UNIVERSITAT DE BARCELONA

Understanding Adiposity through Body Shape Phenotypes: Implications for Cancer Risk, Inflammation, and Prediction

Laia Peruchet Noray

Aquesta tesi doctoral està subjecta a la llicència ***Reconeixement- NoComercial 4.0. Espanya de Creative Commons***.

Esta tesis doctoral está sujeta a la licencia ***Reconocimiento - NoComercial 4.0. España de Creative* Commons**.

This doctoral thesis is licensed under the ***Creative Commons Attribution-NonCommercial 4.0. Spain License***.

Understanding Adiposity through Body Shape Phenotypes: Implications for Cancer Risk, Inflammation, and Prediction

Doctoral thesis presented by

LAIA PERUCHET NORAY

To obtain the PhD degree under the supervision of

Dr. Robert Carreras-Torres

Dr. Heinz Freisling

and tutorship of **Dr. Víctor Raul Moreno Aguado**

Doctorate in Biomedicine

Facultat de Medicina i Ciències de la Salut

Universitat de Barcelona

2024

UNIVERSITAT DE BARCELONA

International Agency for Research on Cancer

World Health Organization

El Dr. **Robert Carreras Torres**, de l'Institut d'Investigació Biomèdica de Girona Dr. Josep Trueta (IDIBGI) i Dr. **Heinz Freisling**, de l'Agència Internacional de Recerca sobre el Càncer (IARC/WHO)

Certifiquen,

Que la tesi doctoral titulada "*Understanding Adiposity through Body Shape Phenotypes: Implications for Cancer Risk, Inflammation, and Prediction"* presentada per **Laia Peruchet Noray**, i co-dirigida per ells reuneix els mèrits per ser defensada davant del tribunal corresponent per a optar al grau de Doctora.

I perquè així consti, signen la present.

Barcelona, setembre de 2024

Laia Peruchet Noray
Doctoranda

Dr. Robert Carreras Torres
Co-director

Dr. Heinz Freisling
Co-director

À ma mamie

ACKNOWLEDGEMENTS

This thesis is the culmination of remarkable experiences over the past three years, made possible by the unwavering professional and personal support of incredible individuals who have stood by my side throughout this journey. I would therefore like to take these lines to express my heartfelt gratitude.

I would like to deeply thank Dr. Heinz Freisling for offering me the opportunity to undertake this thesis. I am truly thankful for your welcome at IARC, for fostering my curiosity, and for allowing me the space to grow independently.

Vull expressar el meu profund agraïment al Dr. Robert Carreras-Torres, no només per ser el meu supervisor, sinó també el meu mentor. Segurament no estaria escrivint aquestes línies si els nostres camins no s'haguessin creuat ara ja fa cinc anys. Tanco aquesta etapa amb el més gran dels somriures (i alguna llàgrima), immensament agraïda per l'oportunitat d'haver après tant de tu.

Thanks to Dr. Niki Dimou to be such a great guidance and support as well as for how our relationship has evolved across the years.

Thanks to Pr. Marc Gunter for being so implicated in this project and for his helpful and valuable advice.

Thanks to Dr. Víctor Raul Moreno Aguado for being my PhD tutor and for facilitating the entire process to achieve this thesis.

Thanks to all the NCM colleagues Alem, Quan, Reynalda, Sarah, Karina, Vivian, Pietro, for all their scientific advice. Specially thanks to Emma for being my partner in crime in this journey.

Thanks to Dr. Anja Sedlmeier for sharing the passion of the body shape phenotypes and to Dr. Laure Dessous for embracing me in her projects.

Thanks to Chrysovalantou, Eileen, Marie, Neimar, Niki, Niko, Ramon, Sabine, and all the current and former NME and IARC colleagues who made this experience so special and unique. Specially thanks to Veronica, my precious gem from IARC, and to Martina, for showing me the importance of balancing seriousness with fun.

Thanks to Anna, Ariadna, Charlotte, Emma, Esther, Hana, and Mira for being my family away from home and for the wonderful memories: Lebanon, Venice, shared meals, coffee breaks, matcha teas, board games, and countless moments I had the pleasure to live with you. My vision of the world has broadened thanks to each of you.

Merci à Henri, Sandrine et Sylvia pour leur gentillesse y a Isabelle por su hospitalidad cuando toda esta aventura empezó.

Tampoc puc acabar aquests agraïments sense mirar endarrere.

Gràcies a tots els Veggies, però sobretot a l'Amaia i la Laura per fer de la vida universitària la millor de les experiències. Estic orgullosa que cadascuna haguem trobat el nostre camí en la ciència.

Gràcies a l'Elsa i la Jorgina per ser tan diferents i tan complementàries. A la Núria i la Sarai per tots els moments compartits al llarg dels anys. I a l'Andreu, per gaudir de créixer junts.

Gràcies als meus pares, Xavier i Claire, per donar-me els valors de l'esforç i el sacrifici i per sempre confiar en mi. Sou els meus referents. Al Jan, per ser el millor dels germans i ensenyar-me que no tot és tan important. I a l'Albert, per viure amb mi les il·lusions i les alegries i afrontar les decepcions. Quina sort que m'acompanyis a cada pas del camí.

« The pursuit of knowledge is the noblest quest »

Hypatia of Alexandria

« Pour les uns, qui voyagent, les étoiles sont des guides »

Antoine de Saint-Exupéry

Table of Contents

ABSTRACT **15**

ABSTRACT (English) 17

ABSTRACT (Spanish) 19

ABSTRACT (Catalan) 21

SCIENTIFIC WORK **23**

ABOUT THE THESIS 25

ABOUT THE PhD CANDIDATE 25

SCIENTIFIC ARTICLES 26

SCIENTIFIC CONFERENCES 30

ACADEMIC TRAINING 31

LIST OF FIGURES AND TABLES **33**

LIST OF ABBREVIATIONS **37**

INTRODUCTION **41**

1. ADIPOSITY **43**

1.1. Definition and epidemiology 43

1.2. Risk factors of obesity 44

1.3. Measurement of adiposity 45

1.3.1. Traditional adiposity indicators: Body mass index (BMI) 45

1.3.2. Traditional adiposity indicators: Waist circumference (WC) 47

1.3.3. Traditional adiposity indicators: Ratios 47

1.3.4. Complex adiposity indicators: A Body Shape Index (ABSI) 48

1.3.5. Complex adiposity indicators: Hip Index (HI) 49

1.3.6. Complex adiposity indicators: Body shape phenotypes 49

1.4. Adipose tissue and inflammation 51

1.5. Prediction of adiposity gain 52

2. CANCER **55**

2.1. Definition and epidemiology 55

2.2. Cancer classification 56

2.3. Hallmarks of cancer 57

3. ADIPOSITY AND CANCER 59
3.1. Epidemiology 59
3.2. Obesity-related cancers and aetiological pathways 60
3.3. Breast cancer 62
3.3.1. Epidemiology of breast cancer 62
3.3.2. Physiopathology of breast cancer 63
3.3.3. Breast cancer classification 64
3.3.4. Aetiology of breast cancer 65
3.4. Colorectal cancer 69
3.4.1. Epidemiology of colorectal cancer 69
3.4.2. Physiopathology of colorectal cancer 69
3.4.3. Aetiology of colorectal cancer 71
4. GENETIC EPIDEMIOLOGY 77
4.1. Genome-Wide Association Studies (GWAS) 77
4.2. Polygenic Risk Scores (PRS) 79
4.3. Mendelian randomization (MR) 80
4.4. Genetics of adiposity 85
5. DATA SOURCES 88
5.1. UK Biobank 88
5.1.1. Anthropometric measurements 89
5.1.2. Genetic data 90
5.1.3. Biomarker measurements 91
5.2. European Prospective Investigation in Cancer and Nutrition (EPIC) 91
5.2.1. Anthropometric measurements 93
5.2.2. Genetic data 93
5.2.3. Biomarker measurements 95
5.3. Genotype-Tissue Expression (GTEx) project 95
5.4. Genetic consortia data for breast and colorectal cancer 97
5.4.1. Genetic data on breast cancer: BCAC 97
5.4.2. Genetic data on colorectal cancer: CORECT, CCFR, and GECCO 98
HYPOTHESES 99
THESIS AIM AND OBJECTIVES 101

SUPERVISORS REPORT **107**

RESULTS **111**

1. STUDY I **113**

2. STUDY II **131**

3. STUDY III **145**

4. STUDY IV **161**

DISCUSSION **185**

1. MAIN FINDINGS AND INTERPRETATION **187**

1.1. The body shape phenotypes 187

1.2. Body shape phenotypes and cancer risk 189

1.3. Molecular pathways between body shape phenotypes and cancer: Inflammation 191

1.4. Preventive strategies for adiposity gain and cancer burden: Prediction 192

2. STRENGTHS AND LIMITATIONS **194**

2.1. Strengths: Data sources 194

2.2. Strengths: Triangulation 194

2.3. Strengths: Sensitivity analysis 195

2.4. Limitations: Body shape phenotypes assessment 196

2.5. Limitations: Methodology and study design 196

2.6. Limitations: Ancestry diversity 197

3. IMPLICATIONS, PUBLIC HEALTH MESSAGES, AND FUTURE DIRECTIONS **198**

CONCLUSIONS **199**

REFERENCES **203**

ANNEXES **227**

1. ANNEX I: Supplementary material Study I 229

2. ANNEX II: Supplementary material Study II 305

3. ANNEX III: Supplementary material Study III 373

4. ANNEX IV: Supplementary material Study IV 405

ABSTRACT

ABSTRACT (English)

Introduction. Obesity is characterized by excess body fat (adiposity) and is a major determinant of disability. Obesity is mainly measured by body mass index (BMI) although it presents several limitations. For instance, BMI does not inform about adiposity distribution nor distinguishes between fat and fit which have different metabolic implications. To overcome these limitations, more comprehensive adiposity indicators such as body shape phenotypes have been proposed. Four distinct body shape phenotypes were derived from a principal component (PC) analysis (PCA) of six anthropometric traits: BMI, height, hip and waist circumferences (WC), weight, and waist-to-hip ratio (WHR); obtaining different subtypes of adiposity. However, it remains unclear whether these phenotypes can enhance our understanding of the pathways associated with disease risk.

Objectives. This thesis integrates findings from multiple large-scale analyses to explore adiposity through body shape phenotypes and investigate their role in cancer risk, inflammatory potential, and adiposity gain prediction. Specifically, this thesis aimed to 1) explore the biological basis of the body shape phenotypes, 2) investigate associations between body shape phenotypes and the risk of major cancers including of the breast and colorectum, 3) assess the associations between traditional and complex adiposity indicators and inflammatory biomarkers, and 4) develop and validate a prediction model of adiposity gain combining environmental and genetic factors.

Methods. This thesis is based on the compilation of four studies. All of them include large-scale epidemiological analyses such as genome-wide association studies and genetic functional analysis for the body shape phenotypes, complementary observational and Mendelian randomization analyses for the associations of the body shapes and breast and colorectal cancer as well as 10 inflammatory biomarkers. Additionally, 5-years adiposity gain prediction models were developed and validated combining environmental factors and polygenic risk scores for 5 adiposity indicators (BMI, WHR, and three body shape phenotypes).

Results. The findings of this thesis revealed that four body shape phenotypes were replicated across different populations. High values of body shape PC1 described overall adiposity, PC2 tall individuals with low WHR, PC3 tall individuals with high WHR, and PC4 athletic individuals. Additionally, body shape phenotypes were associated with independent genetic variants as well as specific gene expression patterns suggesting that they operate through separate molecular pathways. Additionally, their European genetic distribution revealed that individuals from northern countries are genetically more susceptible to higher adiposity than individuals from southern European countries.

PC1 and PC3 were associated with colorectal cancer, by sex, and subsites. For breast cancer, PC1 was inversely associated with overall breast cancer risk, particularly in ER− subtypes. PC2 was weakly linked to an increased risk of breast cancer. More robust positive associations were found between PC2 and Luminal A breast cancer subtype.

This research also identified sex- and phenotype-specific associations between adiposity indicators and inflammatory biomarkers. Traditional obesity measures such as BMI, WC, and WHR and PC1 were positively associated with pro-inflammatory biomarkers like C-reactive protein (CRP), especially in women. In contrast, height and PC2 were inversely associated with inflammation. Interestingly, the association of PC3 and CRP varied by sex being positively associated among men and negatively among women adding a valuable layer of understanding that extends beyond traditional measures of adiposity.

Finally, environmental prediction models for adiposity gain at mid-late adulthood achieved a remarkable predictive ability although were not improved by genetic factors.

Conclusions. Body shape phenotypes could be a valuable tool in research and primary care, enhancing traditional adiposity measures by capturing more subtle underlying biological aspects of adiposity. This approach may improve the accuracy of cancer risk assessment and uncover patterns of systemic inflammation. Additionally, this research provides a practical model for predicting adiposity gain, which could be incorporated into obesity prevention strategies.

ABSTRACT (Spanish)

Introducción. La obesidad se caracteriza por un exceso de grasa corporal (adiposidad) y está considerada como un factor determinante del detrimento de la salud. Principalmente, se mide mediante el índice de masa corporal (IMC), aunque este presenta varias limitaciones. Por ejemplo, no informa sobre la distribución de la adiposidad ni distingue entre grasa y musculatura, lo cual plantea distintas implicaciones metabólicas. Para intentar superar estas limitaciones, se han desarrollado nuevos indicadores de adiposidad más holísticos como los fenotipos de la forma corporal. Estos se derivan de un análisis de componentes principales (ACP) de seis rasgos antropométricos: altura, circunferencia de la cintura (CC) y la cadera, IMC, índice cintura-cadera (ICC) y peso; obteniendo cuatro subtipos de adiposidad distintos e independientes. Sin embargo, aún queda por determinar si estos fenotipos pueden facilitar la comprensión de las vías moleculares asociadas al riesgo de enfermedad.

Objetivos. En esta tesis, se han integrado los hallazgos de múltiples análisis a gran escala para explorar la adiposidad, a través de los fenotipos de la forma corporal, e investigar su papel en el riesgo de cáncer, su potencial inflamatorio y su utilidad en la predicción de aumento de adiposidad. Específicamente, se propuso 1) explorar más en profundidad la base biológica de los fenotipos de la forma corporal, 2) investigar las asociaciones entre los fenotipos de la forma corporal y el riesgo de cánceres principales, como el de mama y el colorrectal, 3) evaluar las asociaciones entre los indicadores de adiposidad tradicionales y complejos y los biomarcadores inflamatorios y 4) desarrollar y validar un modelo de predicción del aumento de adiposidad que combine factores ambientales y genéticos.

Métodos. Este trabajo se ha basado en cuatro estudios. Todos ellos incluyen análisis epidemiológicos a gran escala, como estudios de asociación del genoma completo y análisis genéticos funcionales para los fenotipos de forma corporal, análisis observacionales y de aleatorización mendeliana para las asociaciones entre las formas corporales con el cáncer de mama y colorrectal, así como con 10 biomarcadores inflamatorios. También se incluyen modelos de predicción de aumento de adiposidad que combinan factores ambientales y puntuaciones de riesgo poligénico para 5 indicadores de adiposidad (IMC, ICC y tres fenotipos de forma corporal).

Resultados. Los hallazgos de esta tesis revelaron que los fenotipos de forma corporal se replican entre poblaciones distintas. Valores altos de la forma corporal PC1 describió la adiposidad general, PC2, individuos altos con bajo ICC, PC3, individuos altos con gran ICC y PC4, individuos atléticos. Estos fenotipos de forma corporal se asociaron a variantes genéticas independientes, así como a patrones específicos de expresión génica, sugiriendo que operan a través de vías moleculares independientes.

Además, su distribución genética en Europa reveló que los individuos de los países septentrionales son genéticamente más susceptibles a una mayor adiposidad que los de los países del sur de Europa.

Específicamente, las PC1 y PC3 se asociaron con el cáncer colorrectal, por sexo y subtipos. Para el cáncer de mama, la PC1 estaba inversamente asociado con el riesgo global de cáncer de mama, particularmente con los subtipos ER-. Sin embargo, la PC2 se relacionó débilmente con un mayor riesgo de cáncer de mama. En concreto, se encontraron asociaciones positivas más sólidas entre la PC2 y el subtipo de cáncer de mama Luminal A.

Nuestra investigación también identificó asociaciones específicas de sexo y fenotipo entre indicadores de adiposidad y biomarcadores inflamatorios. Los indicadores de obesidad tradicionales (IMC, CC y ICC) y la PC1 se asociaron positivamente con biomarcadores proinflamatorios como la proteína C reactiva (PCR), especialmente en mujeres. En cambio, la estatura y la PC2 se asociaron inversamente con la inflamación. Curiosamente, la asociación entre la PC3 y la PCR varió en función del sexo, siendo positiva en hombres y negativa en mujeres, revelando más información que los indicadores de adiposidad tradicionales.

Por último, los modelos ambientales de predicción de incremento de la obesidad a medianos y final de la edad adulta alcanzaron una notable capacidad predictiva, aunque no mejoraron con factores genéticos.

Conclusiones. Los fenotipos de la forma corporal podrían ser una herramienta valiosa en investigación y atención primaria dada su capacidad para captar aspectos biológicos subyacentes más sutiles de la adiposidad, complementando así a los actuales indicadores tradicionales. Específicamente, estos fenotipos pueden mejorar la precisión de la evaluación del riesgo de cáncer y revelar patrones de inflamación sistémica. Además, nuestra investigación proporciona un modelo viable para predecir el aumento de la adiposidad, que podría incorporarse a las estrategias de prevención de la obesidad.

ABSTRACT (Catalan)

Introducció. L'obesitat es caracteritza per un excés de greix corporal (adipositat) i està considerada com un factor determinant del deteriorament de la salut. Principalment, es mesura mitjançant l'índex de massa corporal (IMC), tot i que aquest presenta diverses limitacions. Per exemple, no proporciona informació sobre la distribució de l'adipositat ni distingeix entre greix i musculatura, el que planteja diferents implicacions metabòliques. Per intentar superar aquestes limitacions, s'han desenvolupat nous indicadors d'adipositat més holístics com els fenotips de la forma corporal. Aquests es deriven d'una anàlisi de components principals (ACP) de sis trets antropomètrics: alçada, circumferència de la cintura (CC) i del maluc, IMC, índex cintura-maluc (ICM) i pes; obtenint quatre subtipus d'adipositat diferents i independents. No obstant, encara queda per determinar si aquests fenotips poden facilitar la comprensió de les vies moleculars associades al risc de malaltia.

Objectius. En aquesta tesi, s'han integrat els resultats de múltiples anàlisis a gran escala per explorar l'adipositat, a través dels fenotips de la forma corporal, i investigar-ne el paper en el risc de càncer, el seu potencial inflamatori i la seva utilitat en la predicció de l'augment de l'adipositat. Concretament, es va proposar 1) explorar més profundament la base biològica dels fenotips de la forma corporal, 2) investigar les associacions entre els fenotips de la forma corporal i el risc dels principals càncers, com el de mama i el colorectal, 3) avaluar les associacions entre els indicadors tradicionals i complexos d'adipositat i els biomarcadors inflamatoris, i 4) desenvolupar i validar un model de predicció de l'augment de l'adipositat que combini factors ambientals i genètics.

Mètodes. Aquest treball s'ha basat en quatre estudis. Tots ells inclouen anàlisis epidemiològiques a gran escala, com a estudis d'associació del genoma complet i anàlisis genètiques funcionals pels fenotips de forma corporal, anàlisis observacionals i d'aleatorització mendeliana per a les associacions entre les formes corporals amb el càncer de mama i colorectal, així com amb 10 biomarcadors inflamatoris. També s'inclouen models de predicció d'augment d'adipositat que combinen factors ambientals i puntuacions de risc poligènic per a 5 indicadors d'adipositat (IMC, ICM i tres fenotips de la forma corporal).

Resultats. Les troballes d'aquesta tesi van revelar que els fenotips de la forma corporal es repliquen entre poblacions diferents. Valors alts de la forma corporal PC1 descrivien l'adipositat general; la PC2, individus alts amb un baix ICM; la PC3, individus alts amb un gran ICM; i la PC4, individus atlètics. Aquests fenotips de la forma corporal es van associar a variants genètiques independents, així com a patrons específics d'expressió gènica, suggerint que operen a través de vies moleculars independents.

A més, la seva distribució genètica a Europa va revelar que els individus dels països septentrionals són genèticament més susceptibles a una major adipositat que els dels països del sud d'Europa.

Específicament, les PC1 i PC3 es van associar amb el càncer colorectal, per sexe i subtipus. Pel que fa al càncer de mama, la PC1 estava inversament associada amb el risc global de càncer de mama, particularment amb els subtipus ER-. No obstant això, la PC2 es va relacionar dèbilment amb un major risc de càncer de mama. En concret, es van trobar associacions positives més sòlides entre la PC2 i el subtipus de càncer de mama Luminal A.

Aquesta investigació també va identificar associacions específiques de sexe i fenotip entre indicadors d'adipositat i biomarcadors inflamatoris. Els indicadors tradicionals d'obesitat (IMC, CC i ICM) i la PC1 es van associar positivament amb biomarcadors proinflamatoris com la proteïna C reactiva (PCR), especialment en dones. En canvi, l'alçada i la PC2 es van associar inversament amb la inflamació. Curiosament, l'associació entre la PC3 i la PCR va variar en funció del sexe, sent positiva en homes i negativa en dones, revelant més informació que els indicadors tradicionals d'adipositat.

Finalment, els models ambientals de predicció d'increment de l'obesitat a mitjana i avançada edat van aconseguir una notable capacitat predictiva, encara que no van millorar amb factors genètics.

Conclusions. Els fenotips de la forma corporal podrien ser una eina valuosa en recerca i atenció primària, donada la seva capacitat per captar aspectes biològics subjacents més subtils de l'adipositat, complementant així els actuals indicadors tradicionals. Específicament, aquests fenotips poden millorar la precisió de l'avaluació del risc de càncer i revelar patrons d'inflamació sistèmica. A més, aquesta investigació proporciona un model viable per predir l'augment de l'adipositat, que podria incorporar-se a les estratègies de prevenció de l'obesitat.

SCIENTIFIC WORK

ABOUT THE THESIS

This thesis is presented as a compendium of publications and has been conducted during the last three years at the University of Barcelona in Spain and the International Agency for Research on Cancer/World Health Organisation (IARC/WHO) in Lyon, France, under the co-supervision of Dr. Robert Carreras-Torres from the Girona Biomedical Research Institute (IDIBGI) and Dr. Heinz Freisling from IARC as well as close collaboration with Dr. Niki Dimou from IARC and Pr. Marc J. Gunter, former head of the Nutrition and Metabolism Branch, IARC, and current Chair in Cancer Epidemiology and Prevention at Imperial College of London.

This research aimed to understand adiposity through novel, comprehensive adiposity indicators; i.e., multi-trait body shape phenotypes. Thus, it includes research on the role of adiposity in major public health concerns such as its impact on cancer risk and its inflammatory potential. Additionally, the study aimed to improve adiposity prediction as a preventive health strategy. This work includes four original studies. Three articles were published in high-impact peer-review international journals and the other one is currently under review. All of them were included in the results section of this dissertation.

Laia Peruchet-Noray was funded by the World Cancer Research Fund (AdCoCanS project, grant number: IIG_2019_1978) as part of the World Cancer Research Fund International grant program, the French National Cancer Institute (ShapeCancer project, grant number: INCA_14108), and the German Research Foundation (DFG-ShapeSurv project, grant number: BA 5459/2-1).

Where authors are identified as personnel of the International Agency for Research on Cancer/World Health Organisation, the authors alone are responsible for the views expressed in the articles of this thesis and they do not necessarily represent the decisions, policy, or views of the International Agency for Research on Cancer/World Health Organisation.

ABOUT THE PhD CANDIDATE

Laia Peruchet-Noray obtained a degree in Biomedical Sciences from the Universitat de Barcelona in 2020 and a MSc in Bioinformatics and Biostatistics from the Universitat Oberta de Catalunya (UOC) and Universitat de Barcelona in 2021. During her MSc, she joined the Nutrition and Metabolism Branch at IARC under the supervision of Dr. Heinz Freisling in Lyon, France. She continued being part of IARC while she developed her PhD at the University of Barcelona. In 2023, she joined the European Cancer Leagues as Youth Ambassador for the European Code Against Cancer. The scientific work developed during her PhD, including articles, conferences, and other relevant activities are detailed as follows.

SCIENTIFIC ARTICLES

Scientific output of the thesis

1) **Laia Peruchet-Noray,** Anja M. Sedlmeier, Niki Dimou, et al. Tissue-specific genetic variation suggests distinct molecular pathways between body shape phenotypes and colorectal cancer. 2024. *Science Advances*. https://doi.org/10.1126/sciadv.adj1987

   - Mentioned in more than 50 international newspapers and online resources: https://scienceadvances.altmetric.com/details/162667308/news.
   - Laia Peruchet-Noray and Robert Carreras-Torres were interviewed in *El País* journal: "Dos formas corporales se asocian con un mayor riesgo de cáncer de colon". Available at: https://elpais.com/ciencia/2024-04-19/dos-formas-corporales-se-asocian-con-un-mayor-riesgo-de-cancer-de-colon.html

2) **Laia Peruchet-Noray**, Niki Dimou, Anja M. Sedlmeier, et al. Body Shape Phenotypes And Breast Cancer Risk: A Mendelian Randomization Analysis. 2023. *Cancers*. https://doi.org/10.3390/cancers15041296

   - Most Viewed Papers in 2023 in the Section "Cancer Epidemiology and Prevention": https://www.mdpi.com/journal/cancers/announcements/6890
   - Selected Papers in 2023 in the Section "Cancer Epidemiology and Prevention": https://www.mdpi.com/journal/cancers/announcements/8055

3) Esther M. González-Gil*, **Laia Peruchet-Noray***, Anja M. Sedlmeier, et al. Association of body shape phenotypes and body fat distribution indexes with inflammatory biomarkers in the European Prospective Investigation into Cancer and Nutrition (EPIC) and UK Biobank. 2024. *BMC Medicine*. https://doi.org/10.1186/s12916-024-03544-3

   *These authors contributed equally.

4) **Laia Peruchet-Noray**, Niki Dimou, Reynalda Cordova, et al. Nature or nurture: genetic and environmental predictors of adiposity gain in adults. *Under review in EBioMedicine*. http://dx.doi.org/10.2139/ssrn.4898446

Other articles: Published

1) Patricia Bohmann, Michael J. Stein, Hansjörg Baurecht, Emma Fontvieille, **Laia Peruchet-Noray**, et al. Association between distinct body shape phenotypes of multiple anthropometric traits and all-cause and cause-specific mortality in the UK Biobank. 2024. *Epidemiology.* [In press]

2) Hwayoung Noh*, Jeeyoo Lee*, Nazlisadat Seyed Khoei, **Laia Peruchet-Noray**, et al. Serum bilirubin levels and risk of colorectal cancer in Korean adults: Results from the Korean Genome and Epidemiology Study-Health Examinee (KoGES-HEXA) Cohort Study. 2024. *British Journal of Cancer*. [In press]

*These authors contributed equally.

3) Michael J. Stein, Hansjörg Baurecht, Patricia Bohmann, Béatrice Fervers, Emma Fontvieille, Heinz Freisling, Christine M Friedenreich, Julian Konzok, **Laia Peruchet-Noray**, et al. Diurnal timing of physical activity and risk of colorectal cancer in the UK Biobank. 2024. *BMC Medicine.* https://doi.org/10.1186/s12916-024-03632-4

4) Amina Amadou, Heinz Freisling, Anja M Sedlmeier, Patricia Bohmann, Emma Fontvieille, Andrea Weber, Julian Konzok, Michael J. Stein, **Laia Peruchet-Noray**, et al. Multi-Trait Body Shape Phenotypes and Breast Cancer Risk in Postmenopausal Women: A Causal Mediation Analysis in the UK Biobank Cohort. 2024. *Journal of Epidemiology and Global Health*. https://doi.org/10.1007/s44197-024-00226-4

5) Anna Jansana, Aviane Auguste, Marina Kvaskoff, Agnès Fournier, Emma Fontvieille, **Laia Peruchet-Noray**, et al. Impact of pre-existing cardiometabolic diseases on metastatic cancer stage at diagnosis: a prospective multinational cohort study. 2024. *Cancer communications*. https://doi.org/10.1002/cac2.12526

6) Emma Fontvieille, Vivian Viallon, Martina Recalde, Reynalda Cordova, Anna Jansana, **Laia Peruchet-Noray**, et al. Body mass index and cancer risk among adults with and without cardiometabolic diseases: evidence from the EPIC and UK Biobank prospective cohort studies. 2023. *BMC Medicine*. https://doi.org/10.1186/s12916-023-03114-z

7) Reynalda Cordova, Vivian Viallon, Emma Fontvieille, **Laia Peruchet-Noray**, et al. Consumption of ultra-processed foods and risk of multimorbidity of cancer and cardiometabolic diseases: a multinational cohort study. 2023. *Lancet Regional Health-Europe*. https://doi.org/10.1016/j.lanepe.2023.100771

8) Michael J. Stein, Hansjörg Baurecht, Anja M. Sedlmeier, Julian Konzok, Patricia Bohmann, Emma Fontvieille, **Laia Peruchet-Noray**, et al. Association between circadian physical activity patterns and mortality in the UK Biobank. 2023. *International Journal of Behavioral Nutrition and Physical Activity*. https://doi.org/10.1186/s12966-023-01508-z

9) Sofia Christakoudi, Konstantinos K. Tsilidis, Laure Dossus, [...], **Laia Peruchet-Noray,** Heinz Freisling, Elio Riboli. A body shape index (ABSI) is associated inversely with post-menopausal progesterone-receptor-negative breast cancer risk in a large European cohort. 2023. *BMC Cancer.* https://doi.org/10.1186/s12885-023-11056-1

10) Anja M. Sedlmeier, Vivian Viallon, Pietro Ferrari, **Laia Peruchet-Noray**, et al. Body shape phenotypes of multiple anthropometric traits and cancer risk: a multi-national cohort study. 2023. *British Journal of Cancer.* https://doi.org/10.1038/s41416-022-02071-3

Other articles: Under review or in preparation

1) **Laia Peruchet-Noray**, Anja M. Sedlmeier, Niki Dimou, et al. Body shape phenotypes and cancer risk: an observational and Mendelian randomization analysis. *In preparation.*

2) Niki Dimou, **Laia Peruchet-Noray**, Daniela Mariosa, et al. Healthy lifestyle index and risks of colorectal, breast, and pancreatic cancer: A genome-wide association and Mendelian randomization study. *Under review in BMC Medicine.*

3) Rola F. Jaafar, **Laia Peruchet-Noray**, Esther Gonzalez-Gil, et al. Association between adiposity phenotypes and inflammation and metabolic biomarkers among premenopausal women: a cross-sectional study in Latin America. *Under review in Journal of Public Health Research.*

4) Michael J. Stein, Hansjörg Baurecht, Patricia Bohmann, Pietro Ferrari, Béatrice Fervers, Emma Fontvieille, Heinz Freisling, Christine M Friedenreich, Marc J. Gunter, **Laia Peruchet-Noray**, et al. Usual walking pace and risk of 28 types of cancer – an observational and Mendelian randomization study in the UK Biobank. *Under review in BMJ Open Sports and Exercise Medicine.*

5) Emma Fontvieille, Anna Jansana, **Laia Peruchet-Noray**, et al. Body mass index and breast cancer risk among postmenopausal women with and without cardiometabolic diseases: findings from the EPIC and UK Biobank prospective cohort studies. *Under review in JACC CardioOncology.*

6) Patricia Bohmann*, Michael J. Stein*, Amina Amadou, Hansjörg Baurecht, Béatrice Fervers, Emma Fontvieille, Heinz Freisling, Christine M Friedenreich, Julian Konzok, **Laia Peruchet-Noray**, et al. WHO guidelines on waist circumference and physical activity and their joint association with cancer risk. *Under review in British Journal of Sports Medicine.*

*These authors contributed equally.

7) Emma Fontvieille, Amina Amadou, **Laia Peruchet-Noray**, et al. Body mass index and cardiometabolic diseases in relation to mortality among adults with obesity-related cancer: a multinational cohort study. *In preparation.*

8) Emma Fontvieille, Vivian Viallon, **Laia Peruchet-Noray**, et al. Associations of incident CVD with overall and lifestyle-related cancer risk, in two large European prospective cohorts. *In preparation.*

9) Patricia Bohmann, Michael J. Stein, Hansjörg Baurecht, Emma Fontvieille, **Laia Peruchet-Noray**, et al. Association between distinct body shape phenotypes of multiple anthropometric traits and all-cause and cause-specific mortality in cancer survivors in EPIC. *In preparation.*

10) Marie Breeur, Joshua Atkins, **Laia Peruchet-Noray**, et al. Autoencoders Reveal PUFA-Related Metabolic Signatures Linked to Cancer Risk. *In preparation.*

11) Maria Pfeifer, Michael F Leitzmann, Patricia Bohmann, Michael J. Stein, Lam C. Tsoi, James T. Elder, Phil Stuart, Emma Fontvieille, Heinz Freisling, **Laia Peruchet-Noray**, et al. Using body shapes refines risk profiles in psoriasis: A Mendelian Randomization study. *In preparation.*

12) Quan Gan, Emma Fontvieille, Reynalda Cordova, **Laia Peruchet-Noray**, et al. Circadian physical activity, and risk of multiple diseases and death in UK Biobank. *In preparation.*

13) Quan Gan, Anna Jansana, Emma Fontvieille, **Laia Peruchet-Noray**, et al. Imaging-derived adiposity phenotypes and prediction of mortality and cancer and cardiometabolic diseases. *In preparation.*

14) Alem Abraha, Emma Fontvieille, Quan Gan, **Laia Peruchet-Noray**, et al. Physical activity and cancer risk among adults with and without cardiometabolic diseases: evidence from the EPIC and UK Biobank prospective cohort studies. *In preparation.*

15) Manon Cairat, Elea Olivier, Julie Neau, **Laia Peruchet-Noray,** et al. Quality evaluation of previous studies on glucocorticoid and risk-specific cancers: a systematic review. *In preparation.*

16) Fernanda Morales Berstein, Joshua Atkins, Marie Breeur, Peter van der Most, Sinara Rossato, Kiara Chang, Neha Khandpur, Niki Dimou, Ruhina Laskar, **Laia Peruchet-Noray**, et al. Genome-wide association study of the consumption of foods by their degree of processing. *In preparation.*

SCIENTIFIC CONFERENCES

1) **Laia Peruchet-Noray**, Niki Dimou, Hansjörg Baurecht, Amina Amadou, Robert Carreras-Torres, Heinz Freisling. Body shape phenotypes and risk of six obesity-related cancers: a Mendelian randomization study. 2024. *6th Mendelian randomization conference.* **Oral presentation**

2) **Laia Peruchet-Noray**, Anja M. Sedlmeier, Niki Dimou, Hansjörg Baurecht, Béatrice Fervers, Vivian Viallon, Pietro Ferrari, Robert Carreras-Torres, Marc J. Gunter, Heinz Freisling. Genetic characterization of body shape phenotypes and associations with colorectal cancer risk. 2023. *30th European Congress on Obesity.* **Poster presentation**

3) **Laia Peruchet-Noray**, Anja M. Sedlmeier, Niki Dimou, Hansjörg Baurecht, Béatrice Fervers, Vivian Viallon, Marc J. Gunter, Pietro Ferrari, Robert Carreras-Torres, Heinz Freisling. Body shape phenotypes and colorectal cancer risk: a triangulation approach. 2022. *American Institute for Cancer Research (AICR) Research Conference.* **Poster presentation**

4) **Laia Peruchet-Noray**, Niki Dimou, Anja M. Sedlmeier, Béatrice Fervers, Isabelle Romieu, Vivian Viallon, Marc J. Gunter, Pietro Ferrari, Robert Carreras-Torres, Heinz Freisling. Body shape phenotypes and breast cancer risk: a Mendelian randomization analysis. 2022. *Society for Social Medicine & Population Health Annual Scientific Meeting*. **Poster presentation**

5) **Laia Peruchet-Noray**, Niki Dimou, Anja M. Sedlmeier, Béatrice Fervers, Isabelle Romieu, Vivian Viallon, Marc J. Gunter, Pietro Ferrari, Robert Carreras-Torres, Heinz Freisling. Silhouette corporelle et probabilité de développer un cancer du sein: une étude génétique. 2022. *Soirée «Alimentation et cancer», Cancéropôle Lyon Auvergne Rhône-Alpes (CLARA*). **Poster presentation**

ACADEMIC TRAINING

1) **Intermediate Mendelian randomization course**, University of Bristol, 2024.
2) **Complex Trait Analysis of Next Generation Sequence Data Course**, Max Delbrück Center for Molecular Medicine, 2023.
3) **R Shiny for beginners**, International Agency for Research on Cancer (IARC/WHO), 2023.
4) **Tartu Winter School of Evolution, Genomics and Medicine**, University of Tartu, 2022.
5) **Effective Scientific Posters**, International Agency for Research on Cancer (IARC/WHO), 2022.
6) **Science Communication**, International Agency for Research on Cancer (IARC/WHO), 2022.
7) **Introduction to Bayesian Statistics**, International Agency for Research on Cancer (IARC/WHO), 2022.
8) **Multivariate analysis for -omics data integration: principles and applications**, International Agency for Research on Cancer (IARC/WHO) in collaboration with Swiss Institute of Bioinformatics (SIB), 2021.

LIST OF FIGURES AND TABLES

LIST OF FIGURES

Figure 1. Estimates of prevalence of obesity (BMI ≥30 kg/m²) in adults worldwide.

Figure 2. Body shape phenotypes loadings.

Figure 3. Age-standardized cancer incidence rate per 100,000 worldwide in 2022.

Figure 4. Incidence and mortality absolute numbers for cancer sites in the WHO European Region (2022).

Figure 5. Hallmarks of cancer.

Figure 6. Fraction of all cancer cases attributable to high BMI worldwide (2012).

Figure 7. Cancer cases attributable to high BMI by anatomical site in Europe (2012).

Figure 8. Age-standardized breast cancer incidence rates per 100,000 worldwide in 2022.

Figure 9. Age-standardized breast cancer mortality rates per 100,000 worldwide in 2022.

Figure 10. Age-standardized colorectal cancer incidence rates per 100,000 worldwide in 2022.

Figure 11. Age-standardized colorectal cancer mortality rates per 100,000 worldwide in 2022.

Figure 12. Comparison of RCT and MR study designs illustrated with the assessment of the association between serum calcium levels and coronary heart disease.

Figure 13. MR assumptions exemplified with the potential causal association between alcohol intake and coronary heart disease.

Figure 14. Examples of horizontal (A) and vertical (B) pleiotropy in MR.

Figure 15. UK Biobank 22 assessment centres in England, Scotland, and Wales.

Figure 16. EPIC assessment centres across Europe.

Figure 17. Tissue samples included in the GTEx project.

LIST OF TABLES

Table 1. Classification of adults according to BMI.

Table 2. Main characteristics of molecular cancer subtypes.

Table 3. Genotyping platform and sample size for each EPIC case-control study.

Table 4. Details on sample size and tumour heterogeneity for the BCAC data according to tumour marker and grade.

Table 5. Details on author's role, journal, and impact factor (2023) for each study included in this thesis.

LIST OF ABBREVIATIONS

ABSI: A Body Shape Index

AUC: Area Under the ROC Curve

BCAC: Breast Cancer Association Consortium

BMI: Body Mass Index

CCFR: Colon Cancer Family Registry

CI: Confidence Interval

CORECT: Colorectal Transdisciplinary Study

CRP: C-Reactive Protein

DALY: Disability-Adjusted Life Years

EPIC: European Prospective Investigation into Cancer and Nutrition

eQTL: Expression Quantitative Trait Loci

ER: Oestrogen Receptor

GECCO: Epidemiology of Colorectal Cancer Consortium

GTEx: Genotype-Tissue Expression project

GWAS: Genome-Wide Association Study

HC: Hip Circumference

HER2: Human Epidermal Growth Factor Receptor

HI: Hip Index

HRC: Haplotype Reference Consortium

HR: Hazard Ratio

HRT: Hormonal Replacement Therapy

IARC: International Agency for Research on Cancer

IGF: Insulin-like Growth Factor

IL: Interleukins

INF-γ: Interferon-Gamma

LD: Linkage Disequilibrium

MAF: Minor Allele Frequency

MR: Mendelian Randomization

MRI: Magnetic Resonance Imaging

NCD: Non-Communicable Disease

OR: Odds Ratio

PC: Principal Component

PC1: Body shape phenotype 1 (overall obesity)

PC2: Body shape phenotype 2 (tall, low WHR)

PC3: Body shape phenotype 3 (tall, high WHR)

PC4: Body shape phenotype 4 (athletic)

PCA: Principal Component Analysis

PR: Progesterone Receptor

PRS: Polygenic Risk Score

RCT: Randomized Control Trial

RNA-Seq: RNA Sequencing

RR: Relative Risk

SNP: Single Nucleotide Polymorphisms

TNF-α: Tumour Necrosis Factor-Alpha

WC: Waist Circumference

WGS: Whole Genome Sequencing

WCRF: World Cancer Research Fund

WHO: World Health Organization

WHR: Waist-to-Hip Ratio

WHtR: Waist-to-Height Ratio

INTRODUCTION

1. ADIPOSITY

1.1. Definition and epidemiology

Adiposity is defined as the degree of body fat accumulation and is used to denote excess body fat.[1] Overall adiposity is usually known as obesity, a chronic, relapsing, and multifactorial disease.[2] Obesity is an important public health challenge worldwide and is associated with several non-communicable diseases (NCDs) such as certain cancers, cardiovascular diseases, and type 2 diabetes mellitus.[3,4]

The prevalence of obesity is rising globally in both men and women irrespective of the socioeconomic position.[3] Differences in the prevalence of obesity across countries are presented in Figure 1. Additionally, the prevalence of obesity doubled among adults (≥18 years old) from 1990 (7% of population) to 2022 (16% of population)[5] when more than 1 billion individuals worldwide were living with obesity.[6] Developed regions such as parts of America, Oceania, and Europe show higher and plateauing levels while emerging countries show a fast level rise indicating that the biggest impact is yet to come.[3] The main reason is likely to be the double burden of malnutrition (i.e., coexistence of undernutrition and overweight, obesity, or diet related NCDs) that prevails in these countries.[3,5]

In Europe, 23% of adults are currently living with obesity, and the prevalence is projected to increase by 30% in 2030, accounting for approximately 215 million individuals.[3] Additionally, 25% of the disability-adjusted life years (DALYs; i.e., amount of ill health, including premature death and disability, due to specific diseases[7]) and 21.58% of deaths result from high body mass index (BMI), being a major determinant of disability and death in the World Health Organization (WHO) European Region.[3,4]

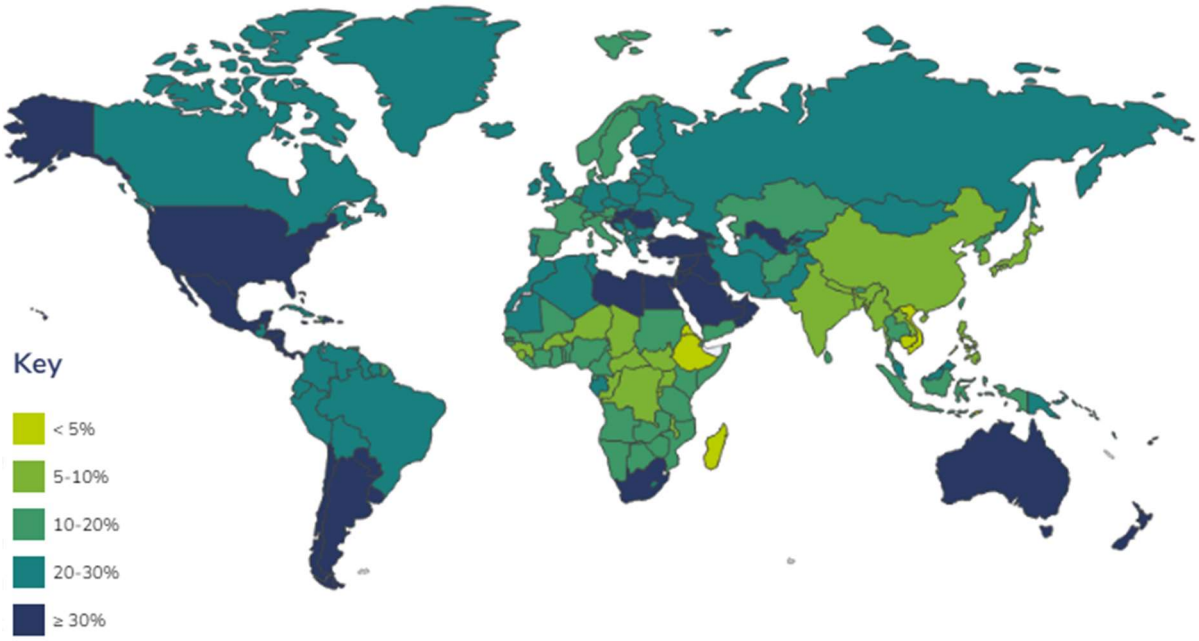


Figure 1. Estimates of prevalence of obesity (BMI ≥30 kg/m²) in adults worldwide. Source: NCD RisC available at https://www.ncdrisc.org/data-downloads-adiposity.html and World Obesity Federation available at https://data.worldobesity.org.

1.2. Risk factors of obesity

The growth of adipose tissue results from an energy imbalance that occurs when the energy intake is higher than the energy expended over a period of time which may in turn result in obesity.[8] Obesity is a multifactorial disease caused by a complex interplay between biological, psychosocial, and behavioural factors.[8] In the late 1990s, the term "obesogenic environment" appeared aiming to describe "the sum of influences that the surroundings, opportunities or conditions of life have on promoting obesity in individuals or populations".[9] This term describes all the environmental factors that act in either energy intake or expenditure, also including costs, laws, policies, social and cultural attitudes, and values.[10]

The relationship between environment and health is not obvious given the complex nature of environments. Simplistically, environments can be categorized as supportive or unsupportive of health which, in the context of obesity, translates to environments that support or are unsupportive of healthy eating patterns and physical activity.[11,12] Further research has also described the environment as an interaction between the microenvironments (e.g., school, workplace, home, neighbourhood) and the macroenvironments (education and health systems, govern policy, and society's attitudes and beliefs).[9]

Food environment is a key aspect of the obesogenic environment which includes availability and accessibility to food, advertising, and marketing.[13] European dietary patterns have experienced nutrition transition (i.e., nutrition change based on rising incomes and food supply)[14,15] and a decrease in occupational and habitual physical activity due to the technology development.[16–18] Additionally, and closely related to the advancements in the technology field, there is a current rising concern on the commercial determinants of obesity which influence the food environment. These determinants include the availability, promotion, and pricing of food items,[19] social media and related-digital food advertising and marketing,[20] and the food and beverage industries influencing the policy-making process, especially in more vulnerable ages (childhood).[21,22]

The food environment is closely related to the built environment. Built environment includes its physical design, land use patterns (residential, commercial, office, industrial, and other activities), and the transportation systems.[23] How the environment is built affects mainly the physical activity levels by factors that encourage walking and cycling. For instance, increased residential densities, neighbourhood design features such as local shops, the presence and quality of pavements and footpaths, and enjoyable scenery, and perception of safety.[24]

Other factors that influence the development of obesity include behavioural patterns, socio-demographic characteristics such as age (individuals gain weight while they age although it decreases in late adulthood), gender (women present higher rates of obesity than men in most countries), ethnicity and cultural influences, socioeconomic status, among others.[3,24,25]

Finally, biological aspects such as genetic, hormonal, and gut microbiome related factors, prenatal exposures, sleep deprivation, and psychological factors can also lead to obesity.[26] Genetic bases of adiposity, which are of main interest for this thesis, are further described in another section of the introduction (see section 4.4. Genetics of adiposity).

1.3. Measurement of adiposity

Different methods to estimate adiposity have been developed which mainly involve traditional indicators such as BMI, waist circumference (WC), waist-to-hip ratio (WHR), skinfolds, as well as more advanced techniques such as bioelectrical impedance analysis (BIA), dual energy x-ray absorptiometry (DEXA), computerized tomography (CT), and magnetic resonance imaging (MRI), among others.[27–29]

While underwater weighing (densitometry), air-displacement plethysmography, dilution method (hydrometry), DEXA, CT, and MRI are considered direct methods to assess adiposity as well as reference standards due to their high accuracy,[27–29] they will not be further presented as they are not typically used in large cohort epidemiological research studies rather in small sample population given their limitations. These include that they are expensive, time consuming, based on immovable equipment, and may expose to small doses of radiation which is then restricted to some population groups (e.g., not applicable to pregnant women).[27–29]

Other indirect methods such as BMI, WC, and WHR, are widely used in epidemiological studies to assess overall adiposity or its distribution given their ease of calculation, their global acceptance by both clinicians and researchers, their high correlation to body fat measured by direct methods, and their inexpensiveness.[27–29]

1.3.1. Traditional adiposity indicators: Body mass index (BMI)

BMI is assessed by dividing weight (kg) by the squared of the height (m^2).[4,27–29] BMI is the goal standard metric in clinical and research to estimate the levels of total adiposity of an individual given that height and weight measurements are non-invasive, are included routinely in clinical and population health questionnaires, and no skills or expensive equipment are required.[4,27–29]

WHO has defined standardized age- and sex-independent cut-offs for underweight, normal, weight, overweight, and obesity status (Table 1).[4,27–30] Being able to categorize BMI in risk categories is of high importance for several reasons. First, it allows meaningful weight comparisons both within and between populations that are meaningful. Second, it is useful in discriminate individuals and groups at higher risk of morbidity and mortality. Third, it helps to identify the priorities for intervention at individual and community levels. Finally, BMI provides a solid foundation for evaluating interventions.[29]

Table 1. Classification of adults according to BMI.[4,27–30]

Category	BMI
Underweight	<18.5
Normal weight	18.5 to <25
Overweight	25 to <30
Obesity	≥30
Obesity class I	30 to <35
Obesity class II	35 to <40
Obesity class III	≥40

Although BMI is a useful metric to quantify obesity, it needs to be considered with the following limitations:

i. BMI is an indirect and imperfect measurement that cannot efficiently distinguish between adipose and other tissues such as lean body mass.[27–29,31] Thus, BMI cannot discriminate individuals with excess body fat but with a healthy weight nor, conversely, individuals with high levels of lean body mass but high weight. This was particularly shown in a previous meta-analysis aimed to assess the performance of BMI to determine obesity among men and women.[32] Specifically, sensitivity and specificity among men were 49.6% and 97.3%, respectively, while were 51.4% and 95.4% among women.[32] This demonstrates that BMI fails to classify 50% of individuals with excess of body fat as individuals living with obesity.

ii. Although BMI cut-offs are supposed to be age- and sex-independent, individuals scoring the same BMI may not reflect the same amount of fat mass.[4,27–30] This can be applicable to different populations, certainly by sex, age, and ethnicity:[33–41] BMI predicts body fat better in young and middle-aged adults than in the elderly, and for the same BMI, women show higher percentages of body fat than men, Asians have 3-5% higher total body fat than white Europeans,[38] blacks

have lower body fat and higher lean muscle mass than whites,[39,40] and Hispanic women have a higher % body fat than black and white American women.[41] The most pronounced differences are in Asian populations, which has led to WHO recommending lower cut-offs values for overweight and obesity than for Caucasian populations.[28,29,42]

iii. BMI is not capable to inform about the distribution of the body fat, especially among individuals with a BMI below 30 kg/m^2.[27,29,31] Abdominal fat was associated with a higher risk of health outcomes such as cardiovascular diseases and type 2 diabetes than overall adiposity (measured by BMI).[4,43–48] Additionally, the risk differs depending on the anatomical subsite of abdominal adiposity. For instance, it is higher when abdominal fat is visceral or intra-abdominal (i.e., fat surrounding the organs of the abdominal cavity) than subcutaneous (i.e., fat found between the dermis and the underlying fascia).[4,43–48]

1.3.2. Traditional adiposity indicators: Waist circumference (WC)

WC is a surrogate marker of abdominal adiposity.[27,49–51] Higher fat levels in the abdominal region are shown to be an important factor in health, independently of BMI.[4,44–48] WC can be measured in up to 8 different ways which can affect the reproducibility and comparability with different classifications.[28,52] However, WHO recommends the use of the midpoint WC measurement, between the lowest rib and the iliac crest.[51,53] WC is easy to measure, inexpensive, correlates well to abdominal fat assessed by most accurate direct methods, predicts the development of disease and death, and provides commonly used cut-offs.[4,27–29] These cut-offs are decided based on the substantial risk of metabolic complications such as cardiovascular diseases, risk factors of cardiovascular diseases, and type 2 diabetes.[51] Contrary to BMI, cut-offs are sex-dependent being >102 and >88 cm in men and women, respectively.[51] WC may be more difficult to measure in individuals with a BMI of 35 or higher leading to less accurate measurements.[27,29]

Given the independent and additive information to BMI of predicting morbidity and mortality, WC is highly recommended to be used in combination to BMI as their combination confers a better prediction of disease risk.[28,54,55]

1.3.3. Traditional adiposity indicators: Ratios

WHR is, likewise WC, a surrogate marker of abdominal adiposity.[4,27–29,49,51] It is calculated dividing the WC by hip circumference (HC) in the same units.[27,29,51] Cut-offs indicating a substantially increased risk of metabolic complications are also sex-dependent, being ≥0.90 for men and ≥0.85 for women.[51] WHR is inexpensive to measure, well correlated to body fat measurements of direct approaches, and is associated with morbidity and mortality, likely achieving a better prediction of adiposity for the latest

than BMI.[27,29,43,56] Compared to WC, WHR is less interpretable as its high values can be from increased abdominal fat or decreased lean muscle mass around the hips.[27,29] Additionally, WHR relies on two measurements: WC and HC, being more prone to measurement error. WHR is less accurate in individuals with a BMI of 35 or higher.[27,29]

Waist-to-height ratio (WHtR) is an emerging indicator to assess obesity and it is calculated dividing the WC by height, both measured in the same units.[28] Measuring WC without accounting for height can lead to overestimating fat mass in taller individuals and underestimating it in shorter ones.[57] WHtR has been increasingly used as it is inexpensive to measure, easy to report, highly correlated to abdominal fat measured by imaging techniques,[58] and may predict early disease risk,[59] morbidity, and mortality better than BMI.[60] The cut-off to define obesity is >0.5 and is invariant by sex, age (including children), and ethnicity group, simplifying public health messages.[60,61]

Despite the aforementioned limitations, traditional indicators still have a role as primary tool for classifying individuals with excess adiposity. However, complex multi-trait adiposity indicators are being developed to overcome some of the limitations.

1.3.4. Complex adiposity indicators: A Body Shape Index (ABSI)

ABSI aims to discern the impact on health from body shape (central adiposity proxying abdominal fat deposits) than from body size.[62] WC is sensitive to body size and fat percentage and distribution as it is highly correlated to BMI, HC, weight, WHR, and WHtR. Therefore, all these adiposity indicators may be interchangeable and may not add much information in adiposity assessment. However, ABSI is uncorrelated to BMI, weight, and HC, has a modest correlation ($r \approx 0.4$-0.5) with WC and WHtR, and higher correlation ($r \approx 0.6$-0.8) with WHR.[62,63] ABSI is an allometric (i.e. scale body dimensions[64,65]) trait derived from WC, height, and weight (Equation 1), and its interpretation is not straightforward.[62] High ABSI values are interpreted as a higher WC than expected for a given height and weight or, in other words, the body volume is more concentrated in the centre of the individual and smaller fraction of mass as limb muscle.[62] ABSI was a more reliable indicator than BMI and other indices of abdominal obesity to predict all-cause mortality.[62,63]

$$ABSI = \frac{WC}{BMI^{\frac{2}{3}}\, height^{\frac{1}{2}}} \qquad Equation\ 1$$

1.3.5. Complex adiposity indicators: Hip Index (HI)

Comparable to ABSI and WC, HI was developed as an allometric indicator of body composition reflecting HC without accounting for weight and height.[66] HI is calculated as following:

$$HI = HC\left(\frac{H}{[H]}\right)^{0.310}\left(\frac{W}{[W]}\right)^{-0.482} \qquad Equation\ 2$$

with H denoting height in cm, W weight in kg, and [H] and [W] the sample average values. [66] HI is positively correlated to HC (r ≈ 0.3-0.4), negatively to WHR (r ≈ -0.5), and uncorrelated to weight, height, BMI, WC, WHtR, and ABSI.[63,66] Thus, HI, together with BMI and ABSI, are indicators of body size and shape that capture potential risk patterns related to body fat.

1.3.6. Complex adiposity indicators: Body shape phenotypes

Body shape phenotypes are based on a principal component (PC) analysis (PCA) of traditional adiposity indicators,[67] and are of high importance for this thesis.

PCA is a multivariate statistical method that aims to reduce data dimensions.[68] PCA linearly combines information from several correlated variables into PCs which reflect the main features of the baseline variables. Each derived PC accounts for an orthogonal major proportion of the total of variance of the original variables (i.e., not correlated and therefore capturing independent variance in the data). PCs are constructed based on the coefficient of the variables (also called loadings) that informs on the contribution of each baseline variable to each PC. This contribution can be positive or negative. From a PCA, the maximum PCs obtained are equal to the number of baseline variables. PC1 is representative of the summary of what baseline variables have most in common and, therefore, is the one that most correlates to all baseline variables. From the variance still unexplained by PC1, PC2 will attempt to capture the most variance remaining. This process will be further applied until the number of PCs equal the number of baseline variables and will reach the sum of variance explained by the PCs, the total variance of the original variables.[68]

Body shape phenotypes are calculated using a PCA of BMI, height, HC, WC, weight, and WHR.[67] Body shape phenotypes have been first derived in 173,278 individuals from the Genetic Investigation of ANthropometric Traits (GIANT) Consortium.[67] The first four PCs explained more than 99% of the variance and reflected different body dimensions.[67] The first PC explained 64.4% of the included traits with high loadings in all traits, except for height. PC1 reflects, therefore, overall adiposity. The second PC explained 18.5% of the variation and showed high but opposite loadings for height and WHR. PC2 characterized short individuals with large WHR to tall individuals with low WHR. PC3 explained 13.8% of the variance and broadly showed high and same direction loadings for height and WHR. Then, PC3

could be describing tall individuals with high WHR and short individuals with low WHR. Lastly, PC4 explained 3% of the total variance. It showed high loadings on BMI and weight but low ones on HC and WC. Although it is the PC harder to interpret, it is likely to be describing an athletic phenotype.[67]

Body shape phenotypes were derived in 340,152 individuals from the European Prospective Investigation into Cancer and Nutrition (EPIC) showing similar loadings to the previous study in GIANT (Figure 2)[69] and among men and women.[67,69] Previous literature on the genetic bases of body shape phenotypes and their associations with cancer risk concluded that these phenotypes may reveal underlying adiposity related biological pathways that seem undetected by traditional indicators.[67,69]

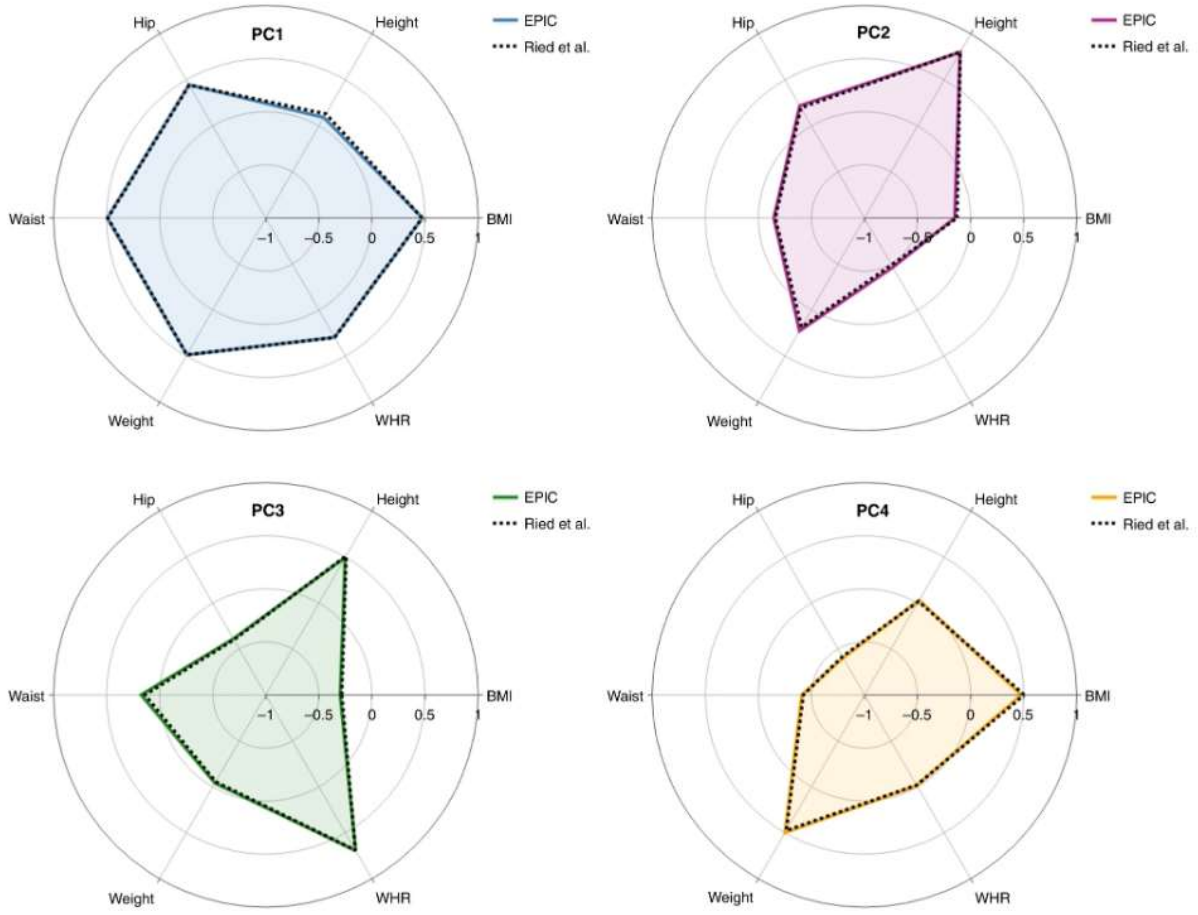


Figure 2. Body shape phenotypes loadings. Source: Sedlmeier, A. M. et al. Body shape phenotypes of multiple anthropometric traits and cancer risk: a multi-national cohort study. Br J Cancer 128, (2023).

The genetic basis of the body shape phenotypes has been described in another section (see section 4.4. Genetics of adiposity) as well as their association with cancer risk (see section 3. Adiposity and cancer).

This thesis aimed to enhance the molecular understanding and characterization of body shape phenotypes, investigating their potential in complementing traditional adiposity indicators, thereby improving their accuracy in assessing adiposity subtypes.

1.4. Adipose tissue and inflammation

Adipose tissue is composed in its majority by adipocytes (fat cells) which contain a single large lipid droplet. It is also composed by preadipocytes (fat stem cells), fibroblasts, blood cells, endothelial cells, macrophages, leukocytes, and other cells involved in inflammatory processes.[70–73] Adipose tissue is present in different body regions being 80% of total body fat under the skin – known as subcutaneous adipose tissue or SAT – and the remaining 20% around digestive organs – known as mesenteric and omental adipose tissue or OAT.[74] Adipose tissue can be classified into 3 main categories that distinguish its morphology and metabolic functions: white, brown, and beige (also known as brite, brown-in-white, brown-like).[75,76] White adipose tissue is primarily involved in energy storage, brown is predominantly responsible for non-shivering thermogenesis certainly in small mammals and human neonates, and beige is a hybrid form of adipose tissue that shares characteristics with white and brown adipose tissues expending energy to generate heat during cold exposure (i.e., cold-induced thermogenesis).[77–80] Although adipose tissue's main function is to store energy in form of triacylglycerols (given that white adipose tissue represents most of the proportion of the total adipose tissue), it is considered an active secretory organ as it sends and respond to signals that influence the appetite, energy expenditure, insulin sensitivity, endocrine and reproductive systems, bone metabolism, and inflammation and immunity modulation.[80–83] Several studies suggest that adipose tissue can secrete approximately more than 50 hormones and signalling molecules referred to as adipokines that play an essential role in inflammation.[84,85]

Inflammation is an adaptative immune response triggered by infection, tissue or cell injury, or damage.[86] Obesity is associated with a chronic low-grade systemic inflammation that is also related to alterations in insulin resistance, hypertension, atherosclerosis, and cancer.[84,87–89] Importantly, inflammation is one of the main mechanistic pathways reported that could explain the association between obesity and cancer.[90] While adipose tissue of lean individuals showed to secrete anti-inflammatory adipokines such as interleukins (IL) IL-1, IL-4, IL-10, IL-13, receptor antagonist (IL-1Ra), adiponectin, and interferon-gamma (INF-γ), among others; adipose tissue of individuals with obesity secretes pro-inflammatory adipokines such as IL-1β, IL-6, IL-8, IL-17, and IL-18, C-reactive protein (CRP), leptin, and tumour necrosis factor-alpha (TNF-α), among others.[84,91] In short, IL are a type of cytokine that play essential roles to modulate growth, differentiation, and activation of immune cells during inflammatory and immune responses.[92] CRP is a widely used marker of acute inflammation as its levels increase and decrease fast in response to a variety of cytokines in presence of trauma and its resolution, respectively.[93] Adiponectin controls glucose uptake and lipids metabolism, by reducing gluconeogenesis and enhancing glycolysis and fatty acid oxidation in the liver.[94] Leptin is a hormone that acts to regulate appetite and energy balance.[95] TNF-α is produced in acute inflammation processes

by macrophages and acts in diverse range of signalling events within cells, leading to necrosis or apoptosis.[96] INF-γ increases macrophage accumulation[97] which has been correlated to adiposity and adipocyte size.[98–100]

Traditional adiposity indicators such as weight, BMI, HC, WC, and WHR showed similar associations with inflammatory biomarkers. Specifically, BMI was positively associated with CRP, leptin, IL-6, and TNF-α levels[101–105] as well as neutrophil, monocyte, and lymphocyte count,[106] whereas it was inversely associated with adiponectin.[107,108] Positive associations were found for weight and other adiposity distribution indicators such as HC, WC, and WHR with CRP, IL-6, and TNF-α levels.[102,103,105] Additionally, WHR was inversely associated with adiponectin levels.[108] Regarding complex adiposity indicators, evidence of a positive and inverse association between ABSI and HI, respectively, and CRP, neutrophils, monocytes, and lymphocytes count were reported.[106] However, the vast majority of these studies were based on small sample sizes (hundred or a few thousands of individuals) as well as they were focused on few inflammatory biomarkers and anthropometric traits.

This thesis aimed to better understand the inflammatory profile associated with traditional and complex adiposity indicators, and in particular the body shape phenotypes. This was further extended to sex-specific associations.

1.5. Prediction of adiposity gain

A clinical prediction model is designed to estimate the likelihood of a specific outcome based on multiple predictors.[109] These models help personalize diagnostic and therapeutic decision-making in healthcare practice by assessing the probability of the presence, occurrence, or future progression of an outcome.[109]

Prediction models highly rely on the predictors they incorporate, making the selection of these predictors crucial to the model's development and validity.[110] Prediction selection is normally performed before and during the modelling.[110] Before modelling, predictors are selected based on clinical reasoning, relevant literature, expert knowledge, and the cost or burden of measurement.[110] Following this preselection, candidate variables are often chosen based on their univariable associations with the outcome, without further adjustments. However, this method has limitations, as it fails to account for confounding factors from other predictors, which can lead to incorrect inclusion or exclusion decisions.[110] Alternative methods for predictor selection include automated techniques such as forward selection, backward elimination, or stepwise selection, which typically result in more streamlined models. These methods, however, rely on different statistical criteria, like the F-statistic or Akaike information criterion (AIC), to decide which variables to include or exclude. As a result, predictor selection can become unstable, influenced by random variations in the data.[110]

The measures of association are not directly linked to a predictor's ability to classify a participant.[111] Thus, the performance of the prediction models is typically evaluated using various statistics that measure their discriminative ability. Common metrics include the area under the receiver operating characteristic (ROC) curve (AUC).[112] The AUC compare sensitivity (i.e., proportion of subjects with the target condition who correctly receive a positive test results) versus specificity (i.e., proportion of subjects without the target condition who correctly receive a negative test result) across a range of values for the ability to predict a dichotomous outcome.[112] AUC ranges from 0.5, indicating no discriminatory power, to 1, representing perfect discrimination.[112] These metrics are important when comparing different prediction models, as improvements in the AUC reflect better model performance.

Additionally, prediction models require validation which can be internal and external to ensure their reliability and generalizability, respectively. Internal validation assesses the reproducibility of the model within the original cohort, while external validation is crucial for testing how well the model performs in independent populations.[110]

Prediction of adiposity gain is of importance to discriminate individuals at higher risk of adiposity accumulation and potentially guide public health policies to reduce the burden of obesity. Previous studies developed prediction models restricted to environmental factors such as socio-demographic, anthropometric traits, dietary, and lifestyle factors. Steffen et al. included 13 different predictors: age, sex, baseline weight, level of education, smoking status, physical activity, alcohol intake, and consumption of red and processed meat, poultry, fish, bread, cake and biscuits, and soft drinks.[113] However, this model showed a rather low predictive ability [AUC: 0.57; 95% confidence interval (CI): 0.56-0.58] highlighting differences across European regions in its predictive performance. For instance, the model performed better in Italy-Naples (AUC: 0.67; 95% CI: 0.64-0.71) and Germany-Heidelberg (AUC: 0.66; 95% CI: 0.64-0.69) than France (AUC: 0.56; 95% CI: 0.55-0.57) and the United Kingdom (AUC: 0.58; 95% CI: 0.57-0.59).[113] Additionally, another work built on the previous study also including sleep disorders, consumption of fruits and vegetables, and chocolate as predictors.[114] Compared to the Steffen et al. model,[113] this showed a higher predictive ability (AUC: 0.71; 95% CI: 0.67-0.75), however, its applicability maintaining the same level of accuracy across Europeans cannot be ensured as it was developed on German populations. Therefore, the existent models may not translate to implementable tools for obesity prevention strategies for huge range of European countries.

Thus, given the importance of a high-performance adiposity gain prediction model in obesity-related prevention strategies, it is crucial to improve the model by finding new relevant predictors. This thesis aimed to develop and validate an adiposity gain prediction model applicable across Europe adding novel environmental and genetic factors.

MAIN INSIGHTS: ADIPOSITY

Obesity is a major public health challenge, reaching more than 1 billion individuals worldwide in 2022.

Obesity is usually assessed by BMI. However, this measurement presents several limitations. For instance, it is not informative of the body fat distribution nor distinguishes between adipose and other tissues.

Body shape phenotypes are derived from a PCA of six anthropometric traits: BMI, height, HC, WC, weight, and WHR.

Body shape phenotypes may capture underlying information of adiposity-related biological pathways beyond the six anthropometric traits.

Body shape phenotypes may be complementary useful adiposity indicators.

2. CANCER

2.1. Definition and epidemiology

Cancer defines a large group of diseases that can be developed across all the body. Until now, more than 100 types of cancer have been classified.[115,116] Cancer is characterized by the rapid, uncontrolled, and abnormal cell growth.[115,116] Tumours mainly arise from mutations in the DNA that damage cells leading to an unregulated cell proliferation beyond their usual boundaries. The damaged cells have the potential to invade or spread into nearby tissues (malignant tumours or cancers) as well as may travel to other organs to form new tumours, process known as metastasis. Widespread metastases are the primary cause of death from cancer.[115,116] Contrarily, benign tumours do not spread and normally do not grow again when they are removed. Although called benign tumours, they may also be life threating and cause symptoms depending on their location such as in the central nervous system.[116]

Cancer remains one of the leading causes of morbidity and mortality worldwide.[115] According to the latest estimates by the International Agency for Research on Cancer (IARC), there were nearly 20 million new cancer cases and 10 million cancer deaths globally in 2022.[117,118] As shown in Figure 3, the world regions with the highest age-standardized incidence rates of cancer in 2022 were Europe, North America, and Oceania.[117,118]

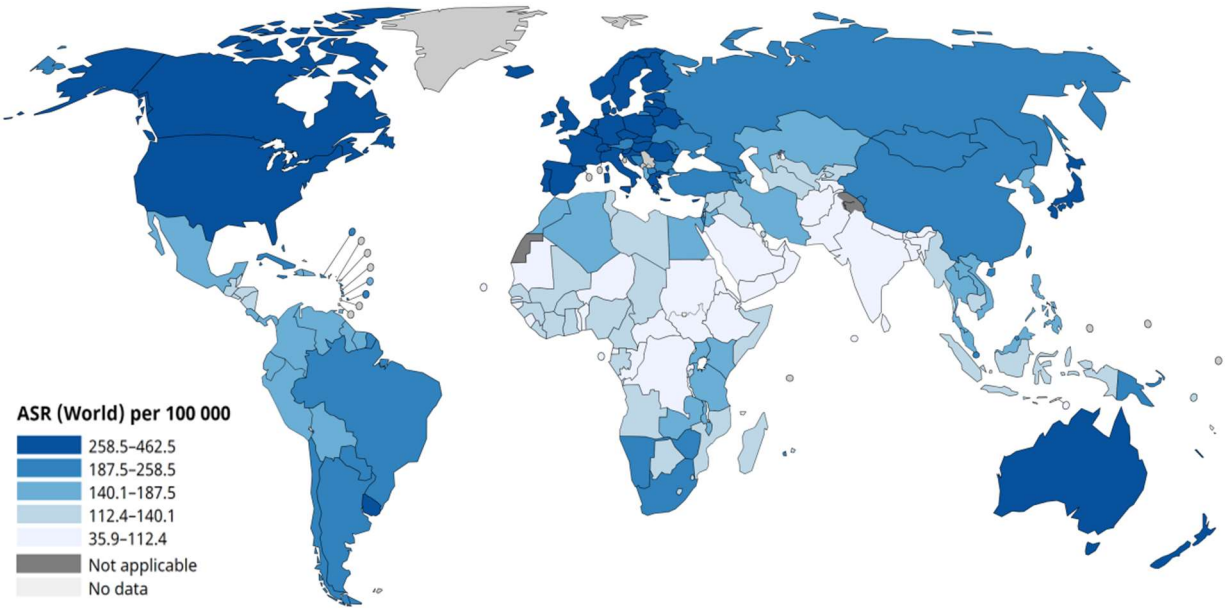


Figure 3. Age-standardized cancer incidence rate per 100,000 worldwide in 2022. Source: Ferlay, J. et al. Global Cancer Observatory: Cancer Today (version 1.1). Lyon, France: International Agency for Research on Cancer. https://gco.iarc.fr/today/ (2024).

In the WHO European region, more than 4.8 million incident cancer cases and nearly 2.2 million cancer deaths were estimated in 2022.[117,118] Leading incident cancer sites were breast, accounting for 604,941 (12.4%) cancer incidence cases and 160,043 (7.2%) of cancer deaths, and colorectum, accounting for 574,953 (11.8%) cancer incidence cases and 267,355 (12.1%) of cancer deaths. However, regarding mortality, lung cancer remains the leading cancer accounting for 427,939 (19.4%) cancer deaths.[117,118] Further details on incidence and mortality rates can be found in Figure 4.

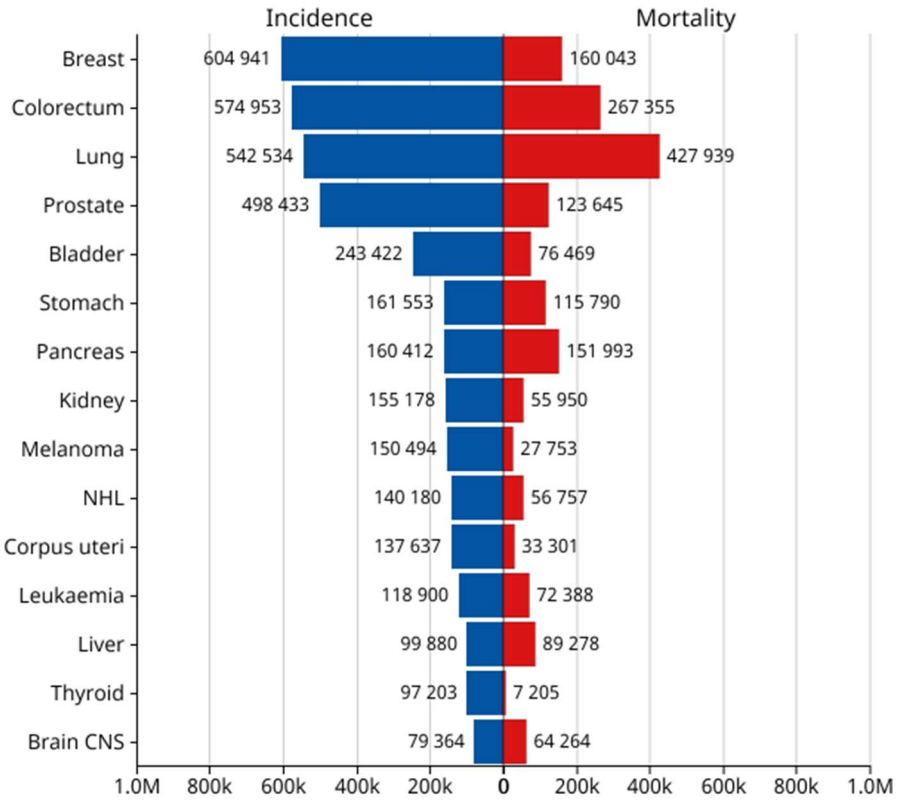


Figure 4. Incidence and mortality absolute numbers for cancer sites in the WHO European Region (2022). Source: Ferlay, J. et al. Global Cancer Observatory: Cancer Today (version 1.1). Lyon, France: International Agency for Research on Cancer. https://gco.iarc.fr/today/ (2024).

2.2. Cancer classification

Cancer is normally named by the organ (e.g., breast cancer) or the type of cell (e.g., carcinoma in the epithelial cells, sarcomas in connective tissue) where it originates.[116]

Cancer classification relies on the International Classification of Diseases (ICD) and the International Classification of Diseases for Oncology (ICD-O) both developed by the WHO and encompassed in the WHO Family of International Health Related Classifications.[119,120] ICD and ICD-O are in continuous update. ICD is the international standard for systematic recording, reporting, analysis, interpretation, and comparison of mortality and morbidity data.[119] Each health condition is assigned an ICD code, which is employed broadly for clinical documentation, health statistics, billing, public health surveillance, and epidemiological research. Specifically, ICD classification of tumours is mainly focused on topography (site) and behaviour (malignant, benign, in situ, or not specified) of neoplasms, both

information being contained in the same topographical code.[119] ICD-O is specifically designed for coding tumours.[120] It is primarily used in cancer registries and pathology to classify the incidence, type, and location of neoplasms. These classifications are coding the topography, morphology, behaviour, and histologic grading (differentiation) of neoplasms, obtained normally from a pathology report.

2.3. Hallmarks of cancer

Cancer hallmarks were first described in 2000[121] and expanded in 2011[122] and 2022.[123] The hallmarks of cancer represent the complex biological capabilities that contributes to the development and progression of malignant tumours. Until today, 14 hallmarks have been identified (Figure 5).

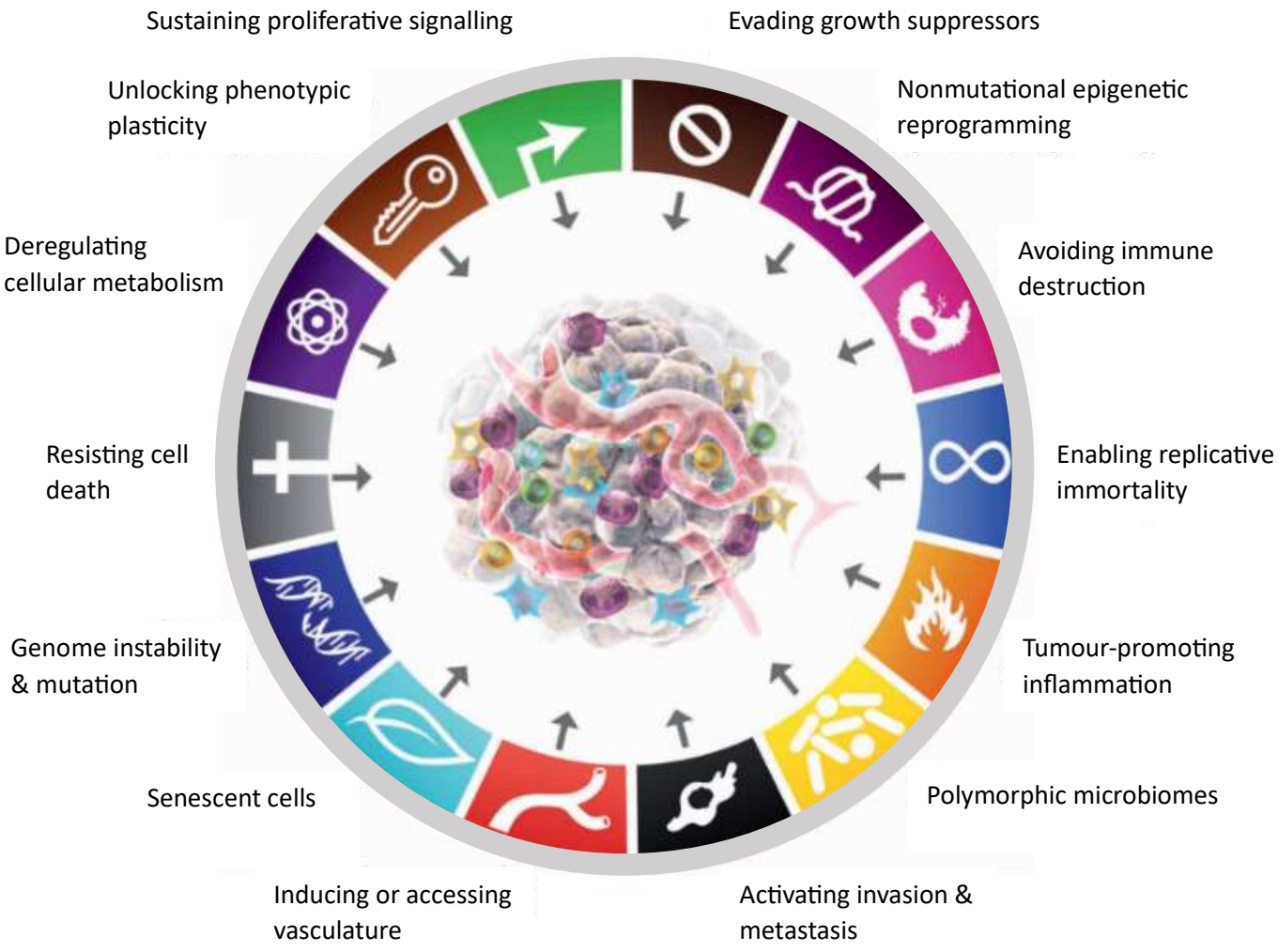


Figure 5. Hallmarks of cancer. Source: Hanahan, D. Hallmarks of Cancer: New Dimensions. Cancer Discov 12, (2022).

MAIN INSIGHTS: CANCER

In 2022, 20 million new cancer cases and 10 million cancer deaths were estimated globally. Specially in the WHO European region, more than 4.8 million incident cancer cases and nearly 2.2 million cancer deaths were approximated.

Cancer hallmarks represent the underlying biological capabilities acquired during the multistep development of human tumours. Up to 14 hallmarks have been identified.

3. ADIPOSITY AND CANCER

3.1. Epidemiology

In 2012, approximately 481,000 cancer cases among both sexes were attributable to high BMI, 136,000 men and 345,000 women.[124,125] Differences among world regions were found. Developed regions, specifically Europe and North America, presented higher cancer burden related to high BMI compared to other regions less developed (Figure 6). Specifically, up to 82% of all new cancer cases in high-income countries were attributable to a high body weight while in low-income countries the respective percentage was 18%.[125] However, this obesity-attributable cancer burden is likely underestimated given the BMI limitations.[126]

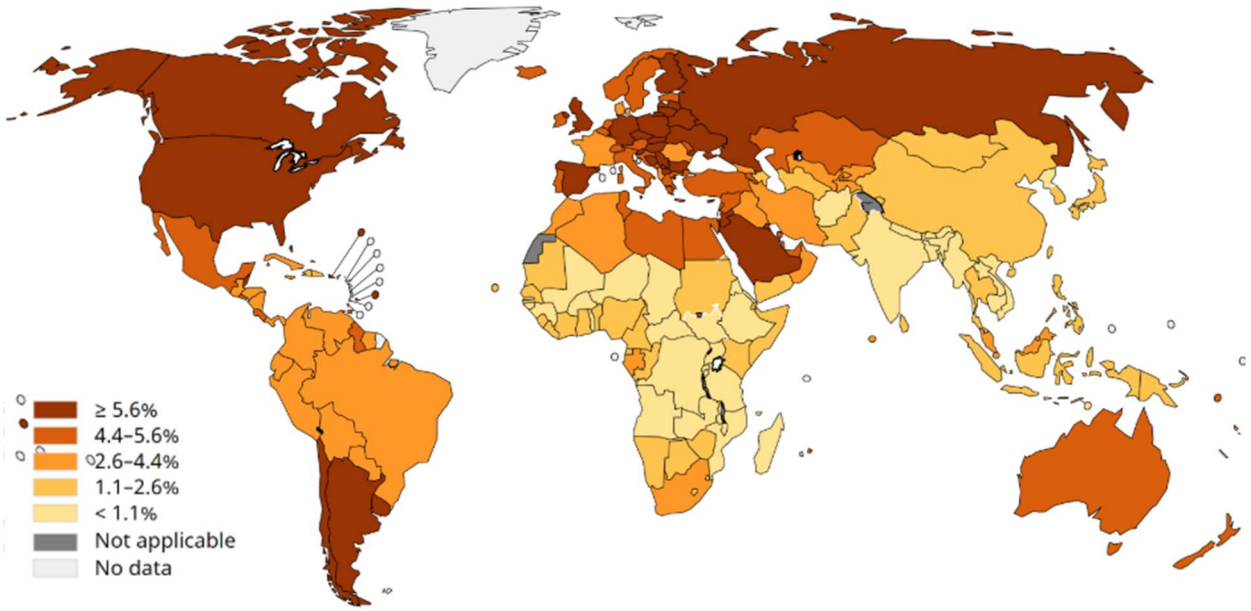


Figure 6. Fraction of all cancer cases attributable to high BMI worldwide (2012). Source: Arnold M, Lam F, Ervik M & Soerjomataram I. Cancer and Obesity: Global burden of cancer attributable to excess weight. Lyon, France: International Agency for Research on Cancer http://gco.iarc.fr/obesity (2015).

In Europe, the attributable fraction of cancer cases to high BMI is estimated in approximately 200,000 cases (60,000 men and 140,000 women).[124,125] Among those, more than half (64%) are presented in 3 different cancer sites: postmenopausal breast, corpus uteri, and colon cancer (Figure 7). [124,125]

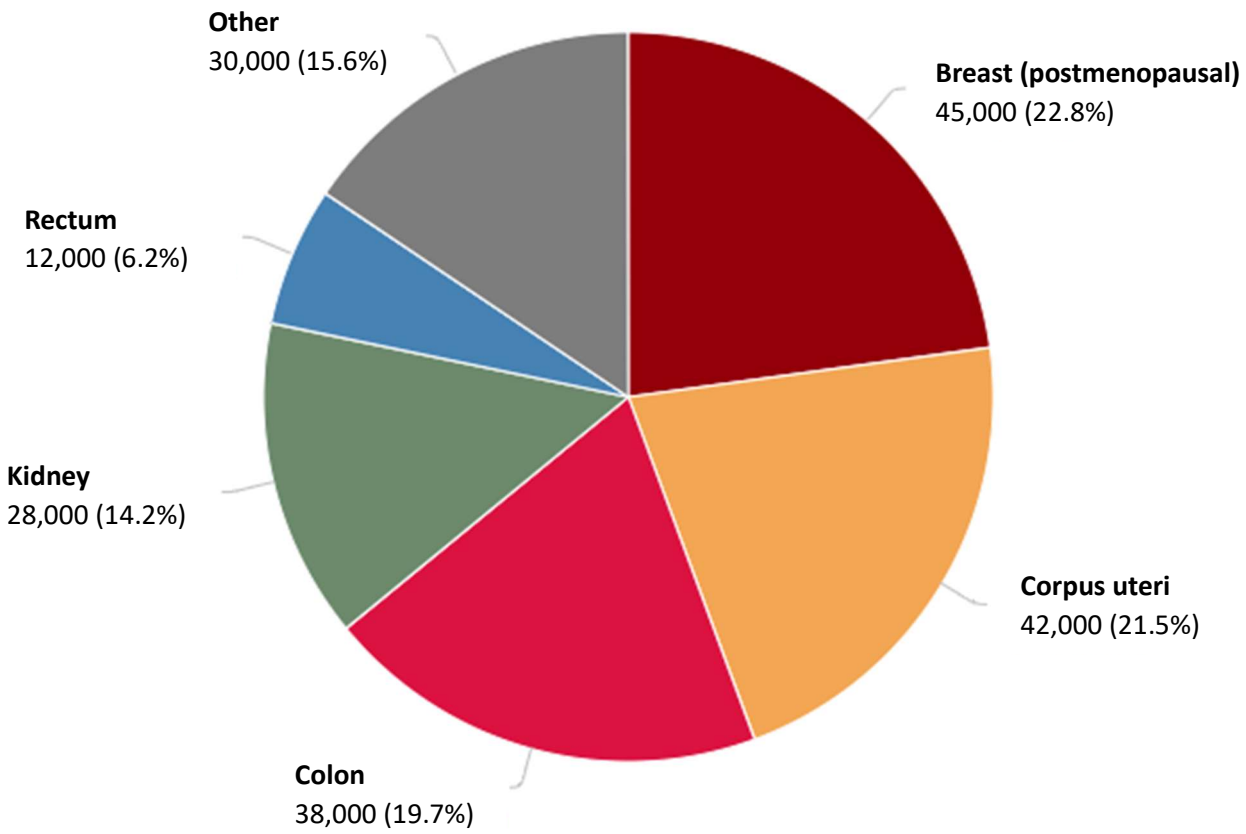


Figure 7. Cancer cases attributable to high BMI by anatomical site in Europe (2012). Source: Arnold M, Lam F, Ervik M & Soerjomataram I. Cancer and Obesity: Global burden of cancer attributable to excess weight. Lyon, France: International Agency for Research on Cancer http://gco.iarc.fr/obesity (2015).

3.2. Obesity-related cancers and aetiological pathways

Obesity is an established risk factor for at least 13 cancer sites, known as obesity-related cancers.[127,128] This group of malignancies were classified based on evidence from more than 100 epidemiologic studies and included oesophagus (adenocarcinoma), gastric cardia, colon and rectum, liver, gallbladder, pancreas, breast (postmenopausal), corpus uteri, ovary, kidney (renal cell), meningioma, thyroid, and multiple myeloma.[127] Regarding other cancers such as non-Hodgkin lymphoma, lung, skin, advanced prostate, and testis, among others, limited or inadequate evidence was found about their relation to obesity.[127] Further evidence is based on the World Cancer Research Fund (WCRF) report,[128] where BMI showed convincing increased risk of oesophagus (adenocarcinoma), pancreas, liver, colorectum, breast (postmenopausal), endometrium, kidney, and probable strong evidence of mouth, pharynx and larynx, stomach (cardia), gallbladder, ovary, and advanced prostate cancer.[128] Although the slight differences between both reports, these studies shed light on strong association between BMI and a huge number of cancer sites.[127,128] Recently, another study showed that it is likely that obesity is related to even more cancer sites such as leukaemia, non-Hodgkin lymphoma, head and neck, and bladder cancers which are yet not considered as obesity-related cancers.[129]

Although all these results were mostly derived from observational settings using BMI, WC, or WHR to assess adiposity, studies based on other adiposity indicators and other approaches are being conducted. For instance, in an observational analysis performed by our group including more than 340,000 participants from 9 European countries, four distinct body shape phenotypes were associated with the incidence of 17 different cancers. These results highlighted novel and positive associations between adiposity subtypes and cancer risk of liver, prostate, oesophageal squamous cell carcinoma (SCC), and malignant melanoma.[69] The study suggested that current cancer burden may be underestimated by traditional adiposity indicators and that body shape phenotypes may capture phenotype characteristics beyond them. Alternatively, further investigation using other study designs to complement observational settings may provide more robust evidence of the complex adiposity-cancer causality via triangulation.[130] Observational settings are likely to suffer from potential confounding due to the limited and lack of harmonization of the variable adjustment, reverse causation, selection bias, and attenuation by measurement errors which complicates the causal inference.[131–133] Thus, several studies have used other study designs such as Mendelian randomization (MR) aiming to overcome these limitations. MR results agreed with the observational analyses on the positive associations with several cancers including oesophagus (adenocarcinoma), stomach, colorectum, pancreas, liver, gallbladder, endometrium, ovarian, and kidney.[134,135] However, they showed an inverse association with breast, prostate, and non-melanoma skin cancer, a positive association with bladder and lung cancer, while no consistent findings were found for other cancers.[135]

The interplay between adiposity and cancer is complex and involves a network of hormonal, inflammatory, and metabolic pathways. Excess body fat disrupts normal cellular and systemic processes, creating an environment conducive to cancer initiation, promotion, and progression. It is hypothesized that the adiposity-cancer link is mediated by three main biological mechanisms including sex hormone metabolism, insulin and insulin-like growth factor (IGF) signalling, and adipokine pathophysiology and systemic inflammation.[90,136–139] In short, sex hormone hypothesis is based on the higher conversions of androgens to oestrogens (oestradiol) in adipose tissue, enhancing breast, endometrial, and ovarian cancers. Less consistently proved, obesity lowers testosterone in men which could explain the association with aggressive prostate cancer. Insulin and IGF signalling theory is based on the hyperinsulinemia (i.e., insulin resistance and increased circulating levels) that individuals with high BMI can experience. This helps cancer development through direct growth signalling and higher free IGF1 levels. At same time, it increases the IGF1 receptors that trigger essential pathways for cell survival and proliferation.[140] Lastly, adipokine pathophysiology and inflammation relies on the levels of leptin and adiponectin and biomarkers of chronic inflammation. Leptin promotes cancer through mitogenic, anti-apoptotic, pro-inflammatory, and angiogenic effects that support tumour growth.[141,142]

Adiponectin has anti-inflammatory and anti-proliferative properties, reducing cancer risk.[143] Obesity-related inflammation, marked by increased CRP, TNF-α, and ILs, is associated with cancer development as the inflammatory processes affects immune suppression, tissue remodelling, DNA damage, and promotion of cell proliferation.[144] Understanding these pathways provides insights into potential preventive and therapeutic strategies to mitigate the increased cancer risk associated with obesity. Thus, it is crucial to understand how obesity is associated with cancer risk and how the current anthropometric traits used in epidemiological settings characterize the inflammatory patterns.

3.3. Breast cancer

3.3.1. Epidemiology of breast cancer

Breast cancer is the most common and mortal cancer among women worldwide while is extremely rare in men (less than 1% of cases).[117,118] In 2022, the estimated age-standardized incidence and mortality rates were 46.8 and 12.7 per 100,000 women, respectively, with 2,296,840 new cancer cases and 666,103 deaths in 2022 worldwide (Figure 8 and 9).[117,118]

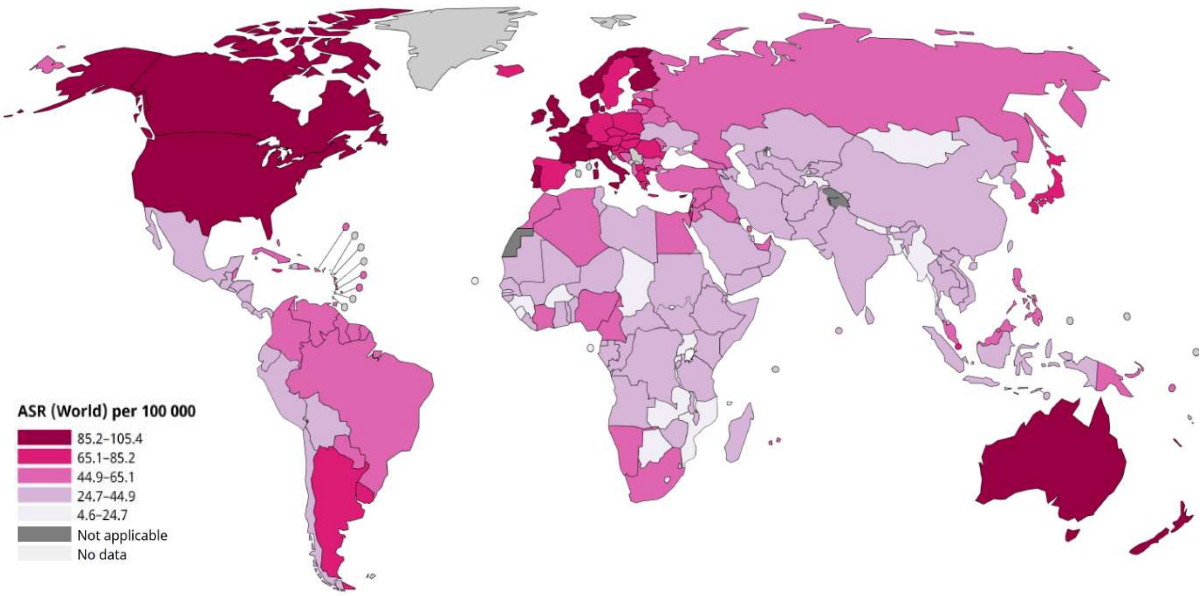


Figure 8. Age-standardized breast cancer incidence rates per 100,000 worldwide in 2022. Source: Ferlay, J. et al. Global Cancer Observatory: Cancer Today (version 1.1). Lyon, France: International Agency for Research on Cancer. https://gco.iarc.fr/today/ (2024).

Disparities in the incidence of breast cancer by income are easily found across the globe. For instance, high and upper middle-income countries present higher rates of breast cancer incidence compared to lower middle- and low-income countries. However, different trends are shown for mortality, where the highest rates correspond to lower middle-income countries.[117,118]

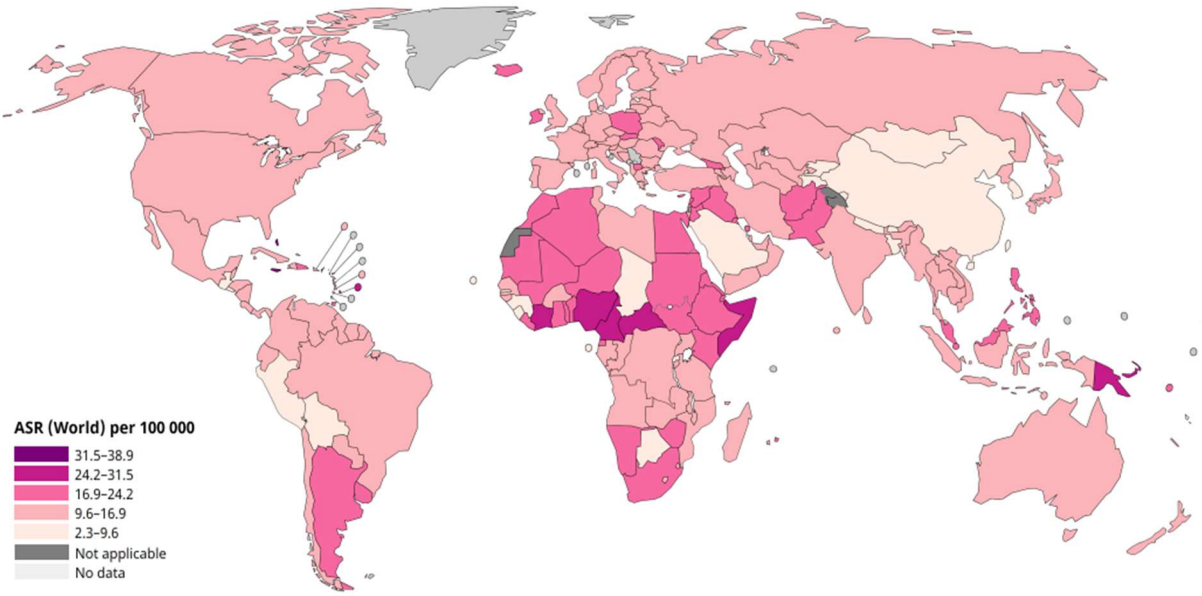


Figure 9. Age-standardized breast cancer mortality rates per 100,000 worldwide in 2022. Source: Ferlay, J. et al. Global Cancer Observatory: Cancer Today (version 1.1). Lyon, France: International Agency for Research on Cancer. https://gco.iarc.fr/today/ (2024).

Specifically in Europe, 557,873 new cases were diagnosed in 2022, and 144,510 individuals died from breast cancer. The age-standardized incidence and mortality rates were 75.6 and 14.6, respectively. Huge increases of the number of cases were observed in the last decades although mortality showed a downward trend.[117,118]

3.3.2. Physiopathology of breast cancer

Breast tissue includes fat, glandular tissue (arranged in 15-20 lobes formed by lobules containing milk production glands), ducts (responsible to carry milk to the nipple), and connective tissue.[145–147] Human mammary gland starts to develop in the embryonic life stages with a main development period during puberty, pregnancy, and lactation in response to different hormones such as oestrogens, progesterone, insulin, and growth factor receptor signalling, as well as other environmental influences. The gland atrophies in the post-menopausal period.[146,147]

Breast cancer involves distinct malignancies from the mammary glands, mostly from the lobules and ducts.[146] It is a highly heterogenous and silent disease which is normally detected through routine screening.[145] Most of the breast cancers are carcinomas of the epithelial cells lining the ducts as consequence of DNA damage and genetic mutations influenced by hormones that modulates the cell structure and growth.[145–147] Additionally, breast cancer itself can also produce hormones which have the capacity to create a more comfortable microenvironment to promote tumoral cell growth and expansion.[146,147]

3.3.3. Breast cancer classification

Breast cancer is characterized by a high biologic, morphologic, and clinical heterogeneity that leads to different biological behaviour and response to therapy.[148–150] Therefore, breast cancer can be classified differently depending on the pathological stage, tumour differentiation, and molecular subtypes.

3.3.3.1. Pathological stage

Breast cancer stage is key for disease prognosis given the differences in survival rates between early-stage and metastatic breast cancer. This classification is based on the confirmation of primary tumour size, infiltration of local structures, presence of lymph node metastases, and estimation of nodal disease burden.[148]

Despite several systems to define the pathological stage, the Tumour Node Metastasis (TNM) remains the most widely used, relying on clinical and pathological examinations to classify breast cancer based on primary tumour size (T), nodal involvement (N), and metastasis (M).[148]

3.3.3.2. Tumour differentiation

The histomorphological classification is considered the root of all other classifications as it remains key in breast cancer diagnosis. It strongly depends on pathologist expertise and performance, without accounting for molecular tests. Overall, this methodology aims to classify *in situ* and invasive disease, tumour typing and grading, and the distinction of primary breast cancers from their mimics.[148]

3.3.3.3. Molecular subtypes

Invasive cancers can be further classified based on their molecular characteristics. This classification includes four breast cancer subtypes (Table 2) and is determined by the presence of the following specific hormone receptors:[150]

- **Oestrogen Receptor (ER):** 70-75% of invasive breast carcinomas. Important diagnostic and prognostic determinant.
- **Progesterone receptor (PR):** More than 50% of ER-positive patients. Nearly no expressed in ER-negative patients. PR expression is regulated by ER, then, PR informs on the functional ER pathway. Important diagnostic and prognostic determinant.
- **Human epidermal growth factor receptor (HER2):** 15-25% of breast cancers. Mainly relevant for treatment decisions.
- **Ki67:** Marker of cell proliferation. Reflects the aggressiveness of the breast cancer. Most immunohistochemistry studies combine the receptor expression information with the levels of Ki67 to classify the different breast cancer subtypes more accurately.

Although a molecular categorization of breast cancer could help to better discriminate individuals with beneficial targeted therapy, it is still not clear whether these molecular characteristics are clinically relevant.[148,150]

Table 2. Main characteristics of molecular cancer subtypes.[146,150–152]

Breast cancer subtype	Hormone receptors	Ki67 levels	Characteristics
Luminal A	ER+ PR+ HER2-	Low	Low grade, slow growing, best prognosis, less incidence of relapse and higher survival rate. 50% of all breast cancers. Hormonal therapy. No mutations.
Luminal B	ER+ PR+/- HER2-	High	Grow faster, worse prognosis than Luminal A. Low expression of ER and increased expression of proliferation and cell cycle gens. Lower survival. 10% of all breast cancers. Hormonal/Chemotherapy. *BRCA2* mutations.
HER2	ER- PR- HER2+	High	Grow faster, worse prognosis, more aggressive than luminal A and B. 20% of all breast cancers. Targeted therapies to HER2. Higher response to chemotherapy.
Triple Negative	ER- PR- HER2-	High	Aggressive, early relapse, greater tendency to present in advance stages. High proliferation rate, alteration in DNA repair genes and increased genomic instability. Bad prognosis. 15% breast cancers.

3.3.4. Aetiology of breast cancer

Breast cancer is associated with numerous modifiable and non-modifiable factors including environmental, nutritional, lifestyle, hormonal, and heritable elements, with these factors varying by menopausal status. This section will present the most relevant breast cancer risk factors to date.

3.3.4.1. Adiposity

Adiposity and breast cancer risk relationship is complex and changes depending on the period of life, molecular breast cancer subtype, anthropometric trait proxying adiposity, and the study design (i.e., observational or genetic analyses).[69,135,147,153–156] For instance, in a dose-response meta-analysis performed by the WCRF of BMI (per 5 kg/m^2) and premenopausal breast cancer (16,371 cases) that included thirty-seven observational studies, higher levels of BMI were inversely associated with premenopausal breast cancer risk [relative risk (RR): 0.93 (0.90, 0.97)].[147] This association was attenuated towards the null when stratified by hormone receptor type [RR_{ER+}: 1.02 (95% CI: 0.90, 1.15); RR_{ER-}: 1.01 (95% CI: 0.94, 1.08)].[147] However, positive associations were found between BMI and postmenopausal breast cancer risk [RR: 1.12 (1.09, 1.15)] in a dose-response meta-analysis including fifty-six studies (80,404 cancer cases).[147] Associations by hormone receptor status showed heterogenous results, being consistent for ER+, PR+, and ER+PR+ but not associated with ER-, PR-, ER+PR-, and ER-PR-.[147] Additionally, WC and WHR showed similar results for the association with pre and postmenopausal breast cancer risk. No associations were found for both WC and WHR and premenopausal breast cancer, although they presented stronger positive associations when adjusting for BMI.[147] However, both proxies of adiposity where positively associated with postmenopausal breast cancer risk, regardless the BMI adjustment.[147] No data was provided by WCRF report on breast cancer subtypes when adiposity was assessed by WC or WHR.[147]

Additionally, one previous study, led by our group, investigated associations between the body shapes and the risk of cancer across 24 anatomical sites including pre (2318 cases) and postmenopausal (4988 cases) breast cancers in an observational setting in EPIC.[69] Findings showed positive associations between PC2 (tall individuals with low WHR) with premenopausal breast cancer risk [hazard ratio (HR): 1.08 (95% CI: 1.03, 1.12)], and between PC1 (overall adiposity) and PC2 with postmenopausal breast cancer [HR_{PC1}: 1.10 (95% CI: 1.07, 1.03); HR_{PC2}: 1.10 (95% CI: 0.07, 1.13)]. No associations were found between PC1 and premenopausal breast cancer, nor between PC3 (tall individuals with high WHR) and PC4 (athletic phenotype) with both premenopausal and postmenopausal breast cancer risk.

Genetically predicted BMI was inversely associated with breast cancer risk [odds ratios (OR) between 0.66 to 0.87], independently of the individual's menopausal status.[135,153–156] Inverse associations were consistent by subtype breast cancer reporting OR close to 0.8 for both ER+ and ER-.[154] Results for genetically predicted WHR were in the same line than BMI, showing OR between 0.73 and 0.85.[155,156] Scarce evidence could be found in the literature for associations between genetically predicted WC and the body shape phenotypes and breast cancer risk and by subtypes.

3.3.4.2. Height

Previous evidence revealed the positive association between height and pre and postmenopausal breast cancer risk.[147,157,158] Potential mechanisms are based on the rate of cell divisions in fetal life, childhood, and adolescence that are determined by the hormonal and metabolic pathways influenced by diet.[159,160] Nutritional status can influence the hormonal profiles modulating the tissue growth and sexual maturity. Hence, nutrition at early-stage life and adolescence could influence both height and cancer risk. Specific tissues in taller individuals are exposed to higher levels of hormones such as insulin, pituitary-derived growth hormone, and IGFs, that amplify cell divisions.[147] This can contribute to a higher number of errors during DNA replication, resulting in a higher probability to develop cancer.[147]

3.3.4.3. Alcohol

Alcohol drinking increases the risk of pre and postmenopausal breast cancer for all levels of alcohol intake.[147] Although the mechanisms through which alcohol impacts the risk of breast cancer are still not yet understood, several potential theories have been developed. For instance, alcoholic beverages contain a toxic metabolite called acetaldehyde which may disrupt DNA synthesis and repair.[161] Also, individuals with higher alcohol intake are likely to follow poorer diets lacking in essential nutrients, such as folate,[147] which plays a role in gene transcription and cell replication and survival.[162]

3.3.4.4. Physical activity

According to the WCRF report, all types and intensities of physical activity show strong evidence of an inverse association with postmenopausal breast cancer risk.[147] Additionally, vigorous-intensity physical activity (e.g., aerobic dancing, fast cycling, swimming, tennis, and running) is inversely associated with premenopausal breast cancer risk.[147] Potential mechanisms underlying the relationship between physical activity and breast cancer include the reduction of circulating oestrogen levels, ovulation insulin resistance, and inflammation as well as the increase of menstrual cycle length.[163,164]

3.3.4.5. Heritable factors

Inherited DNA defects or pro-cancerous genes such as *BRCA1*, *BRCA2*, and *p53* can increase the risk of breast cancer.[145,147] While these genes are implicated in less than 30% of breast cancer cases, up to 25% of cases are linked to rare but highly penetrant genes including *BRCA1*, *BRCA2*, *PTEN*, *TP53*, *CDH1*, and *STK11*.[165] These genes can increase the risk of breast cancer to as much as 80% over a lifetime.[165] Additionally, other genes such as *CHEK2* and *ATM*, among others, are considered rare and moderately penetrant, contributing to 2-3% of breast cancer cases and doubling the overall risk.[165]

Additionally, the risk of developing breast cancer is double for women with a first-degree family (i.e., mother, sister, and daughter) history of breast cancer compared to women without breast cancer family history. This risk increases up to the triple for women with two first-degree relatives with history of breast cancer.[166,167]

3.3.4.6. Age at menarche and menopause

Early menarche and late menopause increase breast cancer risk.[168] Even if this increased risk appears to be related to longer exposure to oestrogen levels, the risk of breast cancer is higher for each year of earlier menarche than for each year of later menopause. This suggests that the hormones released by the ovaries during a woman's fertile period play a significant role in breast cancer risk, and that the incidence of breast cancer is not solely due to the duration of high oestrogen exposure.[166,168]

3.3.4.7. Reproductive factors and breastfeeding

Reproductive factors and breastfeeding decrease the risk of breast cancer as they reduce the number of menstrual cycles and, in consequence, the exposure to endogenous hormones.[169] Both seem to influence the differentiation of the breast cells forcing them to mature and produce milk. Mature cells may be more resistant to become tumoral cells than the immature ones.[170,171]

Having birth, breastfeeding for at least one year, age at pregnancy, and the number of births is associated with breast cancer risk.[172–175] Pregnancy at age of 20 and having 5 births or more reduces the risk of breast cancer by half compared to women who are pregnant after age of 30 and are not pregnant, respectively.[172,173]

3.3.4.8. Hormonal replacement therapy (HRT)

HRT is an hormonal treatment that helps to reduce the symptoms of menopause.[176] These include hot flashes, night sweats, mood changes, among others, and are the body response to the decrease of oestrogen and progesterone levels produced by the ovaries.[176] It is estimated that 5 years of HRT increases breast cancer incidence by 1 in every 50 women of oestrogen and progesterone daily therapy, 1 in every 70 of oestrogen and intermittent progestogen, and 1 in every 200 women of only oestrogen.[177] Additionally, excess risk due to HRT is already existent with 1-4 years of use, achieving progressively higher risks with the time of use.[177]

3.4. Colorectal cancer

3.4.1. Epidemiology of colorectal cancer

Colorectal cancer is the third most incident cancer and the second leading cancer death worldwide. In 2022, the estimated age-standardized incidence rate was 10.7 per 100,000 individuals, with 1,142,286 new cancer cases. The age-standardized mortality rate was 4.7 per 100,000 individuals with 538,167 deaths worldwide.[117,118]

High and upper middle-income countries present higher rates of colorectal cancer incidence compared to lower middle- and low-income countries (Figure 10). However, mortality trends are higher in eastern Europe and Oceania (Figure 11).[117,118]

In Europe, 538,262 new cases were diagnosed, and 247,842 individuals died from colorectal cancer in 2022. The age-standardized incidence and mortality rates were 30.5 and 12.1.[117,118]

3.4.2. Physiopathology of colorectal cancer

The adult large intestine is composed by the colon and the rectum.[178] The intestinal functions are region dependent.[178] While the proximal colon (right side, includes cecum, ascending colon and proximal two thirds of transverse colon) mainly absorb water and some nutrients, the distal colon (left side, distal one third of transverse colon, descending colon, and sigmoid colon) aims to store and excrete feces.[178] The main physiological function of the rectum is defecation, but it also absorbs a small amount of water, salt, glucose, and some drugs.[178] Proximal colon, distal colon, and rectum present molecular, embryological, biological, and anatomical differences adapted to their specific function leading to differences in the cancers originated in these regions.[179]

Colorectum presents an epithelial layer based on a single cell column of epithelial cells structured in crypts. Crypts are finger- and gland-like invaginations that reach the underlying connective tissue.[180] The niche at the base of the crypts is populated by multipotential stem cells that are the responsible for continuously regenerating the epithelial lining of the intestine by producing all intestinal cell types.[180] Genetic mutations in stem cells lead to uncontrolled cell division that ends up with the formation of polyps (i.e., abnormal growths of tissue) that may transform into malignant tumours.[179]

Colorectal cancer (95% of colon adenocarcinoma[181]) arises sporadically (94% of cases), from a hereditary origin (5%), or from chronic inflammatory bowel disease such as Crohn's disease and ulcerative colitis (1%).[182] Polyps' incidence increases with age[181] and while most polyps are benign, some types such as adenomatous (adenomas, 70–90% of colorectal cancers) and serrated (10–20% of colorectal cancers), have significant potential to become cancerous.[179] Hyperplastic and juvenile polyps generally have low to no malignant potential.[181]

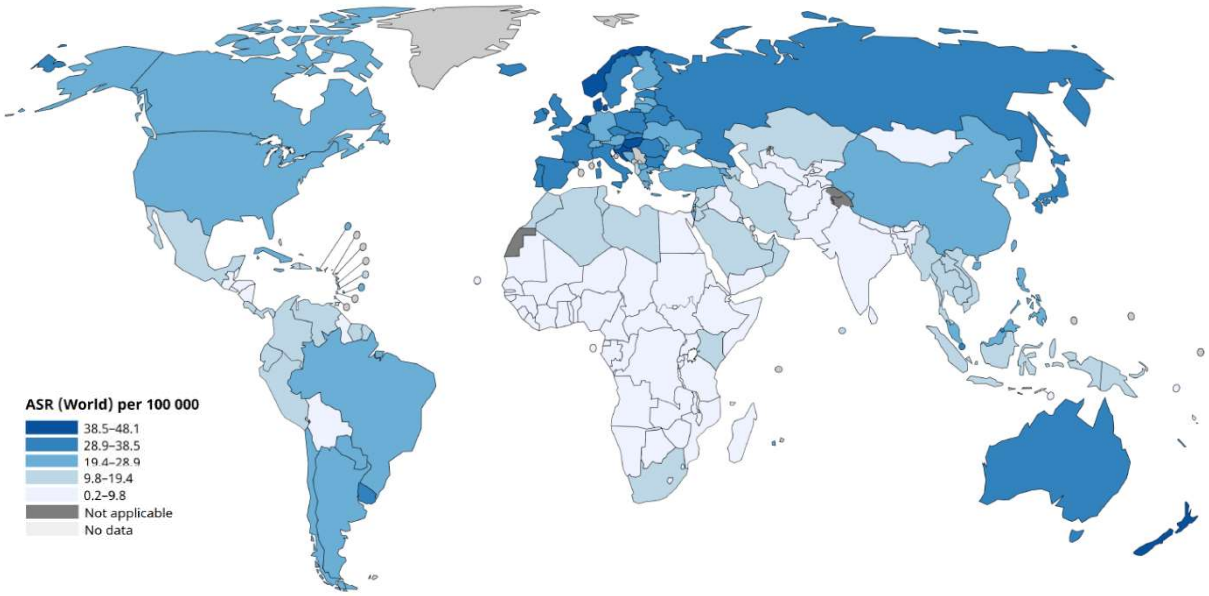


Figure 10. Age-standardized colorectal cancer incidence rates per 100,000 worldwide in 2022. Source: Ferlay, J. et al. Global Cancer Observatory: Cancer Today (version 1.1). Lyon, France: International Agency for Research on Cancer. https://gco.iarc.fr/today/ (2024).

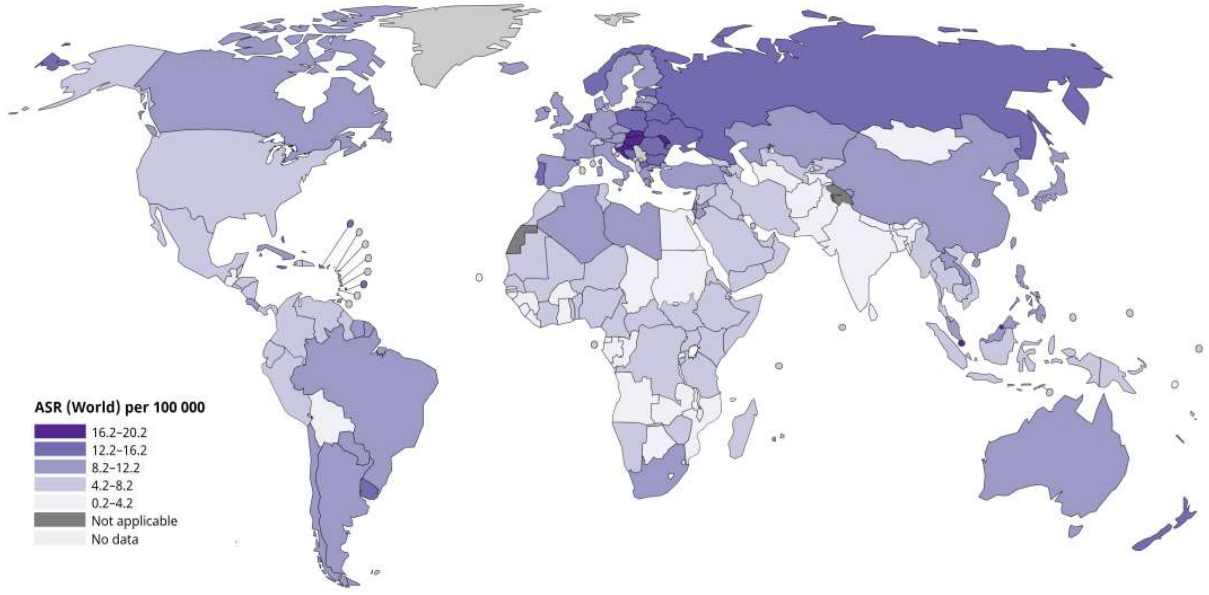


Figure 11. Age-standardized colorectal cancer mortality rates per 100,000 worldwide in 2022. Source: Ferlay, J. et al. Global Cancer Observatory: Cancer Today (version 1.1). Lyon, France: International Agency for Research on Cancer. https://gco.iarc.fr/today/ (2024).

The development of colorectal cancer from polyps is a multi-step process involving initiation, progression, dysplasia, and invasion. It initiates with mutations in the stem cells of the crypts, often influenced by genetic predispositions, environmental factors, or a combination of both.[179,180] Progression develops as the mutated stem cell divides forming a polyp.[179,180] Over time, additional mutations accumulate, especially in genes like *APC*, *KRAS*, *MLH1*, and *TP53*.[179,181] Polyps may then become dysplastic, showing an abnormal cell appearance although they are yet not cancerous.[180,181] Finally, with increasing number of genetic alterations, dysplastic cells may invade the surrounding tissue resulting in the transition from benign polyp to invasive colorectal cancer. Although stem cells are typically the origin of tumours, progenitor cells in the crypts can also acquire mutations that contribute to neoplasia.[180]

3.4.3. Aetiology of colorectal cancer

Colorectal cancer is a multi-factorial disease. Known colorectal cancer risk factors include heritable factors, anthropometric traits such as adiposity and height, lifestyle factors, alcohol intake, smoking, and poor diet which are outlined in this section.

3.4.3.1. Adiposity

The relationship between adiposity and colorectal cancer risk is well-documented and complex, involving various biological mechanisms.[183] Strong evidence on the positive association between overall and abdominal adiposity and the risk of colorectal cancer is provided by the WCRF report. This included a dose-response meta-analysis (71,089 colorectal cancer cases) based on thirty-eight observational studies and showed a RR of 1.05 (95% CI: 1.03, 1.07) on the association between BMI (per 5 kg/m^2) and colorectal cancer.[183] Differences in the associations were found depending on sex, being slightly higher in men [RR: 1.08 (95% CI: 1.04, 1.011)] than in women [RR: 1.05 (95% CI: 1.02, 1.08)], and on subsites, being higher for colon [RR: 1.07 (95% CI: 1.05, 1.09)] and distal colon [RR: 1.08 (95% CI: 1.04, 1.11)] than proximal colon [RR: 1.05 (95% CI: 1.03, 1.08)] and rectal [RR: 1.02 (95% CI: 1.01, 1.04)].[183] A similar dose-response meta-analysis including nine studies (4,301 colorectal cancer cases) was performed to assess the association between WC (per 10 cm) and colorectal cancer.[183] Results showed a positive association with overall colorectal cancer [RR: 1.02 (95% CI: 1.02, 1.03)].[183] Risk estimates did not differ by sex [RR_{men}: 1.02 (95% CI: 1.00, 1.04); RR_{women}: 1.03 (95% CI: 1.02, 1.04)] nor by colorectal subsites [RR_{colon}: 1.04 (95% CI: 1.02, 1.06); RR_{rectal}: 1.02 (95% CI: 1.00, 1.03)].[183] Abdominal adiposity was also assessed using WHR (per 0.1 unit) and the meta-analysis included five studies (2,564 colorectal cancer cases) showing similar results than for WC [1.02 (95% CI: 1.02, 1.03)]. Overall, similar colorectal cancer risk estimates have been observed for BMI, WC, and WHR, which are not providing distinct insight into colorectal cancer aetiology nor risk discrimination.[183]

Additionally, associations between the body shapes and the risk of colon (3368 cases) and rectal (1857 cases) cancers were estimated in an observational setting in EPIC.[69] Findings showed positive associations between PC1 (overall adiposity) and PC3 (tall individuals with high WHR) with colon subsite [HR_{PC1}: 1.18 (95% CI: 1.14, 1.23); HR_{PC3}: 1.09 (95% CI: 1.05, 1.13)] and rectum [HR_{PC1}: 1.08 (95% CI: 1.03, 1.13); HR_{PC3}: 1.04 (95% CI: 0.99, 1.09)]. No associations were found for PC2 (tall individuals with low WHR) and PC4 (athletic phenotype).

Further evidence on a positive association between adiposity and colorectal cancer was provided by one of the largest MR study in literature.[184] This used 312 and 209 sex-combined genetic variants for BMI and WHR, respectively, as well as sex-specific genetic variants for BMI (152 for men and 185 for women) and WHR (64 for men and 153 for women) from a meta-analysis of 806,810 participants from the GIANT consortium and UK Biobank.[184] Higher BMI (per 4.8 kg/m^2) increased the risk of overall colorectal cancer (58,221 cases) by 16% [OR: 1.16 (95% CI: 1.07, 1.26)], showing stronger associations in men [OR: 1.23 (95% CI: 1.08, 1.38)] than in women [OR: 1.09 (95% CI: 0.97, 1.22)]. BMI associations were consistent across colorectal cancer subsites. Associations were slightly stronger for WHR than for BMI. Higher WHR (per 0.09 ratio) was positively associated with overall colorectal cancer risk [OR: 1.28 (95% CI: 1.16, 1.42)] being similar in men [OR: 1.22 (95% CI: 1.02, 1.46)] but attenuated towards the null in women [OR: 1.04 (95% CI: 0.86, 1.26)]. Contrary to BMI, WHR associations were more consistent for colon rather than rectal subsites.[184] Finally, no evidence of genetic predicted body shape phenotypes and their association with colorectal cancer was found in the literature.

3.4.3.2. Height

Adult attained height is positively associated with colorectal cancer risk. Current evidence does not show differences between sex and subsites, estimating a 5% higher risk per 5 cm increase in height.[183] Higher levels of growth factors such as growth hormone and IGFs in childhood and early adulthood are proposed mechanisms acting in the relationship between height and colorectal cancer.[185,186] Additionally, cell number and cell proliferation also plays a role in height-colorectal cancer relationship.[187] Taller individuals have a higher number of cells which translates to a higher opportunity for mutations leading to cancer to arise.[187] Similarly, taller adults have larger intestines which present not only more cells that can mutate, also more surface that can be exposed to carcinogen agents.[183]

3.4.3.3. Alcohol

In 2020, up to 160,000 and 59,000 new cancer cases worldwide and in Europe, respectively, were attributable to alcohol drinking.[188] Epidemiological studies consistently show that alcohol consumption is associated with a higher risk of colorectal cancer and appears to increase with the amount of alcohol consumed.[183] Similar increased risk of colorectal cancer is observed for all types of alcoholic beverages, including beer, wine, and spirits suggesting that the amount of alcohol consumed is more important than the type of alcohol. One proposed mechanism suggests that alcohol intake increases the levels of acetaldehyde and induce oxidative stress, lipid peroxidation, pro-inflammatory responses, and folate deficiency, overall leading to colorectal cancer.[189]

3.4.3.4. Diet

Diet plays a significant role in the risk of developing colorectal cancer, with various dietary components either increasing the risk such as read and processed meats[183,189,190] and high fat and low fibre diets or decreasing it with diet rich in dietary fibres such as intake of wholegrains, fibre, fruits, vegetables, legumes, and dairy products.[183,189,191–198] High consumption of red and processed meats is strongly linked to increased risk due to carcinogens such as heterocyclic amines (HCAs), polycyclic aromatic hydrocarbons (PAHs), and N-nitroso compounds (NOCs).[199–204] Dietary fiber lowers colorectal cancer risk through mechanisms like short-chain fatty acid production, anti-inflammatory effects, improved insulin sensitivity, and increased fecal bulk that limits the exposure to carcinogens.[183,189,205–207] Whole grains are rich in bioactive compounds (e.g., vitamin E, selenium, copper, zinc, phytochemicals, among others) with anti-carcinogenic properties.[183,205,208] Fruits and vegetables contain phytochemicals known to be antitumorigenic such as beta-carotene, vitamins A, C, E, and folate.[183,189,209] Diary products contain protective components like probiotics, vitamin D, and lactoferrin although they mainly decrease the risk of colorectal for the calcium component on it.[210,211] Calcium binds potentially harmful compounds in the gastrointestinal tract reducing their toxic effects[212] and modulates cell-signalling pathways preventing colon carcinogenesis genetic mutations.[213–215]

3.4.3.5. Physical activity

Physical activity has been associated with a reduced risk of colorectal cancer.[183] Observational studies suggest that the risk reduction could be of around 20% for total and 15% for occupational physical activity.[183] Potential mechanisms that could explain the relationship between physical activity and colorectal cancer include reduction in insulin resistance and inflammation through reduction of adiposity.[216–219] Other mechanisms proposed involve changes in gastrointestinal transit time, alterations in prostaglandin levels, shifts in IGFs, bile acid secretion, serum cholesterol levels, and modifications in gastrointestinal and pancreatic hormone profiles.[220] To corroborate this evidence, several studies have investigated the effect of sedentary lifestyle on colorectal cancer finding a positive association between prolonged television viewing, occupational sitting time, and total sitting time and colorectal cancer risk.[221]

3.4.3.6. Smoking

Cigarette smoking increases the risk of colorectal cancer in a dose-dependent manner with intensity and duration.[161,222] After 25 years of quitting smoking the negative effect of smoking may be cancelled out.[222] The associations between smoking and colorectal cancer differ by sex and subsite.[223] For instance, men smokers have a higher risk of distal colon cancer while for women smokers is higher in proximal colon and rectal sites.[223] Over 5300 toxic compounds[224] have been identified in tobacco smoke, with 70 among them classified as carcinogens.[225] Inhaling, these carcinogens directly may cause genetic mutations in the colorectum.[161]

3.4.3.7. Heritable factors

Approximately 5% of colorectal cancer cases occur from an hereditary colorectal cancer syndrome including Lynch syndrome (LS), familial adenomatous polyposis (FAP), attenuated FAP, MUTYH-associated polyposis (MAP), Peutz-Jeghers syndrome (PJS), juvenile polyposis syndrome (JPS), and hyperplastic polyposis (HPP).[226] While there are some clinical similarities across the syndromes, each one presents unique clinical characteristics, genetic determinants, and distinct probabilities of cancer developement.[226] Additionally, all these syndromes are autosomal dominant disorders, except MAP which is autosomal recessive.[226] Most common syndromes in the population are LS and FAP.

LS is responsible for 2-4% of all colorectal cancers although this condition also predisposes to other types of cancers such as endometrial and stomach, among others.[227,228] LS increases the risk of developing colorectal cancer by a 50-80%[228] being more likely to develop the disease and polyps at a younger age. These polyps and cancer are characterized by an excessive microsatellite instability (MSI-H), which arises from defective DNA mismatch repair (NMR) genes.[226]

FAP prevalence is 1 in 10,000 individuals ranking second as most commonly inherited colorectal cancer syndrome. Individuals with FAP develop hundreds of thousands of colonic adenomas which will then develop colorectal cancer in an average age of diagnosis of 39 years (7% of individuals by age 21 and 95% by age 50) if FAP is not treated.[226] The syndrome arises from germline mutations in the *APC* gene.[226]

MAIN INSIGHTS: ADIPOSITY AND CANCER

In 2012, the attributable fraction of cancer cases to high BMI was estimated in 481,000 cancer cases worldwide and 200,000 in Europe.

Obesity-related cancers include at least 13 cancer sites for which obesity is an established risk factor.

Breast and colorectal rank 1st and 2nd most incident cancers worldwide accounting for 2,296,840 and 1,142,286 new cases in 2022, respectively.

Breast and colorectal cancers are considered obesity-related cancers, although the relationship between subtypes of adiposity and these cancers remains unknown.

4. GENETIC EPIDEMIOLOGY

Genetic epidemiology is the field that applies the epidemiologic principles to investigate the role of genetic factors in disease susceptibility in populations.[131] By elucidating the genetic basis of diseases, we may better understand the mechanisms, pathophysiology, aetiology, and prevention of diseases as well as improve their early detection, treatment, and prognosis. Genetic epidemiology plays a key role in expanding the knowledge of the genetic basis of diseases informing on more personalized medicine approaches.

Several approaches are used within the field of genetic epidemiology including genome-wide association studies (GWAS), polygenic risk scores (PRS), and MR. This section focuses on the description of the methods which have been used in this thesis.

4.1. Genome-Wide Association Studies (GWAS)

Prior to GWAS, genetic linkage studies considered Mendelian diseases, caused by mutations in a single or a few genes with large effects, and focused the sampling on families with affected and unaffected individuals.[229] In this family-based studies, the transmission of genetic variants was tested between family members. Tested variants were representative of long-range haplotypes covering several genetic regions (loci) which included genetic variants in linkage disequilibrium (LD) with the tested variants. LD refers to the non-random association of alleles at different loci within a population, indicating that certain combinations of genetic variants occur together more frequently than would be expected by chance. Long-range haplotypes are determined by recombination points, which define the boundaries between segments of the genome where specific alleles are inherited together as a block, reflecting the historical recombination events that have shaped the genetic structure of populations. Therefore, a significant transmission of a tested variant to affected individuals indicated that the causal genetic variant and corresponding gene was located in the genetic regions covered by the long-range haplotype.

On the contrary, GWAS approach focuses the sampling on hundreds or thousands of unrelated individuals in order to identify several genetic variants related to phenotypes. GWAS are used to assess the association between genetic variants such as single nucleotide polymorphisms (SNPs) and a specific phenotype.[230,231] This is done by testing for differences in the allele frequency of hundreds of thousands to millions of genotyped genetic variants between individuals that present differences in the phenotype.[230,231] Tested or genotyped variants in population-based studies are representative of shorter genetic regions compared to family-based studies. Significant associations of the genotyped variants are indicating that the causal genetic variant is located in the genetic region (locus) covered by LD by the genotyped variant. However, the LD present between genotyped variants and linked but

ungenotyped variants allows the imputation of allelic variants, which in turn, allows the *in silico* testing of several millions of genetic variants, which could be the causal ones. Imputation methods rely on LD reference panels to infer missing genotype data by exploiting the established correlations between nearby genetic variants. These panels provide a comprehensive map of variant associations, enabling the accurate prediction of untyped or missing alleles in a given sample, thereby improving the completeness and precision of genomic analyses.

To avoid false positive results of different nature, the GWAS methodology applies different type of corrections. For instance, a correction for multiple comparisons is used as standardized significance threshold (p-value $<5x10^{-8}$) which allows comparison and consistent replication between studies.[232] Additionally, given the background of genetic differences between ancestries, GWAS are normally restricted to one specific ethnic group (e.g., Caucasians).[230,231]

Over the past decade, GWAS revolutionized the field of complex diseases such as diabetes, heart illness, cancer, among others, which are characterised by being highly polygenic.[231] After more than 15 years of the application of GWAS, more than 5,700 GWAS have been performed on more than 3,300 traits[231] benefiting from the availability of millions of genetic variants sequenced of the human genome.[233,234] However, in the context of multifactor phenotypes, GWAS loci altogether normally explain a modest proportion of the heritability of the trait in study given the small effect sizes of individual locus.[235]

The GWAS hypothesis-free nature allows the discovery of novel genetic associations without previous insights of the biological mechanisms underlying a disease.[236,237] In other words, the technique allows the identification of unexpected candidate genes implicated in a specific phenotype unravelling its genetic architecture (i.e., characteristics of the genetic variants that contribute to the variability of a phenotype that is heritable).[237,238] However, GWAS solely cannot infer the functional consequences of the genetic variants associated with the phenotype. Thus, further functional studies are needed to help to determine the affected gene as well as to identify its contribution to disease susceptibility.[230] For instance, GWAS results can be integrated with information of loci associated with RNA expression; i.e., expression quantitative trait loci (eQTL). Variants associated with a trait in GWAS can be mapped to the genes they potentially regulate in specific tissues and the molecular processes mediating these associations.[230]

4.2. Polygenic Risk Scores (PRS)

GWAS results are the source to develop PRSs which have a huge range of applications. These include risk-stratification for prevention or clinical decisions, the study of potential interactions between genetic predisposition and environmental factors for disease risk, and the study of the disease aetiology.

A PRS aims to condense the genetic susceptibility of an individual to a specific trait into a single parameter estimate. The mathematical representation of the PRS is provided in Equation 3, where S denotes the variants included in the risk score, w the weight for variant i, and x the number alleles for variant i.

$$PRS_j = \sum_{i \in S} w_i \, x_{ij} \qquad Equation\ 3$$

To generate and assess the utility and attributes of PRSs, the analyses should be performed based on two independent samples: base and target.[239] Base sample is where a GWAS is derived and, in consequence, where genetic variants are weighted in relation to the trait of interest. The target sample is where the PRS is estimated accounting for the GWAS results from the base sample. Compared to the base sample, the target sample should be independent to avoid overfitting[239] and homogenous to avoid underpowered or biased analysis from differences in allele frequency, population structure, and potential different source of confounding factors intervening differently in heterogenous populations.[240]

Classical methods to derive PRSs are likely the most used approach and are based on clumping (i.e., selection of independent genetic variants based on LD retaining one per locus) and p-value thresholding (clumping + p-value, C+P).[239] Hence, genetic variants in LD are not used although vast information is lost, certainly to estimate the heritability explained by the PRS.[241] However, novel methodologies to derive the PRS including a larger number of genetic variants can improve its predictive power.[239,241] LDpred is one of the successful examples.[241–243]

In short, LDpred is a Bayesian approach that relies in LD information combing GWAS results and a LD reference panel.[241–243] This method has achieved to estimate larger heritability than C+P methods overcoming the potential biases presented by classic methodologies.[241–243]

4.3. Mendelian randomization (MR)

Identifying causal relationships is fundamental to implement public health interventions to reduce or increase exposure to prejudicial or beneficial agents. Randomized control trials (RCTs) are the gold standard to infer causality.[244,245] RCTs are considered a robust study design for causality inference given the random allocation of participants in intervention or control groups without participants (and in best cases also trialists) knowing in which group are assigned.[245] Random allocation ensures no systematic differences between study groups from known or unknown factors that may affect the outcome. All the differences observed are then attributable to the study intervention.[244,245] However, RCTs are sometime unfeasible (due to ethical or practical aspects) or require excessive time to fit in decision making.[244,246] Thus, observational studies are normally used for potential causal inference in epidemiology and public health fields, reinforced by further evidence, if possible.[246]

Observational studies present numerous limitations which should be carefully considered when assessing an exposure-outcome relationship.[131–133] Confounding bias and reverse causation are some of the main issues that can lead to biased conclusions in observational analyses.[132] Confounders, (i.e., variables that are associated with an exposure and outcome but are not in the causal pathways between both, if they exists) should be controlled to remove bias.[133] However, it is impossible to control for all the bias introduced (known as unmeasured confounding), as confounding variables can be poorly measured or not measured at all. Reverse causation is a specific case of confounding where the relationship assessed (A causing B) is occurring in the opposite direction (B causing A) that can also mislead the study conclusions.[133]

MR is a methodological approach that uses genetic variants as instrumental variables to investigate potential causal associations between an exposure and an outcome.[247,248] Its name originates from the concept of Mendel's law of random assortment (known as law of independent assortment) which describes the random transmission of genes from parents to offspring during gamete formation.[248,249] It is thought that this process ensures the random allocation of the genetic variants in a population, mirroring the random assignment of interventions or treatments in traditional RCTs (Figure 12).[247,248] Additionally, the distribution of these genetic variants is highly unrelated to the socioeconomic and behavioural confounders[248] which are a potential source of biased results in observational analyses. In other words, study groups defined by individual's genotypes should theoretically only differ by that genotype rather than other variables.

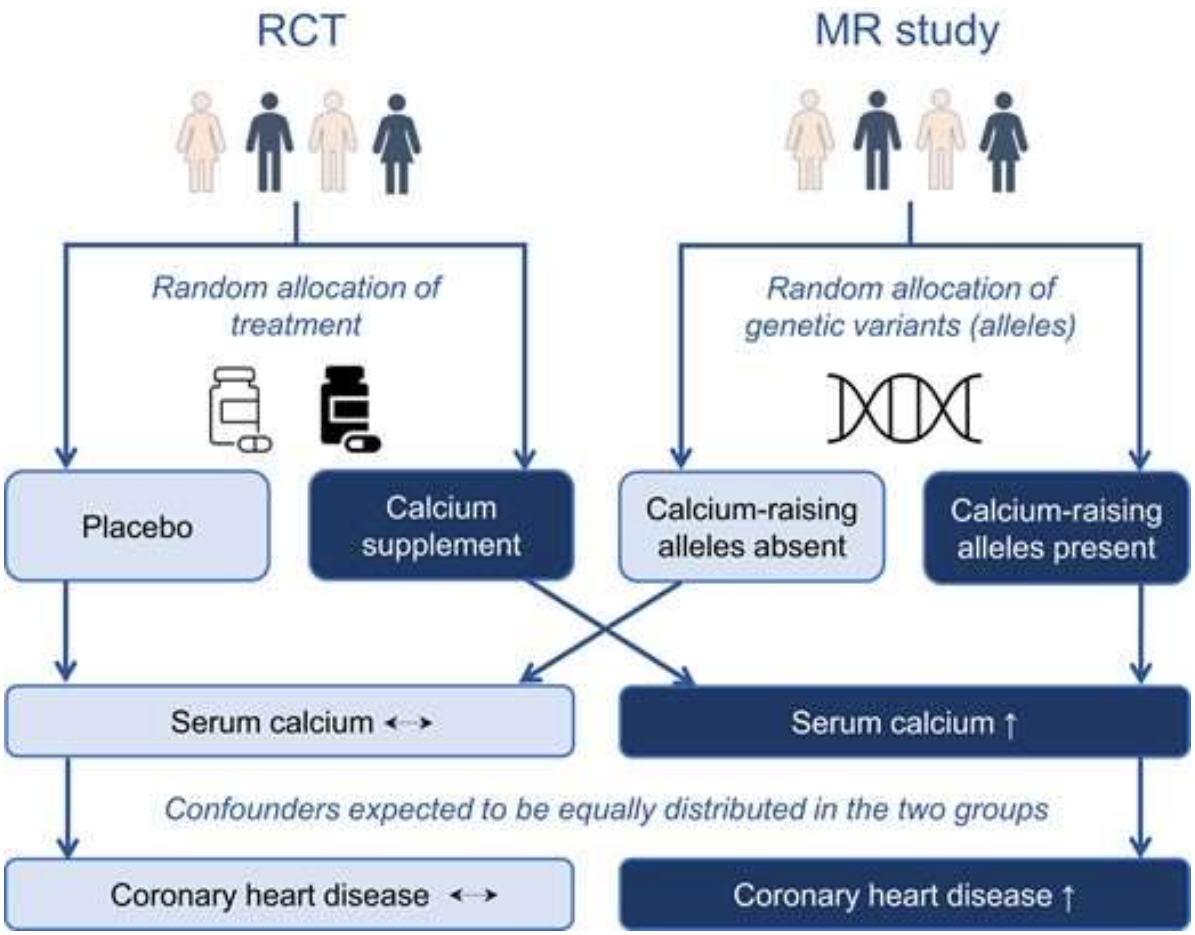


Figure 12. Comparison of RCT and MR study designs illustrated with the assessment of the association between serum calcium levels and coronary heart disease. Source: Larsson, S. C., Butterworth, A. S. & Burgess, S. Mendelian randomization for cardiovascular diseases: principles and applications. Eur Heart J 44, (2023).

MR can be performed as one- or two-sample designs.[248,250] In one-sample MR, the sample used to assess the associations between genetic instruments and exposure and the genetic instruments and outcome is the same; whereas, in two-sample MR, these two populations are independent (usually using summary level data from GWASs on the exposure and outcome).[248,250] Both study designs suffer from some limitations. For instance, one-sample MR is more prone to overfitting while two-sample MR may be biased if the underlying population of both samples are heterogeneous. Both analyses can suffer from weak instrument bias as well.[251] While, in one-sample design, it biases the estimate towards the confounded multivariable regression effect, in two-sample MR, this happens towards the null.[250]

Thanks to the genetic influence that most of the traits are characterised by, genetic variants present several advantages when are used as instruments:[247]

i. Genetic variants are associated with the phenotype of interest, but these associations cannot occur in the reversed direction (i.e., the phenotype influences the genetic variants).

ii. Genetic variants are useful proxies of a particular trait, while potential confounding can be identified in independent samples.

iii. Genetic variants and their effects present rather little measurement error or bias.

iv. Genetic variants associated with a trait are not required to be causal. The use of a genetic variant in LD with the causal variant will not bias the MR results.

v. Genetic variants related data is extracted from easily available GWAS[232] on increasingly larger, and therefore more powerful, studies. This increase in power may balance for the underperformance of testing an instrument that does not represent the full exposure variability.

Genetic variants are not confounded by the environment and germline genotypes remain stable throughout life. Thus, by using genetic variants as valid instrumental variables, MR analyses can overcome some of the limitations of observational studies such as confounding and reverse causation.[248,252]

Furthermore, the validity of the MR methodology relies in three main assumptions (Figure 13):[247,248,252]

1) The genetic instrument is reliably associated with the exposure (relevance assumption).

2) The genetic instrument is independent of confounders that influence exposure and outcome (independence assumption).

3) The genetic instrument is associated with the outcome only through the exposure (exclusion-restriction assumption).

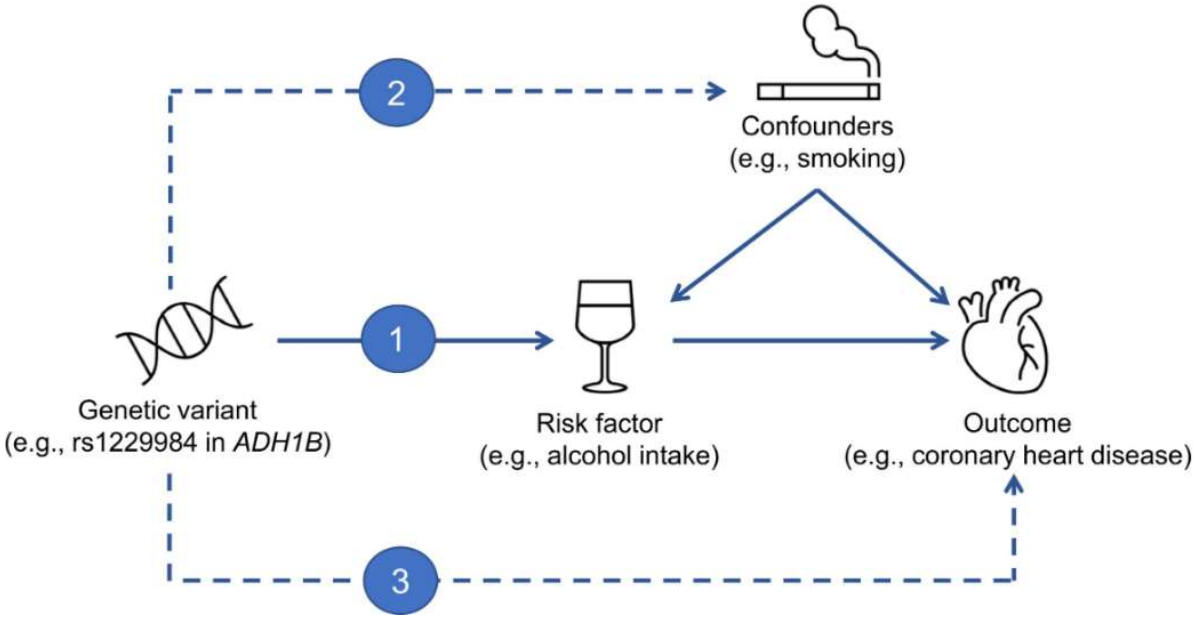


Figure 13. MR assumptions exemplified with the potential causal association between alcohol intake and coronary heart disease. Source: Larsson, S. C., Butterworth, A. S. & Burgess, S. Mendelian randomization for cardiovascular diseases: principles and applications. Eur Heart J 44, (2023).

While the first MR assumption can be formally testable, second and third assumptions present more difficulties to ensure their compliance.[247] The violation of the second and third assumptions occurs for several reasons such as population stratification, pleiotropy, LD, and gene-environment or gene-gene interactions.[252] Population stratification defines the presence of population subgroups with different phenotypic distribution, allele frequencies, and haplotype (LD) structure for genetic variants included as instruments in the MR analysis.[250] This can be mitigated by restricting the study populations to one ancestry and/or by adjusting the analyses for genetic PCs reflecting the population variation in the data.[250] An alternative to account for possible confounding introduced by population structure in the MR analysis is performing MR using data within families.[248,250] However, obtain data from parents and offspring is not straightforward and can lead to lower statistical power.[248] On the other side, pleiotropy describes the potential of genetic variants being associated with several phenotypes.[247,253,254] There are two types of pleiotropy: horizontal and vertical (Figure 14).[247,253,254] Horizontal pleiotropy refers to the phenomenon when a genetic variant is associated with another exposure which influences the outcome. Horizontal pleiotropy leads to a violation of the second MR assumptions.[247,253,254] Additionally, pleiotropy is labelled as balanced when the average pleiotropy effects of the genetic variants included in the analysis is 0.[252] In other cases, pleiotropy is labelled as directional. Vertical pleiotropy occurs when the genetic variant included in the study influence a phenotype that is within the pathway that the exposure is causing the outcome, without affecting the MR analysis (third assumption is not violated).

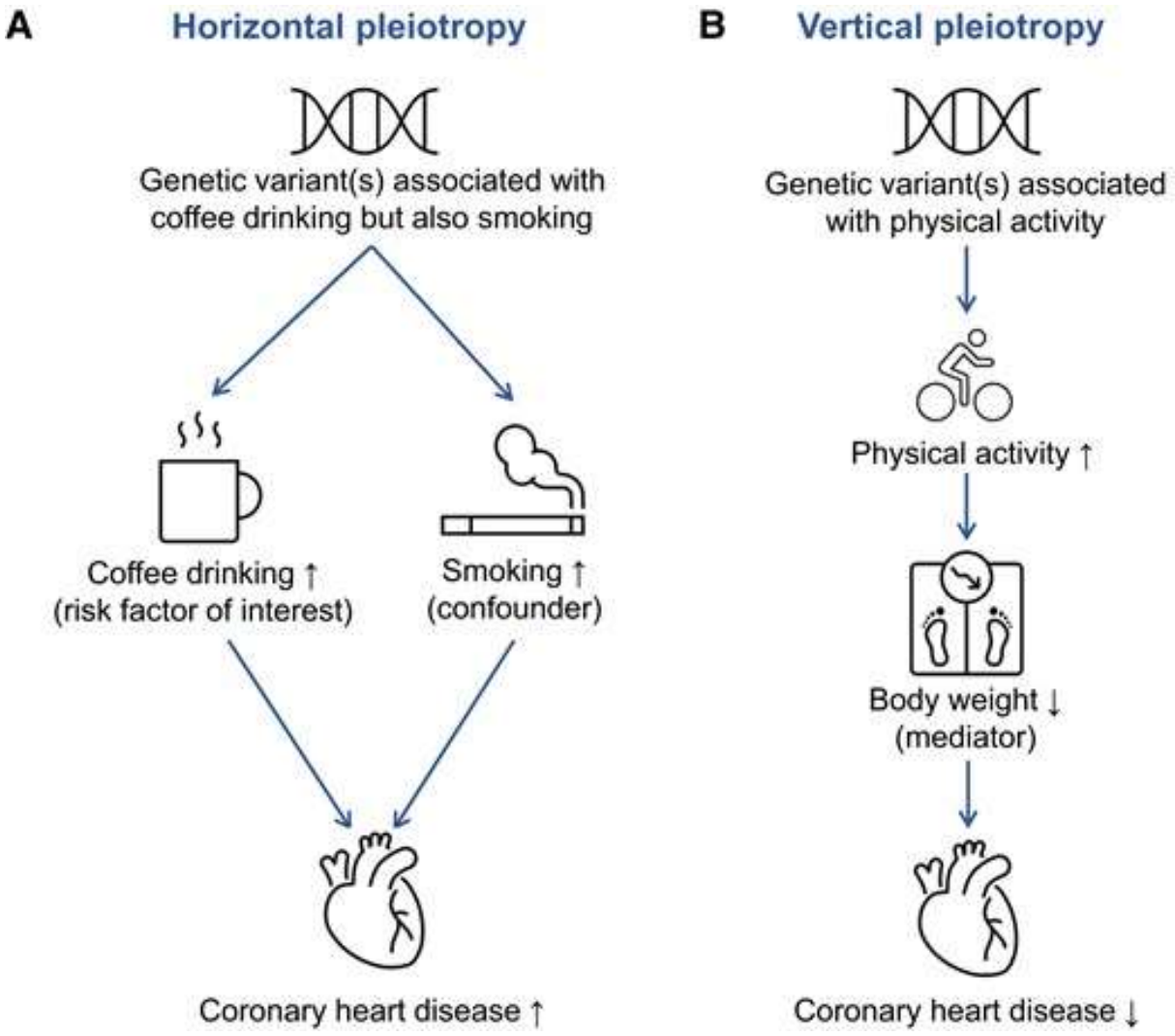


Figure 14. Examples of horizontal (A) and vertical (B) pleiotropy in MR. Source: Larsson, S. C., Butterworth, A. S. & Burgess, S. Mendelian randomization for cardiovascular diseases: principles and applications. Eur Heart J 44, (2023).

Several strategies can be applied to indirectly assess if the genetic instruments are valid and, in consequence, the MR assumptions are hold. For instance, it can be tested by the highly reproducibility of the MR estimates in different studies.[252] Pleiotropy can be identified in sources of GWAS summary statistics of large datasets, for instance the GWAS Catalog.[255,256] Additionally, some MR methods that provide unbiased results under the violation of some of the MR assumptions have been developed being the MR-Egger,[257] weighted median,[258] and pleiotropy residual sum and outlier (MR-PRESSO)[259] the most used examples.

MR is now widely used across various fields such as cardiovascular disease, metabolic disorders, and cancer. Although MR offers insight into causal effect assessment, this approach should be complementary to observational and experimental studies aiming to provide more robust evidence of causality via triangulation.[130]

4.4. Genetics of adiposity

Two types of genetic predisposition to obesity can be described: monogenic and polygenic (or common) obesity.[260] Monogenic obesity is based on a Mendelian heritability pattern becoming a rare, early-onset, and sever obesity.[260] However, polygenic obesity behaves as a multifactorial complex trait involving thousands of genetic variants and resulting from and interaction between them and the environment.[260] Although the distinction between monogenic and polygenic obesity, previous literature unveiled convergent biological mechanisms.[260]

In the past two decades, GWASs on adiposity-related proxies such as BMI and WHR have been successfully developed to identify genetic loci associated with these traits.[261–274] In 2007, a genetic locus in the *FTO* gene was robustly associated with BMI becoming the first genetic variant associated with BMI, and in consequence, with obesity risk.[261,262] *FTO* gene is in chromosome 16 and encodes for an enzyme known as fat mass and obesity-associated protein or alpha-ketoglutarate-dependent dioxygenase *FTO* that plays a key role in the regulation of food intake and energy expenditure.[275] Across the years, large sample meta-analysis of GWAS found over 900 independent genetic variants associated with BMI.[263–266] Other studies have undertaken GWAS on other adiposity-related traits such as WHR and WHR adjusted for BMI (WHRadjBMI),[266,267] childhood obesity,[268] extreme and/or early onset obesity.[269,270] GWAS on most complex traits such as body fat percentage,[271,272] fat-free mass,[273] imaging-derived adipose tissue[274] can also be found in literature. However, these complex traits are more difficult to assess than BMI or WHR ending up in analyses with a reduced sample size.

Although most of the GWAS performed until now are based on common variants [minor allele frequency (MAF) ≥5%], further studies (mainly on BMI) have extended these analyses using whole exome sequencing (WES) data including low-frequency (MAF: 1 to 5%) and rare coding variants (MAF <1%).[276–279] Findings showed novel genetic variants associated with adiposity although less than expected.[260]

Heritability (i.e., variation in a trait due to variation in genetic factors) of these traits was as well estimated. For instance, BMI and WHR heritability widely differs between studies designs. While twin-based settings estimated that heritability of BMI and WHR ranges 60-75%[280,281] and 30-60%[267,282], respectively, family-based analyses attributed a 40-45%[281] to BMI and 20-50%[267,283] to WHR, and population-based analyses a 20-40%[264,284,285] and ~10%.[267,286] This observed variation is mainly due to the ability of the methodologies on better isolating the genetic influences from shared environments.

Most of all adiposity-related GWAS were performed in large-scale European populations and focused on traditional adiposity indicators. Especially relevant for this thesis, it is worth highlighting a GWAS on body shape phenotypes published in 2016.[67] This work was performed on 173,278 individuals from the GIANT Consortium and aimed to overcome the limitations of focusing on one single adiposity indicator (i.e., capture differences in body shape between individuals who are similar in one trait but differ in others) using the body shape phenotypes to assess adiposity more holistically. This work found 6 novel loci across 4 body shape phenotypes that were not identified before in much larger GWAS meta-analyses for BMI[264], WHRadjBMI[267], and height[287] concluding that body shape phenotypes may capture further underlying biological characteristics than traditional adiposity indicators alone.

The translation of these GWAS results to a biological interpretation is, despite its importance, not straightforward. However, functional enrichment analyses showed the implication of the central nervous system, specifically the hypothalamus and the pituitary gland (appetite regulation sites) as well as the hippocampus and limbic system (learning, cognition, emotion, and memory) for BMI-associated genetic variants[264,288,289] while WHR-genetic variants were related to adipogenesis, angiogenesis, and insulin resistance.[267,290] These findings shed light on the plausible biological pathways underlying adiposity.

MAIN INSIGHTS: GENETIC EPIDEMIOLOGY

Genetic epidemiology applies the epidemiologic principles to investigate the role of genetic factors in disease susceptibility in populations.

GWAS are used to assess the associations between genetic variants and a specific phenotype.

PRS estimates the genetic susceptibility of an individual to a specific trait.

MR is a methodological approach that uses genetic variants as instrumental variables to investigate potential causal associations between an exposure and an outcome.

Genetic studies on adiposity revealed more than 900 genetic variants associated with BMI accounting for a heritability of 20-40%.

Body shape phenotypes were associated with loci that were not identified before for other anthropometric traits highlighting their potential in capture novel genetic adiposity-related information.

5. DATA SOURCES

Several data sources were used for this thesis, including large European prospective cohorts, transcriptomics data, and large genetic consortia on cancer outcomes. Data from two prospective cohorts were used namely UK Biobank[291] and EPIC.[292] For transcriptomics, it was used data from the Genotype-Tissue Expression (GTEx) project.[293,294] Finally, the genetic consortia data on breast and colorectal cancer included the most recent GWAS on Breast Cancer Association Consortium (BCAC)[295] and the GWAS meta-analysis of the Colorectal Transdisciplinary Study (CORECT), the Colon Cancer Family Registry (CCFR), and Genetics and Epidemiology of Colorectal Cancer Consortium (GECCO)[296] consortia, respectively.

5.1. UK Biobank

UK Biobank is a prospective cohort study with over 500,000 participants aged approximately 40-69 years recruited between 2006 and 2010 from 22 centres in England, Scotland, and Wales (Figure 15).[291,297] The cohort aims to study a wide range of important diseases such as cancer, heart disease, diabetes, dementia, stroke, among others, and to further understand their causes. UK Biobank includes a huge range of data involving extensive baseline questionnaires and physical measures.[291,297] Additionally, blood and urine samples were collected and stored to allow different types of investigations such as genetic, proteomic, metabolomic, biochemical, and haematological analyses.[291,297,298]

Figure 15. UK Biobank 22 assessment centres in England, Scotland, and Wales. Source: UK Biobank (available at: https://www.ukbiobank.ac.uk/).

All participants from the UK Biobank have provided written informed consent to participate. UK Biobank has ethical approval from the Northwest Multi-Centre Research Ethics Committee.

Participants were asked to attend their assessment visit in an assigned center.[291,297] The first visit consisted of an electronic signed consent, a self-completed touch-screen questionnaire, a brief computer-assisted interview, physical and functional measures, and collection of biological samples such as blood, urine, and saliva.[291,297] UK Biobank baseline questionnaire includes lifestyle and health-related data via self-completed questionnaires and interviews, focusing on known and potential risk factors for health. In short, they cover sociodemographic and occupational descriptors, family history, early life exposures such as birth weight, breastfeeding, and parental health, general health and disability such as medical and reproductive history, environmental factors such as smoking and alcohol parameters, dietary habits, physical activity, and psychological and cognitive state.[291,297]

The UK Biobank collected 40-50ml of blood and a random urine sample from participants during the baseline assessment visit.[297,298] Samples were procured throughout the day (from 8 AM to 9 PM), devoid of any stipulated fasting prerequisites. Approximately 15 million aliquot tubes are stored across two geographical separate locations: a "working" archive for initial research use, holding 9 million tubes at -80°C with automated storage systems, and a "backup" archive for additional samples, holding 6 million tubes in liquid nitrogen vapour (-196°C).[297,298] Samples are processed according to specific protocols. Minimal sample processing was done in the assessment centre. For instance, blood in the serum separator tube allowed to clot for 25-30 minutes before centrifugation at 2500g for 10 minutes. All samples were maintained at appropriate temperatures (4 or 18°C) until were packed and send to the central laboratory. The samples were transported in temperature-controlled shipping boxes by a commercial courier for further processing and storage. [297,298]

5.1.1. Anthropometric measurements

The inclusion and exclusion of anthropometric traits measurements at the baseline assessment was decided based on health relevance (e.g., associations with health outcomes in other epidemiological studies), reliability (e.g., quality assurance framework involving calibration, maintenance, ease of use, training, monitoring, and data transfer on IT systems), and resources.[297]

Anthropometric measures were recorded by trained personnel.[297] Height and weight were measured using a Seca 202 stadiometer and a Tanita BC-418 body composition analyser, respectively. BMI was calculated as body weight (in kilograms) divided by height (in meters squared). WC was measured at the natural indent or the umbilicus and HC at the widest point of the participants. WHR was calculated as WC (in centimetres) divided by HC (in centimetres). Measurements of bioimpedance were also recorded although are not relevant for this work.[297]

5.1.2. Genetic data

The UK Biobank genetic data includes the genotypes of 488,377 participants.[299] A subgroup of participants of 49,950 were genotyped at 807,411 markers by a custom Affymetrix UK BiLEVE Axiom Array chip while the other 438,427 participants were genotyped at 825,927 markers by a custom Affymetrix UK Biobank Axiom Array chip, by 106 sequential batches.[299] Both arrays shared 95% of the markers content and ended up, after the quality control, of 805,426 markers.[299] Genotypification was carried out by Affymetrix Research Services Laboratory.[299]

Quality control was performed based on a PCA to account for population structure and the removal of poor-quality markers. For the latest, consistency of experimental factors such as array or batch, missing rate, and heterozygosity metrics were checked.[299] Additionally, sex discrepancies using mismatches between self-reported and genetic inferred sex were assessed which can be due to transgender or intersex individuals, or instances of rare genetic variation, such as sex-chromosome aneuploidies.[299,300] Further quality control and analysis are specified somewhere else.[299] Markers that failed quality control in more than one batch, overall missing rate >5%, and MAF <0.0001 were also removed as well as samples identified as outliers for heterozygosity and missing rate. At this stage, the dataset included 487,442 samples with 670,739 autosomal markers.[299]

Imputation was performed in the IMPUTE4 program and mainly using the Haplotype Reference Consortium (HRC)[301] data as reference panel. HRC consisted of 64,976 of broadly European haplotypes at 39,235,157 SNPs.[299] Additionally, the merged UK10K and 1000 Genomes phase 3 reference panels,[302] which has 87,696,888 bi-allelic markers, were also used, although HRC panel was the one considered when a genetic variant was in all panels. As a result, the UK Biobank dataset included 487,442 participants with 93,095,623 autosomal SNPs.[299]

5.1.3. Biomarker measurements

Biochemical markers were obtained from the biological samples collected at baseline in all 500,000 participants.[303] Overall, 34 biomarkers were selected for assay as they represented established risk factors for diseases, were clinical diagnostic measures, or because they characterised phenotypes not otherwise well assessed. [303]

Analysis of serum biomarkers utilised 10 immunoassay analysers (6x DiaSorin Liaison XL & 4x Beckman Coulter DXI 800) and 4 clinical chemistry analysers (2x Beckman Coulter AU5800 & 2x Siemens Advia 1800).[303] Specifically, Beckman Coulter AU5800 was used to analyse CRP levels through high sensitivity immunoturbidimetry. Immune complexes formed in solution scatter light in proportion to their size, shape, and concentration. Turbidimeters measure the reduction of incidence light due to reflection, absorption, or scatter. In this procedure, the measurement of the rate of decrease in light intensity transmitted (increase in absorbance) through particles suspended in solution is the result of complexes formed during the CRP-antibody reaction. The analytical range was between 0.08 mg/L and 80 mg/L.[303]

5.2. European Prospective Investigation in Cancer and Nutrition (EPIC)

The EPIC study is also a prospective cohort with approximately 520,000 participants mostly aged 35-65 years recruited between 1992 and 2000 from 23 centres across 10 European countries: Denmark, France, Germany, Greece, Italy, the Netherlands, Norway, Spain, Sweden, and the United Kingdom (Figure 16).[292,304] The EPIC cohort was designed to further understand the aetiology of cancer as well as other chronic diseases, basically, through environmental factors including diet and lifestyle.[292,304]

Participants were mainly selected from the general population.[292,304] Exceptionally, participants from France were school university employees, Spanish and Italian centres recruited blood donors, Utrecht and Florence centres breast cancer participants, and half of the participants in Oxford were from group of vegetarians and vegans. Additionally, in France, Norway, Utrecht, and Naples only women were recruited.[292,304]

All participants provided written informed consent, and approval for the study was obtained from IARC ethics review panel (No. 20-34) and from all recruiting institutions.

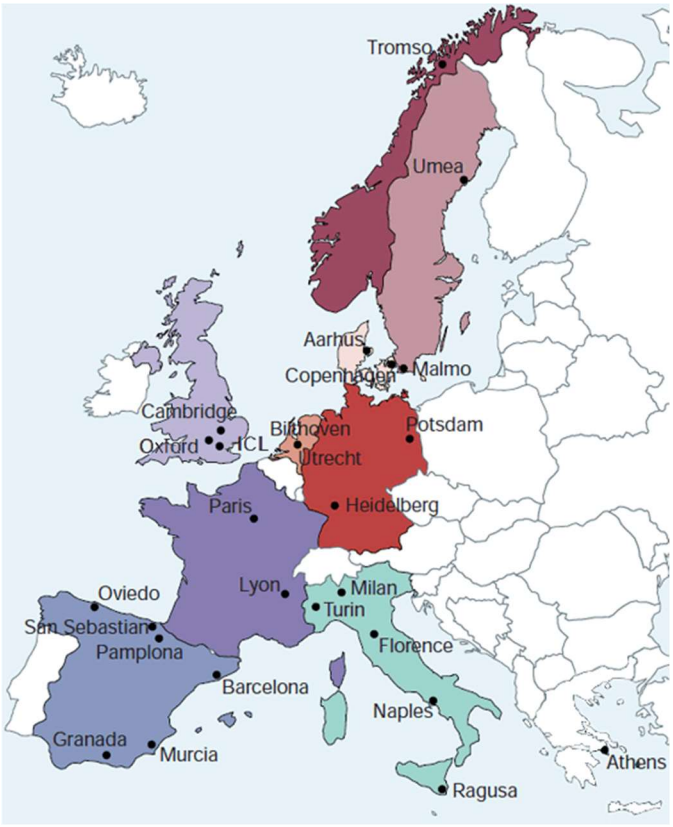


Figure 16. EPIC assessment centres across Europe. Source: IARC/WHO (available at: https://epic.iarc.fr/).

At recruitment, an informed consent was collected together with detailed questionnaires on socioeconomic factors, history of previous illnesses, reproductive factors, anthropometric traits, and lifestyle such as smoking, physical activity, education level, and diet.[304] Participants reported their average consumption of each food over the past year. Food intake (gram/day) was obtained using the frequency intake as well as the portion size.[304]

Blood samples were additionally collected from 387,889 participants (88% of the overall sample; 246,000 women) across all countries.[304] A small proportion of the participants were fasting. Most of the countries including France, Germany, Greece, Italy, the Netherlands, Norway, and the UK followed standard protocols. Plasma, serum (except in Norway), erythrocytes (except in Norway), and buffy coat were separated and aliquoted in 28 laboratory plastic straws of 0.5ml. Samples were stored for long-term in liquid nitrogen (-196°C) at the IARC centralized biobank and mirrored in EPIC collaborating centres. Exceptionally, blood fractions in Norway were collected in 20 laboratory plastic straws of 0.5ml sending half of them to central IARC storage. In Denmark and Sweden, blood samples were collected in tubes instead of plastic straws and were stored in deep freezers (-70°C, Denmark) and in nitrogen vapor (-150°C, Sweden) at local repositories, not mirroring them at IARC.[304] Overall, EPIC biorepositories reach more than 9 million aliquots.[304]

5.2.1. Anthropometric measurements

Anthropometric measurements were generally collected following standard protocols.[304,305] However, in France and Oxford, anthropometric traits were only measured for a subgroup of individuals although all participants provided self-reported measurements of weight and height.[304–307] Therefore, prediction equations based on baseline data from participants who provided both measured and self-reported information were used to enhance the accuracy of the self-reported measures.[305,306] Additionally, in Norway and Umeå, only self-reported information was collected for height and weight.[305] A second anthropometric measurement was registered at follow-up being mainly self-reported, except for UK-Norfolk and NL-Doetinchem. Furthermore, weight at 20 years old was self-reported at recruitment.

Body weight was measured to the nearest 0.1 kg without shoes while height was recorded to the nearest 0.1 cm or 0.5 cm[305] BMI was calculated as body weight (in kilograms) divided by height squared (in meters squared).[305] WC was measured at the narrowest part of the torso or halfway between the lowest rib and the top of the iliac crest.[305] HC was taken horizontally at the widest part of the hips or above the buttocks.[305] Both circumferences were rounded to the nearest centimetre. The WHR was calculated by dividing WC (cm) by HC (cm).[305] Body weight, WC, and HC were adjusted for clothing to avoid differences in the measurement protocols across centres.[305]

5.2.2. Genetic data

DNA samples of individuals from 22 case-control EPIC studies were genotyped through different genotyping platforms (Table 3). Genetic data were normalized, centralised, and imputed at IARC. Normalization across studies was performed to complete information on chromosome, position, and allele codes, harmonize the genome build version between studies, fix the strand orientation on the positive strand, and standardize the genetic variants annotation. Centralisation was based on the following exclusions: sample and genetic variants call rate (cut off >90%), sex discrepancies between genotype and phenotype, close relatives (>0.8), and population outliers to mitigate the variance introduced by diverse ancestries. Imputation was performed by the Michigan imputation server using the 1000 Genomes Project Phase 3 v5[308] as reference panel in the Genome Reference Consortium Human Build 37. Finally, post-imputation quality control was performed keeping the genetic variants by MAF >0.01 and imputation info-score >0.3.

Table 3. Genotyping platform and sample size for each EPIC case-control study. CVD, cardiovascular disease; UADT, upper aerodigestive tract.

Study acronym	Endpoint	Genotyping platform	N
GW_BREA_01	Breast cancer	Illumina Human 660W-Quad	1,011
GW_BREA_02	Breast cancer	Illumina Infinium OncoArray-500k	7,489
GW_CLRT_01	Colorectal cancer	Illumina Human OmniExpress Exome-8v1-2	4,449
GW_ECVD_01	CVD	Illumina HumanCoreExome v24	9,425
GW_ECVD_02	CVD	Customised Illumina CardioMetabochip	8,818
GW_ECVD_03	CVD	Customised Illumina Exomechip	8,572
GW_GLBD_01	Gallbladder cancer	Illumina Infinium Global Screening Array	116
GW_INTE_01	Diabetes	Illumina Human 660W-Quad	9,290
GW_INTE_02	Diabetes	Illumina Human CoreExome v12	7,391
GW_INTE_03	Diabetes	Illumina Human CoreExome v24	6,328
GW_KIDN_01	Renal cancer	Illumina Infinium 610-Quad	354
GW_KIDN_02	Renal cancer	Illumina Infinium Omni5	265
GW_LUNG_01	Lung cancer	Illumina Infinium OncoArray-500k	2,425
GW_LYMP_01	Lymphoma	Illumina OmniExpress	459
GW_OVAR_01	Ovarian cancer	Illumina Infinium OncoArray-500k	1,301
GW_PANC_01	Pancreatic cancer	Illumina HumanHap550	706
GW_PANC_02	Pancreatic cancer	Illumina Human OmniExpress	175
GW_PROS_01	Prostate cancer	Illumina Human 660W-Quad	856
GW_PROS_03	Prostate cancer	Illumina Infinium OncoArray-500k	1,135
GW_PROS_04	Prostate cancer	Illumina Infinium Global Screening Array	1,472
GW_STOM_01	Stomach cancer	Illumina Human 660W-Quad	311
GW_UADT_01	UADT cancer	Illumina Infinium OncoArray-500k	211
TOTAL			**72,559**

5.2.3. Biomarker measurements

Inflammatory biomarkers were measured (some of them more than once) in different nested case-control and case-cohort studies within EPIC participants. Serum was used for most centres except for Norway and Umeå (Sweden) where citrated plasma and heparin plasma were used, respectively. Laboratory procedures for assessing inflammatory biomarkers in EPIC are described in detail somewhere else.[309–319] Values that fell below LOD (Limit of Detection), below LLOQ (Lower Limit of Quantification), or above ULOQ (Upper Limit of Quantification) were set to LOD/2, LLOQ/2 and ULOQ, respectively.

5.3. Genotype-Tissue Expression (GTEx) project

The adult GTEx project is a public resource aiming to study the human gene expression and regulation across tissues.[293,294] Samples from 54 healthy tissue sites were collected from 948 post-mortem individuals achieving 17,382 samples (Figure 17).[294] Participants were aged between 21 and 70 with an average age of 53.4 years. Samples were genotyped through whole genome sequencing (WGS) to assess genetic variation within participants. Gene expression in each tissue was analysed through RNA sequencing (RNA-seq). Additionally, eQTLs were identified as genetic variants associated with expression changes in neighbouring genes. Overall, GTEx offers valuable insights into eQTLs, both shared and tissue-specific, highlighting the importance of cell type composition as well as the mechanistic interpretation of non-coding genetic variants linked to common human diseases.[294]

In the last released version of the data (version 8), eQTLs were identified among 15,201 samples from 838 donors and 49 tissues for those who had at least 70 individuals with both RNA-seq and genotype data WGS available.[294] Of the 838 donors, 557 (66.5%) were men and 281 (33.5%) women while the majority were European American (715, 85.3%) followed by African American (103, 12.3%), Asian Hispanic (16, 1.9%), and American (4, 0.5%).[294]

After quality control, 43,066,422 single-nucleotide variants were identified from the WGS performed for each donor.[294] RNA of each of the tissue samples was sequenced to a median depth of 82.6 million reads, with further details on the alignment, quantification, and quality control described somewhere else.[294] Genetic loci related to the genetic expression or splicing (i.e., eQTL or sQTL) were mapped in *cis* or *trans*, highlighting regulatory associations with almost all gens. Across all tissues, data showed cis-eQTLs for up to 23,368 genes and 4,278,636 genetic variants that were significant in at least one tissue.[294]

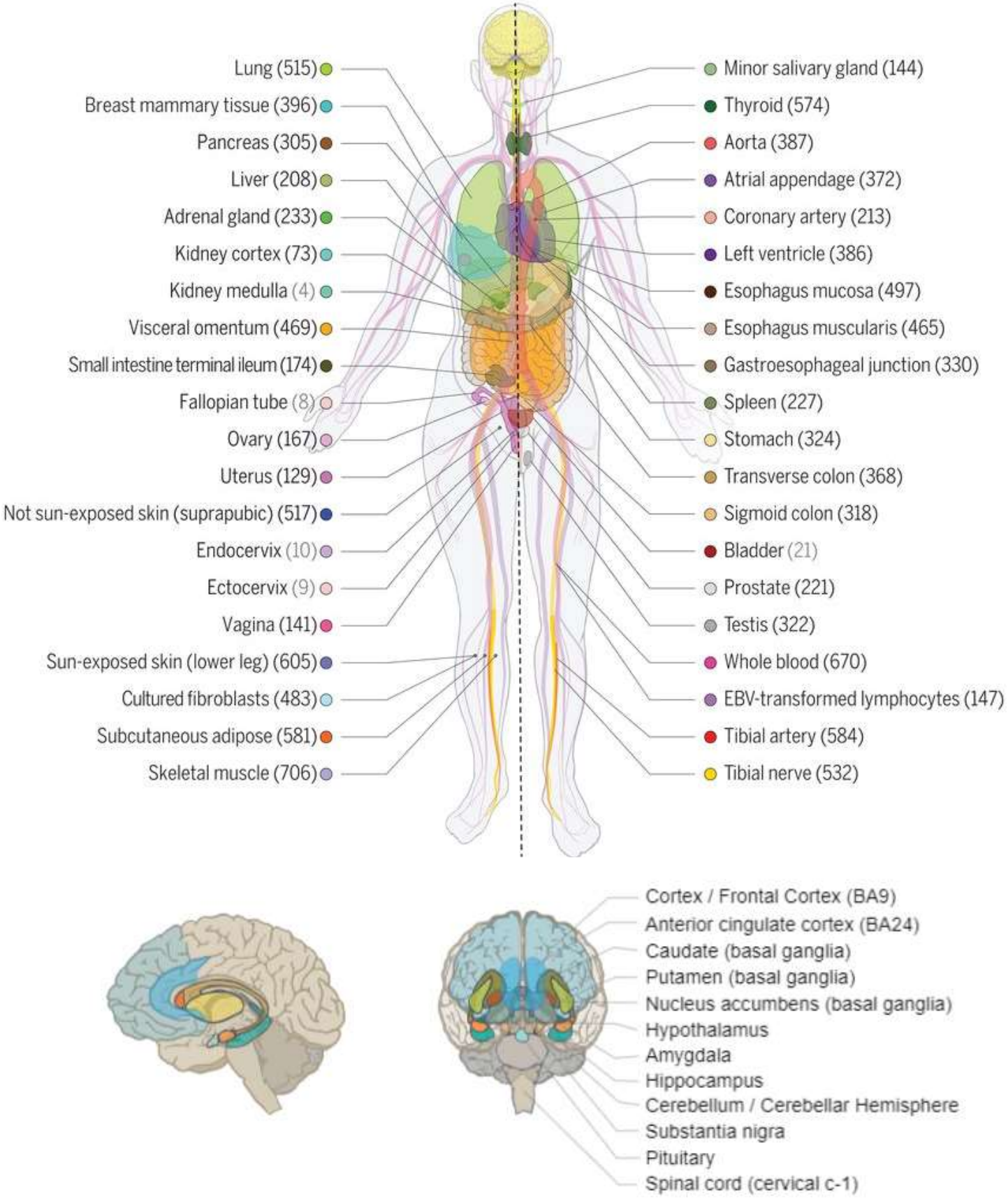


Figure 17. Tissue samples included in the GTEx project. 54 tissue types were examined, being 11 brain regions. Number of donors genotyped are in parenthesis. Source: Aguet, F. et al. The GTEx Consortium atlas of genetic regulatory effects across human tissues. Science 369, (2020).

5.4. Genetic consortia data for breast and colorectal cancer

Summary level data from genetic consortia on breast and colorectal cancer were obtained to perform two-sample MR analyses to assess the potential causal associations between adiposity and these cancer risks.

5.4.1. Genetic data on breast cancer: BCAC

BCAC data involves 82 different studies, mostly case-controls, from the general population or hospital setting of over 20 countries.[295] Data were genotyped using two Illumina custom arrays: iCOGS and OncoArray; and imputed to the 1000 Genomes Project (phase 3) reference panel.[308] Controls, invasive breast cancer, carcinoma *in situ* as well as unknown invasiveness cases were included. All participating studies were approved by their appropriate ethics or institutional review board and all participants provided informed consent. The total sample size of the data comprised 133,384 cases and 113,789 controls.[295]

In a more recent GWAS of 81 BCAC studies data on breast cancer molecular subtypes were released.[295] Contrarily to the main data, these only included controls and invasive breast cancer cases. This study included data on luminal A (7,325 cases), luminal B (1,682 cases), HER2+ (718 cases), triple negative (2,006 cases), and luminal B/HER2 (1,779 cases) invasive breast cancer subtypes, and 20,815 controls.[295] Further details on sample size and tumour heterogeneity are provided in Table 4.

Table 4. Details on sample size and tumour heterogeneity for the BCAC data according to tumour marker and grade.[295]

Breast cancer marker	Endpoint	Sample size
ER status	Negative	16,883
	Positive	69,963
	Unknown	19,432
PR status	Negative	24,260
	Positive	51,546
	Unknown	30,472
HER2 status	Negative	47,645
	Positive	9,502
	Unknown	49,131
Grade	1	15,566
	2	37,532
	3	24,360
	Unknown	28,820

5.4.2. Genetic data on colorectal cancer: CORECT, CCFR, and GECCO

Summary statistics for colorectal cancer were obtained from the meta-analysis of three large genetic consortia: CORECT, CCFR, and GECCO.[296] Data consisted of 58,131 colorectal cancer cases and 67,347 controls from 45 studies. Meta-analysis was performed in 2 stages. The first stage included 30 studies with 34,869 cases and 29,051 controls mainly of European ancestry (91.7% of the sample). The second stage was based on 22 studies including 23,262 cases and 38,296 controls, all from European ancestry. All participants provided written informed consent, and each study was approved by the relevant research ethics committee or institutional review board.[296]

Different genotyping platforms were used across the studies included in the meta-analyses which were described somewhere else.[296] Imputation was performed using the HRC panel[301] in the University of Michigan Imputation Server[320] due to its high imputation quality which enables accurate imputation of variants with MAFs as low as 0.1%.

For this thesis, UK Biobank participants were not included to avoid sample overlap between the exposures and outcomes in the two-sample MR analyses. Therefore, the dataset included 98,715 participants of European ancestry (52,775 cases and 45,940 controls).[296] Data on colorectal cancer by sex (24,568 women and 28,207 men cases) and by subsite [colon (27,817 cases), rectal (13,713 cases), distal colon (14,016 cases), and proximal colon (12,360 cases) cancer] were additionally used.[296]

HYPOTHESES

H1 Investigating adiposity through more holistic indicators such as body shape phenotypes may capture the underlying biological information beyond traditional indicators.

H2 Body shape phenotypes, characterizing independent subtypes of adiposity, may be differentially associated with risks of major cancer site risks such as breast and colorectum.

H3 Body shape phenotypes may relate to more subtle inflammatory patterns than traditional adiposity indicators.

H4 Adiposity gain prediction models may be improved by including environmental and genetic factors.

THESIS AIM AND OBJECTIVES

The main aim of this thesis was to understand adiposity through the body shape phenotypes and investigate their role in cancer risk, inflammation, and adiposity gain prediction.

Accordingly, the four objectives to achieve this aim were:

1) To further explore the biological basis of the body shape phenotypes.

2) To investigate associations between body shape phenotypes and risk of major cancers namely breast and colorectal.

3) To assess the sex-specific associations between traditional and complex adiposity indicators and inflammatory biomarkers.

4) To develop and validate a prediction model of adiposity gain combining environmental factors and PRSs of adiposity indicators such as BMI, WHR, and body shape phenotypes.

OBJECTIVE 1: To further explore the biological basis of the body shape phenotypes

1) To perform a GWAS of 460,198 UK Biobank participants to genetically characterize body shape phenotypes.

2) To identify novel genetic variants associated with the body shape phenotypes and seek for common variants with previous anthropometric traits including BMI, height, HC, WC, weight, and WHR.

3) To perform tissue expression enrichment analyses using GTEx V8 dataset to identify functional genetic variants of body shape phenotypes and unravel potential molecular mechanisms.

OBJECTIVE 2: To investigate associations between body shape phenotypes and risk of major cancers namely breast and colorectal

1) To conduct a two-sample MR analysis to investigate the potential causal associations between the body shape phenotypes and the risk of breast cancer using summary level data from 133,384 breast cancer cases and 113,789 controls from BCAC.
2) To extend these analyses by hormonal receptor status breast cancer subtypes.
3) To triangulate associations between the body shape phenotypes and colorectal cancer risk by conducting a prospective observational analysis in 329,828 UK Biobank participants (3728 incident colorectal cancer cases) and a MR analysis using data from large colorectal genetic consortia (CORECT, CCFR, and GECCO) including 98,715 participants of European ancestry (52,775 cases and 45,940 controls).
4) To further explore the body shape phenotype-colorectal cancer associations by sex and colorectal subsite (colon, distal colon, proximal colon, and rectum).

OBJECTIVE 3: To assess the sex-specific associations between traditional and complex adiposity indicators and inflammatory biomarkers

1) To investigate sex-specific associations between adiposity indicators and CRP levels in EPIC and UK Biobank and perform a meta-analysis.
2) To extend these associations with additional inflammatory biomarkers such as IL, adiponectin, and leptin in the EPIC cohort.
3) To compare results between traditional (e.g., BMI, height, WC, HC, WHR) and complex (e.g., ABSI, HI, the body shape phenotypes) adiposity indicators to assess whether complex indicators provide additional information on the inflammatory mechanisms beyond traditional indicators.

OBJECTIVE 4: To develop and validate a prediction model of adiposity gain combining environmental and PRSs of adiposity indicators such as BMI, WHR, and body shape phenotypes

1) To develop and validate a prediction model for a 5-years adiposity gain (proxied by BMI and WHR) based on environmental predictors in 275,652 EPIC participants from 8 European countries.

2) To compute Bayesian-based PRSs for adiposity indicators such as BMI, WHR, and three distinct body shape phenotypes.

3) To train the predictive ability of the PRSs in 47,014 individuals from UK Biobank and test their predictive ability as well as combined with environmental risk factors in EPIC.

SUPERVISORS REPORT

UNIVERSITAT DE BARCELONA

Informe dels directors sobre les publicacions incloses en la tesi

Dr. Robert Carreras Torres i Dr. Heinz Freisling, com a directors de la tesi doctoral titulada "Understanding Adiposity through Body Shape Phenotypes: Implications for Cancer Risk, Inflammation, and Prediction" emetem el següent:

La tesi presentada per la estudiant Laia Peruchet Noray segueix el format de compendi de publicacions, incloent un total de quatre articles que contribueixen de manera significativa als camps d'estudi abordats. Tres d'aquestes publicacions han estat acceptades i una es troba en procés de revisió en revistes de prestigi amb índexs d'impacte destacats: 4.5 [Q1], 11.7 [D1], 7.0 [D1] i 9.7 [D1]. La estudiant és primera autora en totes les publicacions excepte en un únic cas on és co-primera autora. En aquesta, la seva aportació ha estat rellevant, assumint la responsabilitat dels anàlisis, la creació de figures i taules, la participació parcial en la redacció de la secció de mètodes i resultats i la revisió general de l'article. També ha contribuït en les revisions sol·licitades per la revista i en l'acceptació de les galerades.

Finalment, es confirma que cap d'aquests articles ha estat utilitzat en altres tesis doctorals, garantint així l'exclusivitat de les publicacions en el context de la present tesi.

Barcelona, 16 de setembre de 2024.

Dr Robert Carreras Torres (co-director)

Dr Heinz Freisling (co-director)

RESULTS

In this section are presented the four studies conducted and included in this thesis. Three of them were published in high impact peer-review international journals. Table 5 summarizes the main relevant details of these studies.

Table 5. Details on author's role, journal, and impact factor (2023) for each study included in this thesis.

Study	Title	Author's role	Journal, Category, and Rank	Impact factor (2023)
Study I	Tissue-specific genetic variation suggests distinct molecular pathways between body shape phenotypes and colorectal cancer	First author	Science Advances, Multidisciplinary Sciences, Q1 (D1)	11.7
Study II	Body shape phenotypes and breast cancer risk: A Mendelian randomization analysis	First author	Cancers, Oncology, Q1	4.5
Study III	Association of body shape phenotypes and body fat distribution indexes with inflammatory biomarkers in the European Prospective Investigation into Cancer and Nutrition (EPIC) and UK Biobank	First co-author	BMC Medicine, Medicine, General & Internal, Q1 (D1)	7.0
Study IV	Nature or nurture: genetic and environmental predictors of adiposity gain in adults	First author	EBioMedicine (under review), Medicine, General & Internal, Q1 (D1)	9.7

STUDY I

Tissue-specific genetic variation suggests distinct molecular pathways between body shape phenotypes and colorectal cancer

Laia Peruchet-Noray, Anja M. Sedlmeier, Niki Dimou, …,
Robert Carreras-Torres, Marc J. Gunter, Heinz Freisling

Sci. Adv. **10, eadj1987 (2024)**

EPIDEMIOLOGY

Tissue-specific genetic variation suggests distinct molecular pathways between body shape phenotypes and colorectal cancer

Laia Peruchet-Noray[1,2], Anja M. Sedlmeier[3,4,5], Niki Dimou[1], Hansjörg Baurecht[5], Béatrice Fervers[6], Emma Fontvieille[1], Julian Konzok[5], Kostas K. Tsilidis[7,8], Sofia Christakoudi[7,9], Anna Jansana[1], Reynalda Cordova[1,10], Patricia Bohmann[5], Michael J. Stein[5], Andrea Weber[5], Stéphane Bézieau[11], Hermann Brenner[12,13,14], Andrew T. Chan[15], Iona Cheng[16], Jane C. Figueiredo[17], Koldo Garcia-Etxebarria[18,19], Victor Moreno[2,20,21,22], Christina C. Newton[23], Stephanie L. Schmit[24,25], Mingyang Song[15,26], Cornelia M. Ulrich[27], Pietro Ferrari[1], Vivian Viallon[1], Robert Carreras-Torres[28]†*, Marc J. Gunter[1,7]†*, Heinz Freisling[1]†*

Copyright © 2024 The Authors, some rights reserved; exclusive licensee American Association for the Advancement of Science. No claim to original U.S. Government Works. Distributed under a Creative Commons Attribution NonCommercial License 4.0 (CC BY-NC).

It remains unknown whether adiposity subtypes are differentially associated with colorectal cancer (CRC). To move beyond single-trait anthropometric indicators, we derived four multi-trait body shape phenotypes reflecting adiposity subtypes from principal components analysis on body mass index, height, weight, waist-to-hip ratio, and waist and hip circumference. A generally obese (PC1) and a tall, centrally obese (PC3) body shape were both positively associated with CRC risk in observational analyses in 329,828 UK Biobank participants (3728 cases). In genome-wide association studies in 460,198 UK Biobank participants, we identified 3414 genetic variants across four body shapes and Mendelian randomization analyses confirmed positive associations of PC1 and PC3 with CRC risk (52,775 cases/45,940 controls from GECCO/CORECT/CCFR). Brain tissue–specific genetic instruments, mapped to PC1 through enrichment analysis, were responsible for the relationship between PC1 and CRC, while the relationship between PC3 and CRC was predominantly driven by adipose tissue–specific genetic instruments. This study suggests distinct putative causal pathways between adiposity subtypes and CRC.

INTRODUCTION

Colorectal cancer (CRC) is the third most common cancer and the second leading cause of cancer death worldwide with more than 1.9 million incident cases and nearly 1 million deaths in 2020 (*1*, *2*). There is convincing evidence that individuals with overweight or obesity [body mass index (BMI) ≥ 25 kg/m^2] have a higher risk of CRC (*3*). Waist or hip circumferences (WC or HC) and waist-to-hip ratio (WHR) represent surrogate markers of body fat distribution and have shown associations with CRC risk similar to BMI, without providing additional insight into CRC etiology or risk discrimination (*4*). Jointly interrogating these anthropometric traits may provide information on the role of body shapes in cancer development and advance knowledge on how adiposity subtypes are differentially associated with CRC risk.

A promising way to define body shape was proposed by Ried *et al.* in 2016 (*5*). This approach was derived from data on 170,000 individuals of European ancestry and was based on a principal components analysis (PCA) on BMI, weight, height, WC, HC, and WHR. We reported previously that body shape phenotypes were associated with a higher risk of 17 different cancers in an observational analysis in the European Prospective Investigation into Cancer and Nutrition (EPIC) (*6*). Two distinct and orthogonal body shapes characterizing a generally obese and a tall, centrally obese body shape, respectively, were both strongly positively associated with CRC risk

[1]International Agency for Research on Cancer (IARC/WHO), Nutrition and Metabolism Branch, 69366 Lyon CEDEX 07, France. [2]Department of Clinical Sciences, Faculty of Medicine, University of Barcelona, Barcelona, Spain. [3]Center for Translational Oncology, University Hospital Regensburg, Regensburg, Germany. [4]Bavarian Cancer Research Center (BZKF), Regensburg, Germany. [5]Department of Epidemiology and Preventive Medicine, University of Regensburg, Regensburg, Germany. [6]Département Prévention Cancer Environnement, Centre Léon Bérard, Lyon, France. [7]Department of Epidemiology and Biostatistics, School of Public Health, Imperial College London, St Mary's Campus, Norfolk Place, London W2 1PG, UK. [8]Department of Hygiene and Epidemiology, University of Ioannina School of Medicine, Ioannina, Greece. [9]Department of Inflammation Biology, School of Immunology & Microbial Sciences, King's College London, London, UK. [10]Department of Nutritional Sciences, University of Vienna, Vienna, Austria. [11]Service de Génétique Médicale, Centre Hospitalier Universitaire (CHU) Nantes, Nantes, France. [12]Division of Clinical Epidemiology and Aging Research, German Cancer Research Center (DKFZ), Heidelberg, Germany. [13]Division of Preventive Oncology, German Cancer Research Center (DKFZ) and National Center for Tumor Diseases (NCT), Heidelberg, Germany. [14]German Cancer Consortium (DKTK), German Cancer Research Center (DKFZ), Heidelberg, Germany. [15]Clinical and Translational Epidemiology Unit, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA. [16]Department of Epidemiology and Biostatistics, University of California, San Francisco, San Francisco, CA, USA. [17]Department of Medicine, Samuel Oschin Comprehensive Cancer Institute, Cedars-Sinai Medical Center, Los Angeles, CA, USA. [18]Biodonostia, Gastrointestinal Genetics Group, San Sebastián, Spain. [19]Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBERehd), Barcelona, Spain. [20]Unit of Biomarkers and Susceptibility (UBS), Oncology Data Analytics Program (ODAP), Catalan Institute of Oncology (ICO), L'Hospitalet del Llobregat, 08908 Barcelona, Spain. [21]ONCOBELL Program, Bellvitge Biomedical Research Institute (IDIBELL), L'Hospitalet de Llobregat, 08908 Barcelona, Spain. [22]Consortium for Biomedical Research in Epidemiology and Public Health (CIBERESP), 28029 Madrid, Spain. [23]Department of Population Science, American Cancer Society, Atlanta, GA, USA. [24]Genomic Medicine Institute, Cleveland Clinic, Cleveland, OH, USA. [25]Population and Cancer Prevention Program, Case Comprehensive Cancer Center, Cleveland, OH, USA. [26]Departments of Epidemiology and Nutrition, Harvard T. H. Chan School of Public Health, Boston, MA, USA. [27]Huntsman Cancer Institute and Department of Population Health Sciences, University of Utah, Salt Lake City, UT, USA. [28]Digestive Diseases and Microbiota Group, Girona Biomedical Research Institute (IDIBGI), Salt, Girona, Spain.
†These authors contributed equally to this work.
*Corresponding author. Email: freislingh@iarc.who.fr (H.F.); m.gunter@imperial.ac.uk (M.J.G.); rcarreras@idibgi.org (R.C.-T.)

Downloaded from https://www.science.org at World Health Organization on August 22, 2024

in the observational analysis in EPIC (*6*). These initial findings require replication in a different study population and assessment of their potential causal basis. Moreover, colorectal carcinogenesis is characterized by a variety of genetic and molecular changes (*7*), and body shapes may operate through such distinct, but currently unknown, molecular pathways.

The genetic analysis of the body shapes identified genetic variants not previously associated with anthropometric traits in isolation (*5*). However, several genetic variants that were identified in the latest single-trait genome-wide association studies (GWASs) were not found in the study by Ried *et al.* (*5*). Thus, an updated GWAS in a larger sample of study participants could find additional genetic variants and provide more accurate estimates of the associations with body shapes.

Mendelian randomization (MR) studies use genetic variants as instrumental variables for a given exposure to provide evidence of potential causality in exposure-outcome associations (*8*). The key sources of bias in MR studies are unrelated to those of observational analyses, which means that both approaches complement each other and could thus provide more robust evidence of causality via triangulation (*9*). In addition, genetic variants can be grouped through enrichment analysis based on the tissue in which their mapped genes show different expression levels as compared to other tissues. Enrichment (i.e., differential expression) of BMI- and WHR-associated genes has been observed in tissues of the central nervous system and of the digestive and urogenital systems, respectively (*10*, *11*). Trait-associated genes that show differential expression across tissues may reflect different tissue contribution to a phenotype with distinct effects on disease risk (*12*). Such an approach has the potential to identify more specific molecular targets to intervene on the obesity-CRC relationship.

This analysis aimed to triangulate the association between four distinct body shapes and the risk of CRC, by subsite (colon, distal colon, proximal colon, and rectum) and by sex, and to unravel potential mechanisms by examining the role of tissue-specific gene expression of the body shapes in CRC development. We performed (i) a prospective observational analysis in 329,828 UK Biobank participants (3728 incident CRC cases), (ii) a genome-wide association of 460,198 UK Biobank participants and a tissue expression enrichment analysis in the Genotype-Tissue Expression project (GTEx) V8 dataset to identify functional genetic instruments of body shapes, and (iii) an MR analysis using data from large CRC genetic consortia including 98,715 participants of European ancestry (52,775 cases and 45,940 controls) (Fig. 1).

RESULTS

Body shape phenotypes

The first four PCs as derived in UK Biobank participants captured more than 99% of the variation in BMI, height, weight, WHR, WC, and HC (table S1), defining four distinct body shapes with high consistency to previous studies (*5*, *6*), ancestries (fig. S1), and by sex

Downloaded from https://www.science.org at World Health Organization on August 22, 2024

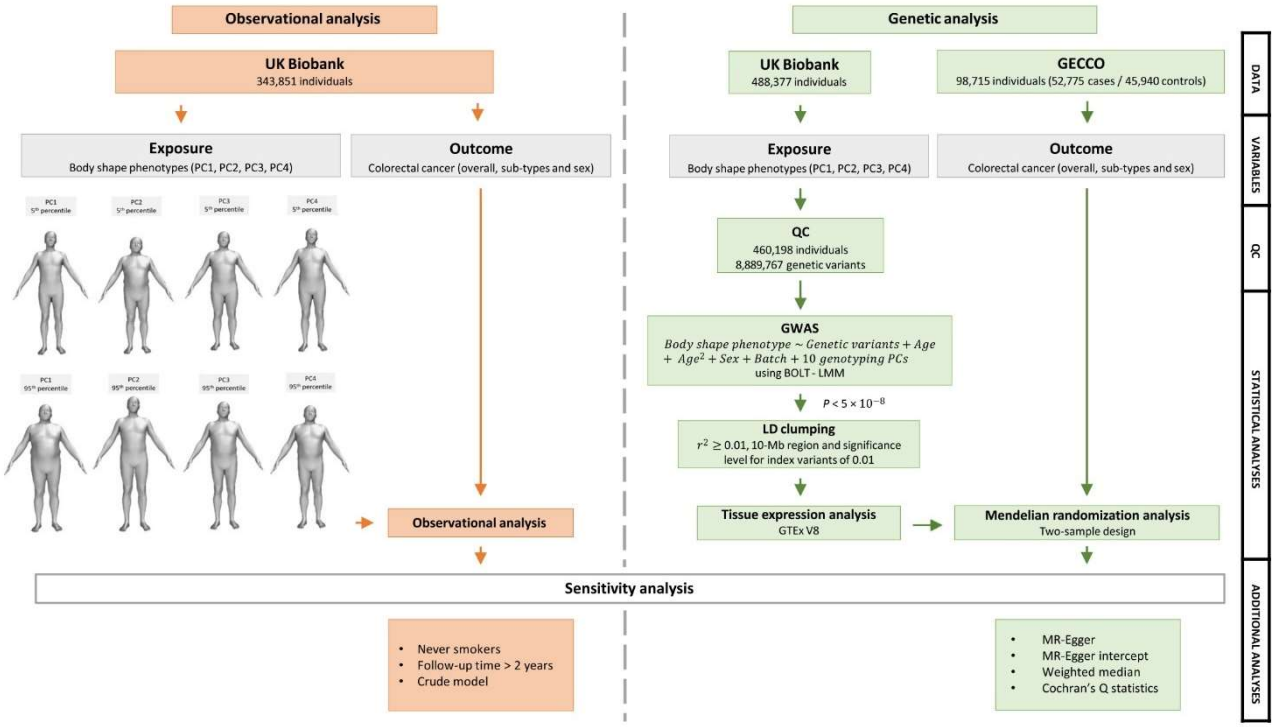


Fig. 1. Flowchart summarizing study methods. Body shape phenotypes have been derived by a PCA on six anthropometric traits (BMI, weight, height, WHR, WC, and HC). PC1 showed high and same sign loadings for all traits except height. PC2 showed high but opposite loadings for height and WHR. PC3 was characterized by high and same direction loadings for height and WHR. PC4 showed high loadings for weight and BMI and low loadings for HC and WC. QC, quality control.

(table S2). The first PC (PC1) accounted for 66.2% of total variation of the six traits describing a generally obese body shape. PC2 explained 19.4% of total variation defining tall individuals with low WHR. PC3 explained 12.3% of total variation characterizing a tall, centrally obese body shape. PC4 explained 2.0% of total variation defining an athletic body shape. Figure 1 shows these four body shapes graphically.

Observational analysis of body shape phenotypes and CRC risk

We investigated whether the four body shapes were associated with the risk of CRC in an observational analysis in UK Biobank. Baseline characteristics of the study population by sex-specific quintiles of PC1 are presented in table S3. Men and women in the lowest quintile (versus the highest quintile) of PC1 tended to have lower weight, height, BMI, WC, HC, and WHR; used less nonsteroidal anti-inflammatory drugs (NSAIDs); were more physically active; were less sedentary; tended to be never smokers; and had higher levels of education and a healthier diet. During a median follow-up time of 10.9 years (interquartile range: 10.1 to 11.6 years; 3,467,670 person-years), a total of 3728 incident CRC cases were recorded. The multivariable-adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) per 1-SD increment of PC1 was 1.13 (95% CI: 1.09 to 1.17), with similar results among men (HR: 1.17; 95% CI: 1.11 to 1.23) and women (HR: 1.09; 95% CI: 1.03 to 1.15) (*P* value for interaction by sex = 0.06). Positive associations were found for colon cancer (HR: 1.16; 95% CI: 1.11 to 1.21), regardless of its subsites (distal colon: HR: 1.15; 95% CI: 1.07 to 1.23; proximal colon: HR: 1.17; 95% CI: 1.11 to 1.24; *P* value for subsites heterogeneity = 0.10), and rectal cancer (HR: 1.07; 95% CI: 1.01 to 1.14). PC3 was also associated with an increased CRC risk with an HR of 1.09 per 1-SD increment (95% CI: 1.05 to 1.13), which was similar between men (HR: 1.09; 95% CI: 1.04 to 1.15) and women (HR: 1.08; 95% CI: 1.03 to 1.13), and for cancers of the colon (HR: 1.10; 95% CI: 1.06 to 1.14) and rectum (HR: 1.07; 95% CI: 1.01 to 1.14). PC2 and PC4 were not associated with CRC risk (Fig. 2 and table S4). Sensitivity analyses excluding current and former smokers, the two initial years of follow-up, and a crude model that included all four PCs supported the risk estimates of the main model for all four body shapes (table S4).

Genome-wide association study

We performed a GWAS in 460,198 UK Biobank participants for each of the four body shapes. We identified 3414 independent genetic variants that reached genome-wide significance ($P < 5 \times 10^{-8}$) after linkage disequilibrium (LD) clumping (see Materials and Methods). Of these, 570 variants were not previously associated with any of the six single anthropometric traits that built the body shapes; 59 (1.7%) genetic variants were shared between two or more body shapes (fig. S2). Manhattan plots, Q-Q plots, and the summary statistic results can be found in Fig. 3, fig. S3, and data S1, respectively.

For PC1, we identified 678 genetic variants ($P < 5 \times 10^{-8}$), of which 21 were not previously linked to the six anthropometric traits. Among these genetic variants, rs10803149, in the *AKT3* gene (chromosome 1), was strongly associated with PC1 (β A versus T = 0.039; $P = 2.00 \times 10^{-10}$). This gene is of interest because it encodes a protein of the serine/threonine protein kinase family, which has a key role in regulating cell survival, insulin signaling, angiogenesis, and tumor formation (*13*, *14*). Another lead genetic variant strongly associated with PC1 (rs1421085, β T versus C = −0.140; $P = 1.90 \times 10^{-241}$) in the *FTO* gene (chromosome 16) has been previously linked to BMI, weight, WC and HC, and WHR (*15*–*19*). The *FTO* gene acts as a regulator of fat mass, adipogenesis, and energy homeostasis (*13*, *14*).

For PC2, of a total of 1802 genetic variants ($P < 5 \times 10^{-8}$), 224 were not previously linked to the six anthropometric traits. Among these 224, the most strongly associated was rs9270074 (β T versus C = 0.040; $P = 2.4 \times 10^{-41}$), an intronic variant in the *HLA-DRB1* gene (chromosome 6). This gene is likely providing antitumor immunity in several solid and hematological malignancies (*13*, *14*). Of all genetic variants associated with PC2, rs6440003 and rs143384 were most strongly associated (β G versus A = −0.086; $P < 1.4 \times 10^{-217}$ and β A versus G = −0.092; $P < 1.4 \times 10^{-217}$, respectively). Rs6440003 is in the gene *ZBTB38* (chromosome 3), which plays an important role in regulating DNA replication (*13*, *14*), while rs143384 is in the *GDF5* gene (chromosome 20), which encodes a growth factor involved in bone and cartilage formation (*13*, *14*).

For PC3, we identified 741 genetic variants ($P < 5 \times 10^{-8}$), of which 220 were not previously linked to the six anthropometric traits. Among these 220 genetic variants, rs114496946, located in the gene *RAF1* (β T versus C = 0.077; $P = 1.50 \times 10^{-24}$), which encodes a serine/threonine protein kinase that regulates cell fate decisions including proliferation, differentiation, apoptosis, survival, and oncogenic transformation (*13*, *14*). The genetic variant rs72959041 (β G versus A = −0.149; $P = 1.20 \times 10^{-277}$) is located in the gene *RSPO3* (chromosome 6), which is involved in the regulation of angiogenesis (*13*, *14*). This variant was the strongest associated genetic variant with waist-to-hip index and WHR adjusted for BMI in a recent GWAS on allometric indices (*20*).

For PC4, we identified 193 genetic variants ($P < 5 \times 10^{-8}$), of which 105 were not previously known for these six anthropometric traits. Among these, rs12952730 (β G versus A = −0.005; $P = 1.50 \times 10^{-12}$) in the *RPS6KB1* gene (chromosome 17) encodes a mammalian target of rapamycin (mTOR) responding protein signaling to promote protein synthesis, cell growth, and cell proliferation. This gene has been associated with human cancer (*13*, *14*). Another genetic variant strongly associated with PC4 was rs9907540 (β A versus G = −0.009; $P = 9.90 \times 10^{-36}$), located in the *VPS53* gene (chromosome 17), which is involved in cellular retrograde transport from early and late endosomes to the trans-Golgi network and in endocytic recycling (*13*, *14*).

Overall, 192 of 207 (92.75%) genetic variants associated with the body shapes reported by Ried *et al.* were also identified in our GWAS (27 of 31 for PC1, 115 of 124 for PC2, 44 of 45 for PC3, and 6 of 7 for PC4). The genetic effects (measured by GWAS betas) of genetic variants associated with PC1 were larger than for genetic variants associated with the other PCs (Fig. 4A). This was reflected in the proportion of variability in the body shapes explained by these independent genetic variants, which were 30.9% for PC1, 34.8% for PC2, 7.8% for PC3, and 0.2% for PC4.

Tissue expression enrichment analysis

A tissue expression enrichment analysis of the body shape GWAS results was carried out using the Multi-marker Analysis of GenoMic Annotation (MAGMA) gene set analysis. This test uses the full distribution of GWAS *P* values to test for gene expression enrichment in 54 specific tissues across 30 general tissues of the GTEx V8 dataset (see Materials and Methods). The results are shown in Fig. 4B and fig. S4. Briefly, PC1 was enriched for gene expression in the

Downloaded from https://www.science.org at World Health Organization on August 22, 2024

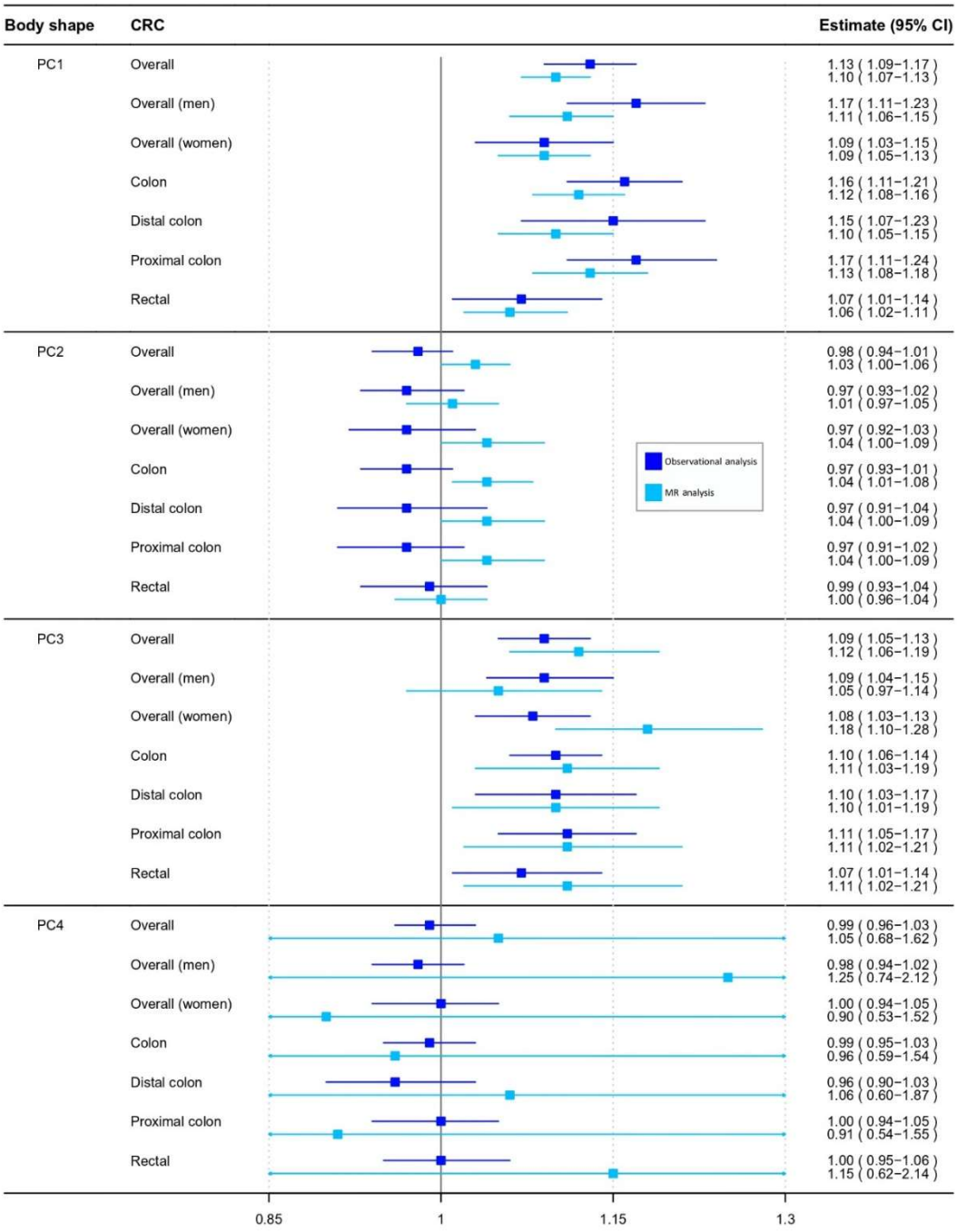


Fig. 2. Observational (dark blue) and MR (light blue) estimates of associations between body shape phenotype PC1, PC2, PC3, and PC4, per 1 standard deviation increments, and the risk of CRC (overall, among men, among women, and CRC subsites). CI, confidence interval; CRC, colorectal cancer; PC, principal component. For observational and MR analyses, cancer cases were 3728 and 52,775 for overall CRC, 2239 and 28,207 among men, 1489 and 24,568 among women, 2443 and 27,817 colon, 1285 and 13,713 rectal, 966 and 14,016 distal colon, and 1370 and 12,360 proximal colon subsites, respectively.

Downloaded from https://www.science.org at World Health Organization on August 22, 2024

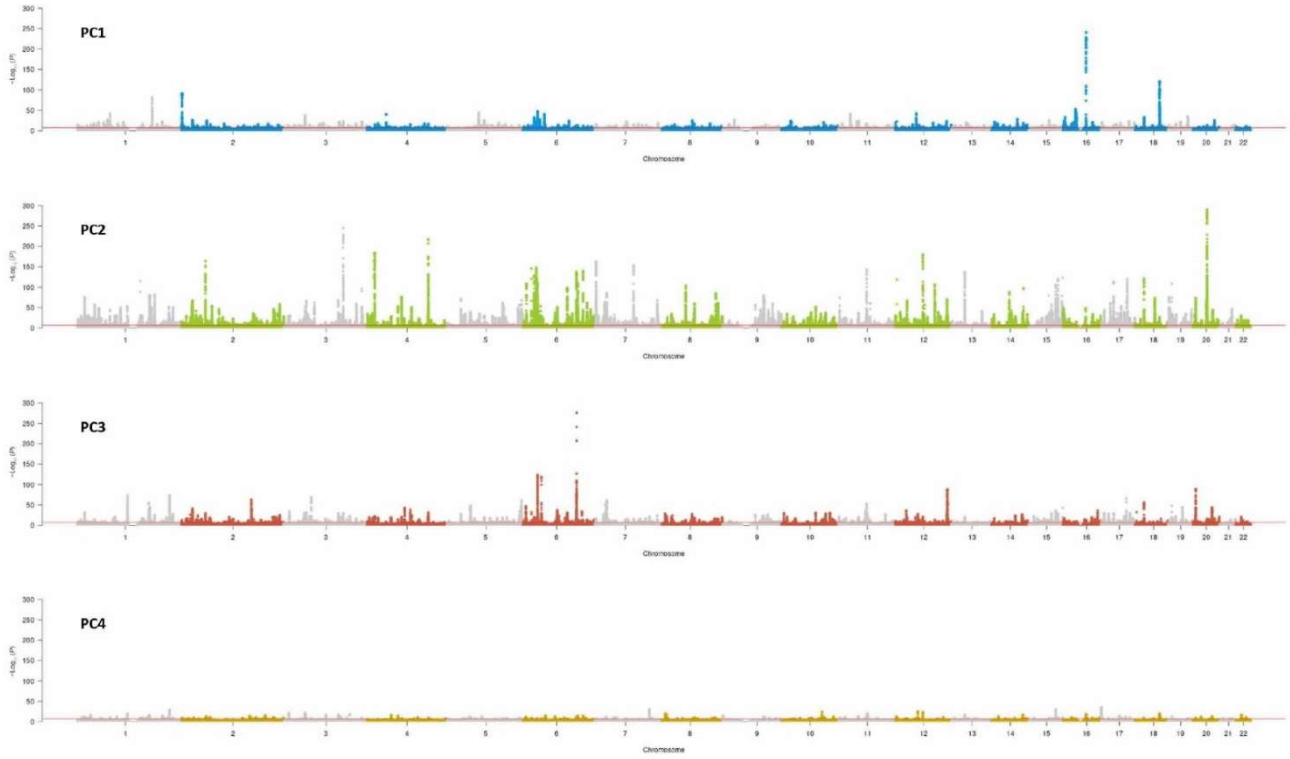


Fig. 3. Manhattan plots showing the genetic associations of the four body shapes.

brain and in the pituitary gland ($P < 7.67 \times 10^{-08}$); PC2 was enriched in the uterus, tibial nerve, ovary, cervix uteri, and blood vessels tissues ($P < 1.06 \times 10^{-3}$); PC3 showed enrichment in the adipose tissue, nerve, cervix uteri, uterus, blood vessel, breast, fallopian tube, and ovary ($P < 2.26 \times 10^{-4}$); and PC4 showed enrichment in uterus, blood vessel, adipose tissue, and muscle ($P < 2.13 \times 10^{-4}$). Overall, PC1 was enriched for gene expression corresponding to the neural broad transcription program (tissues with high proportion of neural cells), while PC2 to PC4 were enriched by gene expression corresponding to the mesenchymal broad transcription program (tissues with high proportion of mesenchymal cells) (*21*).

We further explored whether the genome-wide independent genetic variants were identified as expression quantitative trait loci (eQTL) or in LD ($r^2 > 0.8$) with an eQTL. For PC1, 204 and 110 variants of the 678 variants were identified as eQTLs in the brain tissues and the pituitary gland, respectively. Regarding the other PC GWAS results, several of the initially associated variants were also eQTLs of the tissues enriched for gene expression (PC2: 601 eQTLs in blood vessel, 592 in nerve, 144 in ovary, and 89 in uterus tissue; PC3: 278 eQTLs in adipose tissue, 259 in blood vessel, 154 in breast, 267 in nerve, 65 in ovary, and 40 in uterus tissue; and PC4: 83 eQTLs in adipose tissue, 79 in blood vessel, 68 in muscle, and 13 in uterus tissue). The eQTL with the lowest *P* value corresponded to rs72634819 for PC1 ($P = 1.7 \times 10^{-60}$), rs55938136 for PC2 ($P = 1.9 \times 10^{-184}$), rs34856835 for PC3 ($P = 2. \times 10^{-102}$), and rs10876864 for PC4 ($P = 1.1 \times 10^{-247}$), regulating the gene expression of *SLC35E2B*, *RPS26*, *XKR9*, and *LINC02210* genes, respectively.

MR of body shape phenotypes and CRC risk

Genetic variants related to body shape for the first three PCs identified by our GWAS formed strong instruments for the MR analysis (*F* statistic = 301.79 for PC1, 134.55 for PC2, and 52.22 for PC3) but not for PC4 (*F* statistic = 5.20 for PC4). Summary statistics for genetic associations with CRC risk for the 3414 genetic instruments of body shapes (672 for PC1, 1774 for PC2, 734 for PC3, and 193 for PC4) were obtained from a large CRC consortium [meta-analysis of Colorectal Transdisciplinary Study (CORECT), Colon Cancer Family Registry (CCFR), and Genetics and Epidemiology of Colorectal Cancer Consortium (GECCO)] (*22*).

PC1 was positively associated with overall CRC risk [inverse-variance weighted (IVW) odds ratio (OR) per 1 SD = 1.10; 95% CI: 1.07 to 1.13] and all subsites (colon, rectal, colon proximal, and colon distal) (Fig. 2). There was evidence of heterogeneity across genetic variants (Cochran's Q $P < 0.001$), with no evidence for directional pleiotropy as quantified using the MR Egger intercept test (table S5). Results in sensitivity analyses (MR Egger and weighted median approaches) supported the main IVW MR risk estimates (fig. S5).

PC3 was similarly positively associated with overall CRC risk (IVW OR = 1.12; 95% CI: 1.06 to 1.20), again consistent with the observational findings (Fig. 2) and sensitivity analyses (fig. S6). Heterogeneity was also detected ($P < 0.001$) (table S5). PC3 was positively associated with risk across all the CRC subsites and among women (IVW OR = 1.18; 95% CI: 1.10 to 1.28) (Fig. 2 and fig. S6).

MR estimates for PC2 showed a weak positive association with overall CRC but with a CI including the null (IVW OR = 1.03; 95%

Downloaded from https://www.science.org at World Health Organization on August 22, 2024

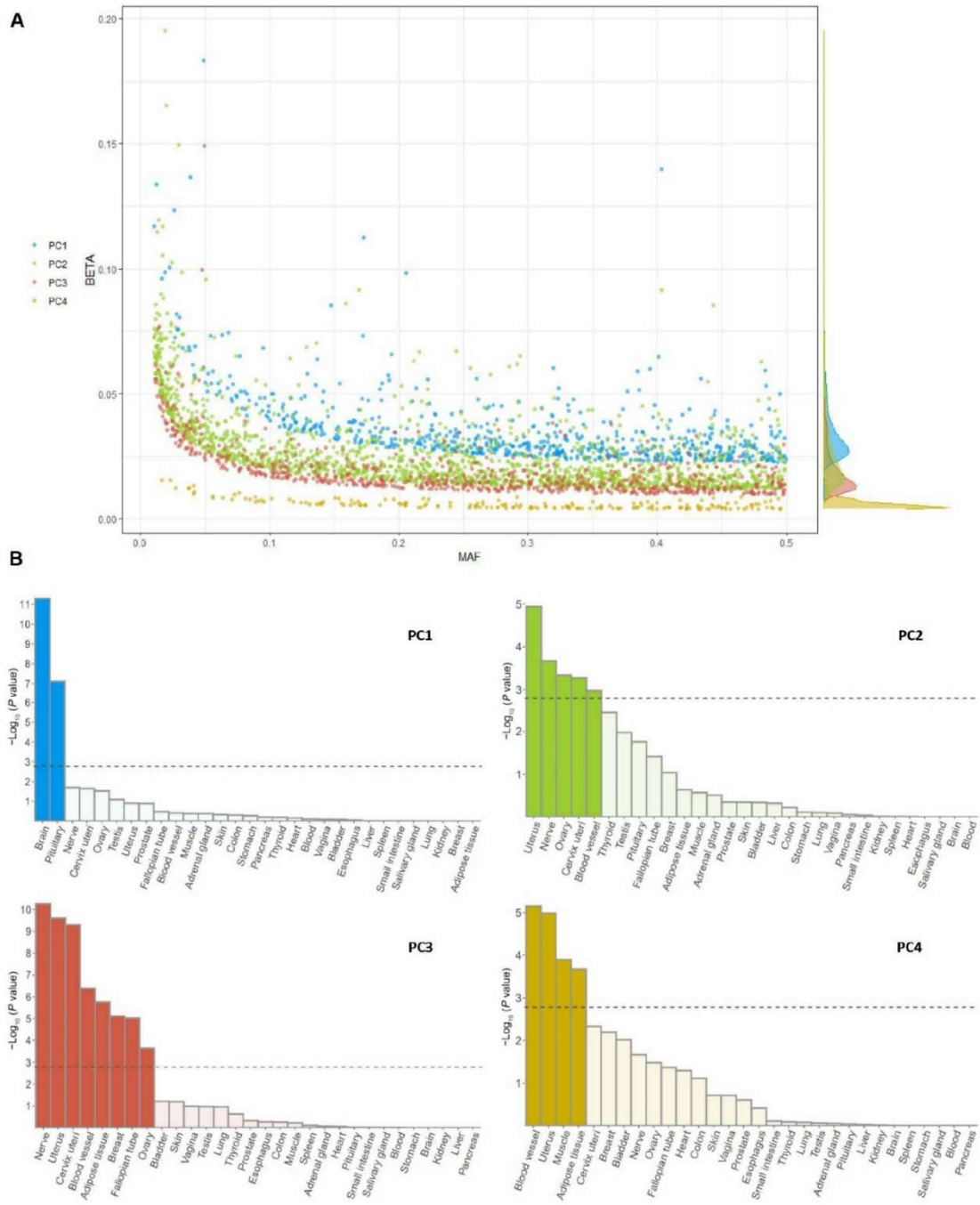


Fig. 4. Genetic architecture and tissue expression profile analyses of the four body shape phenotypes (PC1 to PC4). Genetic architecture (**A**) and tissue expression profile (**B**). Tissues reaching a *P* value of $<1.67 \times 10^{-3}$, after Bonferroni correction, are highlighted in darker colors. MAF, minor allele frequency.

Downloaded from https://www.science.org at World Health Organization on August 22, 2024

CI: 1.00 to 1.06) (Fig. 2). Associations were similar among men and women, and CRC subsites (Fig. 2). However, neither the MR sensitivity analyses (fig. S7) nor the results obtained from the observational analysis supported these findings.

PC4 showed inconclusive associations with CRC risk (IVW OR = 1.05; 95% CI: 0.68 to 1.62) (Fig. 2 and fig. S8). The scatterplots depicting the genetic associations of the body shape–related instruments with the risk of overall CRC are shown in figs. S9 to S12.

MR of tissue-specific variants of body shapes and CRC

We next defined groups of tissue-specific genetic instruments for each of the four body shapes to assess whether these tissue-grouped associations with CRC risk show evidence of divergent mechanisms. Figure S13 shows the number of genetic instruments included in the MR analysis for each tissue and the number of genetic instruments shared between tissues.

The group of brain tissue–specific genetic instruments for PC1 (204 variants) was positively associated with overall CRC risk (IVW OR per 1 SD = 1.12; 95% CI: 1.05 to 1.19), while the PC1–pituitary gland expression instrument (110 variants) showed a more modest positive association (IVW OR = 1.07; 95% CI: 0.99 to 1.16) (Fig. 5). Sensitivity analyses supported these positive observations (fig. S14). The group of adipose tissue– and tibial nerve–genetic instruments for PC3 (278 and 267 variants, respectively) showed positive associations with overall CRC risk (IVW OR = 1.15; 95% CI: 1.05 to 1.27, IVW OR = 1.14; 95% CI: 1.03 to 1.27, respectively) (Fig. 5). Other tissue-gene expression instruments for PC3 showed less strong and/or robust associations with CRC risk (Fig. 5).

In an exploratory MR analysis of PC3 and CRC risk, we subdivided adipose tissue–specific genetic instruments and found no substantial differences in risk estimates for CRC with ORs equal to 1.15 (95% CI: 1.00 to 1.34) and 1.13 (95% CI: 1.01 to 1.27) for visceral and subcutaneous adipose tissue, respectively. Further details on the heterogeneity and overall directional pleiotropy assessment can be found in table S6.

DISCUSSION

We conducted complementary observational and MR analyses to investigate the role of distinct body shapes in CRC development. We found that a generally obese body shape and a tall, centrally obese body shape were both robustly positively associated with overall CRC risk, its subsites (colon, distal colon, proximal colon, and rectal cancer), and in men and women. We also found that the generally obese body shape was associated with gene expression patterns in tissues with a high proportion of neural cells, whereas the tall and centrally obese body shape was associated with gene expression patterns in mesenchymal cells. This suggests that these two distinct body shapes may operate via separate downstream molecular pathways.

Traditionally, overall adiposity is quantified by BMI, while abdominal adiposity or body fat distribution is quantified by WC, HC, or WHR. However, BMI is correlated with height and body fat distribution measures (*23*), and the use of these indicators provides nonspecific risk estimates of the exposures under investigation (*24*, *25*). To overcome this limitation, body shapes have been proposed to characterize different phenotypes of adiposity not fully captured by individual anthropometric traits. The body shapes in UK Biobank were extremely similar with those previously computed in the GIANT consortium (*5*), in the EPIC study (*6*), and between different ancestries available in UK Biobank (i.e., Caucasian, African,

Downloaded from https://www.science.org at World Health Organization on August 22, 2024

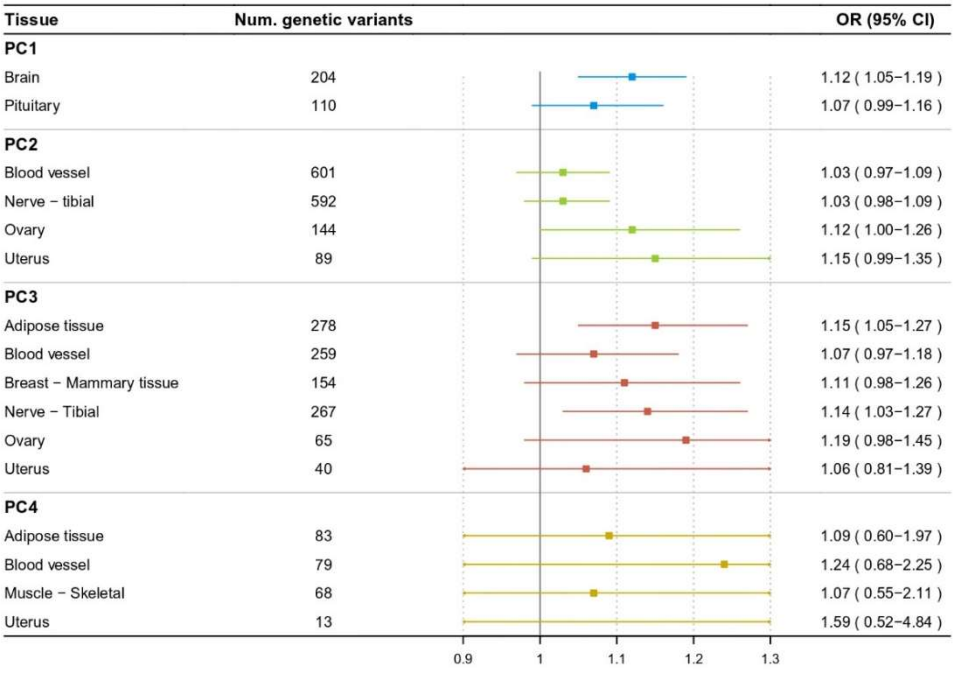


Fig. 5. Associations between body shape phenotype (PC1 to PC4) grouped gene sets and the risk of overall CRC. OR, odds ratio.

Asian, and Chinese). This emphasizes that body shape phenotypes can be built consistently across populations.

Although the body shapes may be more specific in assessing CRC risk in terms of adiposity and body size, the interpretability of the PCs is not straightforward. To facilitate the interpretation of the CRC risk estimates, we computed the means and the difference in SD units of each anthropometric trait for study participants in the top and bottom 5% of each body shape (table S7). For example, comparing top to bottom 5% of PC1 corresponded to almost uniform increments of 3.5 to 4.0 SDs for BMI, weight, WC, and HC, while increments in WHR and height were 1 and 0.4 SDs, respectively. In contrast, for PC3, we observed a 2-SD, 1-SD, and 0.3-SD increment in WHR, height, and WC, respectively, as well as decreases in HC (1.8 SD), BMI (1.3 SD), and weight (0.5 SD). Further detail and respective comparisons for PC2 and PC4 are shown in table S7.

To our knowledge, only one previous study, led by our group, investigated associations between these body shapes and the risk of cancer across 24 anatomical sites including colon and rectal cancers in an observational setting in EPIC (*6*). Our current findings are congruent and support potential causality of associations between body shapes and the risk of colon and rectal cancers observed in EPIC (*6*). Moreover, our study adds evidence for tissue-grouped causal associations of body shapes with CRC risk based on the tissue in which the body shape–mapped genes show markedly different expression levels.

Previous observational findings showed that excess body fat—measured by BMI—increased overall CRC risk by 5% per 1-SD increment (*3*), while an MR study estimated a 16% (per 1 SD) increased risk (*26*). Our findings for PC1 (generally obese body shape) showed more consistent estimates between observational and MR analyses, suggesting a risk increment per 1 SD of 13 and 10%, respectively. A meta-analysis of observational studies and an MR analysis, which used sex-specific genetic variants for BMI, showed stronger associations in men (8 and 23% increased risk) than in women (5 and 9% increased risk) (*3*, *26*). Our results (both observational and MR) are congruent with a stronger association in men than women. We did not derive sex-specific genetic variants for our MR analysis because the loadings of the body shapes between women and men were very similar. This allowed for a larger sample size to identify the genetic instruments. The mean PC scores of the body shapes were also similar between men and women (table S8), except for slightly higher PC1 scores among men than women, suggesting that the prevalence of general obesity (PC1) was higher among men than women.

Our results for PC3 (tall, centrally obese) are probably best compared with previous observational and MR analyses that have linked abdominal adiposity (indicated by WHR) to CRC risk (*3*, *26*). However, these previous studies differed in the estimates reporting 2% (per 1 SD) and 28% (per 1 SD) higher CRC risk for observational and MR analysis, respectively (*3*, *26*). As in PC1, our estimates for both association studies were more consistent (9 and 12% increased risk per 1 SD). This could be explained by the specificity of body shape phenotype PC3 that also captures the contribution of other anthropometric traits such as height.

Also relevant is the finding that associations of PC2 (tall with a low WHR) with the risk of CRC were at best suggestive of a weak positive association based on the MR analysis, which, however, was not robust in MR sensitivity analyses and were conflicting with the observational analysis. This suggests that the association of height with CRC incidence might have been overestimated in previous studies because of the difficulty to separate out the effect of height from WHR [WHR was not accounted for in previous studies (*3*, *27*, *28*)]. The differences with our results suggest that WHR may have an important role in the association between height and CRC risk, which is also supported by the results we obtained for PC3. Mechanistically, increased cancer risk due to height independently of (central) adiposity could be explained by an increased cell number in taller individuals (*29*). However, some biologic overlap with adiposity due to shared mechanistic pathways [e.g., elevated insulin-like growth factor 1 (IGF-1) levels] (*30*) cannot be ruled out and requires further investigation.

Viewed from a different mechanistic perspective with total bilirubin as a unifying indicator of metabolic health (*31*), PC2 was positively associated with total bilirubin in a UK Biobank study (*31*). This indicated a favorable metabolic health for individuals with higher PC2 scores [i.e., a lower trunk fat mass, lower circulating levels of triglycerides and of low-density lipoprotein (LDL)–cholesterol, and lower blood pressure]. In contrast, both PC1 and PC3, except for PC3 among women, were inversely associated with total bilirubin, indicating a less favorable metabolic health (*31*). Total bilirubin itself could potentially also play a causal role in CRC development, whereby higher circulating levels tended to be inversely associated with CRC risk in UK Biobank (*32*).

There is an intricate relationship between metabolic health, in particular dyslipidemia (i.e., imbalance of lipids such as cholesterol and triglycerides), and inflammation (*33*), which could present a mechanistic link to CRC. However, it is thought that inflammation leads to changes in lipid metabolism rather than the other way round; for example, tumor necrosis factor–α (TNF-α) stimulates triglyceride synthesis in hepatic cell lines (*33*). It is also likely that statins (which is a drug prescribed to reduce LDL-cholesterol levels) could confound the dyslipidemia-CRC associations. Findings from prospective and MR studies of either dyslipidemia or statins with CRC risk are inconsistent in this respect (*34*–*37*). Collectively, it remains to be clarified whether dyslipidemia plays a causal role in CRC development or is only a bystander.

Our GWAS identified 3414 independent genetic variants that were robustly associated with at least one of the four body shapes and expands prior knowledge. Ried *et al.* (*5*) had identified 207 independent genetic variants, of which 92.75% were replicated in our GWAS, which clearly shows the importance of our study with an augmented sample size [N = 460,198 current study versus N = 173,278 in Ried *et al.* (*5*)]. A total of 59 genetic variants were common with at least two of the body shapes. Overall, our results suggest different genetic architectures among body shapes.

In our tissue expression enrichment analyses, we found that the genetic variants related to PC1 showed gene expression enrichment in tissues with high proportion of neural cells (brain and pituitary gland tissues), while genetic variants related to PC3 showed gene expression enrichment in tissues with high proportion of mesenchymal cells (adipose, breast, nerve, blood vessel tissues, and the reproductive tissues of uterus, cervix, ovary, and fallopian tube) (*21*). Overall, the observed difference in genetic and tissue expressions suggests that PC1 and PC3 may capture different molecular origins and metabolic consequences of these body shapes and may reflect divergent mechanisms by which body shapes influence the risk of CRC. One mechanism by which PC1-influencing genetic variants expressed in brain tissue likely exert their effects is via energy homeostasis, which is strongly controlled by the central nervous system (*38*). Conforming

Downloaded from https://www.science.org at World Health Organization on August 22, 2024

with this notion, genetic variants strongly associated with PC1 were found in the *AKT3* and *FTO* genes, which are known to be involved in insulin signaling and energy homeostasis, respectively (*13*, *14*). Perturbed energy homeostasis can lead to neurogenic adiposity causing chronic, systemic inflammation mainly through the overexpression of proinflammatory adipokines (*39*). In contrast, PC3-influencing genetic variants expressed in adipose tissue might exert their effects through an unfavorable fat distribution characterized by less subcutaneous fat storage and/or less fat accumulation at legs and hips (*40*). This could lead to metabolically harmful ectopic fat storage (e.g., in liver and muscle) and may result in increased insulin resistance (*40*). In addition to nerves and adipose tissue, PC3 also showed enrichment in female-specific reproductive tissues such as the uterus. Whether this could explain the heterogeneity between men and women in the MR estimates for PC3 and CRC risk needs further study.

The main strength of this study is the combination of prospective observational and instrumental analyses using two large independent datasets: UK Biobank for the observational and GWAS analyses, and the CRC genetic consortia dataset for the MR approach. Second, we identified strong genetic instruments in the GWAS analysis (except for PC4), which allowed us to reliably estimate CRC risk in our MR analysis. Third, we performed multiple sensitivity analyses to evaluate the influence of residual confounding by smoking and reverse causation bias in the observational setting and to assess the potential violation of the MR assumptions.

Our findings should be interpreted considering the following limitations. Despite adjusting for the main confounders, residual confounding can be present in the risk estimates of prospective observational analysis. Second, a one-point-in-time assessment of body shapes may underestimate cumulative exposure over the life course or miss changes in body shapes. Other limitations include that, in general, the MR studies can be slightly biased because of uncontrolled confounding from family effects such as assortative mating, dynastic effects, and population structure (*41*). We minimized this bias from population stratification performing a two-sample MR analysis in samples composed of European ancestry individuals. Last, although our tissue-specific MR results suggest divergent mechanisms across tissues, we acknowledge that the observed differences in risk across tissues could be influenced by varying instrument strength/power. Future studies could use genetic colocalization to verify the functional relationship between the body shape PCs and gene expression.

In these complementary observational and MR analyses, we found that a generally obese and a distinctly tall, centrally obese body shape were both robustly associated with a higher CRC risk. While the former was enriched for gene expression in the brain and pituitary gland, the latter was enriched in adipose, nerve, blood vessel, breast, and reproductive tissues. Together with the results of the tissue-specific MR analyses, our work suggests that these two distinct body shapes may operate via separate molecular pathways through which they influence the risk of CRC. Future studies that examined these two pathways in mechanistic/experimental studies would be welcomed.

MATERIALS AND METHODS

Ethics statement

All participants from the UK Biobank have provided written informed consent to participate. UK Biobank has ethical approval from the Northwest Multi-Centre Research Ethics Committee. All participants from the GECCO, CORECT, and CCFR consortium provided written informed consent, and each study was approved by the relevant research ethics committee or institutional research board. GECCO is approved under Fred Hutch Cancer Center IRB file no. 3995.

UK Biobank

UK Biobank is a prospective cohort study with over 500,000 individuals with an age range of 38 to 73 years at recruitment between 2006 and 2010 from 22 study centers in England, Scotland, and Wales. Data on anthropometry, lifestyle, health-related indicators, and biological samples were collected (*42*, *43*). Up to 488,377 individuals were genotyped using either a custom Affymetrix UK Biobank Axiom Array chip or a custom Affymetrix UK BiLEVE Axiom Array chip (*43*).

Body shape phenotypes

Anthropometric measures were recorded by trained personnel. Height and weight were measured using a Seca 202 stadiometer and a Tanita BC-418 body composition analyzer, respectively. BMI was calculated as body weight (in kilograms) divided by height (in meters squared). WC was measured at the natural indent or the umbilicus and HC at the widest point of the participants. WHR was calculated as WC (in centimeters) divided by HC (in centimeters) (*42*). Weight and WC were not recorded for women, who were pregnant at baseline, and were thus excluded in our analysis because of missing exposure information.

Body shapes were derived from a PCA on the residuals of the six anthropometric traits (BMI, height, weight, WHR, WC, and HC) computed by regressing each trait on sex, age, and recruitment center. The distributions of PC data were winsorized at 1 and 99% to reduce the influence of point anomalies (*44*). Details regarding PC loadings and its proportion of variance explained can be found in table S1. We computed the arithmetic mean of each anthropometric trait of participants in the top and bottom 5% across all four body shape phenotypes to facilitate its interpretation (table S7). We also derived the body shape phenotypes in other ancestries available in UK Biobank (i.e., African, Asian, and Chinese).

Genome-wide association study for body shape phenotypes

We excluded participants for excess of heterozygosity, extensive missingness (rate > 5%), sex discrepancy, aneuploidy, and discordance across control replicates ($N = 1865$). We restricted our analysis to European ancestry individuals based on self-reported ancestry and categories derived using *k*-means algorithm to UK Biobank genetic PCs (fig. S15). Last, we also excluded individuals showing nonadherence to follow-up appointments, obtaining a final sample size of 460,198 European individuals. A total of 8,889,767 genetic variants remained for the GWAS after applying filters in missingness < 0.05, minor allele frequency (MAF) > 0.01, imputation info-score > 0.1, and Hardy-Weinberg equilibrium (HWE) test $P > 1 \times 10^{-8}$. These quality control steps were performed using PLINK2 except for the *k*-means algorithm, which was implemented using the "stats" package in the statistical software R 4.2.1 and RStudio 2022.7.0.548 (*45*–*48*).

Genome-wide association testing was implemented using Bayesian linear mixed-model analysis BOLT-LMM v2.3.5 (*49*). BOLT-LMM requires three primary components to be performed: the imputed genetic data for the association testing, a reference panel of LD scores per genetic variant, and genotype data used to approximate

Downloaded from https://www.science.org at World Health Organization on August 22, 2024

a genetic relationship matrix (GRM). As our sample was restricted to European ancestry individuals, we were able to use the LD score reference panel provided by BOLT-LMM, which is based on 1000 Genomes samples using the LD Score Regression (LDSC) software (*50*). The genetic variant selection for the GRM was as follows: missingness < 0.01, HWE < 1×10^{-08}, MAF > 0.01, and imputation info-score > 0.8. The remaining genetic variants were hard called using a threshold of 0.25 and pruned at $r^2 < 0.2$. Some conflictive genomic regions such as the lactase locus on chromosome 2, the major histocompatibility complex (MHC) on chromosome 6, and inversions on chromosomes 8 and 17 were removed. Last, the GRM included 836,810 genetic variants.

BOLT-LMM was applied using the standard infinitesimal model adjusting for age, age^2, sex, genotyping batch, and 10 genetic PCs. To identify independent genetic variants associated with each body shape, we performed an LD clumping on genetic variants with a *P* value of $<5 \times 10^{-08}$ in windows of 10 Mb, with a clumping threshold at $r^2 = 0.01$, using the "ieugwasr" package in R 4.2.1 and RStudio 2022.7.0.548 (*47*, *48*, *51*, *52*).

Genetic variants—not previously linked to BMI, weight, height, WHR, WC, and HC—were defined on the basis of databases from the NHGRI-EBI GWAS Catalog, the MRC IEU OpenGWAS project, the Open Targets Genetics, and PhenoScanner (accessed in February 2023) (*15*–*19*, *52*, *53*). In addition, we also compared our results with the latest GWAS on height (sample size of 5.4 million individuals) (*54*).

Tissue expression enrichment analysis

A tissue expression enrichment analysis on the GWAS summary statistics of each of the four body shapes was carried out using the MAGMA gene set analysis implemented in the Functional Mapping and Annotation (FUMA) of GWAS software (*55*, *56*). This analysis was performed for 30 general tissue types (e.g., brain tissue) and separately for 54 tissue types that included specific subtypes (e.g., 13 brain subregions). Some tissues had no subtypes (e.g., lung) and were included in both analyses. In the first step, among all genetic variants of the GWAS on body shapes, only the genetic variants mapped to a protein-coding gene were selected. Second, a regression model was fitted using the normalized GWAS-derived *P* values of the genetic variants identified in the first step as the outcome and the average gene expression per tissue type and several technical confounders as covariables. The tissues were derived from a total of 838 postmortem donors of the GTEx V8 dataset (*57*). The sample numbers from genotyped donors across the 54 tissue types are given in table S9.

Genetic variants related to body shape phenotypes

From the identified independent genetic variants across the four body shapes, we estimated the variance explained by the genetic variants related to each body shape, as a function of the effect size (β) for the phenotype in SD units and the MAF of the variants included [cumulative of $2 \times \beta^2 \times \text{MAF} \times (1 - \text{MAF})$] (*58*). We also calculated the *F* statistic to quantify the strength of the relationship between each genetic instrument and its body shape. The *F* statistic is an estimation of the magnitude of the instrument bias (with an *F* statistic of <10 indicating weak instruments) (*59*).

For the tissue-specific MR analysis, we selected genetic instruments that were found in the GWAS and identified as an eQTL or in LD ($r^2 > 0.8$) with an eQTL through MAGMA gene set analysis. We restricted our tissue-specific MR analyses to the 30 general tissues using as genetic instruments all genetic variants identified for each tissue subtype (e.g., genetic instruments for adipose tissue included genetic instruments mapped to subcutaneous and visceral adipose tissues). Further details of the number of genetic variants mapped in each specific tissue and the different specific tissues composing the general ones can be found in table S10.

Genetic variants related to CRC risk

Summary statistics for CRC risk of the genetic variants related to body shapes were obtained from three large CRC genetic consortia: GECCO, CORECT, and CCFR. These datasets did not include UK Biobank participants to avoid sample overlap between exposures and outcomes. The dataset consisted of 98,715 participants of European ancestry (52,775 cases and 45,940 controls). Further analyses by subsite [colon (27,817 cases), rectal (13,713 cases), distal colon (14,016 cases), and proximal colon (12,360 cases) cancer] and by sex (24,568 women and 28,207 men cases) were performed (*22*).

MR analysis

MR analysis is an approach that uses genetic variants as instruments to seek potential causal associations between an exposure and an outcome. MR is based on three main assumptions: (i) The genetic variants are strongly associated with the exposure, (ii) the genetic variants are not associated with any potential confounder, and (iii) the genetic variants are associated with the outcome only through the exposure (*60*–*62*).

Two-sample summary-based MR approach consists of the application of MR methods to summary-level data of a GWAS on the exposures (the four body shapes) and a GWAS on the outcomes (overall CRC, by subsites, and by sex) (*63*). Random-effects IVW MR method was used as the primary analysis (*64*).

We used scatterplots to present the genetic associations between body shapes and CRC risk to visually examine the consistency of MR estimates and the potential associated bias.

Last, we also performed the same MR analysis design for the tissue-specific MR approach.

Sensitivity analyses

The first MR assumption (i.e., the genetic variants are associated with the exposure) is likely to be met as we selected genetic variants with a rigorous *P* value of $<5 \times 10^{-8}$. The second (i.e., the genetic variants are not associated with any potential confounder) and third (i.e., the genetic variants are associated with the outcome only through the exposure) MR assumptions are more difficult to test (*65*). Thus, several sensitivity analyses were implemented to assess the potential violation of these assumptions.

We used the Cochran's *Q* test to evaluate heterogeneity among causal effects derived from each of the selected variants, considering the existence of heterogeneity with a *P* value of <0.05 (*66*). MR-Egger regression was also implemented providing a statistical test for overall directional pleiotropy (intercept term different from zero) (*67*). We performed the weighted median approach as it allows for the violations of the second and the third assumptions when up to 50% of the genetic variants are invalid (i.e., violation of one or more MR assumptions) (*68*, *69*). Both tests provide valid MR estimates in the presence of overall directional pleiotropy but suffer from reduced power (*64*, *67*). All analyses were conducted using the "MendelianRandomization" in R 4.2.1 and RStudio 2022.7.0.548 (*47*, *48*, *70*).

Downloaded from https://www.science.org at World Health Organization on August 22, 2024

Observational analysis

CRC incident cases

Data on cancer diagnoses were provided by National Health Service (NHS) Digital and Public Health England for participants from England and Wales and by NHS Central Register (NHSCR) for participants residing in Scotland. Detailed information about the record linkage and cancer registry information can be found at https://biobank.ndph.ox.ac.uk/~bbdatan/CancerNumbersReport.html. Type of cancer cases was coded using the International Classification of Diseases (ICD), and information on tumor morphology and histology was derived using the third revision of the International Classification of Diseases for Oncology (*71*). Date of complete follow-up was 29 February 2020 for England and Wales and 31 January 2021 for Scotland. CRC was defined as ICD C18-C20 (3728 cases), colon cancer as C18 (2443 cases), and rectal cancer as C19-C20 (1285 cases) using the 10th Edition of the International Classification of Diseases (ICD-10). Further subdivided, proximal colon cancer was defined as C18.0-C18.5 (1370 cases) and distal colon cancer as C18.6-C18.7 (966 cases).

Covariables

We identified potential confounding variables using directed acyclic graphs (Fig. 6 and fig. S16) (*72*, *73*). These were socioeconomic factors: age, sex, recruitment center, Townsend deprivation index, and education (university/college degree, A levels/AS levels/National Vocational Qualification/Higher National Diploma/Higher National Certificate or equivalent/other professional qualification, O levels/Certificate of Secondary Education or equivalent, none of the above); ethnicity (white, mixed, Asian/British Asian, Black/Black British, Chinese, other); lifestyle factors: tobacco smoking (never, previous, current), physical activity (metabolic equivalent-minutes per week), sedentary behavior (hours per day spent watching television/using computer/driving), adherence to a healthy diet score based on several food items (processed meat, red meat, oily fish, milk type, spread type, cereal intake, and fruit and vegetables) (*74*), milk intake (<150, 150 to 299, ≥300 ml/day), and alcohol intake frequency (daily or almost daily, three or four times a week, once or twice a week, one to three times a month, special occasions only, never); medication use: NSAIDs and hormone therapy in postmenopausal women; bowel (CRC) cancer screening and family history of CRC (father and/or mother). Further details on these variables are provided in the UK Biobank protocol (http://ukbiobank.ac.uk).

We did not adjust for comorbidities, such as type 2 diabetes, because we assumed that this comorbidity would rather be a mediator (i.e., in the pathway from body shapes to CRC) than a confounder. Unmeasured (known) confounders are inflammatory bowel syndrome and Lynch syndrome; both phenotypes are difficult to diagnose clinically, and data availability in UK Biobank was therefore limited. However, as indicated in the DAG, we assumed that the confounding paths for both phenotypes are at least partly blocked by accounting for bowel (CRC) cancer screening and family history of CRC. After the exclusion of participants with prevalent cancer at baseline, and missing, incomplete, or implausible information on exposures or in at least one covariable, the sample for observational analyses comprised 329,828 participants (51.1% women; fig. S17).

Statistical analysis

Cox proportional hazards models with age as the underlying timescale were used. We estimated HRs and 95% CIs per 1-SD increment of each PC. Models were stratified by sex, age (in 5-year categories), and recruitment center and adjusted for covariables (see above) in the main models. Proportional hazards assumptions were tested with scaled Schoenfeld residuals (*75*), and log-likelihood ratio tests were used to assess potential departure from linearity for all exposure variables.

Sensitivity analyses

As sensitivity analyses, we excluded the current and former smokers to address potential residual confounding by smoking, excluded the two initial years of follow-up to control for reverse causation, and additionally fitted a crude model that included all four PCs.

All statistical tests were two-sided and P values < 0.05 were considered statistically significant. All analyses were performed with R version 4.2.3 using the packages "FactoMineR" and "rms" (*47*, *76*, *77*).

Downloaded from https://www.science.org at World Health Organization on August 22, 2024

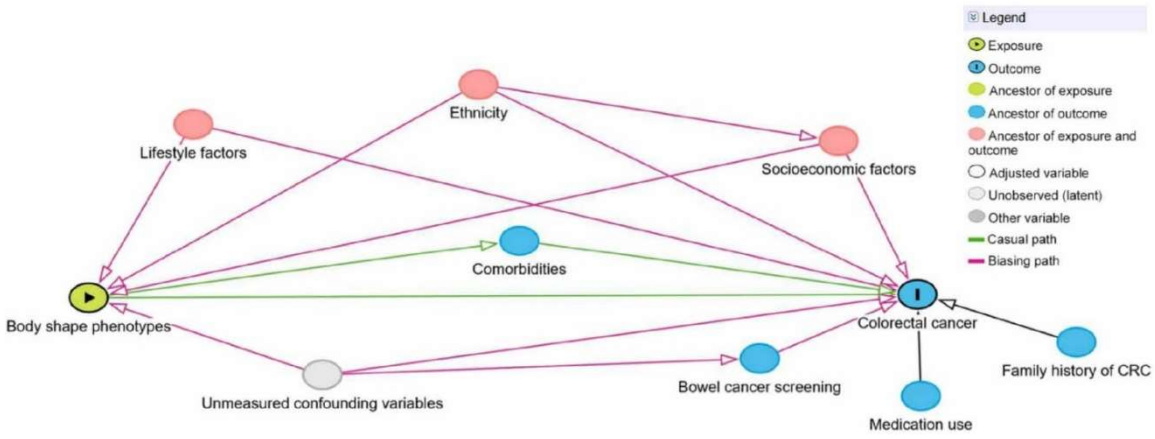


Fig. 6. Directed acyclic graph depicting the assumed causal relationship between body shape phenotypes and CRC risk with its confounding and mediating paths.

Supplementary Materials

This PDF file includes:
Figs. S1 to S17
Tables S1 to S10
Supplementary Text

Other Supplementary Material for this manuscript includes the following:
Data S1

REFERENCES AND NOTES

1. H. Sung, J. Ferlay, R. L. Siegel, M. Laversanne, I. Soerjomataram, A. Jemal, F. Bray, Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J. Clin.* **71**, 209–249 (2021).
2. J. Ferlay, M. Colombet, I. Soerjomataram, D. M. Parkin, M. Piñeros, A. Znaor, F. Bray, Cancer statistics for the year 2020: An overview. *Int. J. Cancer* **149**, 778–789 (2021).
3. World Cancer Research Fund/American Institute for Cancer Research. Continuous Update Project Expert Report, Diet, nutrition, physical activity and colorectal cancer (2018).
4. H. Freisling, M. Arnold, I. Soerjomataram, M. G. O'Doherty, J. M. Ordóñez-Mena, C. Bamia, E. Kampman, M. Leitzmann, I. Romieu, F. Kee, K. Tsilidis, A. Tjønneland, A. Trichopoulou, P. Boffetta, V. Benetou, H. B. Bueno-De-Mesquita, J. M. Huerta, H. Brenner, T. Wilsgaard, M. Jenab, Comparison of general obesity and measures of body fat distribution in older adults in relation to cancer risk: Meta-analysis of individual participant data of seven prospective cohorts in Europe. *Br. J. Cancer* **116**, 1486–1497 (2017).
5. J. S. Ried, J. M. Jeff M, A. Y. Chu, J. L. Bragg-Gresham, J. van Dongen, J. E. Huffman, T. S. Ahluwalia, G. Cadby, N. Eklund, J. Eriksson, T. Esko, M. F. Feitosa, A. Goel, M. Gorski, C. Hayward, N. L. Heard-Costa, A. U. Jackson, E. Jokinen, S. Kanoni, K. Kristiansson, Z. Kutalik, J. Lahti, J. Luan, R. Mägi, A. Mahajan, M. Mangino, C. Medina-Gomez, K. L. Monda, I. M. Nolte, L. Pérusse, I. Prokopenko, L. Qi, L. M. Rose, E. Salvi, M. T. Smith, H. Snieder, A. Stančáková, Y. J. Sung, I. Tachmazidou, A. Teumer, G. Thorleifsson, P. van der Harst, R. W. Walker, S. R. Wang, S. H. Wild, S. M. Willems, A. Wong, W. Zhang, E. Albrecht, A. C. Alves, S. J. L. Bakker, C. Barlassina, T. M. Bartz, J. Beilby, C. Bellis, R. N. Bergman, S. Bergmann, J. Blangero, M. Blüher, E. Boerwinkle, L. L. Bonnycastle, S. R. Bornstein, M. Bruinenberg, H. Campbell, Y.-D. I. Chen, C. W. K. Chiang, P. S. Chines, F. S. Collins, F. Cucca, L. A. Cupples, F. D'Avila, E. J. C. de Geus, G. Dedoussis, M. Dimitriou, A. Döring, J. G. Eriksson, A.-E. Farmaki, M. Farrall, T. Ferreira, K. Fischer, N. G. Forouhi, N. Friedrich, A. P. Gjesing, N. Glorioso, M. Graff, H. Grallert, N. Grarup, J. Gräßler, J. Grewal, A. Hamsten, M. N. Harder, C. A. Hartman, M. Hassinen, N. Hastie, A. T. Hattersley, A. S. Havulinna, M. Heliövaara, H. Hillege, A. Hofman, O. Holmen, G. Homuth, J.-J. Hottenga, J. Hui, L. L. Husemoen, P. G. Hysi, A. Isaacs, T. Ittermann, S. Jalilzadeh, A. L. James, T. Jørgensen, P. Jousilahti, A. Jula, J. M. Justesen, A. E. Justice, M. Kähönen, M. Karaleftheri, K. T. Khaw, S. M. Keinanen-Kiukaanniemi, L. Kinnunen, P. B. Knekt, H. A. Koistinen, I. Kolcic, I. K. Kooner, S. Koskinen, P. Kovacs, T. Kyriakou, T. Laitinen, C. Langenberg, A. M. Lewin, P. Lichtner, C. M. Lindgren, J. Lindström, A. Linneberg, R. Lorbeer, M. Lorentzon, R. Luben, V. Lyssenko, S. Männistö, P. Manunta, I. M. Leach, W. L. M. Ardle, B. Mcknight, K. L. Mohlke, E. Mihailov, L. Milani, R. Mills, M. E. Montasser, A. P. Morris, G. Müller, A. W. Musk, N. Narisu, K. K. Ong, B. A. Oostra, C. Osmond, A. Palotie, J. S. Pankow, L. Paternoster, B. W. Penninx, I. Pichler, M. G. Pilia, O. Polašek, P. P. Pramstaller, O. T. Raitakari, T. Rankinen, D. C. Rao, N. W. Rayner, R. Ribel-Madsen, T. K. Rice, M. Richards, P. M. Ridker, F. Rivadeneira, K. A. Ryan, S. Sanna, M. A. Sarzynski, S. Scholtens, R. A. Scott, S. Sebert, L. Southam, T. H. Sparsø, V. Steinthorsdottir, K. Stirrups, R. P. Stolk, K. Strauch, H. M. Stringham, M. A. Swertz, A. J. Swift, A. Tönjes, E. Tsafantakis, P. J. van der Most, J. V. Van Vliet-Ostaptchouk, L. Vandenput, E. Vartiainen, C. Venturini, N. Verweij, J. S. Viikari, V. Vitart, M.-C. Vohl, J. M. Vonk, G. Waeber, E. Widén, G. Willemsen, T. Wilsgaard, T. W. Winkler, A. F. Wright, L. M. Yerges-Armstrong, J. H. Zhao, M. C. Zillikens, D. I. Boomsma, C. Bouchard, J. C. Chambers, D. I. Chasman, D. Cusi, R. T. Gansevoort, C. Gieger, T. Hansen, A. A. Hicks, F. Hu, K. Hveem, M.-R. Jarvelin, E. Kajantie, J. S. Kooner, D. Kuh, J. Kuusisto, M. Laakso, T. A. Lakka, T. Lehtimäki, A. Metspalu, I. Njølstad, C. Ohlsson, A. J. Oldehinkel, L. J. Palmer, O. Pedersen, M. Perola, A. Peters, B. M. Psaty, H. Puolijoki, R. Rauramaa, I. Rudan, V. Salomaa, P. E. H. Schwarz, A. R. Shudiner, J. H. Smit, T. I. A. Sørensen, T. D. Spector, K. Stefansson, M. Stumvoll, A. Tremblay, J. Tuomilehto, A. G. Uitterlinden, M. Uusitupa, U. Völker, P. Vollenweider, N. J. Wareham, H. Watkins, J. F. Wilson, E. Zeggini, G. R. Abecasis, M. Boehnke, I. B. Borecki, P. Deloukas, C. M. van Duijn, C. Fox, L. C. Groop, I. M. Heid, D. J. Hunter, R. C. Kaplan, M. I. M. Carthy, K. E. North, J. R. O'Connell, D. Schlessinger, U. Thorsteinsdottir, D. P. Strachan, T. Frayling, J. N. Hirschhorn, M. Müller-Nurasyid, R. J. F. Loos, A principal component meta-analysis on multiple anthropometric traits identifies novel loci for body shape. *Nat. Commun.* **7**, 13357 (2016).
6. A. M. Sedlmeier, V. Viallon, P. Ferrari, L. Peruchet-Noray, E. Fontvieille, A. Amadou, N. Seyed Khoei, A. Weber, H. Baurecht, A. K. Heath, K. Tsilidis, R. Kaaks, V. Katzke, E. Inan-Eroglu, M. B. Schulze, K. Overvad, C. Bonet, E. Ubago-Guisado, M.-D. Chirlaque, E. Ardanaz, A. Perez-Cornago, V. Pala, R. Tumino, C. Sacerdote, F. Pasanisi, K. B. Borch, C. Rylander, E. Weiderpass, M. J. Gunter, B. Fervers, M. F. Leitzmann, H. Freisling, Body shape phenotypes of multiple anthropometric traits and cancer risk: A multi-national cohort study. *Br. J. Cancer* **128**, 594–605 (2022).
7. L. H. Nguyen, A. Goel, D. C. Chung, Pathways of colorectal carcinogenesis. *Gastroenterology* **158**, 291–302 (2020).
8. G. D. Smith, G. Hemani, Mendelian randomization: Genetic anchors for causal inference in epidemiological studies. *Hum. Mol. Genet.* **23**, R89–R98 (2014).
9. D. A. Lawlor, K. Tilling, G. D. Smith, Triangulation in aetiological epidemiology. *Int. J. Epidemiol.* **45**, 1866–1886 (2016).
10. A. E. Locke, B. Kahali, S. I. Berndt, A. E. Justice, T. H. Pers, F. R. Day, C. Powell, S. Vedantam, M. L. Buchkovich, J. Yang, D. C. Croteau-Chonka, T. Esko, T. Fall, T. Ferreira, S. Gustafsson, Z. Kutalik, J. Luan, R. Mägi, J. C. Randall, T. W. Winkler, A. R. Wood, T. Workalemahu, J. D. Faul, J. A. Smith, J. H. Zhao, W. Zhao, J. Chen, R. Fehrmann, Å. K. Hedman, J. Karjalainen, E. M. Schmidt, D. Absher, N. Amin, D. Anderson, M. Beekman, J. L. Bolton, J. L. Bragg-Gresham, S. Buyske, A. Demirkan, G. Deng, G. B. Ehret, B. Feenstra, M. F. Feitosa, K. Fischer, A. Goel, J. Gong, A. U. Jackson, S. Kanoni, M. E. Kleber, K. Kristiansson, U. Lim, V. Lotay, M. Mangino, I. M. Leach, C. Medina-Gomez, S. E. Medland, M. A. Nalls, C. D. Palmer, D. Pasko, S. Pechlivanis, M. J. Peters, I. Prokopenko, D. Shungin, A. Stančáková, R. J. Strawbridge, Y. J. Sung, T. Tanaka, A. Teumer, S. Trompet, S. W. van der Laan, J. van Setten, J. V. Van Vliet-Ostaptchouk, Z. Wang, L. Yengo, W. Zhang, A. Isaacs, E. Albrecht, J. Ärnlöv, G. M. Arscott, A. P. Attwood, S. Bandinelli, A. Barrett, I. N. Bas, C. Bellis, A. J. Bennett, C. Berne, R. Blagieva, M. Blüher, S. Böhringer, L. L. Bonnycastle, Y. Böttcher, H. A. Boyd, M. Bruinenberg, I. H. Caspersen, Y.-D. I. Chen, R. Clarke, E. W. Daw, A. J. M. de Craen, G. Delgado, M. Dimitriou, A. S. F. Doney, N. Eklund, K. Estrada, E. Eury, L. Folkersen, R. M. Fraser, M. E. Garcia, F. Geller, V. Giedraitis, B. Gigante, A. S. Go, A. Golay, A. H. Goodall, S. D. Gordon, M. Gorski, H.-J. Grabe, H. Grallert, T. B. Grammer, J. Gräßler, H. Grönberg, C. J. Groves, G. Gusto, J. Haessler, P. Hall, T. Haller, G. Hallmans, C. A. Hartman, M. Hassinen, C. Hayward, N. L. Heard-Costa, Q. Helmer, C. Hengstenberg, O. Holmen, J.-J. Hottenga, A. L. James, J. M. Jeff, Å. Johansson, J. Jolley, T. Juliusdottir, L. Kinnunen, W. Koenig, M. Koskenvuo, W. Kratzer, J. Laitinen, C. Lamina, K. Leander, N. R. Lee, P. Lichtner, L. Lind, J. Lindström, K. S. Lo, S. Lobbens, R. Lorbeer, Y. Lu, F. Mach, P. K. E. Magnusson, A. Mahajan, W. L. McArdle, S. M. Lachlan, C. Menni, S. Merger, E. Mihailov, L. Milani, A. Moayyeri, K. L. Monda, M. A. Morken, A. Mulas, G. Müller, M. Müller-Nurasyid, A. W. Musk, R. Nagaraja, M. M. Nöthen, I. M. Nolte, S. Pilz, N. W. Rayner, F. Renstrom, R. Rettig, J. S. Ried, S. Ripke, N. R. Robertson, L. M. Rose, S. Sanna, H. Scharnagl, S. Scholtens, F. R. Schumacher, W. R. Scott, T. Seufferlein, J. Shi, A. V. Smith, J. Smolonska, A. V. Stanton, V. Steinthorsdottir, K. Stirrups, H. M. Stringham, J. Sundström, M. A. Swertz, A. J. Swift, A.-C. Syvänen, S.-T. Tan, B. O. Tayo, B. Thorand, G. Thorleifsson, J. P. Tyrer, H.-W. Uh, L. Vandenput, F. C. Verhulst, S. H. Vermeulen, N. Verweij, J. M. Vonk, L. L. Waite, H. R. Warren, D. Waterworth, M. N. Weedon, L. R. Wilkens, C. Willenborg, T. Wilsgaard, M. K. Wojczynski, A. Wong, A. F. Wright, Q. Zhang, The LifeLines Cohort Study, E. P. Brennan, M. Choi, Z. Dastani, A. W. Drong, P. Eriksson, A. Franco-Cereceda, J. R. Gådin, A. G. Gharavi, M. E. Goddard, R. E. Handsaker, J. Huang, F. Karpe, S. Kathiresan, S. Keildson, K. Kiryluk, M. Kubo, J.-Y. Lee, L. Liang, R. P. Lifton, B. Ma, S. A. M. Carroll, A. J. M. Knight, J. L. Min, M. F. Moffatt, G. W. Montgomery, J. M. Murabito, G. Nicholson, D. R. Nyholt, Y. Okada, J. R. B. Perry, R. Dorajoo, E. Reinmaa, R. M. Salem, N. Sandholm, R. A. Scott, L. Stolk, A. Takahashi, T. Tanaka, F. M. van't Hooft, A. A. E. Vinkhuyzen, H.-J. Westra, W. Zheng, K. T. Zondervan, The ADIPOGen Consortium; The AGEN-BMI Working Group; The CARDIOGRAMplusC4D Consortium; The CKDGen Consortium; The GLGC; The ICBP; The MAGIC Investigators, The MuTHER Consortium, The MIGen Consortium, The PAGE Consortium; The ReproGen Consortium; The GENIE Consortium; The International Endogene Consortium; A. C. Heath, D. Arveiler, S. J. L. Bakker, J. Beilby, R. N. Bergman, J. Blangero, P. Bovet, H. Campbell, M. J. Caulfield, G. Cesana, A. Chakravarti, D. I. Chasman, P. S. Chines, F. S. Collins, D. C. Crawford, L. A. Cupples, D. Cusi, J. Danesh, U. de Faire, H. M. den Ruijter, A. F. Dominiczak, R. Erbel, J. Erdmann, J. G. Eriksson, M. Farrall, S. B. Felix, E. Ferrannini, J. Ferrières, I. Ford, N. G. Forouhi, T. Forrester, O. H. Franco, R. T. Gansevoort, P. V. Gejman, C. Gieger, O. Gottesman, V. Gudnason, U. Gyllensten, A. S. Hall, T. B. Harris, A. T. Hattersley, A. A. Hicks, L. A. Hindorff, A. D. Hingorani, A. Hofman, G. Homuth, G. K. Hovingh, S. E. Humphries, S. C. Hunt, E. Hyppönen, T. Illig, K. B. Jacobs, M.-R. Jarvelin, K.-H. Jöckel, B. Johansen, P. Jousilahti, J. W. Jukema, A. M. Jula, J. Kaprio, J. J. P. Kastelein, S. M. Keinanen-Kiukaanniemi, L. A. Kiemeney, P. Knekt, J. S. Kooner, C. Kooperberg, P. Kovacs, A. T. Kraja, M. Kumari, J. Kuusisto, T. A. Lakka, C. Langenberg, L. L. Marchand, T. Lehtimäki, V. Lyssenko, S. Männistö, A. Marette, T. C. Matise, C. A. McKenzie, B. M. Knight, F. L. Moll, A. D. Morris, A. P. Morris, J. C. Murray, M. Nelis, C. Ohlsson, A. J. Oldehinkel, K. K. Ong, P. A. F. Madden, G. Pasterkamp, J. F. Peden, A. Peters, D. S. Postma, P. P. Pramstaller, J. F. Price, L. Qi, O. T. Raitakari, T. Rankinen, D. C. Rao, T. K. Rice, P. M. Ridker, J. D. Rioux, M. D. Ritchie, I. Rudan, V. Salomaa, N. J. Samani, J. Saramies, M. A. Sarzynski, H. Schunkert, P. E. H. Schwarz, P. Sever, A. R. Shuldiner, J. Sinisalo, R. P. Stolk, K. Strauch, A. Tönjes, D.-A. Trégouët, A. Tremblay, E. Tremoli, J. Virtamo, M.-C. Vohl, U. Völker, G. Waeber, G. Willemsen, J. C. Witteman, M. C. Zillikens, L. S. Adair, P. Amouyel, F. W. Asselbergs, T. L. Assimes, M. Bochud, B. O. Boehm, E. Boerwinkle, S. R. Bornstein, E. P. Bottinger, C. Bouchard, S. Cauchi, J. C. Chambers, S. J. Chanock, R. S. Cooper,

Downloaded from https://www.science.org at World Health Organization on August 22, 2024

P. I. W. de Bakker, G. Dedoussis, L. Ferrucci, P. W. Franks, P. Froguel, L. C. Groop, C. A. Haiman, A. Hamsten, J. Hui, D. J. Hunter, K. Hveem, R. C. Kaplan, M. Kivimaki, D. Kuh, M. Laakso, Y. Liu, N. G. Martin, W. März, M. Melbye, A. Metspalu, S. Moebus, P. B. Munroe, I. Njølstad, B. A. Oostra, C. N. A. Palmer, N. L. Pedersen, M. Perola, L. Pérusse, U. Peters, C. Power, T. Quertermous, R. Rauramaa, F. Rivadeneira, T. E. Saaristo, D. Saleheen, N. Sattar, E. E. Schadt, D. Schlessinger, P. E. Slagboom, H. Snieder, T. D. Spector, U. Thorsteinsdottir, M. Stumvoll, J. Tuomilehto, A. G. Uitterlinden, M. Uusitupa, P. van der Harst, M. Walker, H. Wallaschofski, N. J. Wareham, H. Watkins, D. R. Weir, H.-E. Wichmann, J. F. Wilson, P. Zanen, I. B. Borecki, P. Deloukas, C. S. Fox, I. M. Heid, J. R. O'Connell, D. P. Strachan, K. Stefansson, C. M. van Duijn, G. R. Abecasis, L. Franke, T. M. Frayling, M. I. McCarthy, P. M. Visscher, A. Scherag, C. J. Willer, M. Boehnke, K. L. Mohlke, C. M. Lindgren, J. S. Beckmann, I. Barroso, K. E. North, E. Ingelsson, J. N. Hirschhorn, R. J. F. Loos, E. K. Speliotes, Genetic studies of body mass index yield new insights for obesity biology. *Nature* **518**, 197–206 (2015).

11. T. W. Winkler, F. Günther, S. Höllerer, M. Zimmermann, R. J. Loos, Z. Kutalik, I. M. Heid, A joint view on genetic variants for adiposity differentiates subtypes with distinct metabolic implications. *Nat. Commun.* **9**, 1946 (2018).
12. I. Verkouter, R. De Mutsert, R. A. J. Smit, S. Trompet, F. R. Rosendaal, D. Van Heemst, K. Willems Van Dijk, R. Noordam, The contribution of tissue-grouped BMI-associated gene sets to cardiometabolic-disease risk: A Mendelian randomization study. *Int. J. Epidemiol.* **49**, 1246–1256 (2020).
13. G. Stelzer, N. Rosen, I. Plaschkes, S. Zimmerman, M. Twik, S. Fishilevich, T. Iny Stein, R. Nudel, I. Lieder, Y. Mazor, S. Kaplan, D. Dahary, D. Warshawsky, Y. Guan-Golan, A. Kohn, N. Rappaport, M. Safran, D. Lancet, The GeneCards suite: From gene data mining to disease genome sequence analyses. *Curr. Protoc. Bioinformatics* **54**, 1.30.1–1.30.33 (2016).
14. M. Safran, N. Rosen, M. Twik, R. BarShir, T. Iny Stein, D. Dahary, S. Fishilevich, D. Lancet, "The GeneCards Suite" in *Practical Guide to Life Science Databases*, I. Abugessaisa, T. Kasukawa, Eds. (Springer Nature, 2022), pp. 27–56.
15. E. Sollis, A. Mosaku, A. Abid, A. Buniello, M. Cerezo, L. Gil, T. Groza, O. Güneş, P. Hall, J. Hayhurst, A. Ibrahim, Y. Ji, S. John, E. Lewis, J. A. L. MacArthur, A. McMahon, D. Osumi-Sutherland, K. Panoutsopoulou, Z. Pendlington, S. Ramachandran, R. Stefancsik, J. Stewart, P. Whetzel, R. Wilson, L. Hindorff, F. Cunningham, S. A. Lambert, M. Inouye, H. Parkinson, L. W. Harris, The NHGRI-EBI GWAS Catalog: Knowledgebase and deposition resource. *Nucleic Acids Res.* **51**, D977–D985 (2023).
16. M. Ghoussaini, E. Mountjoy, M. Carmona, G. Peat, E. M. Schmidt, A. Hercules, L. Fumis, A. Miranda, D. Carvalho-Silva, A. Buniello, T. Burdett, J. Hayhurst, J. Baker, J. Ferrer, A. Gonzalez-Uriarte, S. Jupp, M. A. Karim, G. Koscielny, S. MacHlitt-Northen, C. Malangone, Z. M. Pendlington, P. Roncaglia, D. Suveges, D. Wright, O. Vrousgou, E. Papa, H. Parkinson, J. A. L. MacArthur, J. A. Todd, J. C. Barrett, J. Schwartzentruber, D. G. Hulcoop, D. Ochoa, E. M. McDonagh, I. Dunham, Open Targets Genetics: Systematic identification of trait-associated genes using large-scale genetics and functional genomics. *Nucleic Acids Res.* **49**, D1311–D1320 (2021).
17. E. Mountjoy, E. M. Schmidt, M. Carmona, J. Schwartzentruber, G. Peat, A. Miranda, L. Fumis, J. Hayhurst, A. Buniello, M. A. Karim, D. Wright, A. Hercules, E. Papa, E. B. Fauman, J. C. Barrett, J. A. Todd, D. Ochoa, I. Dunham, M. Ghoussaini, An open approach to systematically prioritize causal variants and genes at all published human GWAS trait-associated loci. *Nat. Genet.* **53**, 1527–1533 (2021).
18. J. R. Staley, J. Blackshaw, M. A. Kamat, S. Ellis, P. Surendran, B. B. Sun, D. S. Paul, D. Freitag, S. Burgess, J. Danesh, R. Young, A. S. Butterworth, PhenoScanner: A database of human genotype-phenotype associations. *Bioinformatics* **32**, 3207–3209 (2016).
19. M. A. Kamat, J. A. Blackshaw, R. Young, P. Surendran, S. Burgess, J. Danesh, A. S. Butterworth, J. R. Staley, PhenoScanner V2: An expanded tool for searching human genotype-phenotype associations. *Bioinformatics* **35**, 4851–4853 (2019).
20. S. Christakoudi, E. Evangelou, E. Riboli, K. K. Tsilidis, GWAS of allometric body-shape indices in UK Biobank identifies loci suggesting associations with morphogenesis, organogenesis, adrenal cell renewal and cancer. *Sci. Rep.* **11**, 10688 (2021).
21. A. Breschi, M. Muñoz-Aguirre, V. Wucher, C. A. Davis, D. Garrido-Martín, S. Djebali, J. Gillis, D. D. Pervouchine, A. Vlasova, A. Dobin, C. Zaleski, J. Drenkow, C. Danyko, A. Scavelli, F. Reverter, M. P. Snyder, T. R. Gingeras, R. Guigó, A limited set of transcriptional programs define major cell types. *Genome Res.* **30**, 1047–1059 (2020).
22. J. R. Huyghe, S. A. Bien, T. A. Harrison, H. M. Kang, S. Chen, S. L. Schmit, D. V. Conti, C. Qu, J. Jeon, C. K. Edlund, P. Greenside, M. Wainberg, F. R. Schumacher, J. D. Smith, D. M. Levine, S. C. Nelson, N. A. Sinnott-Armstrong, D. Albanes, M. H. Alonso, K. Anderson, C. Arnau-Collell, V. Arndt, C. Bamia, B. L. Banbury, J. A. Baron, S. I. Berndt, S. Bézieau, D. T. Bishop, J. Boehm, H. Boeing, H. Brenner, S. Brezina, S. Buch, D. D. Buchanan, A. Burnett-Hartman, K. Butterbach, B. J. Caan, P. T. Campbell, C. S. Carlson, S. Castellví-Bel, A. T. Chan, J. Chang-Claude, S. J. Chanock, M. D. Chirlaque, S. H. Cho, C. M. Connolly, A. J. Cross, K. Cuk, K. R. Curtis, A. de la Chapelle, K. F. Doheny, D. Duggan, D. F. Easton, S. G. Elias, F. Elliott, D. R. English, E. J. M. Feskens, J. C. Figueiredo, R. Fischer, L. M. FitzGerald, D. Forman, M. Gala, S. Gallinger, W. J. Gauderman, G. G. Giles, E. Gillanders, J. Gong, P. J. Goodman, W. M. Grady, J. S. Grove, A. Gsur, M. J. Gunter, R. W. Haile, J. Hampe, H. Hampel, S. Harlid, R. B. Hayes, P. Hofer, M. Hoffmeister, J. L. Hopper, W. L. Hsu, W. Y. Huang, T. J. Hudson, D. J. Hunter, G. Ibañez-Sanz, G. E. Idos, R. Ingersoll, R. D. Jackson, E. J. Jacobs, M. A. Jenkins, A. D. Joshi, C. E. Joshu, T. O. Keku, T. J. Key, H. R. Kim, E. Kobayashi, L. N. Kolonel, C. Kooperberg, T. Kühn, S. Küry, S. S. Kweon, S. C. Larsson, C. A. Laurie, L. Le Marchand, S. M. Leal, S. C. Lee, F. Lejbkowicz, M. Lemire, C. I. Li, L. Li, W. Lieb, Y. Lin, A. Lindblom, N. M. Lindor, H. Ling, T. L. Louie, S. Männistö, S. D. Markowitz, V. Martín, G. Masala, C. E. McNeil, M. Melas, R. L. Milne, L. Moreno, N. Murphy, R. Myte, A. Naccarati, P. A. Newcomb, K. Offit, S. Ogino, N. C. Onland-Moret, B. Pardini, P. S. Parfrey, R. Pearlman, V. Perduca, P. D. P. Pharoah, M. Pinchev, E. A. Platz, R. L. Prentice, E. Pugh, L. Raskin, G. Rennert, H. S. Rennert, E. Riboli, M. Rodríguez-Barranco, J. Romm, L. C. Sakoda, C. Schafmayer, R. E. Schoen, D. Seminara, M. Shah, T. Shelford, M. H. Shin, K. Shulman, S. Sieri, M. L. Slattery, M. C. Southey, Z. K. Stadler, C. Stegmaier, Y. R. Su, C. M. Tangen, S. N. Thibodeau, D. C. Thomas, S. S. Thomas, A. E. Toland, A. Trichopoulou, C. M. Ulrich, D. J. Van Den Berg, F. J. B. van Duijnhoven, B. Van Guelpen, H. van Kranen, J. Vijai, K. Visvanathan, P. Vodicka, L. Vodickova, V. Vymetalkova, K. Weigl, S. J. Weinstein, E. White, A. K. Win, C. R. Wolf, A. Wolk, M. O. Woods, A. H. Wu, S. H. Zaidi, B. W. Zanke, Q. Zhang, W. Zheng, P. C. Scacheri, J. D. Potter, M. C. Bassik, A. Kundaje, G. Casey, V. Moreno, G. R. Abecasis, D. A. Nickerson, S. B. Gruber, L. Hsu, U. Peters, Discovery of common and rare genetic risk variants for colorectal cancer. *Nat. Genet.* **51**, 76–87 (2019).
23. M. Arnold, M. Leitzmann, H. Freisling, F. Bray, I. Romieu, A. Renehan, I. Soerjomataram, Obesity and cancer: An update of the global impact. *Cancer Epidemiol.* **41**, 8–15 (2016).
24. F. Hu, *Obesity Epidemiology* (Oxford Univ. Press, 2008).
25. F. Q. Nuttall, Body mass index: Obesity, BMI, and health: A critical review. *Nutr. Today* **50**, 117–128 (2015).
26. C. J. Bull, J. A. Bell, N. Murphy, E. Sanderson, G. D. Smith, N. J. Timpson, B. L. Banbury, D. Albanes, S. I. Berndt, S. Bézieau, D. T. Bishop, H. Brenner, D. D. Buchanan, A. Burnett-Hartman, G. Casey, S. Castellví-Bel, A. T. Chan, J. Chang-Claude, A. J. Cross, A. de la Chapelle, J. C. Figueiredo, S. J. Gallinger, S. M. Gapstur, G. G. Giles, S. B. Gruber, A. Gsur, J. Hampe, H. Hampel, T. A. Harrison, M. Hoffmeister, L. Hsu, W.-Y. Huang, J. R. Huyghe, M. A. Jenkins, C. E. Joshu, T. O. Keku, T. Kühn, S.-S. Kweon, L. L. Marchand, C. I. Li, L. Li, A. Lindblom, V. Martín, A. M. May, R. L. Milne, V. Moreno, P. A. Newcomb, K. Offit, S. Ogino, A. I. Phipps, E. A. Platz, J. D. Potter, C. Qu, J. R. Quirós, G. Rennert, E. Riboli, L. C. Sakoda, C. Schafmayer, R. E. Schoen, M. L. Slattery, C. M. Tangen, K. K. Tsilidis, C. M. Ulrich, F. J. B. van Duijnhoven, B. van Guelpen, K. Visvanathan, P. Vodicka, L. Vodickova, H. Wang, E. White, A. Wolk, M. O. Woods, A. H. Wu, P. T. Campbell, W. Zheng, U. Peters, E. E. Vincent, M. J. Gunter, Adiposity, metabolites, and colorectal cancer risk: Mendelian randomization study. *BMC Med.* **18**, 396 (2020).
27. F. Y. Lai, M. Nath, S. E. Hamby, J. R. Thompson, C. P. Nelson, N. J. Samani, Adult height and risk of 50 diseases: A combined epidemiological and genetic analysis. *BMC Med.* **16**, 187 (2018).
28. N. K. Khankari, X.-O. Shu, W. Wen, P. Kraft, S. Lindström, U. Peters, J. Schildkraut, F. Schumacher, P. Bofetta, A. Risch, H. Bickeböller, C. I. Amos, D. Easton, R. A. Eeles, S. B. Gruber, C. A. Haiman, D. J. Hunter, S. J. Chanock, B. L. Pierce, W. Zheng; Colorectal Transdisciplinary Study (CORECT); Discovery, Biology, and Risk of Inherited Variants in Breast Cancer (DRIVE); Elucidating Loci Involved in Prostate Cancer Susceptibility (ELLIPSE); Transdisciplinary Research in Cancer of the Lung (TRICL), Association between adult height and risk of colorectal, lung, and prostate cancer: Results from meta-analyses of prospective studies and mendelian randomization analyses. *PLOS Med.* **13**, e1002118 (2016).
29. L. Nunney, Size matters: Height, cell number and a person's risk of cancer. *Proc. Biol. Sci.* **285**, 20181743 (2018).
30. E. Giovannucci, Nutrition, insulin, insulin-like growth factors and cancer. *Horm. Metab. Res.* **35**, 694–704 (2003).
31. N. Seyed Khoei, K. H. Wagner, A. M. Sedlmeier, M. J. Gunter, N. Murphy, H. Freisling, Bilirubin as an indicator of cardiometabolic health: A cross-sectional analysis in the UK Biobank. *Cardiovasc. Diabetol.* **21**, 54 (2022).
32. N. S. Khoei, K. H. Wagner, R. Carreras-torres, M. J. Gunter, N. Murphy, H. Freisling, Associations between prediagnostic circulating bilirubin levels and risk of gastrointestinal cancers in the UK biobank. *Cancers* **13**, 2749 (2021).
33. E. Esteve, W. Ricart, J. M. Fernández-Real, Dyslipidemia and inflammation: An evolutionary conserved mechanism. *Clin. Nutr.* **24**, 16–31 (2005).
34. Y. Tian, K. Wang, J. Li, J. Wang, Z. Wang, Y. Fan, Y. Ye, G. Ji, Y. Li, The association between serum lipids and colorectal neoplasm: A systemic review and meta-analysis. *Public Health Nutr.* **18**, 3355–3370 (2015).
35. X. Yao, Z. Tian, Dyslipidemia and colorectal cancer risk: A meta-analysis of prospective studies. *Cancer Causes Control* **26**, 257–268 (2015).
36. H. Rodriguez-Broadbent, P. J. Law, A. Sud, K. Palin, S. Tuupanen, A. Gylfe, U. A. Hänninen, T. Cajuso, T. Tanskanen, J. Kondelin, E. Kaasinen, A. P. Sarin, S. Ripatti, J. G. Eriksson, H. Rissanen, P. Knekt, E. Pukkala, P. Jousilahti, V. Salomaa, A. Palotie, L. Renkonen-Sinisalo, A. Lepistö, J. Böhm, J. P. Mecklin, N. A. Al-Tassan, C. Palles, L. Martin, E. Barclay, S. M. Farrington, M. N. Timofeeva, B. F. Meyer, S. M. Wakil, H. Campbell, C. G. Smith, S. Idziaszczyk, T. S. Maughan, R. Kaplan, R. Kerr, D. Kerr, M. N. Passarelli, J. C. Figueiredo,

Downloaded from https://www.science.org at World Health Organization on August 22, 2024

D. D. Buchanan, A. K. Win, J. L. Hopper, M. A. Jenkins, N. M. Lindor, P. A. Newcomb, S. Gallinger, D. Conti, F. Schumacher, G. Casey, L. A. Aaltonen, J. P. Cheadle, I. P. Tomlinson, M. G. Dunlop, R. S. Houlston, Mendelian randomisation implicates hyperlipidaemia as a risk factor for colorectal cancer. *Int. J. Cancer* **140**, 2701–2708 (2017).
37. G. Ibáñez-Sanz, A. Díez-Villanueva, M. Riera-Ponsati, T. Fernández-Villa, P. Fernández Navarro, M. Bustamante, J. Llorca, P. Amiano, N. Ascunce, G. Fernández-Tardón, I. Salcedo Bellido, D. Salas, R. Capelo Álvarez, M. Crous-Bou, L. Ortega-Valín, B. Pérez-Gómez, G. Castaño-Vinyals, C. Palazuelos, J. M. Altzibar, E. Ardanaz, A. Tardón, J. J. Jiménez Moleón, V. Olmos Juste, N. Aragonés, M. Pollán, M. Kogevinas, V. Moreno, Mendelian randomization analysis rules out disylipidaemia as colorectal cancer cause. *Sci. Rep.* **9**, 13407 (2019).
38. A. Gómez-Hernández, N. Beneit, S. Díaz-Castroverde, Ó. Escribano, Differential role of adipose tissues in obesity and related metabolic and vascular complications. *Int. J. Endocrinol.* **2016**, 1216783 (2016).
39. G. J. Farkas, D. R. Gater, Neurogenic obesity and systemic inflammation following spinal cord injury: A review. *J. Spinal Cord Med.* **41**, 378–387 (2018).
40. R. J. F. Loos, T. O. Kilpeläinen, Genes that make you fat, but keep you healthy. *J. Intern. Med.* **284**, 450–463 (2018).
41. B. Brumpton, E. Sanderson, K. Heilbron, F. P. Hartwig, S. Harrison, G. Å. Vie, Y. Cho, L. D. Howe, A. Hughes, D. I. Boomsma, A. Havdahl, J. Hopper, M. Neale, M. G. Nivard, N. L. Pedersen, C. A. Reynolds, E. M. Tucker-Drob, A. Grotzinger, L. Howe, T. Morris, S. Li, A. Auton, F. Windmeijer, W. M. Chen, J. H. Bjørngaard, K. Hveem, C. Willer, D. M. Evans, J. Kaprio, G. Davey-Smith, B. O. Åsvold, G. Hemani, N. M. Davies, Avoiding dynastic, assortative mating, and population stratification biases in Mendelian randomization through within-family analyses. *Nat. Commun.* **11**, 3519 (2020).
42. UK Biobank Coordinating Centre, *UK Biobank: Protocol for a Large-Scale Prospective Epidemiological Resource* (UK Biobank Coordinating Centre, 2007).
43. C. Bycroft, C. Freeman, D. Petkova, G. Band, L. T. Elliott, K. Sharp, A. Motyer, D. Vukcevic, O. Delaneau, J. O'Connell, A. Cortes, S. Welsh, A. Young, M. Effingham, G. McVean, S. Leslie, N. Allen, P. Donnelly, J. Marchini, The UK Biobank resource with deep phenotyping and genomic data. *Nature* **562**, 203–209 (2018).
44. N. J. Salkind, Ed., "Winsorize," in *Encyclopedia of Research Design* (Sage Publications Inc., 2012).
45. S. Purcell, B. Neale, K. Todd-Brown, L. Thomas, M. A. R. Ferreira, D. Bender, J. Maller, P. Sklar, P. I. W. De Bakker, M. J. Daly, P. C. Sham, PLINK: A tool set for whole-genome association and population-based linkage analyses. *Am. J. Hum. Genet.* **81**, 559–575 (2007).
46. C. C. Chang, C. C. Chow, L. C. A. M. Tellier, S. Vattikuti, S. M. Purcell, J. J. Lee, Second-generation PLINK: Rising to the challenge of larger and richer datasets. *Gigascience* **4**, 7 (2015).
47. R Core Team, *R: A Language and Environment for Statistical Computing* (R Foundation for Statistical Computing, 2022).
48. RStudio Team, *RStudio: Integrated Development Environment for R* (RStudio, 2022).
49. P.-R. Loh, G. Kichaev, S. Gazal, A. P. Schoech, A. L. Price, Mixed-model association for biobank-scale datasets. *Nat. Genet.* **50**, 906–908 (2018).
50. B. K. Bulik-Sullivan, P.-R. Loh, H. K. Finucane, S. Ripke, J. Yang; Schizophrenia Working Group of the Psychiatric Genomics Consortium, N. Patterson, M. J. Daly, A. L. Price, B. M. Neale, LD score regression distinguishes confounding from polygenicity in genome-wide association studies. *Nat. Genet.* **47**, 291–295 (2015).
51. Hemani G, ieugwasr: R interface to the IEU GWAS database API. R package (2020).
52. B. Elsworth, M. Lyon, T. Alexander, Y. Liu, P. Matthews, J. Hallett, P. Bates, T. Palmer, V. Haberland, G. Davey, S. 1, J. Zheng, P. Haycock, T. R. Gaunt, G. Hemani, The MRC IEU OpenGWAS data infrastructure. bioRxiv 2020.08.10.244293 [Preprint] (2020); https://doi.org/10.1101/2020.08.10.244293.
53. G. Hemani, J. Zheng, B. Elsworth, K. H. Wade, V. Haberland, D. Baird, C. Laurin, S. Burgess, J. Bowden, R. Langdon, V. Y. Tan, J. Yarmolinsky, H. A. Shihab, N. J. Timpson, D. M. Evans, C. Relton, R. M. Martin, G. Davey Smith, T. R. Gaunt, P. C. Haycock, The MR-base platform supports systematic causal inference across the human phenome. *eLife* **7**, e34408 (2018).
54. L. Yengo, S. Vedantam, E. Marouli, J. Sidorenko, E. Bartell, S. Sakaue, M. Graff, A. U. Eliasen, Y. Jiang, S. Raghavan, J. Miao, J. D. Arias, S. E. Graham, R. E. Mukamel, C. N. Spracklen, X. Yin, S.-H. Chen, T. Ferreira, H. H. Highland, Y. Ji, T. Karaderi, K. Lin, K. Lüll, D. E. Malden, C. Medina-Gomez, M. Machado, A. Moore, S. Rüeger, X. Sim, S. Vrieze, T. S. Ahluwalia, M. Akiyama, M. A. Allison, M. Alvarez, M. K. Andersen, A. Ani, V. Appadurai, L. Arbeeva, S. Bhaskar, L. F. Bielak, S. Bollepalli, L. L. Bonnycastle, J. Bork-Jensen, J. P. Bradfield, Y. Bradford, P. S. Braund, J. A. Brody, K. S. Burgdorf, B. E. Cade, H. Cai, Q. Cai, A. Campbell, M. Cañadas-Garre, E. Catamo, J.-F. Chai, X. Chai, L.-C. Chang, Y.-C. Chang, C.-H. Chen, A. Chesi, S. H. Choi, R.-H. Chung, M. Cocca, M. P. Concas, C. Couture, G. Cuellar-Partida, R. Danning, E. W. Daw, F. Degenhard, G. E. Delgado, A. Delitala, A. Demirkan, X. Deng, P. Devineni, A. Dietl, M. Dimitriou, L. Dimitrov, R. Dorajoo, A. B. Ekici, J. E. Engmann, Z. Fairhurst-Hunter, A.-E. Farmaki, J. D. Faul, J.-C. Fernandez-Lopez, L. Forer, M. Francescatto, S. Freitag-Wolf, C. Fuchsberger, T. E. Galesloot, Y. Gao, Z. Gao, F. Geller, O. Giannakopoulou, F. Giulianini, A. P. Gjesing, A. Goel, S. D. Gordon, M. Gorski, J. Grove, X. Guo, S. Gustafsson, J. Haessler, T. F. Hansen, A. S. Havulinna, S. J. Haworth, J. He, N. Heard-Costa, P. Hebbar, G. Hindy, Y.-L. A. Ho, E. Hofer, E. Holliday, K. Horn, W. E. Hornsby, J.-J. Hottenga, H. Huang, J. Huang, A. Huerta-Chagoya, J. E. Huffman, Y.-J. Hung, S. Huo, M. Y. Hwang, H. Iha, D. D. Ikeda, M. Isono, A. U. Jackson, S. Jäger, I. E. Jansen, I. Johansson, J. B. Jonas, A. Jonsson, T. Jørgensen, I.-P. Kalafati, M. Kanai, S. Kanoni, L. L. Kårhus, A. Kasturiratne, T. Katsuya, T. Kawaguchi, R. L. Kember, K. A. Kentistou, H.-N. Kim, Y. J. Kim, M. E. Kleber, M. J. Knol, A. Kurbasic, M. Lauzon, P. Le, R. Lea, J.-Y. Lee, H. L. Leonard, S. A. Li, X. Li, X. Li, J. Liang, H. Lin, S.-Y. Lin, J. Liu, X. Liu, K. S. Lo, J. Long, L. Lores-Motta, J. Luan, V. Lyssenko, L.-P. Lyytikäinen, A. Mahajan, V. Mamakou, M. Mangino, A. Manichaikul, J. Marten, M. Mattheisen, L. Mavarani, A. F. McDaid, K. Meidtner, T. L. Melendez, J. M. Mercader, Y. Milaneschi, J. E. Miller, I. Y. Millwood, P. P. Mishra, R. E. Mitchell, L. T. Møllehave, A. Morgan, S. Mucha, M. Munz, M. Nakatochi, C. P. Nelson, M. Nethander, C. W. Nho, A. A. Nielsen, I. M. Nolte, S. S. Nongmaithem, R. Noordam, I. Ntalla, T. Nutile, A. Pandit, P. Christofidou, K. Pärna, M. Pauper, E. R. B. Petersen, L. V. Petersen, N. Pitkänen, O. Polašek, A. Poveda, M. H. Preuss, S. Pyarajan, L. M. Raffield, H. Rakugi, J. Ramirez, A. Rasheed, D. Raven, N. W. Rayner, C. Riveros, R. Rohde, D. Ruggiero, S. E. Ruotsalainen, K. A. Ryan, M. Sabater-Lleal, R. Saxena, M. Scholz, A. Sendamarai, B. Shen, J. Shi, J. H. Shin, C. Sidore, C. M. Sitlani, R. C. Slieker, R. A. J. Smit, A. V. Smith, J. A. Smith, L. J. Smyth, L. Southam, V. Steinthorsdottir, L. Sun, F. Takeuchi, D. S. P. Tallapragada, K. D. Taylor, B. O. Tayo, C. Tcheandjieu, N. Terzikhan, P. Tesolin, A. Teumer, E. Theusch, D. J. Thompson, G. Thorleifsson, P. R. H. J. Timmers, S. Trompet, C. Turman, S. Vaccargiu, S. W. van der Laan, P. J. van der Most, J. B. van Klinken, J. van Setten, S. S. Verma, N. Verweij, Y. Veturi, C. A. Wang, C. Wang, L. Wang, Z. Wang, H. R. Warren, W. B. Wei, A. R. Wickremasinghe, M. Wielscher, K. L. Wiggins, B. S. Winsvold, A. Wong, Y. Wu, M. Wuttke, R. Xia, T. Xie, K. Yamamoto, J. Yang, J. Yao, H. Young, N. A. Yousri, L. Yu, L. Zeng, W. Zhang, X. Zhang, J.-H. Zhao, W. Zhao, W. Zhou, M. E. Zimmermann, M. Zoledziewska, L. S. Adair, H. H. H. Adams, C. A. Aguilar-Salinas, F. Al-Mulla, D. K. Arnett, F. W. Asselbergs, B. O. Åsvold, J. Attia, B. Banas, S. Bandinelli, D. A. Bennett, T. Bergler, D. Bharadwaj, G. Biino, H. Bisgaard, E. Boerwinkle, C. A. Böger, K. Bønnelykke, D. I. Boomsma, A. D. Børglum, J. B. Borja, C. Bouchard, D. W. Bowden, I. Brandslund, B. Brumpton, J. E. Buring, M. J. Caulfield, J. C. Chambers, G. R. Chandak, S. J. Chanock, N. Chaturvedi, Y.-D. I. Chen, Z. Chen, C.-Y. Cheng, I. E. Christophersen, M. Ciullo, J. W. Cole, F. S. Collins, R. S. Cooper, M. Cruz, F. Cucca, L. A. Cupples, M. J. Cutler, S. M. Damrauer, T. M. Dantoft, G. J. de Borst, L. C. P. G. M. de Groot, P. L. De Jager, D. P. V. de Kleijn, H. J. de Silva, G. V. Dedoussis, A. I. den Hollander, S. Du, D. F. Easton, P. J. M. Elders, A. H. Eliassen, P. T. Ellinor, S. Elmståhl, J. Erdmann, M. K. Evans, D. Fatkin, B. Feenstra, M. F. Feitosa, L. Ferrucci, I. Ford, M. Fornage, A. Franke, P. W. Franks, B. I. Freedman, P. Gasparini, C. Gieger, G. Girotto, M. E. Goddard, Y. M. Golightly, C. Gonzalez-Villalpando, P. Gordon-Larsen, H. Grallert, S. F. A. Grant, N. Grarup, L. Griffiths, V. Gudnason, C. Haiman, H. Hakonarson, T. Hansen, C. A. Hartman, A. T. Hattersley, C. Hayward, S. R. Heckbert, C.-K. Heng, C. Hengstenberg, A. W. Hewitt, H. Hishigaki, C. B. Hoyng, P. L. Huang, W. Huang, S. C. Hunt, K. Hveem, E. Hyppönen, W. G. Iacono, S. Ichihara, M. A. Ikram, C. R. Isasi, R. D. Jackson, M.-R. Jarvelin, Z.-B. Jin, K.-H. Jöckel, P. K. Joshi, P. Jousilahti, J. W. Jukema, M. Kähönen, Y. Kamatani, K. D. Kang, J. Kaprio, S. L. R. Kardia, F. Karpe, N. Kato, F. Kee, T. Kessler, A. V. Khera, C. C. Khor, L. A. L. M. Kiemeney, B.-J. Kim, E. K. Kim, H.-L. Kim, P. Kirchhof, M. Kivimaki, W.-P. Koh, H. A. Koistinen, G. D. Kolovou, J. S. Kooner, C. Kooperberg, A. Köttgen, P. Kovacs, A. Kraaijeveld, P. Kraft, R. M. Krauss, M. Kumari, Z. Kutalik, M. Laakso, L. A. Lange, C. Langenberg, L. J. Launer, L. L. Marchand, H. Lee, N. R. Lee, T. Lehtimäki, H. Li, L. Li, W. Lieb, X. Lin, L. Lind, A. Linneberg, C.-T. Liu, J. Liu, M. Loeffler, B. London, S. A. Lubitz, S. J. Lye, D. A. Mackey, R. Mägi, P. K. E. Magnusson, G. M. Marcus, P. M. Vidal, N. G. Martin, W. März, F. Matsuda, R. W. McGarrah, M. M. Gue, A. J. McKnight, S. E. Medland, D. Mellström, A. Metspalu, B. D. Mitchell, P. Mitchell, D. O. Mook-Kanamori, A. D. Morris, L. A. Mucci, P. B. Munroe, M. A. Nalls, S. Nazarian, A. E. Nelson, M. J. Neville, C. Newton-Cheh, C. S. Nielsen, M. M. Nöthen, C. Ohlsson, A. J. Oldehinkel, L. Orozco, K. Pahkala, P. Pajukanta, C. N. A. Palmer, E. J. Parra, C. Pattaro, O. Pedersen, C. E. Pennell, B. W. J. H. Penninx, L. Perusse, A. Peters, P. A. Peyser, D. J. Porteous, D. Posthuma, C. Power, P. P. Pramstaller, M. A. Province, Q. Qi, J. Qu, D. J. Rader, O. T. Raitakari, S. Ralhan, L. S. Rallidis, D. C. Rao, S. Redline, D. F. Reilly, A. P. Reiner, S. Y. Rhee, P. M. Ridker, M. Rienstra, S. Ripatti, M. D. Ritchie, D. M. Roden, F. R. Rosendaal, J. I. Rotter, I. Rudan, F. Rutters, C. Sabanayagam, D. Saleheen, V. Salomaa, N. J. Samani, D. K. Sanghera, N. Sattar, B. Schmidt, H. Schmidt, R. Schmidt, M. B. Schulze, H. Schunkert, L. J. Scott, R. J. Scott, P. Sever, E. J. Shiroma, M. B. Shoemaker, X.-O. Shu, E. M. Simonsick, M. Sims, J. R. Singh, A. B. Singleton, M. F. Sinner, J. G. Smith, H. Snieder, T. D. Spector, M. J. Stampfer, K. J. Stark, D. P. Strachan, L. M. 't Hart, Y. Tabara, H. Tang, J.-C. Tardif, T. A. Thanaraj, N. J. Timpson, A. Tönjes, A. Tremblay, T. Tuomi, J. Tuomilehto, M.-T. Tusié-Luna, A. G. Uitterlinden, R. M. van Dam, P. van der Harst, N. Van der Velde, C. M. van Duijn, N. M. van Schoor, V. Vitart, U. Völker, P. Vollenweider, H. Völzke, N. H. Wacher-Rodarte, M. Walker, Y. X. Wang, N. J. Wareham, R. M. Watanabe, H. Watkins, D. R. Weir, T. M. Werge, E. Widen, L. R. Wilkens, G. Willemsen, W. C. Willett, J. F. Wilson, T.-Y. Wong, J.-T. Woo, A. F. Wright, J.-Y. Wu, H. Xu, C. S. Yajnik, M. Yokota, J.-M. Yuan, E. Zeggini, B. S. Zemel, W. Zheng, X. Zhu, J. M. Zmuda, A. B. Zonderman, J.-A. Zwart; 23andMe Research Team; VA Million Veteran Program; DiscovEHR (DiscovEHR, MyCode Community Health Initiative); eMERGE (Electronic Medical Records, Genomics Network); Lifelines Cohort Study; The

Downloaded from https://www.science.org at World Health Organization on August 22, 2024

PRACTICAL Consortium; Understanding Society Scientific Group, D. I. Chasman, Y. S. Cho, I. M. Heid, M. I. McCarthy, M. C. Y. Ng, C. J. O'Donnell, F. Rivadeneira, U. Thorsteinsdottir, Y. V. Sun, E. S. Tai, M. Boehnke, P. Deloukas, A. E. Justice, C. M. Lindgren, R. J. F. Loos, K. L. Mohlke, K. E. North, K. Stefansson, R. G. Walters, T. W. Winkler, K. L. Young, P.-R. Loh, J. Yang, T. Esko, T. L. Assimes, A. Auton, G. R. Abecasis, C. J. Willer, A. E. Locke, S. I. Berndt, G. Lettre, T. M. Frayling, Y. Okada, A. R. Wood, P. M. Visscher, J. N. Hirschhorn, A saturated map of common genetic variants associated with human height. *Nature* **610**, 704–712 (2022).
55. C. A. de Leeuw, J. M. Mooij, T. Heskes, D. Posthuma, MAGMA: Generalized gene-set analysis of GWAS data. *PLOS Comput. Biol.* **11**, e1004219 (2015).
56. K. Watanabe, E. Taskesen, A. Van Bochoven, D. Posthuma, Functional mapping and annotation of genetic associations with FUMA. *Nat. Commun.* **8**, 1826 (2017).
57. GTEx Consortium, The genotype-tissue expression (GTEx) project. *Nat. Genet.* **45**, 580–585 (2013).
58. S. Burgess, F. Dudbridge, S. G. Thompson, Combining information on multiple instrumental variables in Mendelian randomization: Comparison of allele score and summarized data methods. *Stat. Med.* **35**, 1880–1906 (2016).
59. S. Burgess, S. G. Thompson, Avoiding bias from weak instruments in Mendelian randomization studies. *Int. J. Epidemiol.* **40**, 755–764 (2011).
60. G. D. Smith, S. Ebrahim, "Mendelian randomization": Can genetic epidemiology contribute to understanding environmental determinants of disease? *Int. J. Epidemiol.* **32**, 1–22 (2003).
61. D. A. Lawlor, R. M. Harbord, J. A. C. Sterne, N. Timpson, G. D. Smith, Mendelian randomization: Using genes as instruments for making causal inferences in epidemiology. *Stat. Med.* **27**, 1133–1163 (2008).
62. V. Didelez, N. Sheehan, Mendelian randomization as an instrumental variable approach to causal inference. *Stat. Methods Med. Res.* **16**, 309–330 (2007).
63. F. P. Hartwig, N. M. Davies, G. Hemani, G. Davey Smith, Two-sample Mendelian randomization: Avoiding the downsides of a powerful, widely applicable but potentially fallible technique. *Int. J. Epidemiol.* **45**, 1717–1726 (2016).
64. J. Bowden, F. D. G. M, C. Minelli, G. D. Smith, N. Sheehan, J. Thompson, A framework for the investigation of pleiotropy in two-sample summary data Mendelian randomization. *Stat. Med.* **36**, 1783–1802 (2017).
65. N. L. Dimou, K. K. Tsilidis, A primer in Mendelian randomization methodology with a focus on utilizing published summary association data. *Methods Mol. Biol.* **1793**, 211–230 (2018).
66. J. P. T. Higgins, S. G. Thompson, J. J. Deeks, D. G. Altman, Measuring inconsistency in meta-analyses. *BMJ* **327**, 557–560 (2003).
67. J. Bowden, G. D. Smith, S. Burgess, Mendelian randomization with invalid instruments: Effect estimation and bias detection through Egger regression. *Int. J. Epidemiol.* **44**, 512–525 (2015).
68. P. Pagoni, N. L. Dimou, N. Murphy, E. Stergiakouli, Using Mendelian randomisation to assess causality in observational studies. *Evid. Based Ment. Health* **22**, 67–71 (2019).
69. J. Bowden, G. Davey Smith, P. C. Haycock, S. Burgess, Consistent estimation in Mendelian randomization with some invalid instruments using a weighted median estimator. *Genet. Epidemiol.* **40**, 304–314 (2016).
70. O. O. Yavorska, S. Burgess, MendelianRandomization: An R package for performing Mendelian randomization analyses using summarized data. *Int. J. Epidemiol.* **46**, 1734–1739 (2017).
71. World Health Organization, *International Classification of Diseases for Oncology (ICD-O): First Revision* (World Health Organization, ed. 3, 2013).
72. M. A. Hernán, S. Hernández-Díaz, J. M. Robins, A structural approach to selection bias. *Epidemiology* **15**, 615–625 (2004).
73. S. Greenland, J. Pearl, J. M. Robins, Causal diagrams for epidemiologic research. *Epidemiology* **10**, 37–48 (1999).
74. P. Hepsomali, J. A. Groeger, Diet and general cognitive ability in the UK Biobank dataset. *Sci. Rep.* **11**, 11786 (2021).
75. D. F. Moore, *Applied Survival Analysis Using R* (Springer, 2016).
76. S. Lê, J. Josse, F. Husson, FactoMineR: An R package for multivariate analysis. *J. Stat. Softw.* **25**, 1–18 (2008).
77. F. E. Harrel Jr., *Regression Modeling Strategies: With Applications to Linear Models, Logistic and Ordinal Regression, and Survival Analysis* (Springer, 2015).

Acknowledgments: UKB is an open access resource. Bona fide researchers can apply to use the UKB dataset by registering and applying at http://ukbiobank.ac.uk/register-apply/. This research has been conducted using the UKB Resource under application number 55870, and we express our gratitude to the participants and those involved in building the resource. The Genotype-Tissue Expression (GTEx) Project was supported by the Common Fund of the Office of the Director of the National Institutes of Health, and by NCI, NHGRI, NHLBI, NIDA, NIMH, and NINDS. Additional acknowledgements are given in Supplementary Text. **Funding:** This work was supported by the French National Cancer Institute (INCA_14108) and the German Research Foundation (BA 5459/2-1). The National Institute for Health Research (NIHR) Imperial Biomedical Research Centre (BRC) provided infrastructure support for the Department of Epidemiology and Biostatistics at Imperial College London (UK). Study-specific funding sources are given in Supplementary Text. **Author contributions:** Conceptualization: L.P.-N. and H.F. Methodology: L.P.-N. and A.M.S. Investigation: L.P.-N. and A.M.S. Visualization: L.P.-N. Supervision: R.C.-T., M.J.G., and H.F. Writing—original draft: L.P.-N. and A.M.S. Writing—review and editing: L.P.-N., A.M.S., N.D., H.Ba., B.F., E.F., J.K., K.K.T., S.C., A.J., R.C., P.B., M.J.S., A.W., S.B., H.Br., A.T.C., I.C., J.C.F., K.G.-E., V.M., C.C.N., S.L.S., M.S., C.M.U., P.F., V.V., R.C.-T., M.J.G., and H.F. **Competing interests:** The authors declare that they have no competing interests. **Data and materials availability:** All data needed to evaluate the conclusions in the paper are present in the paper and/or the Supplementary Materials. The UK Biobank resource is available to bona fide researchers for health-related research in the public interest. All researchers who wish to access the research resource must register with UK Biobank by completing the registration form in the Access Management System (AMS- https://ams.ukbiobank.ac.uk/ams/). The UK Biobank data can be provided by UK Biobank Limited pending scientific review and a completed material transfer agreement. The transcriptome data information of human subjects can be downloaded from the GTEx portal (https://gtexportal.org/home/, GTEx v8 release phs000424.v8.p8). Genotype data from CCFR, CORECT, and GECCO are available through dbGaP (accession nos. phs001415.v1.p1, phs001315.v1.p1, phs001078.v1.p1, phs001903.v1.p1, phs001856.v1.p1, and phs001045.v1.p1). Requests for the genotype data stratified by colorectal cancer subtypes and by men and women should be submitted to gecco@fredhutch.org. The codes for the computation of the body shape phenotypes, the observational and Mendelian randomization analyses, the GWAS, and the related documentation are available at https://doi.org/10.5281/zenodo.10063272 and at GitHub (https://github.com/LaiaPeruchet/Body_Shape_Colorectal_Cancer).

Submitted 13 June 2023
Accepted 12 March 2024
Published 19 April 2024
10.1126/sciadv.adj1987

Downloaded from https://www.science.org at World Health Organization on August 22, 2024

STUDY II

Body shape phenotypes and breast cancer risk: A Mendelian randomization analysis

Laia Peruchet-Noray, Niki Dimou, Anja M. Sedlmeier, Béatrice Fervers, Isabelle Romieu, Vivian Viallon, Pietro Ferrari, Marc J. Gunter, Robert Carreras-Torres, Heinz Freisling

Cancers **15, 1296 (2023)**

cancers

MDPI

Article

Body Shape Phenotypes and Breast Cancer Risk: A Mendelian Randomization Analysis

Laia Peruchet-Noray [1,2], Niki Dimou [1], Anja M. Sedlmeier [3], Béatrice Fervers [4], Isabelle Romieu [5], Vivian Viallon [1], Pietro Ferrari [1], Marc J. Gunter [1], Robert Carreras-Torres [6] and Heinz Freisling [1,*]

1 International Agency for Research on Cancer (IARC/WHO), Nutrition and Metabolism Branch, CEDEX 08, 69372 Lyon, France
2 Department of Clinical Sciences, Faculty of Medicine, University of Barcelona, 08007 Barcelona, Spain
3 Department of Epidemiology and Preventive Medicine, University of Regensburg, Franz-Josef-Strauss-Allee 11, 93053 Regensburg, Germany
4 Département Prévention Cancer Environnement, Centre Léon Bérard, CEDEX 08, 69373 Lyon, France
5 National Institute of Public Health, Cuernavaca 62100, Morelos, Mexico
6 Digestive Diseases and Microbiota Group, Institut d'Investigació Biomèdica de Girona Dr. Josep Trueta (IDIBGI), 17190 Salt, Spain
* Correspondence: freislingh@iarc.who.int

Simple Summary: Investigating body shapes may offer novel insights into the role of adiposity and body size in breast cancer development. We derived three distinct body shapes from combinations of height, weight, body mass index (BMI), waist and hip circumference, and waist-to-hip ratio (WHR) by a principal component analysis. We then used genetic variants linked to these body shapes and investigated associations with breast cancer risk. A body shape characterizing general adiposity was associated with a lower breast cancer risk, however this is likely because the genetic variants predicting this body shape reflect body fatness during childhood and adolescence rather than during later adulthood. A body shape characterizing tall women with a low WHR was weakly associated with a higher breast cancer risk. A body shape characterizing tall women with a large WHR was not associated with breast cancer risk. These findings can spur wider application in cancer research and possibly risk stratification.

Abstract: Observational and genetic studies have linked different anthropometric traits to breast cancer (BC) risk, with inconsistent results. We aimed to investigate the association between body shape defined by a principal component (PC) analysis of anthropometric traits (body mass index [BMI], height, weight, waist-to-hip ratio [WHR], and waist and hip circumference) and overall BC risk and by tumor sub-type (luminal A, luminal B, HER2+, triple negative, and luminal B/HER2 negative). We performed two-sample Mendelian randomization analyses to assess the association between 188 genetic variants robustly linked to the first three PCs and BC (133,384 cases/113,789 controls from the Breast Cancer Association Consortium (BCAC)). PC1 (general adiposity) was inversely associated with overall BC risk (0.89 per 1 SD [95% CI: 0.81–0.98]; p-value = 0.016). PC2 (tall women with low WHR) was weakly positively associated with overall BC risk (1.05 [95% CI: 0.98–1.12]; p-value = 0.135), but with a confidence interval including the null. PC3 (tall women with large WHR) was not associated with overall BC risk. Some of these associations differed by BC sub-types. For instance, PC2 was positively associated with a risk of luminal A BC sub-type (1.09 [95% CI: 1.01–1.18]; p-value = 0.02). To clarify the inverse association of PC1 with breast cancer risk, future studies should examine independent risk associations of this body shape during childhood/adolescence and adulthood.

Keywords: body shape; breast cancer; height; Mendelian randomization; obesity

check for updates

Citation: Peruchet-Noray, L.; Dimou, N.; Sedlmeier, A.M.; Fervers, B.; Romieu, I.; Viallon, V.; Ferrari, P.; Gunter, M.J.; Carreras-Torres, R.; Freisling, H. Body Shape Phenotypes and Breast Cancer Risk: A Mendelian Randomization Analysis. *Cancers* **2023**, *15*, 1296. https://doi.org/10.3390/cancers15041296

Academic Editor: Antonis Valachis

Received: 17 December 2022
Revised: 11 February 2023
Accepted: 15 February 2023
Published: 17 February 2023

Copyright: © 2023 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (https://creativecommons.org/licenses/by/4.0/).

1. Introduction

Breast cancer is the most frequently diagnosed cancer in women worldwide (2.26 million new cases in 2020) and is the leading cause of cancer mortality in women (684,996 deaths in 2020) [1]. Mammography screening reduces breast cancer mortality effectively by detecting breast cancer at an early and curable stage [2]. In addition, mutations in high penetrance genes (e.g., BRCA1/2) can help to identify individuals at a higher risk of developing breast cancer [3]. However, the breast cancer screening participation rate varies largely across countries and can be as low as 16% [4] and the known genetic predisposing genes account for 5–10% of the total breast cancer burden [5]. The identification of breast cancer risk factors is crucial to reduce incidence and associated mortality, and to risk-stratify the population to optimize screening participation [2].

Established risk factors for female breast cancer include age, family history, alcohol consumption, ionizing radiation exposure, reproductive factors, such as early menarche, late menopause, late age at first pregnancy, low parity, and elevated levels of both endogenous and exogenous estrogen [6].

There is inconsistent evidence from prospective observational and genetic studies linking body fatness, mostly assessed by body mass index (BMI), to breast cancer incidence [6,7]. Mostly from observational studies, BMI has been reported to be either positively or inversely associated with breast cancer depending on menopausal status and the molecular breast cancer sub-type [6]. However, genetically predicted BMI is inversely associated with breast cancer risk, independently of the individual's menopausal status [7]. Additionally, other single anthropometric traits have also been assessed as risk factors for breast cancer risk. For instance, waist circumference (WC) has been positively associated with breast cancer risk among post-menopausal women, while the association with waist-to-hip ratio (WHR) remains inconclusive [6]. Finally, height has been positively associated with a risk of overall and hormone-receptor-positive breast cancer [6,8].

While a correlation between different anthropometric variables exists, individuals with similar values in one trait (e.g., BMI) may differ considerably for others (e.g., WHR) resulting in different body shapes. A promising approach to capture the complexity of body shape phenotypes is to combine multiple traits. In 2016, a principal component analysis (PCA) was performed on six anthropometric traits (height, weight, BMI, WC, hip circumference (HC), and WHR) to define body shape [9]. Each principal component (PC) represented a specific pattern of the six anthropometric traits and captured distinct body shape dimensions. Different biological mechanisms may underlie the heterogeneity of body morphology with breast cancer risk, and the different body shapes may confer differences in breast cancer risk. We have previously shown that these body shapes were differentially associated with breast cancer risk in an observational analysis [10]. For example, a body shape characterizing overall adiposity was positively associated with post-menopausal breast cancer risk, but not associated with pre-menopausal breast cancer risk, while a body shape contrasting tall women with large WHR and short women with low WHR was not associated with either pre- or post-menopausal breast cancer [10]. However, considerable uncertainty remains about the potential causal effect of these anthropometric phenotypes, individually or in combination, on overall breast cancer risk and according to sub-type.

Mendelian randomization (MR) analysis uses genetic variants as instrumental variables (IVs) to strengthen the causal inference in exposure–outcome associations in the absence of pleiotropic effects (i.e., a single genetic locus influences multiple phenotypes). This methodology can overcome some of the limitations of conventional approaches, such as reverse causation and unmeasured confounding, provided that the key assumptions of MR are not violated [11].

In this study, a two-sample MR analysis was conducted to investigate the potential causal associations between three body shape phenotypes, as derived in Ried et al. [9], and the risk of breast cancer using summary level data including 133,384 breast cancer cases and 113,789 controls from the Breast Cancer Association Consortium (BCAC) [12]. We also investigated associations by hormonal receptor status breast cancer sub-types.

2. Materials and Methods

2.1. Body Shape Phenotypes and Related Genetic Variants

Ried et al. performed a PCA of six anthropometric traits (BMI, height, weight, WC, HC, and WHR) obtaining three body shape phenotypes [9]. Each PC represents a specific composition of the six anthropometric traits and thus captures a specific aspect of body shape. The first three PCs explained 96.7% of the variation of these six anthropometric traits [9]. PC1 explained on average 64.4% of the variation in all traits and had equally high positive loadings on all traits, except for height, characterizing individuals with general adiposity. PC2 explained 18.5% of the variation and had high but opposite loadings on height and WHR, capturing variation in a composite body shape that represents tall individuals with a low WHR or vice versa, short individuals with a large WHR. PC3 explained 13.8% of the variation and had high positive loadings on height and WHR, and an opposite loading of nearly the same size on HC. PC3 characterizes tall individuals with a large WHR resulting from a smaller HC or vice versa, short individuals with a low WHR and a high HC [9]. Further details regarding PC loadings can be found in Supplementary Table S1.

Ried et al. also reported a fourth body shape (PC4) characterizing individuals with high BMI and weight with low WC and HC (athletic individuals) and vice versa [9]. Although we also attempted to analyze PC4 as an additional exposure, the results obtained are not reported in this manuscript due to their imprecision and the impossibility of building solid conclusions.

The genome-wide association study (GWAS) to identify genetic variants robustly associated with the body shape phenotypes included more than 170,000 individuals of European descent from 65 studies from the GIANT Consortium. All study participants gave written informed consent and ethic committees approved all studies. The results included significant associations ($p < 5 \times 10^{-8}$) of 200 loci (31 for PC1, 124 for PC2, and 45 for PC3), some of them not previously associated with single anthropometric traits [9]. On this basis, we excluded 11 genetic variants after linkage disequilibrium analysis (LD $r^2 \leq 0.01$) to avoid correlation between genetic variants, using the 1000 Genomes Project European samples. Genetic variant summary statistics for associations with PC1–3 were obtained for the remaining 189 genetic variants (30 for PC1, 115 for PC2, and 44 for PC3, considering 4 genetic variants related to both PC2 and PC3) (Supplementary File S1).

2.2. Breast Cancer Risk Data

Genetic variant summary statistics for associations with the risk of overall breast cancer and 5 sub-types were extracted from a GWAS of 247,173 individuals (133,384 breast cancer cases and 113,789 controls) of European ancestry carried out by the Breast Cancer Association Consortium (BCAC) [12]. The overall breast cancer analyses were based on mostly middle-aged women of European ancestry from 82 BCAC studies from over 20 countries including controls, cases of invasive breast cancer, cases of carcinoma in situ and cases of unknown invasiveness. In the sub-type analyses, 81 BCAC studies were included, restricted to controls and cases of invasive breast cancer. The study comprised data on luminal A (7325 cases), luminal B (1682 cases), HER2+ (718 cases), triple negative (2006 cases) and luminal B/HER2 (1779 cases) invasive breast cancer sub-types, and 20,815 controls. More detailed information on sample size and tumor heterogeneity is provided in Supplementary Table S2. All participating studies were approved by their appropriate ethics or institutional review board and all participants provided informed consent.

For 6 genetic variants, the use of a proxy genetic variant was needed ($r^2 \geq 0.8$; European samples), while for 1 genetic variant, no data were obtained.

2.3. Statistical Analysis

We performed a two-sample MR analysis to estimate the causal relation between independent body shape phenotypes (PC1, PC2 and PC3) and breast cancer risk (Figure 1).

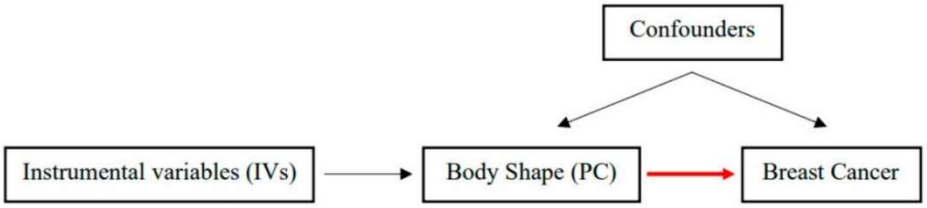


Figure 1. Causal directed acyclic graph (DAG) of Mendelian Randomization analysis. The red arrow highlights the causal association between the body shape (exposure) and breast cancer (outcome) assessed. PC, principal component.

The MR analysis was performed and reported in line with the STROBE-MR guidelines [13,14]. The STROBE-MR guidelines checklist can be found in Supplementary File S2. MR is based on three key assumptions: (1) the genetic variants are associated with the exposure, (2) the genetic variants are not associated with any potentially confounding variable, and (3) the genetic variants are only associated with the outcome through the risk factor [15,16]. To validate the first MR assumption, we used genetic variants identified from a two-stage meta-analysis of GWAS performed on the three first body shapes [9].

We used the fixed-effects inverse-variance weighted (IVW) method as the primary approach [17]. This analysis can be understood as a meta-analysis of the Wald estimates for each genetic variant effects which are calculated as the ratio of the genetic variant-breast cancer over the genetic variant-body shape association [15,18]. The fixed-effects IVW model assumes absence of horizontal pleiotropy and will return an unbiased estimate provided that all variants are valid instrumental variables. We calculated the MR-derived odds ratio (OR) of breast cancer risk for a one standard deviation (SD) increase in genetically predicted body shape phenotype.

2.4. Sensitivity Analyses

As the second (i.e., genetic variants are not associated with any potentially confounding variable) and the third (i.e., genetic variants are only associated with the outcome through the risk factor) MR assumptions are challenging to test [19], further analyses were performed to assess any potential violation of both assumptions.

First, we used PhenoScanner (available at http://www.phenoscanner.medschl.cam.ac.uk, accessed on 12 June 2021) and the GWAS catalog (available at https://www.ebi.ac.uk/gwas/, accessed on 15 June 2021) to investigate whether our selected genetic variants were associated with other traits in previous GWAS [19–21].

Second, we used Cochran's Q test to evaluate the heterogeneity of causal effects for each variant, with a p-value < 0.05 indicating statistical significance [22]. In the case of heterogeneity, likely indicating pleiotropy [23], a random-effects IVW MR analysis was used [24]. This method relaxes the third assumption as the total pleiotropic effect of a single genetic variant no longer needs to be null but assumes a zero mean between all the genetic variants (i.e., balanced pleiotropy) [24]. In addition, we implemented MR-Egger regression [25] and the weighted median approach [26]. The MR-Egger methodology provides an unbiased causal effect estimate even if the third MR assumption is violated and all the variants are invalid instruments. However, the Instrument Strength Independent of Direct Effect (InSIDE) assumption needs to be held. This additional assumption is based on the independency between the horizontal pleiotropic effects and the variants-exposure effects. MR-Egger also provides a statistical test for overall directional pleiotropy based on whether the intercept term is different from zero, as well as the I^2_{GX} statistic, which indicates the potential violation of the NO Measurement Error (NOME) assumption and suggests the unreliability of MR-Egger inferences at values below 90% [25,27]. The weighted median estimator allows for violations of the second and the third assumptions when up to 50% of the genetic variants are invalid (i.e., violation of one or more of the three basic MR assumptions) [23,26]. Both tests provide valid MR estimates in the presence

of overall directional pleiotropy but suffer from reduced power [25,26]. We also used the MR Pleiotropy RESidual Sum and Outlier (MR-PRESSO) method to identify and remove any outlying variants, applying a random-effects IVW model [28]. This method regresses genetic variant-outcome on genetic variant-exposure and uses the square of residuals to identify outliers. Finally, leave-one-genetic-variant-out analyses were used to assess whether any association was driven by specific genetic variants.

A two-sided p-value < 0.05 was considered statistically significant in all analyses.

We used scatter plots to present the genetic associations between body shape phenotypes and breast cancer risk, in combination with funnel plots, to visually examine the consistency of MR estimates and the potential associated bias (Supplementary Figure S1).

All analyses were conducted with the statistical software R 4.0.4 and RStudio 1.4.1106 using the MendelianRandomization 0.6.0 and MRPRESSO 1.0 R packages [28,29].

3. Results

3.1. Body Shape Phenotypes and Risk of Overall Breast Cancer

PC1 was inversely associated with breast cancer risk ($IVW_{random\text{-}effects}$ OR per 1 SD equal to 0.89 [95% CI: 0.81–0.98]; p-value = 0.016) (Figure 2). There was evidence of heterogeneity across genetic variants (p-value < 0.001) and of overall directional pleiotropy (Egger intercept = 0.029 [95% CI: 0.014–0.043]; p-value < 0.001) (Supplementary Table S3). Nevertheless, the results of the random IVW after performing MR PRESSO, MR Egger, and the weighted median supported the inverse association (Egger OR = 0.59 [95% CI: 0.48–0.74]; p-value < 0.001; weighted median OR = 0.81 [95% CI: 0.76–0.88]; p-value < 0.001) (Supplementary Figure S2A). The leave-one-genetic-variant-out analysis showed an estimate closer to the null when excluding the genetic variant rs1121980 (a variant in the FTO gene) (Supplementary Figure S3). This genetic variant along with the rs1582874 variant (associated with height and other traits) (Supplementary File S3) were identified as outliers by the MR-PRESSO method. No distortion of the overall risk estimate by the presence of these two outlier genetic variants was detected (ρ distortion = 0.13) (Supplementary Table S4).

PC2 was weakly positively associated with the risk of breast cancer ($IVW_{random\text{-}effects}$ OR = 1.05 [95% CI: 0.98–1.12]; p-value = 0.135) (Figure 2), but the confidence interval included the null. We found the presence of heterogeneity across genetic variants (p-value < 0.001), but directional pleiotropy was not detected (Supplementary Table S3). Accordingly, the dispersion of the estimates provided by the genetic variants in the funnel plot showed balanced pleiotropy (Supplementary Figure S4). However, MR PRESSO indicated that the presence of five outlier genetic variants was potentially biasing the initial risk estimate (ρ distortion = 0.013) (Supplementary Table S4). The weighted median and IVW random MR approaches without outlier genetic variants estimations were attenuated toward the null (Supplementary Figure S2B).

There was no evidence of an association between PC3 and breast cancer risk ($IVW_{random\text{-}effects}$ OR = 1.04 [95% CI: 0.89–1.21]; p-value = 0.619) (Figure 2). We observed evidence of heterogeneity (p-value < 0.001), but without the presence of overall directional pleiotropy (Supplementary Table S3). The sensitivity analysis supported a null association (Supplementary Figure S2C).

3.2. Body Shape Phenotypes and Risk of Breast Cancer Sub-Types

PC1 was inversely associated with a risk of all five breast cancer sub-types, of which associations were most consistent for HER2+ ($IVW_{random\text{-}effects}$ OR = 0.81 [95% CI: 0.67–0.99]; p-value = 0.043) and triple negative sub-types ($IVW_{random\text{-}effects}$ OR = 0.82 [95% CI: 0.73–0.91]; p-value < 0.001) (Figure 2). Nevertheless, all of the associations showed heterogeneity and overall directional pleiotropy (Supplementary Table S3). Sensitivity analyses accounting for unbalanced pleiotropy and outliers supported the inverse associations of the main analysis (Supplementary Figure S2A). MR-PRESSO classified genetic variants as outliers in all the sub-types but only in luminal A sub-type identified biased association estimates

(ρ distortion = 0.02) (Supplementary Table S4).Comparable to the overall breast cancer risk analysis, PC2 risk estimates included the null, except for luminal A ($IVW_{random\text{-}effects}$ OR = 1.09 [95% CI: 1.01–1.18]; *p*-value = 0.02) (Figure 2) with the presence of balanced pleiotropy (heterogeneity *p*-value luminal A < 0.001; Egger intercept *p*-value luminal A = 0.256) (Supplementary Table S3).

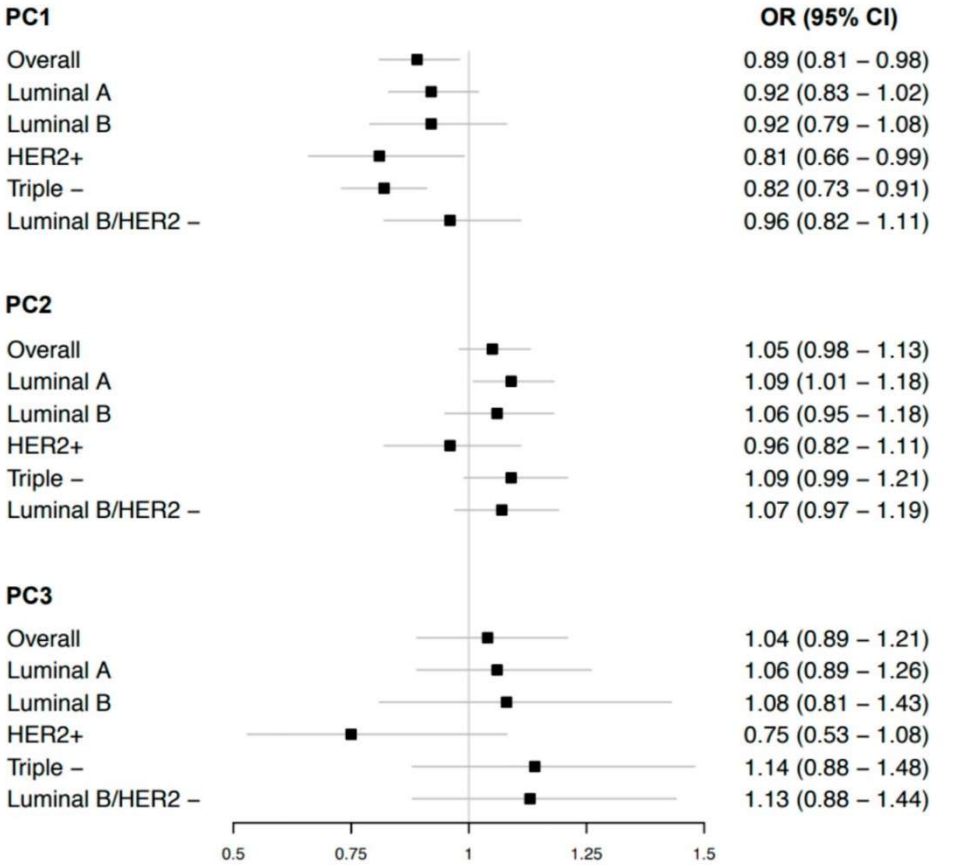


Figure 2. Mendelian randomization estimates between body shape phenotype PC1, PC2, and PC3 and overall breast cancer risk and sub-types. CI, confidence interval; OR, odds ratio; PC, principal component. We report random-effect IVW results due to heterogeneity across the genetic instruments.

PC3 was suggestively inversely associated with the risk of the HER2+ sub-type breast cancer ($IVW_{random\text{-}effects}$ OR = 0.75 [95% CI: 0.53–1.08]; *p*-value = 0.122) (Figure 2), in contrast with other sub-types; triple negative and luminal B/HER2 negative sub-types of breast cancer, although risk estimates were imprecise ($OR_{triple\ negative}$ = 1.14 [95% CI 0.88–1.48]; $OR_{luminal\ B/HER2\ negative}$ = 1.13 [95% CI 0.88–1.44]) (Figure 2). The sensitivity analysis showed comparable results except for the Egger test which presented unreliable results (I^2_{GX}~0%) similar to the overall breast cancer analysis (Supplementary Figure S2C).

4. Discussion

We performed a large-scale MR analysis to estimate potential causal associations between three distinct body shape phenotypes and the risk of overall breast cancer and five breast cancer tumor sub-types. A body shape capturing general adiposity (PC1) was inversely associated with the risk of overall breast cancer. The inverse association was stronger for ER− subtypes as compared to ER+ sub-types. A body shape contrasting tall women with a low WHR to short women with a large WHR (PC2) was weakly positively associated with overall breast cancer risk and most sub-types. There was no evidence of an

association between PC3, a body shape characterizing tall women with a large WHR, and the risk of overall breast cancer. There was suggestive evidence that PC3 was differentially associated with breast cancer sub-types (inversely associated with HER2+, but positively associated with triple negative and luminal B/HER2 negative).

General adiposity has been traditionally assessed using BMI, and in the absence of MR studies using PC1, BMI is an indicator that is closest to the PC1 body shape in our study. Previous MR analyses showed an inverse association between BMI and pre- and post-menopausal breast cancer risk [7,30–33], which is congruent with our findings for PC1. Specifically, a 2019 MR analysis found that BMI was inversely associated with the risk of overall breast cancer, and ER+ (luminal A, luminal B and luminal B/HER2 negative) and ER− (HER2+ and triple negative) sub-types, using a similar dataset—although with less cancer cases—to the BCAC study [31]. However, the associations observed for the ER+ and ER− sub-groups slightly differed from our results. While our results suggest a 10% and 20% reduced risk, in ER+ and ER− related sub-types of breast cancer, respectively, Ooi et al. did not find any difference between ER+/− and reported an OR close to 0.8 for both sub-types [31].

This difference could be due to the specificity of PC1, which captures a body shape that goes beyond BMI. PC1 could thus be complementary to, and potentially more specific than, BMI in characterizing general adiposity. This assertion is supported by the finding that two novel loci for PC1 were identified by Ried et al. that were not identified before in larger GWAS analyses for BMI, WHRadjBMI, and height [9]. In comparison to other research in the field using anthropometric traits, such as BMI, waist circumference, or height individually, we captured body size and adiposity holistically by combining information from six anthropometric traits. The derived body shapes represent anthropometric information that is by construction orthogonal, i.e., mutually adjusted for the six traits and risk associations (here: with breast cancer) are likely less biased due to residual confounding between traits in standard multivariable regression e.g., adjusting WHR for height.

In contrast to the MR results, observational studies have shown that a high BMI throughout adulthood is convincingly associated with a higher risk of post-menopausal breast cancer [6,34]. Observational studies also showed that a high BMI prior to menopause is associated with a lower risk of pre-menopausal breast cancer [6]. Furthermore, a high BMI in young adulthood (18–30 years of age) is associated with a lower risk of pre- and post-menopausal breast cancer [6]. A 2020 MR study provided some potential insights into the apparently divergent findings between observational and MR approaches regarding post-menopausal breast cancer risk [35]. This MR study found that elevated childhood BMI (age 10 years) was associated with a decreased risk of pre- and post-menopausal breast cancer combined, whereas adult BMI (mean age 56.5 years) was suggestive of a positive association (OR = 1.08 [95% CI: 0.93–1.27]) after accounting for childhood BMI [35]. Body fatness in childhood and adolescence (indicated by BMI) has also been linked to a decreased risk of breast cancer among pre- and post-menopausal women in observational studies [36–38], which suggests a long-term effect of body fatness at a young age on breast cancer risk later in life. Mechanistic evidence from in vivo experiments in female rats supports this notion whereby adipose-tissue-derived estrogen in overweight adolescents may induce early breast differentiation and render the breast tissue less susceptible to tumorigenesis [39]. Thus, the genetically predicted PC1 exposure used in our MR analysis may reflect body fatness during childhood and adolescence rather than during later adulthood explaining the inverse association with breast cancer risk.

In post-menopausal women, adipose tissue converts adrenal androgens into estrogen by the aromatase enzyme [40]. The presence of estrogen, alone and with progestin, is directly associated with an increased post-menopausal breast cancer risk [40]. Furthermore, in vivo and in vitro models have shown that macrophages that are stimulated by an obese milieu can increase estrogen signaling in breast cancer cells through the upregulation of ERα expression [41]. Indirectly, higher levels of estrogen may upregulate leptin production, which may also be relevant for breast cancer development [40]. For example, leptin mediates

immune suppression facilitating cancer formation and progression [40]. However, in pre-menopausal women, high vs low BMI is generally associated with longer anovulatory cycles resulting in lower levels of estrogen and progestin [42], thereby potentially providing a barrier to cancer formation. Taken together, the time of onset of excess body fatness and its modulating effects on circulating levels of estrogen and progestin may partly explain the divergent associations of body fatness with breast cancer risk. Although we were not able to differentiate between pre- and post-menopausal breast cancer with our summary-level genetic data, our results remain consistent with other MR analyses that used individual-level data and found that BMI was inversely associated with breast cancer risk, independently of menopausal stage [30,33].

Our findings concerning PC2 (tall with low WHR) are in line with the observational analysis of a previous publication of our group, where PC2 was positively associated with pre- and post-menopausal breast cancer with risk increments of 8–10% per 1 SD increase [10]. Positive associations between height and breast cancer risk using both observational and instrumental approaches have been reported with risk increases of 7–20% per ~10 cm increase [8,43]. Our observational and MR results for PC2 (OR = 1.05 [95% CI: 0.98–0.13]) were slightly weaker than those reported in the literature for height, which can potentially be explained by the contribution of WHR into PC2. However, no clear role of WHR with cancer risk has been observed [32,44].

Regarding breast cancer sub-types, only PC2 showed a positive association with the luminal A (ER+/PR+) tumor subtype. The results of other sub-types showed a confidence interval including the null. Zhang et al. reported a positive association between height and all hormone receptor-positive (ER+/PR+) sub-type breast cancers and no relationship for hormone receptor-negative (ER−/PR−) sub-types [8]. The lack of a consistent positive association between PC2 and other hormone receptor-positive sub-types (i.e., luminal B and luminal B/HER2 negative) in our analysis could be due to the lower number of genetic variants linked to height (114 variants; see Supplementary File S3) when compared to Zhang et al. (168 variants) [8].

Mechanistically, breast tissue in taller women is thought to be exposed to higher levels of insulin, growth hormone and IGF-I, and thus may have undergone more cell divisions contributing to a greater potential for error during DNA replication [6]. Animal models clearly support a key role of growth hormone and its downstream signaling, including the IGF pathway, in breast cancer development [45].

For body shape PC3, indicating body height combined with small HC and large WHR, we found little evidence for an association with breast cancer risk and sub-types, congruent with observational results from our group [10]. However, HER2+ sub-type showed an inverse association trend, in contrast with other breast cancer sub-types. HER2+ sub-type showed inverse associations for all tested PCs, being only statistically significant for PC1. In the previous literature, HER2+ sub-type tumors have been identified as a distinct subset (comprising 20–25%) of breast carcinomas and being differently associated with hormone-related risk factors [46,47].

In this study we employed different MR approaches: IVW-based, Egger regression, and median-based methods. IVW methods are generally more powerful compared to the other methods implemented but they do not account for directional (unbalanced) pleiotropy. MR-Egger accounts for heterogeneity due to pleiotropy and detects directional pleiotropy. The median-based method is more robust to overall pleiotropy as it allows up to 50% of invalid instruments (i.e., violating the second or third assumptions of MR) [48].

Although we checked for associations between our genetic variants and confounders, a violation of the second assumption of the MR approach cannot be entirely excluded due to the potential presence of unknown confounding factors. Other limitations include that our study may be slightly biased due to uncontrolled confounding from family effects, such as assortative mating, dynastic effects, and population structure [49]. We minimized this bias from population stratification by performing a two-sample MR analysis in samples composed of Caucasian individuals only. However, this may cause our findings to not be

generalizable to other ethnic groups. Referring to the body shapes, it is difficult to interpret the effect of PCs on breast cancer as it is not evident to what 1 SD corresponds with in terms of anthropometry. Finally, it is important to highlight that we were not able to differentiate between pre- and post-menopausal breast cancer with the available data.

5. Conclusions

This MR analysis provides evidence of an inverse association between a body shape that reflects general adiposity and the risk of overall breast cancer among women of European decent. The strength of association differed across sub-types of breast cancer suggesting a stronger inverse association for ER− sub-types as compared to ER+ sub-types. The most likely explanation for these inverse associations with overall breast cancer and sub-types is that the genetic instruments for this body shape indicate general adiposity during childhood/adolescence rather than during later adulthood. To test this assertion in future studies, genetic instruments for body shape during both childhood/adolescence and adulthood (age 30+ years) should be identified and their independent risk associations with breast cancer compared in a multivariable MR framework.

Furthermore, we found a weak positive association between a body shape characterizing tall women with a low WHR and overall breast cancer risk and most sub-types. This is in line with previous evidence on height and breast cancer. Our findings add to this evidence base by ruling out confounding by WHR.

A body shape characterizing tall women with a large WHR was not associated with breast cancer risk.

The current study provides complementary evidence to observational studies to interrogate multiple anthropometric measurements in relation to breast cancer risk.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/cancers15041296/s1, Supplementary Figure S1: Scatter plots of associations between body shapes and overall breast cancer and sub-types; Supplementary Figure S2: Mendelian randomization estimates (main and sensitivity analysis) between body shape phenotype PC1, PC2 and PC3 and overall and sub-types breast cancer risk; Supplementary Figure S3: Leave-one SNP-out plot for PC1 and overall breast cancer risk; Supplementary Figure S4: Funnel plot for PC2 and overall breast cancer risk; Supplementary Table S1: Loadings and explained variance of the three PCs; Supplementary Table S2: Detailed information on BCAC sample size and tumor heterogeneity; Supplementary Table S3: Heterogeneity test and Egger intercept results for body shape phenotypes and overall breast cancer risk and sub-types; Supplementary Table S4: Genetic variants considered as outliers for overall and sub-types breast cancer and each body shape phenotype; Supplementary File S1: Genetic instruments for body shape phenotypes; Supplementary File S2: STROBE-MR guidelines checklist; Supplementary File S3: Genetic variants and associated traits in previous GWAS ($p < 5 \times 10^{-8}$).

Author Contributions: Conceptualization, H.F.; methodology, L.P.-N., N.D. and R.C.-T.; software, L.P.-N.; validation, H.F., A.M.S. and N.D.; formal analysis, L.P.-N.; resources, H.F. and N.D.; data curation, L.P.-N.; writing—original draft preparation, L.P.-N. and H.F.; writing—review and editing, L.P.-N., N.D., A.M.S., B.F., I.R., V.V., P.F., M.J.G., R.C.-T. and H.F.; visualization, L.P.-N.; supervision, H.F., N.D., R.C.-T. and M.J.G.; project administration, H.F.; funding acquisition, H.F. All authors have read and agreed to the published version of the manuscript.

Funding: This study was supported by the French National Cancer Institute (l'Institut National du Cancer, INCA_14108).

Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki, and approved by the Ethics Committee of the International Agency for Research on Cancer (No. 20-34) on 12 October 2020.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data presented in this study regarding the body shape phenotypes are available in https://www.nature.com/articles/ncomms13357, accessed on 18 February 2021.

Publicly available datasets were analyzed in this study regarding breast cancer risk. This data can be found here: https://bcac.ccge.medschl.cam.ac.uk/, accessed on 21 February 2021.

Acknowledgments: The breast cancer genome-wide association analyses for BCAC and CIMBA were supported by Cancer Research UK (C1287/A10118, C1287/A16563, C1287/A10710, C12292/A20861, C12292/A11174, C1281/A12014, C5047/A8384, C5047/A15007, C5047/A10692, C8197/A16565), The National Institutes of Health (CA128978, X01HG007492- the DRIVE consortium), the PERSPECTIVE project supported by the Government of Canada through Genome Canada and the Canadian Institutes of Health Research (grant GPH-129344) and the Ministère de l'Économie, Science et Innovation du Québec through Genome Québec and the PSRSIIRI-701 grant, the Quebec Breast Cancer Foundation, the European Community's Seventh Framework Programme under grant agreement n° 223175 (HEALTH-F2-2009-223175) (COGS), the European Union's Horizon 2020 Research and Innovation Programme (634935 and 633784), the Post-Cancer GWAS initiative (U19 CA148537, CA148065 and CA148112—the GAME-ON initiative), the Department of Defence (W81XWH-10-1-0341), the Canadian Institutes of Health Research (CIHR) for the CIHR Team in Familial Risks of Breast Cancer (CRN-87521), the Komen Foundation for the Cure, the Breast Cancer Research Foundation, and the Ovarian Cancer Research Fund. All studies and funders are listed in Zhang H et al. (Nat Genet, 2020).

Conflicts of Interest: The authors declare no conflict of interest.

Disclaimer: Where authors are identified as personnel of the International Agency for Research on Cancer/World Health Organization, the authors alone are responsible for the views expressed in this article and they do not necessarily represent the decisions, policy or views of the International Agency for Research on Cancer/World Health Organization.

References

1. Ferlay, J.; Ervik, M.; Lam, F.; Colombet, M.; Mery, L.; Piñeros, M.; Znaor, A.; Soerjomataram, I.; Bray, F. *Global Cancer Observatory: Cancer Today*; International Agency for Research on Cancer: Lyon, France, 2020. Available online: https://gco.iarc.fr/today (accessed on 29 September 2021).
2. Løberg, M.; Lousdal, M.L.; Bretthauer, M.; Kalager, M. Benefits and harms of mammography screening. *Breast Cancer Res.* **2015**, *17*, 63. [CrossRef] [PubMed]
3. Thorat, M.A.; Balasubramanian, R. Breast cancer prevention in high-risk women. *Best Pract. Res. Clin. Obstet. Gynaecol.* **2020**, *65*, 18–31. [CrossRef] [PubMed]
4. Mandrik, O.; Tolma, E.; Zielonke, N.; Meheus, F.; Ordóñez-Reyes, C.; Severens, J.; Murillo, R. Systematic reviews as a "lens of evidence": Determinants of participation in breast cancer screening. *J. Med. Screen.* **2020**, *28*, 70–79. [CrossRef] [PubMed]
5. Oldenburg, R.; Meijers-Heijboer, H.; Cornelisse, C.; Devilee, P. Genetic susceptibility for breast cancer: How many more genes to be found? *Crit. Rev. Oncol.* **2007**, *63*, 125–149. [CrossRef] [PubMed]
6. World Cancer Research Fund; American Institute for Cancer Research. Continuous Update Project Expert Report 2018. Diet, Nutrition, Physical Activity and Breast Cancer. Available online: dietandcancerreport.org (accessed on 14 September 2021).
7. Larsson, S.C.; Burgess, S. Causal role of high body mass index in multiple chronic diseases: A systematic review and meta-analysis of Mendelian randomization studies. *BMC Med.* **2021**, *19*, 320. [CrossRef]
8. Zhang, B.; Shu, X.-O.; Delahanty, R.J.; Zeng, C.; Michailidou, K.; Bolla, M.K.; Wang, Q.; Dennis, J.; Wen, W.; Long, J.; et al. Height and breast cancer risk: Evidence from prospective studies and mendelian randomization. *Gynecol. Oncol.* **2015**, *107*, djv219. [CrossRef]
9. Ried, J.S.; Jeff, M.J.; Chu, A.Y.; Bragg-Gresham, J.L.; van Dongen, J.; Huffman, J.E.; Ahluwalia, T.S.; Cadby, G.; Eklund, N.; Eriksson, J.; et al. A principal component meta-analysis on multiple anthropometric traits identifies novel loci for body shape. *Nat. Commun.* **2016**, *7*, 13357. [CrossRef]
10. Sedlmeier, A.M.; Viallon, V.; Ferrari, P.; Peruchet-Noray, L.; Fontvieille, E.; Amadou, A.; Khoei, N.S.; Weber, A.; Baurecht, H.; Heath, A.K.; et al. Body shape phenotypes of multiple anthropometric traits and cancer risk: A multi-national cohort study. *Br. J. Cancer* **2022**. [CrossRef]
11. Smith, G.D.; Ebrahim, S. "Mendelian randomization": Can genetic epidemiology contribute to understanding environmental determinants of disease? *Int. J. Epidemiol.* **2003**, *32*, 1–22. [CrossRef]
12. Zhang, H.; Ahearn, T.U.; Lecarpentier, J.; Barnes, D.; Beesley, J.; Qi, G.; Jiang, X.; O'Mara, T.A.; Zhao, N.; Bolla, M.K.; et al. Genome-wide association study identifies 32 novel breast cancer susceptibility loci from overall and subtype-specific analyses. *Nat. Genet.* **2020**, *52*, 572–581. [CrossRef]
13. Skrivankova, V.W.; Richmond, R.C.; Woolf, B.A.R.; Davies, N.M.; Swanson, S.A.; VanderWeele, T.J.; Timpson, N.J.; Higgins, J.P.T.; Dimou, N.; Langenberg, C.; et al. Strengthening the reporting of observational studies in epidemiology using mendelian randomisation (STROBE-MR): Explanation and elaboration. *BMJ* **2021**, *375*, n2233. [CrossRef] [PubMed]

14. Skrivankova, V.W.; Richmond, R.C.; Woolf, B.A.R.; Yarmolinsky, J.; Davies, N.M.; Swanson, S.A.; VanderWeele, T.J.; Higgins, J.P.T.; Timpson, N.J.; Dimou, N.; et al. Strengthening the reporting of observational studies in epidemiology using mendelian randomization: The STROBE-MR Statement. *JAMA* **2021**, *326*, 1614. [CrossRef] [PubMed]
15. Lawlor, D.A.; Harbord, R.M.; Sterne, J.A.C.; Timpson, N.; Smith, G.D. Mendelian randomization: Using genes as instruments for making causal inferences in epidemiology. *Stat. Med.* **2008**, *27*, 1133–1163. [CrossRef] [PubMed]
16. Didelez, V.; Sheehan, N. Mendelian randomization as an instrumental variable approach to causal inference. *Stat. Methods Med. Res.* **2007**, *16*, 309–330. [CrossRef] [PubMed]
17. Burgess, S.; Scott, R.A.; Timpson, N.J.; Smith, G.D.; Thompson, S.G.; EPIC-InterAct Consortium. Using published data in Mendelian randomization: A blueprint for efficient identification of causal risk factors. *Eur. J. Epidemiol.* **2015**, *30*, 543–552. [CrossRef]
18. Burgess, S.; Butterworth, A.; Thompson, S.G. Mendelian randomization analysis with multiple genetic variants using summarized data. *Genet. Epidemiol.* **2013**, *37*, 658–665. [CrossRef]
19. Dimou, N.L.; Tsilidis, K.K. A primer in mendelian randomization methodology with a focus on utilizing published summary association data. *Genet. Epidemiol. Methods Protoc.* **2018**, *1793*, 211–230. [CrossRef]
20. MacArthur, J.; Bowler-Barnett, E.; Cerezo, M.; Gil, L.; Hall, P.; Hastings, E.; Junkins, H.; McMahon, A.; Milano, A.; Morales, J.; et al. The new NHGRI-EBI Catalog of published genome-wide association studies (GWAS Catalog). *Nucleic Acids Res.* **2016**, *45*, D896–D901. [CrossRef]
21. Staley, J.R.; Blackshaw, J.; Kamat, M.A.; Ellis, S.; Surendran, P.; Sun, B.B.; Paul, D.S.; Freitag, D.; Burgess, S.; Danesh, J.; et al. PhenoScanner: A database of human genotype–phenotype associations. *Bioinformatics* **2016**, *32*, 3207–3209. [CrossRef]
22. Higgins, J.P.T.; Thompson, S.G.; Deeks, J.J.; Altman, D.G. Measuring inconsistency in meta-analyses. *BMJ* **2003**, *327*, 557–560. [CrossRef]
23. Pagoni, P.; Dimou, N.L.; Murphy, N.; Stergiakouli, E. Using Mendelian randomisation to assess causality in observational studies. *Evid. Based Ment. Health* **2019**, *22*, 67–71. [CrossRef] [PubMed]
24. Bowden, J.; Del Greco, M.F.; Minelli, C.; Davey Smith, G.; Sheehan, N.; Thompson, J. A framework for the investigation of pleiotropy in two-sample summary data Mendelian randomization. *Stat. Med.* **2017**, *36*, 1783–1802. [CrossRef] [PubMed]
25. Bowden, J.; Davey Smith, G.; Burgess, S. Mendelian randomization with invalid instruments: Effect estimation and bias detection through Egger regression. *Int. J. Epidemiol.* **2015**, *44*, 512–525. [CrossRef] [PubMed]
26. Bowden, J.; Smith, G.D.; Haycock, P.C.; Burgess, S. Consistent Estimation in Mendelian Randomization with Some Invalid Instruments Using a Weighted Median Estimator. *Genet. Epidemiol.* **2016**, *40*, 304–314. [CrossRef]
27. Bowden, J.; Del Greco, M.F.; Minelli, C.; Smith, G.D.; Sheehan, N.A.; Thompson, J.R. Assessing the suitability of summary data for two-sample Mendelian randomization analyses using MR-Egger regression: The role of the I^2 statistic. *Leuk. Res.* **2016**, *45*, 1961–1974. [CrossRef]
28. Verbanck, M.; Chen, C.-Y.; Neale, B.; Do, R. Detection of widespread horizontal pleiotropy in causal relationships inferred from Mendelian randomization between complex traits and diseases. *Nat. Genet.* **2018**, *50*, 693–698. [CrossRef]
29. Yavorska, O.O.; Burgess, S. MendelianRandomization: An R package for performing Mendelian randomization analyses using summarized data. *Leuk. Res.* **2017**, *46*, 1734–1739. [CrossRef]
30. Guo, Y.; Andersen, S.W.; Shu, X.-O.; Michailidou, K.; Bolla, M.K.; Wang, Q.; Garcia-Closas, M.; Milne, R.L.; Schmidt, M.K.; Chang-Claude, J.; et al. Genetically predicted body mass index and breast cancer risk: Mendelian randomization analyses of data from 145,000 women of european descent. *PLoS Med.* **2016**, *13*, e1002105. [CrossRef]
31. Ooi, B.N.S.; Loh, H.; Ho, P.J.; Milne, R.L.; Giles, G.; Gao, C.; Kraft, P.; John, E.M.; Swerdlow, A.; Brenner, H.; et al. The genetic interplay between body mass index, breast size and breast cancer risk: A Mendelian randomization analysis. *Leuk. Res.* **2019**, *48*, 781–794. [CrossRef]
32. Gao, C.; Patel, C.J.; Michailidou, K.; Peters, U.; Gong, J.; Schildkraut, J.; Schumacher, F.R.; Zheng, W.; Boffetta, P.; Stucker, I.; et al. Mendelian randomization study of adiposity-related traits and risk of breast, ovarian, prostate, lung and colorectal cancer. *Leuk. Res.* **2016**, *45*, 896–908. [CrossRef]
33. Shu, X.; Wu, L.; Khankari, N.K.; Shu, X.-O.; Wang, T.J.; Michailidou, K.; Bolla, M.K.; Wang, Q.; Dennis, J.; Milne, R.L.; et al. Associations of obesity and circulating insulin and glucose with breast cancer risk: A Mendelian randomization analysis. *Leuk. Res.* **2018**, *48*, 795–806. [CrossRef] [PubMed]
34. Recalde, M.; Davila-Batista, V.; Díaz, Y.; Leitzmann, M.; Romieu, I.; Freisling, H.; Duarte-Salles, T. Body mass index and waist circumference in relation to the risk of 26 types of cancer: A prospective cohort study of 3.5 million adults in Spain. *BMC Med.* **2021**, *19*, 10. [CrossRef] [PubMed]
35. Richardson, T.G.; Sanderson, E.; Elsworth, B.; Tilling, K.; Smith, G.D. Use of genetic variation to separate the effects of early and later life adiposity on disease risk: Mendelian randomisation study. *BMJ* **2020**, *369*, m1203. [CrossRef] [PubMed]
36. Baer, H.J.; Tworoger, S.; Hankinson, S.E.; Willett, W.C. Body fatness at young ages and risk of breast cancer throughout life. *Am. J. Epidemiol.* **2010**, *171*, 1183–1194. [CrossRef]
37. Yang, T.O.; Cairns, B.J.; Pirie, K.; Green, J.; Beral, V.; Floud, S.; Reeves, G.K. Body size in early life and the risk of postmenopausal breast cancer. *BMC Cancer* **2022**, *22*, 232. [CrossRef]

38. Baer, H.J.; Colditz, G.A.; Rosner, B.; Michels, K.B.; Rich-Edwards, J.W.; Hunter, D.J.; Willett, W.C. Body fatness during childhood and adolescence and incidence of breast cancer in premenopausal women: A prospective cohort study. *Breast Cancer Res.* **2005**, *7*, R314. [CrossRef]
39. Grubbs, C.J.; Farnell, D.R.; Hill, D.L.; McDonough, K.C. Chemoprevention of N-nitroso-N-methylurea-induced mammary cancers by pretreatment with 17β-estradiol and progesterone23. *Gynecol. Oncol.* **1985**, *74*, 927–931. [CrossRef]
40. Picon-Ruiz, M.; Morata-Tarifa, C.; Valle-Goffin, J.J.; Friedman, E.R.; Slingerland, J.M. Obesity and adverse breast cancer risk and outcome: Mechanistic insights and strategies for intervention. *CA Cancer J. Clin.* **2017**, *67*, 378–397. [CrossRef]
41. Blank, D.N.; Hermano, E.; Sonnenblick, A.; Maimon, O.; Rubinstein, A.M.; Drai, E.; Maly, B.; Vlodavsky, I.; Popovtzer, A.; Peretz, T.; et al. Macrophages upregulate estrogen receptor expression in the model of obesity-associated breast carcinoma. *Cells* **2022**, *11*, 2844. [CrossRef]
42. Fichman, V.; Costa, R.D.S.S.D.; Miglioli, T.C.; Marinheiro, L.P.F. Association of obesity and anovulatory infertility. *Einstein* **2020**, *18*, eAO5150. [CrossRef]
43. Lai, F.Y.; Nath, M.; Hamby, S.E.; Thompson, J.R.; Nelson, C.; Samani, N.J. Adult height and risk of 50 diseases: A combined epidemiological and genetic analysis. *BMC Med.* **2018**, *16*, 187. [CrossRef] [PubMed]
44. Chen, G.-C.; Chen, S.-J.; Zhang, R.; Hidayat, K.; Qin, J.-B.; Zhang, Y.-S.; Qin, L.-Q. Central obesity and risks of pre- and postmenopausal breast cancer: A dose-response meta-analysis of prospective studies. *Obes. Rev.* **2016**, *17*, 1167–1177. [CrossRef] [PubMed]
45. Subramani, R.; Nandy, S.B.; Pedroza, D.A.; Lakshmanaswamy, R. Role of growth hormone in breast cancer. *Endocrinology* **2017**, *158*, 1543–1555. [CrossRef] [PubMed]
46. Ménard, S.; Balsari, A.; Casalini, P.; Tagliabue, E.; Campiglio, M.; Bufalino, R.; Cascinelli, N. HER-2-positive breast carcinomas as a particular subset with peculiar clinical behaviors. *Clin. Cancer Res.* **2002**, *8*, 520–525.
47. Balsari, A.; Casalini, P.; Bufalino, R.; Berrino, F.; Ménard, S. Role of hormonal risk factors in HER2-positive breast carcinomas. *Br. J. Cancer* **2003**, *88*, 1032–1034. [CrossRef]
48. Pingault, J.-B.; O'Reilly, P.F.; Schoeler, T.; Ploubidis, G.B.; Rijsdijk, F.; Dudbridge, F. Using genetic data to strengthen causal inference in observational research. *Nat. Rev. Genet.* **2018**, *19*, 566–580. [CrossRef]
49. Brumpton, B.; Sanderson, E.; Heilbron, K.; Hartwig, F.P.; Harrison, S.; Vie, G.; Cho, Y.; Howe, L.D.; Hughes, A.; Boomsma, D.I.; et al. Avoiding dynastic, assortative mating, and population stratification biases in Mendelian randomization through within-family analyses. *Nat. Commun.* **2020**, *11*, 3519. [CrossRef]

Disclaimer/Publisher's Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.

STUDY III

Association of body shape phenotypes and body fat distribution indexes with inflammatory biomarkers in the European Prospective Investigation into Cancer and Nutrition (EPIC) and UK Biobank

Esther M. González-Gil*, **Laia Peruchet-Noray***, Anja M. Sedlmeier, …, Sabina Rinaldi, Heinz Freisling, Laure Dossus

**These authors contributed equally*

***BMC Medicine* 22, 334 (2024)**

González-Gil *et al. BMC Medicine* (2024) 22:334
https://doi.org/10.1186/s12916-024-03544-3

BMC Medicine

RESEARCH Open Access

Association of body shape phenotypes and body fat distribution indexes with inflammatory biomarkers in the European Prospective Investigation into Cancer and Nutrition (EPIC) and UK Biobank

Esther M. González-Gil[1*†], Laia Peruchet-Noray[1,2†], Anja M. Sedlmeier[3,4,5], Sofia Christakoudi[6], Carine Biessy[1], Anne-Sophie Navionis[1], Yahya Mahamat-Saleh[1], Rola F. Jaafar[1], Hansjörg Baurecht[3], Marcela Guevara[7,8,9], Pilar Amiano Etxezarreta[8,10,11], W. M. Monique Verschuren[12,13], Jolanda M. A. Boer[12], Anja Olsen[14,15], Anne Tjønneland[14,16], Vittorio Simeon[17], Carlota Castro-Espin[18,19], Dagfinn Aune[6,20,21], Alicia K. Heath[6], Marc Gunter[6], Sandra M. Colorado-Yohar[8,22,23], Nuno R. Zilhão[24], Christina C. Dahm[24], Erand Llanaj[25,26], Matthias B. Schulze[25,27], Dafina Petrova[8,28,29], Sabina Sieri[30], Fulvio Ricceri[31], Giovanna Masala[32], Tim Key[33], Vivian Viallon[1], Sabina Rinaldi[1], Heinz Freisling[1] and Laure Dossus[1]

Abstract

Background The allometric body shape index (ABSI) and hip index (HI), as well as multi-trait body shape phenotypes, have not yet been compared in their associations with inflammatory markers. The aim of this study was to examine the relationship between novel and traditional anthropometric indexes with inflammation using data from the European Prospective Investigation into Cancer and Nutrition (EPIC) and UK Biobank cohorts.

Methods Participants from EPIC ($n=17,943$, 69.1% women) and UK Biobank ($n=426,223$, 53.2% women) with data on anthropometric indexes and C-reactive protein (CRP) were included in this cross-sectional analysis. A subset of women in EPIC also had at least one measurement for interleukins, tumour necrosis factor alpha, interferon gamma, leptin, and adiponectin. Four distinct body shape phenotypes were derived by a principal component (PC) analysis on height, weight, body mass index (BMI), waist (WC) and hip circumferences (HC), and waist-to-hip ratio (WHR). PC1 described overall adiposity, PC2 tall with low WHR, PC3 tall and centrally obese, and PC4 high BMI and weight with low WC and HC, suggesting an athletic phenotype. ABSI, HI, waist-to-height ratio and waist-to-hip index (WHI) were also calculated. Linear regression models were carried out separately in EPIC and UK Biobank stratified by sex and adjusted for age, smoking status, education, and physical activity. Results were additionally combined in a random-effects meta-analysis.

†Esther M. González-Gil and Laia Peruchet-Noray equally contributed to the present work.

*Correspondence:
Esther M. González-Gil
Full list of author information is available at the end of the article

© The Author(s) 2024. **Open Access** This article is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License, which permits any non-commercial use, sharing, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if you modified the licensed material. You do not have permission under this licence to share adapted material derived from this article or parts of it. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by-nc-nd/4.0/.

Results Traditional anthropometric indexes, particularly BMI, WC, and weight were positively associated with CRP levels, in men and women. Body shape phenotypes also showed distinct associations with CRP. Specifically, PC2 showed inverse associations with CRP in EPIC and UK Biobank in both sexes, similarly to height. PC3 was inversely associated with CRP among women, whereas positive associations were observed among men.

Conclusions Specific indexes of body size and body fat distribution showed differential associations with inflammation in adults. Notably, our results suggest that in women, height may mitigate the impact of a higher WC and HC on inflammation. This suggests that subtypes of adiposity exhibit substantial variation in their inflammatory potential, which may have implications for inflammation-related chronic diseases.

Keywords Body shape, Height, Anthropometric indicators, Inflammation, C-reactive protein

Background

Body fatness has been associated with various comorbidities and cardiometabolic risk [1]. Several studies suggested that abdominal obesity is more strongly associated with cardiovascular risk factors than general obesity usually proxied by body mass index (BMI) [2, 3]. Additionally, waist circumference (WC) is a proxy of abdominal obesity positively associated with body size (mainly weight and BMI, but also height). Thus, the measurement of WC may not provide information on the abdominal deposition of fat beyond BMI.

To overcome the limitations of traditional anthropometric indexes, the allometric body shape index (ABSI) and hip index (HI) [4, 5] were developed to reflect WC and hip circumference (HC) among individuals with the same weight and height [6]. Thus, information on body size is reflected in BMI and height and information on body shape and fat distribution is reflected in ABSI and HI [7]. Alternatively, data-driven body shape phenotypes have been proposed to capture body size and body fat distribution holistically [8]. These phenotypes were derived by a principal component (PC) analysis (PCA) of six anthropometric traits [height, weight, BMI, WC, HC, and waist-to-hip ratio (WHR)] [8]. Four body shape phenotypes were previously identified in the European Prospective Investigation into Cancer and Nutrition (EPIC) study [9] and UK Biobank [10] characterizing overall adiposity (PC1), tall stature with low WHR (PC2), tall stature with central obesity (PC3), and high BMI and weight with low WC and HC likely defining an athletic phenotype (PC4). Previous findings suggested that these complex anthropometric indexes (ABSI, HI, and body shape phenotypes) may be more accurate than traditional anthropometric indexes at capturing information on cardiometabolic and metabolic health [8], cancer risk assessment [9], and mortality risk stratification [11]. However, there is a limited number of studies on the association of these anthropometric indexes or body shape phenotypes with inflammatory biomarkers.

Inflammation has been proposed as a potential biological mechanism linking body fatness to cardiometabolic diseases and cancer [12, 13]. A previous study using data from UK Biobank reported positive associations of ABSI and BMI with inflammatory biomarkers such as C-reactive protein (CRP), neutrophil, monocyte, and lymphocyte counts, while HI was only inversely associated with lymphocyte count [14]. Additionally, it has been observed that a high ABSI value is an independent predictor of endothelial dysfunction in both sexes [15], suggesting its association with inflammatory processes.

Therefore, we used data from EPIC and UK Biobank cohorts to examine cross-sectionally the associations of the traditional anthropometric indexes, ABSI, HI, WHR, waist-to-height ratio (WHtR), waist-to-hip index (WHI), and four body shape phenotypes (PC1-4), with circulating inflammatory biomarkers.

Methods

Study population: EPIC and UK Biobank

EPIC is a multicentre cohort study that included ~ 520,000 participants, aged mainly between 35 and 65 years, recruited from 1992 to 2000 across ten European countries (Denmark, France, Germany, Greece, Italy, the Netherlands, Norway, Spain, Sweden, and the UK). Socio-demographic, dietary, lifestyle, anthropometric, and medical data were collected at recruitment from all participants by country-specific questionnaires. Further details have previously been described elsewhere [16]. Data from Greece were not available for this analysis.

Approximately 386,000 EPIC participants provided a blood sample at recruitment [16]. All participants provided written informed consent and ethical approval for the study was obtained from the International Agency for Research on Cancer (IARC) ethics review panel (No. 20–34) and from all recruiting centres [16].

The UK Biobank is a prospective cohort study with over 500,000 individuals registered with the National Health Service of the United Kingdom [17]. Participants were recruited between 2006 and 2010, aged 40 to 70, and from across 22 study centres in England, Scotland, and

Wales. The study collected a wide range of data, including anthropometric measurements, lifestyle, health-related indexes, and biological samples.

Study population

In EPIC, participants were controls (i.e. cancer-free participants at blood collection) from nested case–control or case-cohort sub-studies conducted on associations between inflammation and cancer [18–28]. All included participants had CRP measured as it was the main inclusion criteria and, some women among the included participants also had additional inflammatory biomarkers measured including interleukin-6 (IL6), IL8, IL10, IL17d, interleukin 1 receptor antagonist (IL1ra), tumour necrosis factor alpha (TNF-α), Interferon-gamma (IFN-γ), leptin, and adiponectin. In total, 17,943 (69.1% women) EPIC participants were included. However, the number of participants included for the analysis of each biomarker was variable due to data availability (Additional file 1: Fig. S1).

The initial UK Biobank study sample included 503,386 individuals. After exclusion of participants with prevalent cancer at baseline and individuals lacking anthropometric measurements, 426,223 UK Biobank participants (53.2% women) who had values for CRP were included (Additional file 1: Fig. S1).

Assessment of anthropometric measurements

All anthropometric measurements included in EPIC followed standardized protocols, apart from Oxford (UK), where body weight and height were self-reported. However, these self-reported data were improved via prediction equations in Oxford and the self-reported data was considered valid for identifying associations [29]. Weight was measured barefoot and rounded to the nearest 0.1 kg whereas height was measured to the nearest 0.1 cm or 0.5 cm. WC was measured either between the lowest rib and the iliac crest or at the narrowest circumference of the torso. HC was horizontally determined at the wider point of the hip or above the buttocks. Additionally, weight, WC and HC measurements were corrected for clothing differences among centres [29]. When certain anthropometric data were missing like the weight, height, WC, and HC, they were imputed for some individuals using centre-, age-, and sex-specific mean values.

In the UK Biobank, trained personnel collected anthropometric measurements, where Seca 202 stadiometer and Tanita BC-418 body composition analyser were utilized to measure height and weight, respectively. WC was assessed at the point of natural indentation or the umbilicus, while HC was gauged at the widest part of the participants' hips.

Anthropometric indexes and body shape phenotypes

BMI was computed as: weight in kg divided by height in squared metres. WHR was determined by dividing WC by HC, both in centimeters. Additionally, other common indexes were computed, including WHtR and WHI [14].

ABSI was calculated as $WC/(BMI^{2/3}height^{1/2})$ [30] while HI was defined as $HC\ (height/[height])^{0.310}\ (weight/[weight])^{-0.482}$ with squared brackets indicating the mean values of the sample [31]. The mean value for height in EPIC was 164.9 cm while for weight was 70.9 kg whereas in the UK Biobank mean height was 168.6 cm and weight was 78.2 kg. Body shape phenotypes were previously derived in EPIC and in UK Biobank [9, 10]. Body shape phenotypes were derived through PCA performed on the standardized residuals of six anthropometric traits: height, weight, BMI, WC, HC, and WHR. For each single anthropometric trait, residuals were derived from a linear regression model of the anthropometric trait onto age, sex, and study centre [8–10]. This further adjustment was performed to remove the additional variability introduced by both age and sex making those traits more comparable across populations. Six PCs were created where each component represented a weighted sum of the six transformed traits and was independent of the other components. Out of the six PCs created, the first four PCs collectively explained 99.8% of the total variation of the six anthropometric variables and were selected for the subsequent analysis. Each of the four identified PCs described a specific body morphology type: PC1, overall adiposity, PC2, tall stature with low WHR, PC3, tall stature with large WHR, and PC4 characterized by high BMI and weight with low WC and HC. Body shape phenotypes showed similar loadings between the two study samples (Additional file 1: Table S1). To facilitate the interpretation of the body shape phenotypes, arithmetic means and SD of age and the six anthropometric traits building the PCs for each study participant in the 5 and 95% of each PC are presented in Additional file 1: Table S2 and S3.

Laboratory measurements

EPIC blood samples were collected (in fasting status in a small proportion of the participants) and stored in liquid nitrogen (− 196 °C) in a centralized biobank. For laboratory analysis, serum was used for most centres except for Norway and Umea (Sweden) where citrated plasma and heparin plasma were used, respectively. Laboratory procedures for assessing inflammatory biomarkers in EPIC have been already described in detail [18–28]. Values that fell below LOD (Limit of Detection), below LLOQ (Lower Limit of Quantification), or above ULOQ (Upper Limit of Quantification) were set to LOD/2, LLOQ/2 and ULOQ,

respectively. In the EPIC cohort, some biomarkers were measured more than once in different nested case–control or case-cohort studies; in these instances, only data from the study with the highest number of quantified values for that biomarker were retained.

Within the UK Biobank, blood samples [32] were procured throughout the day (from 8 AM to 9 PM), devoid of any stipulated fasting prerequisites. CRP serum biomarker concentrations were quantified using the Beckman Coulter AU5800 analyser.

Statistical analysis

Concentrations of the biomarkers were transformed logarithmically to approximate a normal distribution. We implemented a normalization step of the EPIC data as described in a previously published pipeline [33]. Briefly, linear mixed effect models were used for each biomarker. Models corrected for unwanted random effects like variation due to analytical method and analytical batch and fixed effects such as study centre, fasting status (no, in between, yes) and time of blood draw ($\leq$8 h, (8–12 h], (12–16 h), > 16 h), while fixed effects of interest such as anthropometric indexes, sex, and age at recruitment (years; continuous) were preserved. Linear regression models were used to confirm that normalization removed unwanted sources of variation. All the normalized data were then standardized (mean = 0 and standard deviation = 1) to rescale the concentration of the inflammatory biomarkers to enhance comparison.

The characteristics of participants were summarized using percentages for categorical variables and mean and standard deviation for continuous variables. Mann–Whitney tests were used to evaluate differences by sex in both cohorts. Spearman correlation coefficients between anthropometric indexes and CRP were calculated separately for each sex in both studies.

We assessed associations of body shape phenotypes and body fat distribution indexes with inflammatory biomarkers for both sexes in EPIC and UK Biobank using linear regression models adjusted for age at recruitment (years, continuous), smoking status (never, current, former, or unknown), education (primary education, secondary/tech school, university degree or higher, unknown) and physical activity (inactive, moderately inactive, moderately active, active, and unknown in EPIC; MET/week in UK Biobank). Results were combined separately for each sex through random-effects meta-analysis [34]. I^2 was used to assess the proportion of total variability attributable to between-study heterogeneity.

We evaluated interactions of the body shape phenotypes and body fat distribution indexes with age (above vs. below sex-specific median age) and smoking status (never vs. ever smoker), respectively, separately in men and women. Likelihood ratio tests were used to compare models with and without multiplicative interaction terms. *P* values were reported non-adjusted and adjusted for Bonferroni correction.

Sensitivity analyses among women were performed with further adjustment for menopausal status (premenopausal or postmenopausal) and use of menopausal hormonal treatment as well as stratification by menopausal status. Additionally, we performed sensitivity analyses excluding participants with cardiovascular diseases (myocardial infarction, stroke, or hypertension), and those with diabetes at baseline in both study samples. Further sensitivity analyses fitting regressions by sex between anthropometric indexes and CRP levels additionally adjusting by ethnicity (White/mixed/Asian/black/other/prefer not to answer) were performed to account for the potential variation introduced by the difference in anthropometric indexes across ethnic groups. These analyses were restricted in UK Biobank given the lack of ethnicity information in EPIC. Finally, associations between obesity categories [obesity class I (BMI 30 – < 35 kg/m^2), obesity class II (BMI 35 – < 40 kg/m^2), and obesity class III (BMI $\geq$ 40 kg/m^2)] and CRP levels were further investigated.

Sensitivity analyses also included regressions between body shape phenotypes and CRP levels without adjusting by age, a variable already included in the construction of the PCs. Additionally, correlations between the PCs and age have also been performed. These two analyses were reported to further check of potential bias due to overadjustment and collinearity.

Statistical analyses were performed using R 4.1.3. All tests were two-sided and *P* value < 0.05 was considered statistically significant. *P* values were adjusted by Bonferroni correction.

Results

The main characteristics of the study population are presented in Table 1. In EPIC, 69.1% of the participants were women, whereas in UK Biobank women represented 53.2% of the study sample. Additionally, women in both cohorts were generally younger than men. When it comes to anthropometric indexes, men in both EPIC and UK Biobank had higher values compared to women, except for HC and HI, where no such differences were observed and where women had higher values, respectively. Additionally, a higher percentage of men were in the obesity class I whereas a higher percentage of women were found in the obesity classes II and III (Additional file 1: Table S4 and S5). In both study samples, a greater proportion of men were current smokers, had attained higher levels of education, and were more physically active.

Table 1 Main characteristics of the study populations: EPIC and UK Biobank

	EPIC ($n = 17,943$)			UK Biobank ($n = 426,223$)		
	Men	**Women**	***P* value**	**Men**	**Women**	***P* value**
	Mean (SD) or *n* %	Mean (SD) or *n* %		Mean (SD) or *n* %	Mean (SD) or *n* %	
Sex	5546 (30.9%)	12,397 (69.1%)	< 0.001	199,506 (46.8%)	226,717 (53.2%)	< 0.001
Age (years)	53.1 (8.3)	52.5 (8.8)	< 0.001	56.4 (8.2)	56.1 (8.0)	< 0.001
Height (cm)	173.7 (7.3)	161.1 (6.7)	< 0.001	175.7 (6.8)	162.5 (6.3)	< 0.001
Weight (kg)	80.8 (11.6)	66.6 (11.5)	< 0.001	85.9 (14.3)	71.4 (14.1)	< 0.001
BMI (kg/m^2)	26.8 (3.6)	25.7 (4.5)	< 0.001	27.8 (4.2)	27.1 (5.2)	< 0.001
< 25 kg/m^2	1787 (32.2%)	6221 (50.2%)		50,170 (25.1%)	90,233 (39.8%)	
25–30 kg/m^2	2812 (50.7%)	4233 (34.1%)		98,707 (49.5%)	83,154 (36.7%)	
> 30 kg/m^2	947 (17.1%)	1943 (15.7%)		50,629 (25.4%)	53,330 (23.5%)	
Waist circumference (cm)	95.1 (10.1)	81.2 (11.2)	< 0.001	96.9 (11.3)	84.6 (12.5)	< 0.001
Waist to Height ratio	0.5 (0.07)	0.6 (0.06)	< 0.001	0.6 (0.1)	0.5 (0.1)	< 0.001
Hip circumference (cm)	101.0 (6.9)	101.6 (9.1)	< 0.001	103.4 (7.6)	103.3 (10.4)	< 0.001
Waist-to-hip ratio	0.9 (0.1)	0.8 (0.1)	< 0.001	0.9 (0.1)	0.8 (0.1)	< 0.001
Waist-to-hip index	4.1 (0.2)	3.6 (0.3)	< 0.001	4.1 (0.2)	3.6 (0.3)	< 0.001
ABSI	80.7 (4.3)	73.6 (5.0)	< 0.001	79.8 (4.2)	73.9 (5.0)	< 0.001
Hip index	96.7 (3.8)	104.3 (4.3)	< 0.001	100.5 (3.7)	107.2 (4.2)	< 0.001
Inflammatory biomarkers[a]						
CRP (µg/mL)	2.1 (3.07)	2.2 (35.8)	0.3	2.4 (4.2)	2.6 (4.3)	< 0.001
Interleukin 6 (pg/ml)	-	1.1 (1.5)		-	-	
Interleukin 8 (pg/ml)	-	6.9 (65.6)		-	-	
Interleukin 10 (pg/ml)	-	0.2 (0.4)		-	-	
Interleukin 17d (pg/ml)	-	8.5 (15.6)		-	-	
IL1ra (pg/ml)	-	162.9 (266.7)		-	-	
TNF-α (pg/ml)	-	1.4 (2.1)		-	-	
IFN-γ (pg/ml)	-	4.5 (10.4)		-	-	
Leptin (ng/ml)	-	16.6 (14.2)		-	-	
Adiponectin (µg/ml)	-	10.7 (5.2)		-	-	
Cambridge physical activity index (EPIC)			< 0.001			
Inactive	970 (17.5%)	3199 (25.8%)		-	-	
Moderately inactive	1734 (31.3%)	4508 (36.4%)		-	-	
Moderately active	1330 (24.0%)	2490 (20.1%)		-	-	
Active	1423 (25.7%)	2069 (16.7%)		-	-	
Unknown	89 (1.6%)	131 (1.1%)		-	-	
Physical activity (MET-minutes/week) (UK Biobank)	-	-		2821 (2963.2)	2516 (2467.5)	< 0.001
Smoking status			< 0.001			<0.001
Never	1676 (30.2%)	7143 (57.6%)		97,847 (49.1%)	135,953 (60.0%)	
Former	2114 (38.1%)	2623 (21.2%)		75,634 (37.9%)	69,904 (30.9%)	
Current	1692 (30.5%)	2517 (20.3%)		25,015 (12.6%)	19,768 (8.7%)	
Unknown (EPIC)/prefer not to answer (UK Biobank)	64 (1.2%)	114 (0.9%)		1010 (0.4%)	1092 (0.4%)	
Education			< 0.001			< 0.001
None/primary education	2164 (39.0%)	5114 (41.3%)		33,638 (16.9%)	37,380 (16.5%)	
Secondary/Tech school	1862 (33.6%)	4839 (39.0%)		48,209 (24.2%)	65,004 (28.7%)	
University degree or higher	1420 (25.6%)	2184 (17.6%)		115,212 (57.7%)	121,780 (53.7%)	
Unknown (EPIC)/prefer not to answer (UK Biobank)	100 (1.8%)	260 (2.1%)		2447 (1.2%)	2553 (1.1%)	

BMI Body mass index, *ABSI* A body shape index, *CRP* C-reactive protein, *IL1ra* Interleukin-1 receptor antagonist, *TNF-α* Tumour necrosis factor alpha, *IFN-γ* Interferon-gamma

Mann–Whitney tests were used to evaluate differences by sex in both cohorts. Significant when *P* value < 0.05

[a] All inflammatory biomarkers, except CRP, have missing values. See Additional file 1: Fig. 1

Crude correlations between CRP and all the anthropometric indexes were similar in men and women in both EPIC (Additional file 1: Fig. S2a) and UK Biobank (Additional file 1: Fig. S2b), being Bonferroni-adjusted. Specifically, weight, BMI, WC, WHR, WHI, HC, WHtR, and ABSI showed positive correlations with CRP, whereas height was inversely correlated with CRP (P value < 0.005). Additionally, HI showed weak correlations in UK Biobank only. For the body shape phenotypes, PC1 showed positive correlations with CRP, whereas PC2 was inversely correlated with CRP, in both cohorts and both sexes. PC3 and PC4 showed weak or no correlation with CRP.

Linear regression analyses adjusting for age, smoking status, education, and physical activity levels showed that the traditional anthropometric indexes and PC1 (overall adiposity) were all positively associated with CRP, with stronger estimates than the other body shape indexes in both cohorts (Figs. 1 and 2, Additional file 1: Table S6 and S7) and in both men and women. Height and PC2 (tall stature with low WHR) showed inverse associations with CRP, with similar estimates in both study samples and both sexes. Specifically, estimates for the association between height and CRP in men were -0.12 (95% CI: − 0.15, − 0.09) in EPIC and − 0.07 (95% CI: − 0.07, − 0.06) in UK Biobank, whereas in women were − 0.10 (95% CI: − 0.13, − 0.08) in EPIC and − 0.12 (95% CI: − 0.13, − 0.12) in UK biobank. Estimates for the association between PC2 and CRP in men were − 0.09 (95% CI: − 0.12, − 0.07) in EPIC and − 0.11 (95% CI: − 0.11, − 0.10) in UK Biobank, while for women they were − 0.10 (95% CI: − 0.12, − 0.09) in EPIC and − 0.13 (95% CI: − 0.14, − 0.13) in UK Biobank. The other body shape phenotypes, PC3 (tall with high

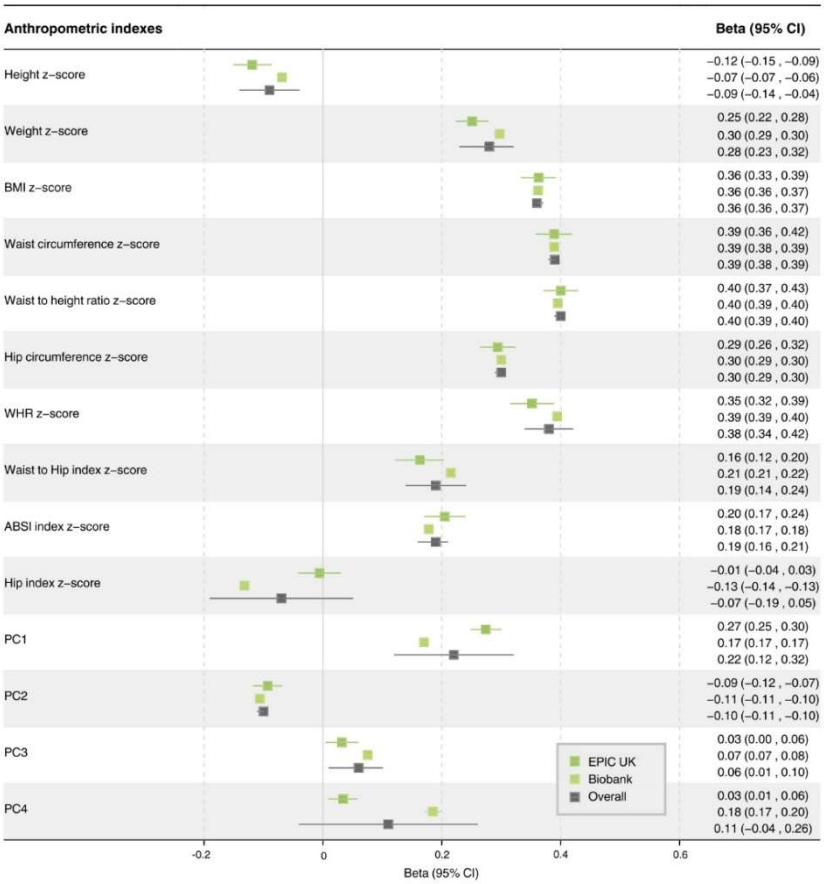


Fig. 1 Associations between anthropometric indexes and C-reactive protein (CRP) among men in the EPIC study and UK Biobank. Adjusted for age at recruitment, smoking status, education, and physical activity. Sample size EPIC: $N = 5546$, sample size UK Biobank: $N = 199{,}506$. BMI, body mass index; WHR, waist-to-hip ratio; ABSI, allometric body shape index. PC1, overall adiposity; PC2, tall with low waist-to-hip ratio; PC3, tall with high waist-to-hip ratio, PC4, high BMI and weight with low waist circumference and hip circumference. *X*-axis represents the beta estimates and the 95% confidence intervals (CI).

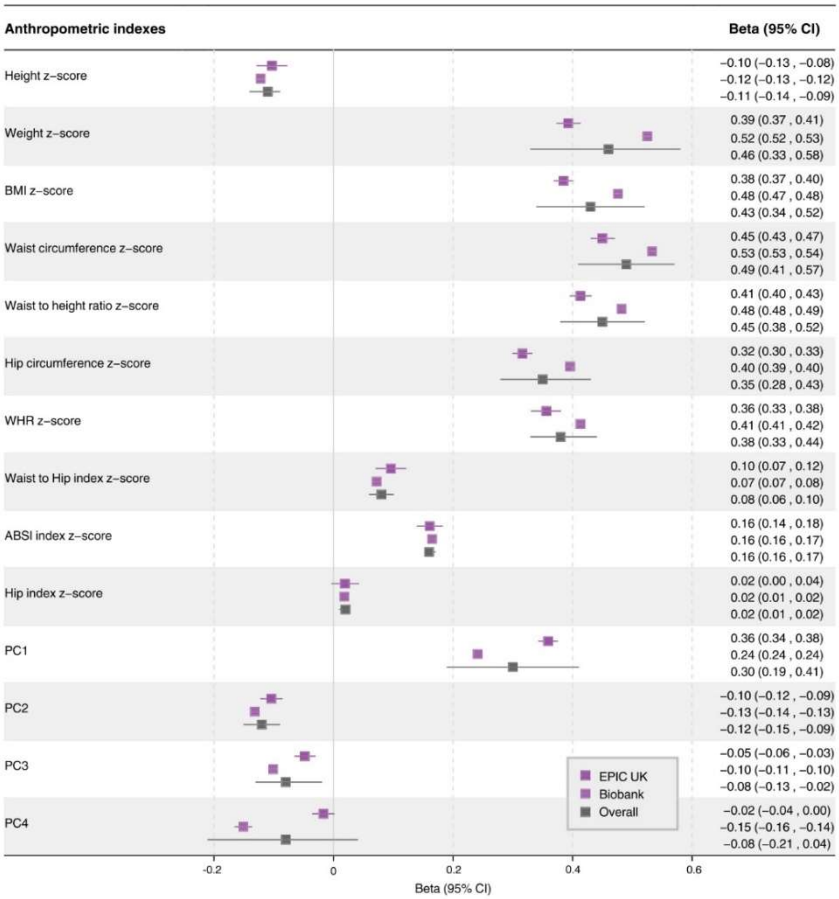


Fig. 2 Associations between anthropometric indexes and C-reactive protein (CRP) among women in the EPIC study and UK Biobank. Adjusted for age at recruitment, smoking status, education, and physical activity. Sample size EPIC: *N* = 12,397, sample size UK Biobank: *N* = 226,717. BMI, body mass index; WHR, waist-to-hip ratio; ABSI, allometric body shape index. PC1, overall adiposity; PC2, tall with low waist-to-hip ratio; PC3, tall with high waist-to-hip ratio; PC4, high BMI and weight with low waist circumference and hip circumference. *X*-axis represents the beta estimates and the 95% confidence intervals (CI).

WHR) and PC4 (high BMI and weight with low WC and HC) were also inversely associated with CRP in women (PC3: − 0.05; 95% CI: − 0.06, − 0.03 in EPIC and − 0.10; 95% CI: − 0.11, − 0.10 in UK Biobank and PC4: − 0.02; 95% CI: − 0.04, 0.00 in EPIC and − 0.15; 95% CI: − 0.16, − 0.14 in UK Biobank). In contrast, positive associations with CRP were observed in men for PC3: 0.03 (95% CI: 0.00, 0.06) in EPIC and 0.07 (95% CI: 0.07, 0.08) in UK Biobank and PC4: 0.03 (95% CI: 0.01, 0.06) in EPIC and 0.18 (95% CI: 0.17, 0.20) in UK Biobank. On the other hand, HI showed an inverse association with CRP for men and a positive association for women, but only consistent in UK Biobank: − 0.13 (95% CI: − 0.14, − 0.13) for men and 0.02 (95% CI: 0.01, 0.02) for women.

Similar estimates were found in the meta-analysis of both studies for both men and women. However, for HI (in men) and PC4, the meta-analysis showed less robust estimates (Figs. 1 and 2 and Additional file 1: Table S8). In most of the analyses, high heterogeneity was found (Additional file 1: Table S8).

Results for the other inflammatory biomarkers measured only in women from the EPIC study are presented in Figs. 3 and 4 and Additional file 1: Table S9. Traditional anthropometric indexes exhibited a greater number of associations and yielded higher effect estimates compared to the complex anthropometric indexes. Weight, BMI, WC, and HC were positively associated with IL6, IL1ra, TNF-α, and leptin, and inversely associated with IL17d and adiponectin. No associations were found

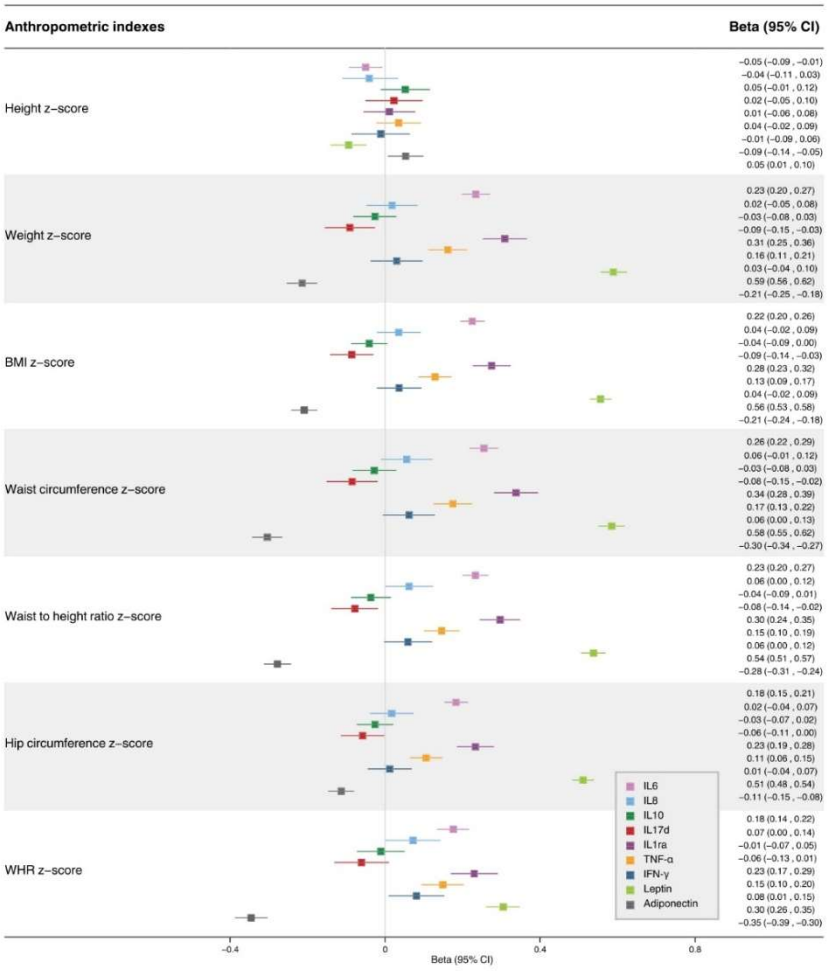


Fig. 3 Associations between simple anthropometric indexes and inflammatory biomarkers among women from the EPIC study. Adjusted for age at recruitment, smoking status, education, and physical activity. BMI, body mass index; WHR, waist-to-hip ratio. *X*-axis represents the beta estimates and the 95% confidence intervals (CI). IL6 (interleukin 6): $n = 3315$; IL8: $n = 1415$, IL10: $n = 2036$; IL17d: $n = 1416$; IL1ra (interleukin-1 receptor antagonist): $n = 1803$; TNF-α (tumour necrosis factor alpha): $n = 2425$; IFN-γ (interferon-gamma): $n = 1415$; leptin: $n = 2722$; adiponectin: $n = 3315$

between the traditional anthropometric indexes and IL8 or IL10. Both WHtR and WHR showed similar associations and were positively associated with IL8. WHR was also positively associated with IFN-γ. Additionally, ABSI was positively associated with IL6, IL1ra, TNF-α, and leptin and inversely associated with adiponectin. HI showed positive associations with leptin and adiponectin. For the body shape phenotypes, PC1 was positively associated with IL6, IL1ra, TNF-α, and leptin, and inversely associated with IL17d and adiponectin. PC2 showed inverse associations with IL6, IL1ra, and leptin and a positive association with adiponectin. PC3 was inversely associated with leptin and adiponectin. PC4 showed no association with any inflammatory biomarker.

In sub-group analyses by age groups and smoking status, estimated associations between anthropometric indexes and CRP were all in the same direction and similar in magnitude (Additional file 1: Table S10–S13). However, several tests for multiplicative interaction may reach statistical significance due to the large sample size, in particular in the UK Biobank.

Sensitivity analyses among women stratifying by menopausal status at recruitment showed similar results in both pre and postmenopausal women for the associations between anthropometric indexes and CRP in both EPIC and UK Biobank (Additional file 1: Table S14 and S15). Results were also similar when models were further adjusted for menopausal hormonal treatment

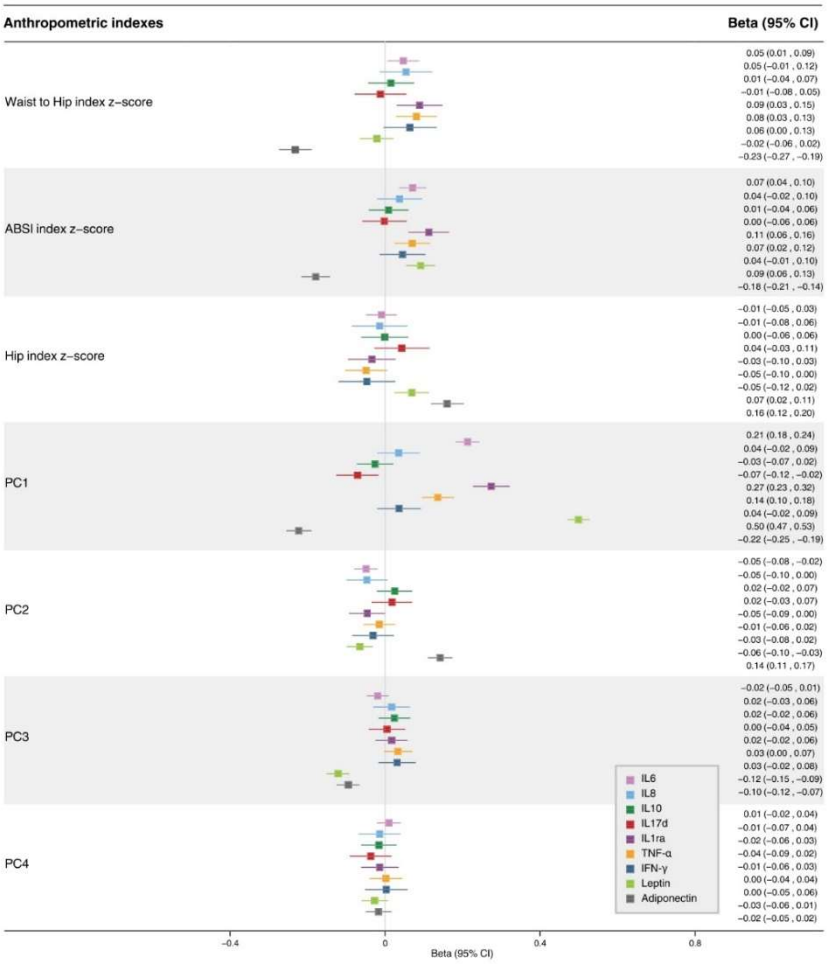


Fig. 4 Associations between complex anthropometric indexes and inflammatory biomarkers among women from the EPIC study. Adjusted for age at recruitment, smoking status, education, and physical activity. ABSI, allometric body shape index. *X*-axis represents the beta estimates and the 95% confidence intervals (CI). PC1, overall adiposity; PC2, tall with low waist-to-hip ratio; PC3, tall with high waist-to-hip ratio; PC4, high BMI and weight with low waist circumference and hip circumference. IL6 (interleukin 6): $n = 3315$; IL8: $n = 1415$, IL10: $n = 2036$; IL17d: $n = 1416$; IL1ra (interleukin-1 receptor antagonist): $n = 1803$; TNF-α (tumour necrosis factor alpha): $n = 2425$; IFN-γ (interferon-gamma): $n = 1415$; leptin: $n = 2722$; adiponectin: $n = 3315$

(postmenopausal women only). The sensitivity analyses excluding participants with cardiovascular diseases (myocardial infarction, stroke, and hypertension) and diabetes at baseline yielded similar results to those from the main analysis (Additional file 1: Table S16 and S17 for EPIC and Additional file 1: Table S18 and S19 for UK Biobank). No differences in the associations by sex between anthropometric indexes and CRP levels models additionally adjusted by ethnicity were found in UK Biobank (Additional file 1: Table S20).

In an exploratory analysis, associations fitted by obesity class showed similar results in both EPIC and UK Biobank presenting a higher and increasing estimate as the categories included higher BMI ranges. Associations for all obesity categories were higher in women than men (Additional file 1: Table S4 and S5).

Finally, analyses excluding age as a confounder were not showing differences in the results (Additional file 1: Table S21 and S22). Slight inverse and positive correlations were found between PC1, PC3, and PC4 and age among men and women in both cohorts, respectively (Additional file 1: Fig. S3).

Discussion

In this study, we identified associations between various body shape phenotypes and body fat distribution indexes and inflammatory biomarkers in both the EPIC and UK Biobank cohorts, revealing significant gender-specific and phenotype-specific associations. Specifically, we found positive associations between the traditional anthropometric indexes (such as BMI, WC, and WHR), ABSI, and PC1 (overall adiposity) and CRP, in both sexes from EPIC and UK Biobank, as well as with IL6, IL1ra, TNF-α, and leptin in women from the EPIC study (no data available for men). On the other hand, height and PC2 (tall with low WHR) showed inverse associations with CRP in both study populations and with IL6, IL1ra, and leptin in EPIC. PC3 (tall with high WHR) was inversely associated with CRP among women but positively associated among men, in both cohorts. PC3 was also inversely associated with leptin and adiponectin in women of the EPIC study. The differential associations of PC3 with CRP in men and women add a valuable layer of understanding that extends beyond traditional measures of adiposity. Additionally, our results suggest an inverse association between height, independent of WC/WHR, and inflammation, especially in women.

The positive associations found between traditional anthropometric indexes and inflammation are in line with existing literature [35]. However, the mechanisms that cause the adipose tissue dysfunction triggering low-grade inflammation are not yet fully understood [36, 37]. In addition, it has been observed that normal weight individuals with abdominal fat accumulation can have metabolic alterations whereas some individuals with obesity can be metabolically healthy [38–40]. However, there is no consensus on the definition of metabolically healthy obesity and further research is needed as literature suggests that the clinical relevance of the associations with metabolic dysfunction is speculative, and mostly based on cross-sectional studies. In this sense, a study using data from the UK Biobank [41] indicated that individuals classified as metabolically healthy obese still face elevated risks of cardiovascular diseases, respiratory disease, diabetes, and all-cause mortality compared to individuals without obesity and without obesity-related risk factors.

Therefore, it would be useful to consider complex anthropometric indexes over single indexes as they may better reflect body fat distribution and could better capture inflammatory status [31]. From the results of our study, BMI, WC, and WHR are interchangeable and do not give additional insight on the association with CRP or IL6.

Two of the most used complex anthropometric indexes, ABSI and HI, have previously shown associations with inflammatory biomarkers [14], endothelial dysfunction [15], and cardiometabolic risk factors [42]. However, literature examining associations of those indexes and inflammatory markers is scarce and focused exclusively on ABSI, rarely considering HI. Large ABSI has also been associated with higher CRP in previous studies [43, 44], and, in agreement with our findings, BMI has also shown stronger positive associations with CRP in women compared to men [44]. In our study, ABSI showed stronger associations with CRP than HI suggesting that ABSI is more closely linked to inflammatory status. A previous study in UK Biobank [14] found that BMI and ABSI were positively associated with CRP showing similar results to ours. However, no associations were found for HI and CRP in that study. Even if BMI seems to show greater associations with inflammation than ABSI, they are independent by design and should be interpreted as complementary. Thus, our results suggest that using complex anthropometric indexes, beyond traditional metrics like BMI, into clinical practice could improve the identification of individuals at higher risk of inflammation-related conditions. This could lead to earlier interventions and better clinical outcomes.

Among the body shape phenotypes, we found that PC1 (overall adiposity) was the one more correlated with single anthropometric indexes. This is expected as PC1 is constructed based on higher loadings in BMI, weight, HC, and WC. Likewise, PC1 and all these anthropometric indexes showed similar associations with CRP. On the other hand, PC2 (tall stature with low WHR) consistently exhibited inverse associations with CRP across both cohorts and sexes. In this sense, the multivariate approach of a PCA simplifies to holistically account for different traditional anthropometric indexes, like adiposity and height. Thus, body shape phenotypes may better reflect body composition than individual indexes for risk assessment and incorporated into clinical practice could help refine models for inflammation-related diseases, enabling more personalized and effective intervention strategies. Previous findings have suggested that WHR may be positively linked to CRP [45], irrespective of age, sex, metabolic and various lifestyle factors in several studies. However, we showed that PC3 (tall stature with high WHR) was inversely associated with concentrations of CRP in women. Overall, our results for PC2, in both sexes, and PC3, in women, suggest that height mitigates the positive association of abdominal adiposity with CRP, especially in women. Women generally have a higher proportion of body fat compared to men [46], even when matched for BMI, and this physiological difference also could contribute to variations in inflammatory markers. These observed associations highlight the importance of tailored public health initiatives that

address gender-specific risk factors and promote lifestyle modifications to mitigate inflammation and its related conditions.

Evidence suggests that height is positively associated with cancer risk [47–50], but also inversely associated with cardiometabolic risk [51] and diabetes [52], for the latter also when adjusting for WC. Although BMI and WC are established variables with which to assess morbidity and mortality risk, adult height is also associated with mortality independently of adiposity measures [53]. Previous research supports that shorter height is positively associated with cardiovascular risk [54] and that this risk might at least in part be mediated by cardiometabolic risk factors relevant for type 2 diabetes, namely blood pressure, blood lipids, and inflammation [55, 56]. Also, in one analysis that studied a sub-sample of the EPIC study, height appeared to be more strongly correlated with CRP among women, playing a stronger role in the association with diabetes in women than in men [52]. These results suggest taller height in women might have some metabolic implications. This stronger inverse association of taller height and CRP in women could explain the divergent result for PC3 as, for women, height can be a major driver than WHR of the association with CRP. However, more studies in different cohorts are needed to support these findings.

In our study based on two cohorts, height emerged as an indicator inversely associated with CRP in both sexes, even in combination with abdominal adiposity in women from both studies. We found similar results when considering menopausal status or when excluding those with cardiovascular diseases or diabetes. Furthermore, height was inversely associated with IL6 and leptin in women from EPIC. These inverse associations suggest that height could be protective for inflammatory status.

Strengths and limitations

The primary strength of our study is the novel results on anthropometric indexes and inflammation in two large cohort studies: EPIC and UK Biobank. These studies were conducted following standardized procedures. The use of several anthropometric indexes is another major strength as it allows comparison between them. Also, we performed sensitivity analyses, excluding those with diabetes and cardiovascular diseases to detect potential shared molecular pathways with adiposity that could bias our results.

The main limitation of our study is the lack of data for some of the inflammatory biomarkers in UK Biobank and in men in EPIC. Furthermore, we cannot determine subcutaneous adipose tissue from overall adipose tissue as we have no body composition data using objective techniques. Also, the cross-sectional design of the study does not allow us to establish causal relationships while one-time-point measurements are not ideal to assess temporal relationships. However, this study could be considered a starting point for further longitudinal studies.

Conclusions

This study adds to our understanding of the relationship between body composition and systemic inflammation. Our findings affirm an inverse relationship between height and inflammation. Notably, our results suggest that a taller height may mitigate the impact of a large WC or a large HC on inflammation in women. PC2 (tall stature with low WHR) and PC3 (tall stature with large WHR) were inversely associated with CRP in both the EPIC and UK Biobank studies. These findings underscore the value of body shape phenotypes suggesting that they could serve as additional tools for risk stratification in epidemiological studies as well as to improve personalized approaches to disease prevention and management. Further longitudinal studies that include more inflammatory markers are needed.

Abbreviations

ABSI	Allometric body shape index
BMI	Body mass index
CRP	C-reactive protein
EPIC	European Prospective Investigation into Cancer and Nutrition study
HC	Hip circumference
HI	Hip index
IARC	International Agency for Research on Cancer
IFN-γ	Interferon gamma
IL	Interleukin
LLOQ	Lower limit of quantification
LOD	Limit of detection
PC1	Overall adiposity
PC2	Tall stature with low WHR
PC3	Tall and with high WHR
PC4	High BMI and weight with low WC and HC
TNF-α	Tumour necrosis factor alpha
ULOQ	Upper Limit of Quantification
WC	Waist circumference
WHR	Waist-to-hip ratio
WHtR	Waist-to-height ratio

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12916-024-03544-3.

Additional file 1: Fig. S1. Flowchart with the included number of subjects in EPIC and UK Biobank. IL1ra: Interleukin-1 receptor antagonist; TNF-α: Tumour necrosis factor alpha; IFN-γ: Interferon-gamma. Fig. S2a. Correlations between adiposity and concentration of C-reactive protein in the EPIC study by sex. Fig. S2b. Correlations between adiposity and concentration of C-reactive protein in UK Biobank study by sex. Fig. S3. Correlations between body shape phenotypes and age in the EPIC and UK Biobank study by sex. Table S1. Loadings of the principal components derived in EPIC ($n = 17,943$) and UK Biobank ($n = 426,223$). Table S2. Mean and standard deviations of age and the six anthropometric traits building the body shape phenotypes for individuals included in the top and bottom 5% of each PC in the EPIC study. Table S3. Mean and standard deviations of age and the six anthropometric traits building the body shape phenotypes for

individuals included in the top and bottom 5% of each PC in UK Biobank study. Table S4. Sample size and associations between individuals with obesity and by obesity class and C-reactive protein (CRP) levels in EPIC. Table S5. Sample size and associations between individuals with obesity and by obesity class and C-reactive protein (CRP) levels in UK Biobank. Table S6. Associations between anthropometric indexes and C-reactive protein (CRP) in the EPIC study. Table S7. Associations between anthropometric indexes and C-reactive protein (CRP) in UK Biobank study. Table S8. Meta-analysis results of the associations between anthropometric indexes and C-reactive protein (CRP) in the EPIC and UK Biobank cohorts. Table S9. Associations between anthropometric indexes and all the inflammatory biomarkers analysed in EPIC. Table S10. Associations between anthropometric indexes and C-reactive protein (CRP) stratifying by sex-specific median age and p-values for likelihood ratio test comparing models without and with interactions in the EPIC study. Table S11. Associations between anthropometric indexes and C-reactive protein (CRP) stratifying by smoking status and p-values for likelihood ratio test comparing models without and with interactions in the EPIC study. Table S12. Associations between anthropometric indexes and C-reactive protein (CRP) stratifying by sex-specific median age and p-values for likelihood ratio test comparing models without and with interactions in UK Biobank study. Table S13. Associations between anthropometric indexes and C-reactive protein (CRP) stratifying by smoking status and p-values for likelihood ratio test comparing models without and with interactions in UK Biobank study. Table S14. Associations between anthropometric indexes and C-reactive protein (CRP) in the EPIC study. Data presented for all women and by menopausal status. Table S15. Associations between anthropometric indexes and C-reactive protein (CRP) in UK Biobank study. Data presented for all women and by menopausal status. Table S16. Associations between anthropometric indexes and C-reactive protein (CRP) in the EPIC study excluding 3,643 participants with CVD at baseline defined as myocardial infarction (heart attack), stroke or hypertension. Table S17. Associations between anthropometric indexes and C-reactive protein (CRP) in the EPIC Study excluding 484 participants with diabetes at baseline. Table S18. Associations between anthropometric indexes and C-reactive protein (CRP) in UK Biobank excluding 102,020 participants with CVD at baseline defined as myocardial infarction (heart attack), stroke, or hypertension. Table S19. Associations between anthropometric indexes and C-reactive protein (CRP) in UK Biobank excluding 26,365 participants with diabetes at baseline. Table S20. Associations between anthropometric indexes and C-reactive protein (CRP) in UK Biobank additionally adjusted for ethnicity. Table S21. Associations between body shape phenotypes and C-reactive protein (CRP) in the EPIC study excluding age as a confounder. Table S22. Associations between anthropometric indexes and C-reactive protein (CRP) in UK Biobank study excluding age as a confounder.

Acknowledgements
The authors thank all EPIC participants and staff for their outstanding contribution to the study. This research has been conducted using the UK Biobank Resource under Application Number 55870 and we express our gratitude to the participants and those involved in building the resource.

IARC disclaimer
Where authors are identified as personnel of the International Agency for Research on Cancer/World Health Organization, the authors alone are responsible for the views expressed in this article and they do not necessarily represent the decisions, policy, or views of the International Agency for Research on Cancer/World Health Organization.

Authors' contributions
EMGG, and LPN analysed the data. EMGG, LPN, AS, SC, CB, AN, YMS, RFJ, PAE, HB, MG, MV, JMAB, AO, AT, VS, CCE, DA, AKH, MG, SMCY, NRZ, CCD, ELL, MBS, DP, SS, FR, GM, TK, VV, SR, HF and LD have drafted the manuscript or substantively revised it. LD conceived and designed the work. EMGG, LPN, SC, HF, and LD contributed to the interpretation of the data. All authors have read and approved the submitted manuscript.

Authors' Twitter handles
Twitter handles: @GonzalezGilEM (Esther M. González-Gil), @LPeruchet (Laia Peruchet-Noray), @MS_Yahya_ (Yahya Mahamat-Saleh), @HFreisling (Heinz Freisling).

Funding
This work was supported by the German Research Fund (DFG) [BA 5459/2–1] and the French National Cancer Institute (l'Institut National du Cancer) [INCa_16643].
The coordination of EPIC is financially supported by the International Agency for Research on Cancer (IARC) and by the Department of Epidemiology and Biostatistics, School of Public Health, Imperial College London, which has additional infrastructure support provided by the NIHR Imperial Biomedical Research Centre (BRC). The national cohorts are supported by:Danish Cancer Society (Denmark); Ligue Contre le Cancer, Institut Gustave Roussy, Mutuelle Générale de l'Education Nationale, Institut National de la Santé et de la Recherche Médicale (INSERM) (France); German Cancer Aid, German Cancer Research Centre (DKFZ), German Institute of Human Nutrition PotsdamRehbruecke (DIfE), Federal Ministry of Education and Research(BMBF) (Germany); Associazione Italiana per la Ricerca sul CancroAIRCItaly,Compagnia di SanPaolo and National Research Council (Italy); Dutch Ministryof Public Health, Welfare and Sports (VWS), Netherlands Cancer Registry (NKR),LK Research Funds, Dutch Prevention Funds, Dutch ZON (Zorg OnderzoekNederland), World Cancer Research Fund (WCRF), Statistics Netherlands(The Netherlands); Health Research Fund (FIS)—Instituto de Salud Carlos III(ISCIII), Regional Governments of Andalucía, Asturias, Basque Country, Murciaand Navarra, and the Catalan Institute of Oncology—ICO (Spain); SwedishCancer Society, Swedish Research Council and County Councils of Skåne andVästerbotten (Sweden); Cancer Research UK (14136 to EPICNorfolk; C8221/A29017 to EPICOxford), Medical Research Council (1000143 to EPIC Norfolk;MR/M012190/1 to EPICOxford) (United Kingdom). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.
The UK Biobank was supported by the Wellcome Trust, Medical Research Council, Department of Health, Scottish Government and the Northwest Regional Development Agency. It has also had funding from the Welsh Assembly Government and the British Heart Foundation.

Availability of data and materials
EPIC data are available for investigators who seek to answer important questions on health and disease in the context of research projects that are consistent with the legal and ethical standard practices of IARC/WHO and the EPIC centres. The primary responsibility for accessing the data belongs to IARC and the EPIC centres. For information on how to submit an application for gaining access to EPIC data and/or biospecimens, please follow the instructions at https://epic.iarc.fr/access/.
The data that support the findings of this study are available from UK Biobank but restrictions apply to their availability. You could also use this statement: UK Biobank is an open access resource. Bona fide researchers can apply to use the UK Biobank dataset by registering and applying at http://ukbiobank.ac.uk/register-apply/. These data were used under licence for the current study, and so are not publicly available. The data are, however, available from the authors upon reasonable request and with permission of UK Biobank.

Declarations

Ethics approval and consent to participate
This study complies with the Declaration of Helsinki. EPIC was approved by the Ethics Committee of the International Agency for Research on Cancer (IARC) (ref IEC 14–02), Lyon, France, as well as the local ethics committees of the study centres. All participants provided written informed consent for data collection and storage as well as individual follow-up.
The UK Biobank study was approved by the Northwest Multi-Centre Research Ethics Committee (reference for UK Biobank is 16/NW/0274) and all participants provided written informed consent to participate in the UK Biobank study. The study protocol is available online (https://www.ukbiobank.ac.uk/media/gnkeyh2q/study-rationale.pdf).

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Author details
[1]Nutrition and Metabolism Branch, International Agency for Research On Cancer, World Health Organization, 69372 Lyon, CEDEX 08, France. [2]Department of Clinical Sciences, Faculty of Medicine, University of Barcelona, Barcelona, Spain. [3]Department of Epidemiology and Preventive Medicine, University of Regensburg, Regensburg, Germany. [4]Center for Translational Oncology, University Hospital Regensburg, Regensburg, Germany. [5]Bavarian Cancer Research Center (BZKF), Regensburg, Germany. [6]Department of Epidemiology and Biostatistics, School of Public Health, Imperial College London, London, UK. [7]Instituto de Salud Pública y Laboral de Navarra, 31003 Pamplona, Spain. [8]Centro de Investigación Biomédica en Red de Epidemiología y Salud Pública (CIBERESP), 28029 Madrid, Spain. [9]Navarra Institute for Health Research (IdiSNA), 31008 Pamplona, Spain. [10]Sub Directorate for Public Health and Addictions of Gipuzkoa, Ministry of Health of the Basque Government, San Sebastian, Spain. [11]Epidemiology of Chronic and Communicable Diseases Group, BioGipuzkoa (BioDonostia) Health Research Institute, San Sebastián, Spain. [12]Centre forPrevention, Lifestyle and Health, National Institute for Public Health and the Environment, PO Box 1, 3720 BA Bilthoven, the Netherlands. [13]Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, The Netherlands. [14]Danish Cancer Institute, Danish Cancer Society, Diet, Cancer and Health Strandboulevarden 49 2100, Copenhagen, Denmark. [15]Department of Public Health, University of Aarhus, Copenhagen, Denmark. [16]Department of Public Health, University of Copenhagen, Copenhagen, Denmark. [17]Dipartimento Di Salute Mentale E Fisica E Medicina Preventiva, Università Degli Studi Della Campania 'Luigi Vanvitelli', Napoli, Italy. [18]Unit of Nutrition and Cancer, Catalan Institute of Oncology-ICO, L'Hospitalet de Llobregat, Barcelona, Spain. [19]Nutrition and Cancer Group, Epidemiology, Public Health, Cancer Prevention and Palliative Care Program, Bellvitge Biomedical Research Institute-IDIBELL, L'Hospitalet de Llobregat, Barcelona, Spain. [20]Department of Research, The Cancer Registry of Norway, Oslo, Norway. [21]Department of Nutrition, Oslo New University College, Oslo, Norway. [22]Department of Epidemiology, Murcia Regional Health Council-IMIB, Murcia, Spain. [23]Research Group On Demography and Health, National Faculty of Public Health, University of Antioquia, Medellín, Colombia. [24]Department of Public Health, Aarhus University, Aarhus, Denmark. [25]Department of Molecular Epidemiology, German Institute of Human Nutrition Potsdam-Rehbruecke, Nuthetal, Germany. [26]German Center for Diabetes Research (DZD), Munchen-Neuherberg, Germany. [27]Institute of Nutritional Science, University of Potsdam, Nuthetal, Germany. [28]Escuela Andaluza de Salud Pública (EASP), 18011 Granada, Spain. [29]Instituto de Investigación Biosanitaria Ibs, GRANADA, 18012 Granada, Spain. [30]Epidemiology and Prevention Unit, Fondazione IRCCS Istituto Nazionale Dei Tumori Di Milano, Milan, Italy. [31]Centre for Biostatistics, Epidemiology, and Public Health (C-BEPH) Department of Clinical and Biological Sciences, University of Turin, Turin, Italy. [32]Clinical Epidemiology Unit, Institute for Cancer Research, Prevention, and Clinical Network (ISPRO), Florence, Italy. [33]Cancer Epidemiology Unit, Nuffield Department of Population Health, University of Oxford, Oxford, UK.

Received: 4 March 2024 Accepted: 29 July 2024
Published online: 15 August 2024

References

1. Nishida C, Ko GT, Kumanyika S. Body fat distribution and noncommunicable diseases in populations: overview of the 2008 WHO Expert Consultation on Waist Circumference and Waist-Hip Ratio. Eur J Clin Nutr. 2010;64(1):2–5.
2. Ashwell M, Gunn P, Gibson S. Waist-to-height ratio is a better screening tool than waist circumference and BMI for adult cardiometabolic risk factors: systematic review and meta-analysis. Obes Rev. 2012;13(3):275–86.
3. Lee JJ, Pedley A, Hoffmann U, Massaro JM, Fox CS. Association of Changes in Abdominal Fat Quantity and Quality With Incident Cardiovascular Disease Risk Factors. J Am Coll Cardiol. 2016;68(14):1509–21.
4. Krakauer NY, Krakauer JC. A New Body Shape Index Predicts Mortality Hazard Independently of Body Mass Index. PLoS One. 2012;7:e39504 (**Public Library of Science**).
5. Krakauer NY, Krakauer JC. An Anthropometric Risk Index Based on Combining Height, Weight, Waist, and Hip Measurements. J Obes. 2016;2016:8094275 (**2016/11/11 edn**).
6. Christakoudi S, Tsilidis KK, Evangelou E, Riboli E. A Body Shape Index (ABSI), hip index, and risk of cancer in the UK Biobank cohort. Cancer Med. 2021;10(16):5614–28.
7. Christakoudi S, Tsilidis KK, Evangelou E, Riboli E. Association of body-shape phenotypes with imaging measures of body composition in the UK Biobank cohort: relevance to colon cancer risk. BMC Cancer. 2021;21(1):1106.
8. Ried JS, Jeff MJ, Chu AY, Bragg-Gresham JL, van Dongen J, Huffman JE, Ahluwalia TS, Cadby G, Eklund N, Eriksson J, et al. A principal component meta-analysis on multiple anthropometric traits identifies novel loci for body shape. Nat Commun. 2016;7:13357.
9. Sedlmeier AM, Viallon V, Ferrari P, Peruchet-Noray L, Fontvieille E, Amadou A, Seyed Khoei N, Weber A, Baurecht H, Heath AK et al. Body shape phenotypes of multiple anthropometric traits and cancer risk: a multinational cohort study. Br J Cancer. 2022.
10. Peruchet-Noray L, Sedlmeier AM, Dimou N, Baurecht H, Fervers B, Fontvieille E, Konzok J, Tsilidis KK, Christakoudi S, Jansana A, et al. Tissue-specific genetic variation suggests distinct molecular pathways between body shape phenotypes and colorectal cancer. Sci Adv. 2024;10(16):eadj1987.
11. Christakoudi S, Tsilidis KK, Muller DC, Freisling H, Weiderpass E, Overvad K, Soderberg S, Haggstrom C, Pischon T, Dahm CC, et al. A Body Shape Index (ABSI) achieves better mortality risk stratification than alternative indices of abdominal obesity: results from a large European cohort. Sci Rep. 2020;10(1):14541.
12. Deng T, Lyon CJ, Bergin S, Caligiuri MA, Hsueh WA. Obesity, Inflammation, and Cancer. Annu Rev Pathol. 2016;11:421–49.
13. Volpe M, Gallo G. Obesity and cardiovascular disease: An executive document on pathophysiological and clinical links promoted by the Italian Society of Cardiovascular Prevention (SIPREC). Front Cardiovasc Med. 2023;10:1136340.
14. Christakoudi S, Riboli E, Evangelou E, Tsilidis KK. Associations of body shape index (ABSI) and hip index with liver, metabolic, and inflammatory biomarkers in the UK Biobank cohort. Sci Rep. 2022;12(1):8812.
15. Kajikawa M, Maruhashi T, Kishimoto S, Yamaji T, Harada T, Hashimoto Y, Han Y, Mizobuchi A, Aoki G, Yoshimura K, et al. A body shape index is associated with endothelial dysfunction in both men and women. Sci Rep. 2021;11(1):17873.
16. Riboli E, Hunt KJ, Slimani N, Ferrari P, Norat T, Fahey M, Charrondiere UR, Hemon B, Casagrande C, Vignat J, et al. European Prospective Investigation into Cancer and Nutrition (EPIC): study populations and data collection. Public Health Nutr. 2002;5(6B):1113–24.
17. Sudlow C, Gallacher J, Allen N, Beral V, Burton P, Danesh J, Downey P, Elliott P, Green J, Landray M, et al. UK biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. PLoS Med. 2015;12(3):e1001779.
18. Aleksandrova K, Boeing H, Jenab M, Bueno-de-Mesquita HB, Jansen E, van Duijnhoven FJ, Fedirko V, Rinaldi S, Romieu I, Riboli E, et al. Total and high-molecular weight adiponectin and risk of colorectal cancer: the European Prospective Investigation into Cancer and Nutrition Study. Carcinogenesis. 2012;33(6):1211–8.
19. Aleksandrova K, Boeing H, Jenab M, Bueno-de-Mesquita HB, Jansen E, van Duijnhoven FJ, Rinaldi S, Fedirko V, Romieu I, Riboli E, et al. Leptin and soluble leptin receptor in risk of colorectal cancer in the European Prospective Investigation into Cancer and Nutrition cohort. Cancer Res. 2012;72(20):5328–37.
20. Aleksandrova K, Boeing H, Nothlings U, Jenab M, Fedirko V, Kaaks R, Lukanova A, Trichopoulou A, Trichopoulos D, Boffetta P, et al. Inflammatory and metabolic biomarkers and risk of liver and biliary tract cancer. Hepatology. 2014;60(3):858–71.
21. Aleksandrova K, Jenab M, Boeing H, Jansen E, Bueno-de-Mesquita HB, Rinaldi S, Riboli E, Overvad K, Dahm CC, Olsen A, et al. Circulating C-reactive protein concentrations and risks of colon and rectal cancer: a nested case-control study within the European Prospective Investigation into Cancer and Nutrition. Am J Epidemiol. 2010;172(4):407–18.
22. Cust AE, Kaaks R, Friedenreich C, Bonnet F, Laville M, Lukanova A, Rinaldi S, Dossus L, Slimani N, Lundin E, et al. Plasma adiponectin levels and

endometrial cancer risk in pre- and postmenopausal women. J Clin Endocrinol Metab. 2007;92(1):255–63.
23. Dossus L, Becker S, Rinaldi S, Lukanova A, Tjonneland A, Olsen A, Overvad K, Chabbert-Buffet N, Boutron-Ruault MC, Clavel-Chapelon F, et al. Tumor necrosis factor (TNF)-alpha, soluble TNF receptors and endometrial cancer risk: the EPIC study. Int J Cancer. 2011;129(8):2032–7.
24. Dossus L, Franceschi S, Biessy C, Navionis AS, Travis RC, Weiderpass E, Scalbert A, Romieu I, Tjonneland A, Olsen A, et al. Adipokines and inflammation markers and risk of differentiated thyroid carcinoma: The EPIC study. Int J Cancer. 2018;142(7):1332–42.
25. Dossus L, Rinaldi S, Becker S, Lukanova A, Tjonneland A, Olsen A, Stegger J, Overvad K, Chabbert-Buffet N, Jimenez-Corona A, et al. Obesity, inflammatory markers, and endometrial cancer risk: a prospective case-control study. Endocr Relat Cancer. 2010;17(4):1007–19.
26. Grote VA, Kaaks R, Nieters A, Tjonneland A, Halkjaer J, Overvad K, Skjelbo Nielsen MR, Boutron-Ruault MC, Clavel-Chapelon F, Racine A, et al. Inflammation marker and risk of pancreatic cancer: a nested case-control study within the EPIC cohort. Br J Cancer. 2012;106(11):1866–74.
27. Grote VA, Rohrmann S, Dossus L, Nieters A, Halkjaer J, Tjonneland A, Overvad K, Stegger J, Chabbert-Buffet N, Boutron-Ruault MC, et al. The association of circulating adiponectin levels with pancreatic cancer risk: a study within the prospective EPIC cohort. Int J Cancer. 2012;130(10):2428–37.
28. Ose J, Schock H, Tjonneland A, Hansen L, Overvad K, Dossus L, Clavel-Chapelon F, Baglietto L, Boeing H, Trichopolou A, et al. Inflammatory Markers and Risk of Epithelial Ovarian Cancer by Tumor Subtypes: The EPIC Cohort. Cancer Epidemiol Biomarkers Prev. 2015;24(6):951–61.
29. Spencer EA, Appleby PN, Davey GK, Key TJ. Validity of self-reported height and weight in 4808 EPIC-Oxford participants. Public Health Nutr. 2002;5(4):561–5.
30. Krakauer NY, Krakauer JC. A new body shape index predicts mortality hazard independently of body mass index. PLoS ONE. 2012;7(7):e39504.
31. Krakauer NY, Krakauer JC. An Anthropometric Risk Index Based on Combining Height, Weight, Waist, and Hip Measurements. J Obes. 2016;2016:8094275.
32. Elliott P, Peakman TC, Biobank UK. The UK Biobank sample handling and storage protocol for the collection, processing and archiving of human blood and urine. Int J Epidemiol. 2008;37(2):234–44.
33. Viallon V, His M, Rinaldi S, Breeur M, Gicquiau A, Hemon B, Overvad K, Tjonneland A, Rostgaard-Hansen AL, Rothwell JA et al. A New Pipeline for the Normalization and Pooling of Metabolomics Data. Metabolites. 2021;11(9).
34. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003;327(7414):557–60.
35. Choi J, Joseph L, Pilote L. Obesity and C-reactive protein in various populations: a systematic review and meta-analysis. Obes Rev. 2013;14(3):232–44.
36. Garske KM, Kar A, Comenho C, Balliu B, Pan DZ, Bhagat YV, Rosenberg G, Koka A, Das SS, Miao Z, et al. Increased body mass index is linked to systemic inflammation through altered chromatin co-accessibility in human preadipocytes. Nat Commun. 2023;14(1):4214.
37. Hildebrandt X, Ibrahim M, Peltzer N. Cell death and inflammation during obesity: "Know my methods, WAT(son)." Cell Death Differ. 2023;30(2):279–92.
38. Ding C, Chan Z, Magkos F. Lean, but not healthy: the "metabolically obese, normal-weight" phenotype. Curr Opin Clin Nutr Metab Care. 2016;19(6):408–17.
39. Iacobini C, Pugliese G, BlasettiFantauzzi C, Federici M, Menini S. Metabolically healthy versus metabolically unhealthy obesity. Metabolism. 2019;92:51–60.
40. Stefan N, Haring HU, Hu FB, Schulze MB. Metabolically healthy obesity: epidemiology, mechanisms, and clinical implications. Lancet Diabetes Endocrinol. 2013;1(2):152–62.
41. Zhou Z, Macpherson J, Gray SR, Gill JMR, Welsh P, Celis-Morales C, Sattar N, Pell JP, Ho FK. Are people with metabolically healthy obesity really healthy? A prospective cohort study of 381,363 UK Biobank participants. Diabetologia. 2021;64(9):1963–72.
42. Bertoli S, Leone A, Krakauer NY, Bedogni G, Vanzulli A, Redaelli VI, De Amicis R, Vignati L, Krakauer JC, Battezzati A. Association of Body Shape Index (ABSI) with cardio-metabolic risk factors: A cross-sectional study of 6081 Caucasian adults. PLoS ONE. 2017;12(9):e0185013.
43. Biolo G, Di Girolamo FG, Breglia A, Chiuc M, Baglio V, Vinci P, Toigo G, Lucchin L, Jurdana M, Praznikar ZJ, et al. Inverse relationship between "a body shape index" (ABSI) and fat-free mass in women and men: Insights into mechanisms of sarcopenic obesity. Clin Nutr. 2015;34(2):323–7.
44. Clark DO, Unroe KT, Xu H, Keith NR, Callahan CM, Tu W. Sex and Race Differences in the Relationship between Obesity and C-Reactive Protein. Ethn Dis. 2016;26(2):197–204.
45. Panagiotakos DB, Pitsavos C, Yannakoulia M, Chrysohoou C, Stefanadis C. The implication of obesity and central fat on markers of chronic inflammation: The ATTICA study. Atherosclerosis. 2005;183(2):308–15.
46. Power ML, Schulkin J. Sex differences in fat storage, fat metabolism, and the health risks from obesity: possible evolutionary origins. Br J Nutr. 2008;99(5):931–40.
47. Vithayathil M, Carter P, Kar S, Mason AM, Burgess S, Larsson SC. Body size and composition and risk of site-specific cancers in the UK Biobank and large international consortia: A mendelian randomisation study. PLoS Med. 2021;18(7):e1003706.
48. Khankari NK, Shu XO, Wen W, Kraft P, Lindstrom S, Peters U, Schildkraut J, Schumacher F, Bofetta P, Risch A, et al. Association between Adult Height and Risk of Colorectal, Lung, and Prostate Cancer: Results from Meta-analyses of Prospective Studies and Mendelian Randomization Analyses. PLoS Med. 2016;13(9):e1002118.
49. Ong JS, An J, Law MH, Whiteman DC, Neale RE, Gharahkhani P, MacGregor S. Height and overall cancer risk and mortality: evidence from a Mendelian randomisation study on 310,000 UK Biobank participants. Br J Cancer. 2018;118(9):1262–7.
50. Research WCRFAIfC: Height and birthweight and the risk of cancer. Continuous Update Project Expert Report 2018. 2018.
51. Stefan N, Haring HU, Hu FB, Schulze MB. Divergent associations of height with cardiometabolic disease and cancer: epidemiology, pathophysiology, and global implications. Lancet Diabetes Endocrinol. 2016;4(5):457–67.
52. Wittenbecher C, Kuxhaus O, Boeing H, Stefan N, Schulze MB. Associations of short stature and components of height with incidence of type 2 diabetes: mediating effects of cardiometabolic risk factors. Diabetologia. 2019;62(12):2211–21.
53. Emerging Risk Factors C. Adult height and the risk of cause-specific death and vascular morbidity in 1 million people: individual participant meta-analysis. Int J Epidemiol. 2012;41(5):1419–33.
54. Paajanen TA, Oksala NK, Kuukasjarvi P, Karhunen PJ. Short stature is associated with coronary heart disease: a systematic review of the literature and a meta-analysis. Eur Heart J. 2010;31(14):1802–9.
55. Nelson CP, Hamby SE, Saleheen D, Hopewell JC, Zeng L, Assimes TL, Kanoni S, Willenborg C, Burgess S, Amouyel P, et al. Genetically determined height and coronary artery disease. N Engl J Med. 2015;372(17):1608–18.
56. Nuesch E, Dale C, Palmer TM, White J, Keating BJ, van Iperen EP, Goel A, Padmanabhan S, Asselbergs FW, Investigators EP-N, et al. Adult height, coronary heart disease and stroke: a multi-locus Mendelian randomization meta-analysis. Int J Epidemiol. 2016;45(6):1927–37.

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

STUDY IV

Nature or nurture: genetic and environmental predictors of adiposity gain in adults

Laia Peruchet-Noray, Niki Dimou, Reynalda Cordova, …,
Catalina Bonet, Heinz Freisling, Robert Carreras-Torres

Under review in eBioMedicine

Title

Nature or nurture: genetic and environmental predictors of adiposity gain in adults

Authors

Laia Peruchet-Noray, MSc[1,2]; Niki Dimou, PhD[1]; Reynalda Cordova, PhD[1,3]; Emma Fontvieille, MSc[1]; Anna Jansana, PhD[1]; Quan Gan, MSc[1]; Marie Breeur, MSc[1]; Hansjörg Baurecht, PhD[4]; Patricia Bohmann, MSc[4]; Julian Konzok, PhD[4]; Michael J. Stein, MSc[4]; Christina C. Dahm, PhD[5]; Nuno Nogueira, PhD[5]; Lene Mellemkjær, PhD[6]; Anne Tjønneland, PhD[6,7]; Rudolf Kaaks, PhD[8]; Verena Katzke, PhD[8]; Elif Inan-Eroglu, PhD[9]; Matthias B. Schulze, PhD[9,10]; Giovanna Masala, MD[11]; Sabina Sieri, PhD[12]; Vittorio Simeon, PhD[13]; Giuseppe Matullo, PhD[14,15]; Esther Molina-Montes, PhD[16,17,18,19]; Pilar Amiano, PhD[17,20,21]; María-Dolores Chirlaque, PhD[17,22]; Alba Gasque, MD[23]; Joshua Atkins, PhD[24]; Karl Smith-Byrne, PhD[24]; Pietro Ferrari, PhD[1]; Vivian Viallon, PhD[1]; Antonio Agudo, PhD[25]; Marc J. Gunter, PhD[1,26]; Catalina Bonet, PhD[25]; Heinz Freisling, PhD[1]*; Robert Carreras-Torres, PhD[27]*

1 International Agency for Research on Cancer (IARC/WHO), Nutrition and Metabolism Branch, 69366 Lyon CEDEX 07, France.

2 Department of Clinical Sciences, Faculty of Medicine, University of Barcelona, Barcelona, Spain.

3 Department of Nutritional Sciences, University of Vienna, Vienna, Austria.

4 Department of Epidemiology and Preventive Medicine, University of Regensburg, Regensburg, Germany.

5 Department of Public Health, Aarhus University, Aarhus, Denmark.

6 Danish Cancer Society Research Center, Copenhagen, Denmark.

7 Department of Public Health, the University of Copenhagen, Copenhagen, Denmark.

8 Division of Cancer Epidemiology, German Cancer Research Center (DKFZ), Heidelberg, Germany.

9 Department of Molecular Epidemiology, German Institute of Human Nutrition Potsdam-Rehbruecke, Nuthetal, Germany.

10 Institute of Nutritional Science, University of Potsdam, Nuthetal, German.

11 Clinical Epidemiology Unit, Institute for cancer research, prevention and clinical network (ISPRO), Florence, Italy.

12 Epidemiology and Prevention Unit, Fondazione IRCCS Istituto Nazionale Dei Tumori Di Milano, Milan, Italy.

13 Department of Mental and Physical Health and Preventive Medicine, University 'Luigi Vanvitelli', Naples, Italy.

14 Department of Medical Sciences, University of Torino, Italy.

15 Genetic Service Unit, Città della Salute e della Scienza di Torino, Italy.

16 Department of Nutrition and Food Science, Campus of Cartuja, University of Granada, Granada, Spain.

17 Centro de Investigación Biomédica en Red de Epidemiología y Salud Pública (CIBERESP), Madrid, Spain.

Under review

18 Instituto de Investigación Biosanitaria ibs.GRANADA, 18012 Granada, Spain.

19 Institute of Nutrition and Food Technology (INYTA) 'José Mataix', Biomedical Research Centre, University of Granada, 18071 Granada, Spain.

20 Ministry of Health of the Basque Government, Sub Directorate for Public Health and Addictions of Gipuzkoa, San Sebastian, Spain.

21 BioGipuzkoa (BioDonostia) Health Research Institute, Epidemiology of Chronic and Communicable Diseases Group, San Sebastián, Spain.

22 Department of Epidemiology, Regional Health Council, IMIB-Arrixaca, Murcia University, Murcia, Spain.

23 Instituto de Salud Pública y Laboral de Navarra, Pamplona, Spain.

24 Cancer Epidemiology Unit, University of Oxford, Oxford, UK.

25 Unit of Nutrition and Cancer, Epidemiology Research Program, Catalan Institute of Oncology (ICO), Bellvitge Biomedical Research Institute (IDIBELL), 08908 L'Hospitalet de Llobregat, Spain.

26 Department of Epidemiology and Biostatistics, School of Public Health, Imperial College London, St Mary's Campus, Norfolk place, London W2 1PG, United Kingdom.

27 Digestive Diseases and Microbiota Group, Girona Biomedical Research Institute (IDIBGI), 17190, Salt, Girona, Spain.

***Correspondence:**

Robert Carreras-Torres. Digestive Diseases and Microbiota Group, Girona Biomedical Research Institute (IDIBGI). **Mail:** rcarreras@idibgi.org

Heinz Freisling. Nutrition and Metabolism Branch. International Agency for Research on Cancer, World Health Organization. **Mail:** freislingh@iarc.who.int

Under review

Abstract

Background Previous prediction models for adiposity gain have not yet achieved sufficient predictive ability for clinical relevance. We investigated whether traditional and genetic factors accurately predict adiposity gain.

Methods A 5-year gain of ≥5% in body mass index (BMI) and waist-to-hip ratio (WHR) from baseline were predicted. Proportional hazards models were fitted in 245,699 participants from the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort to identify robust environmental predictors. Polygenic risk scores (PRS) of 5 proxies of adiposity [BMI, WHR, and three body shape phenotypes (PCs)] were computed using genetic weights from an independent cohort (UK Biobank). Environmental and genetic models were validated in 29,953 EPIC participants.

Findings Environmental models presented a remarkable predictive ability (AUC_{BMI}:0.69, 95% CI:0.68-0.70; AUC_{WHR}:0.75, 95% CI:0.74-0.77). The genetic geographic distribution for WHR and PC1 (overall adiposity) showed higher predisposition in North than South Europe. Predictive ability of PRSs was null (AUC: ~0.52) in mid-late adulthood and did not improve when combined with environmental models. However, PRSs of BMI and PC1 showed some prediction ability for BMI gain in early adulthood (AUC:0.60-0.62; 20 years old).

Interpretation Our study indicates that environmental models to discriminate European individuals at higher risk of adiposity gain can be integrated in standard prevention protocols. PRSs may play a robust role in predicting adiposity gain at early rather than mid-late adulthood suggesting a more important role of genetic factors in this life period.

Funding French National Cancer Institute (INCA_N°2019-176) 1220, German Research Foundation (BA 5459/2-1), Instituto de Salud Carlos III (Miguel Servet Program CP21/00058).

Keywords: Adiposity gain, prediction, polygenic risk scores, environmental factors.

Under review

Research in context

Evidence Before This Study

Previous research has shown that environmental prediction models incorporating socio-demographic and lifestyle factors lack the predictive accuracy necessary for clinical relevance in forecasting adiposity gain. While genetic factors are known to contribute to obesity, their combined predictive ability with environmental factors has not yet been thoroughly evaluated.

Added Value of This Study

This study leverages data from the extensive European Prospective Investigation into Cancer and Nutrition (EPIC) cohort to evaluate both environmental and genetic predictors of adiposity gain. By employing proportional hazards models and polygenic risk scores (PRS) derived from the UK Biobank, we assessed the predictive capabilities of these factors over a 5-year period. Our findings highlight that environmental models alone offer significant predictive ability for BMI and WHR gain. However, the integration of PRSs shows considerable predictive ability specifically for BMI gain in early adulthood, though it remains ineffective in mid-late adulthood.

Implications of All the Available Evidence

Our study underscores the importance of integrating robust environmental models into standard adiposity prevention protocols, as these models can effectively identify individuals at higher risk of adiposity gain. The limited predictive ability of PRSs in mid-late adulthood suggests that genetic factors may play a more crucial role in early adulthood. These insights emphasize the need for age-specific approaches in using genetic data for predicting adiposity, paving the way for more tailored prevention strategies across different life stages. This research supports the potential for personalized prevention programs that account for both environmental and genetic factors, enhancing the overall effectiveness of obesity prevention efforts.

Under review

Introduction

Obesity is characterized by excess body fat and is defined as a body mass index (BMI) ≥30 kg/m^2. In the WHO European Region, approximately 23% of adults are living with obesity, and the prevalence is projected to increase to 30% by 2030.[1] Obesity has substantial economic and societal impacts, it is a major determinant of disability, and 22% of preventable deaths result from a high BMI in the European region.[1]

Among the main drivers of obesity are environmental factors that favour a positive energy balance and weight gain;[2] however, individual predisposition to obesity also has a heritable and genetic basis.[3,4] Genome-wide association studies (GWAS) identified thousands of genetic loci associated with obesity-related anthropometric traits,[3,4] including body shape phenotypes.[5] A single genetic locus has a minimal impact on complex traits; however, the cumulative genetic risk can be substantial.[6] Polygenic risk scores (PRS) have been progressively investigated to predict individuals at higher risk of a particular condition.[7–11] In addition, PRS have also been used to assess the genetic contribution to the European regional differences in anthropometric traits.[12] Recently developed Bayesian approaches for building PRS allow modelling linkage disequilibrium (LD) between genetic variants to generate genome-wide infinitesimal models that outperform the traditional approach of pruning by LD followed by P value threshold.[13] Thus, Bayesian-based PRS on anthropometric traits could improve the predictive ability beyond environmental models.

Several attempts to identify individuals that are more prone to weight gain have been made in the last years, but with little success or generalizability.[14,15] For instance, Steffen *et al.* developed a predictive score for substantial weight gain (10% or more) over 5 years among European adults from the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort.[14] This model included 13 socio-demographic, dietary, and lifestyle factors that showed a rather low predictive ability. Therefore, discovery of other relevant predictors beyond those previously examined is needed. Whether PRS of obesity could improve prediction of adiposity gain has not been investigated.

In this work, we aimed to develop and validate a prediction model for adiposity gain based on environmental predictors and evaluate the added value of PRS in 275,652 EPIC participants across 8 European countries. We first built environmental models to predict 5-years BMI and WHR gain. Second, we computed Bayesian-based PRSs for anthropometric traits (BMI, WHR, and three distinct body shapes). Third, we fitted the PRSs in 47,014 individuals from UK Biobank and assessed their predictive ability beyond the environmental models.

Under review

Methods

Study population: EPIC Cohort

The EPIC study is a European prospective multicentre cohort that recruited approximately 520,000 men and women between 1992 and 2000.[16,17] Most of the participants were aged between 35 and 65 at baseline and were selected from the general population, with few exceptions (Supplemental text), of Denmark, France, Germany, Greece, Italy, the Netherlands, Norway, Spain, Sweden, and the United Kingdom. Exclusion criteria were based on individuals with cancer, unrealistic anthropometric traits measurements, and from Greece and Norway due to administrative reasons (Fig. S1). Sample was divided into two groups: development (N=245,699) and validation (N=29,953) depending on the availability of genetic data to compare the different prediction models in the same group of individuals. Further details on exclusions and sample sizes are included in Supplemental text and Fig. S1.

Anthropometry and lifestyle factors

At baseline, weight, height, waist, and hip circumference were measured by trained personnel following standard protocols, except France and UK-Oxford, where these traits were self-reported (Supplemental text).[18] At follow-up, anthropometric traits were self-reported, except for UK-Norfolk and NL-Doetinchem, where they were measured. The mean time difference between baseline and follow-up assessments was 7.4 years across study centers, ranging between 3.3 and 11.9 years. Data on self-reported weight at age 20 years was also collected.

At baseline, information on socio-demographic and lifestyle factors, and medical history were collected using questionnaires.[17] Further, participants reported their average food consumption over the past year. Food intake (gram/day) was obtained considering the frequency intake as well as the portion size.

Environmental models

A 5-year gain of ≥5% in BMI and WHR from baseline were predicted. The ≥5% threshold was selected to avoid random anthropometric trait variation and for its clinical importance.[19] A total of 245,699 and 44,190 EPIC participants with repeated measurements of BMI and WHR data, respectively, were used to train the environmental models. Potential predictors were selected among 10 socio-demographic and lifestyle parameters and 30 dietary parameters using a stepwise forward model selection based on the Akaike Information Criterion (AIC). Further details on the 40 potential predictors were included in the Supplemental text. Predictors presenting a beta estimate lower than 0.001 (both sides) were removed to achieve a simpler model with the strongest predictors. A model excluding the predictor country was further assessed to enhance generalizability.

We used Cox proportional hazard regression to estimate the coefficients for the predictors and to account for the time of reaching BMI and WHR gain. An event was defined as a ≥5% gain between baseline and second assessment of BMI or WHR, respectively. Time to event for cases assumed a linear BMI or WHR gain. Non-cases were censored at the end of follow-up.

Under review

Five-year absolute risks were estimated by combining the relative risk estimates from the Cox regression with the baseline survivor function (Supplemental text).[20,21] The predictive ability of all models was evaluated in the validation sample of 29,953 (11% of the whole sample) and 6,456 (13%) EPIC participants for BMI and WHR gain, respectively, through cumulative/dynamic time-dependent AUC at time 5 years.[22–24]

Statistical analyses were performed using *timeROC* package[25] in R 4.2.1 and RStudio.[26,27]

Genome-wide data

Genetic data was available from 29,953 EPIC participants (validation prediction sample) from 20 case-control studies. DNA samples were genotyped through different genotyping platforms. Details on genotype data normalization, genotyping platforms, and sample sizes for each case-control study can be found in Supplemental text and Table S1.

Data on 47,014 individuals from UK Biobank with at least two measurements of BMI and WHR were extracted. UK Biobank is a prospective cohort study with over 500,000 individuals from 22 study centers in England, Scotland, and Wales. Participants between 38 and 73 years old were recruited between 2006 and 2010. Data on anthropometry, lifestyle, health-related indicators, and biological samples were collected.[28] Individuals were genotyped using either a custom Affymetrix UK Biobank Axiom Array chip or a custom Affymetrix UK BiLEVE Axiom Array chip.[28,29]

Genome-wide models

To develop Bayesian-based PRSs, we obtained summary statistics from large GWAS on BMI, WHR, and three body shapes (PC1-3).[3,5] PRSs in EPIC were computed for these 5 proxies of adiposity using the LDPred2-auto computation algorithm.[30] LDpred2-auto is a Bayesian approach, which showed better predictive performance compared to other methods for PRS.[30] LDpred2-auto estimates the regional LD structure using GWAS summary level statistics and a LD reference panel based on 1,444,196 genetic variants from HapMap3 (Supplemental text).[30] PRS were standardized through z-score transformation to enhance interpretability. PC1 characterized overall adiposity. In contrast to previous publications,[5,31,32] the PRS of PC2 was reversed defining short individuals with central adiposity. PC3 described tall individuals with central adiposity. The geographic distribution of PRS across EPIC countries was assessed and compared with the geographic distribution of similar PRS of 396 European participants from the 1000 Genomes Project Phase 3 (UK [N=89], Finland [N=96], Italy [N=107], and Spain [N=104]).[33]

Under review

We assessed the association between PRSs and BMI and WHR gain, separately, using Cox proportional hazard models. These were adjusted for age at baseline, country, sex, first ten genetic PCs, batch, and BMI or WHR at baseline. As sensitivity analyses, we additionally adjusted for alcohol intake, smoking status, education level, menopausal status, hormonal-replacement therapy (HRT) intake, physical activity, Mediterranean diet score[34], and energy intake. Analyses were performed by sex, North and South Europe, and above and below median baseline age (55 years) (Supplemental text). PRSs and Cox proportional hazard models were also derived and fitted in UK Biobank sample to independently estimate the coefficients of the PRSs in relation to BMI and WHR gain.

The predictive ability of the 5 PRSs was validated in EPIC (N=29,953 and 6,456 for BMI and WHR gain, respectively) individually and combined with the environmental models. Specifically, for BMI gain, we combined the environmental model with each of the PRS for BMI and the three body shape phenotypes. Likewise, for WHR gain, we combined the environmental model with the PRS of WHR and PC1-3. Correlations between individuals' scores of the environmental models and the PRSs were further investigated. Lastly, we assessed the predictive ability of PRS of BMI for BMI gain at age 20 years.

Ethics statement

This study complies with the Declaration of Helsinki. EPIC was approved by the Ethics Committee of the International Agency for Research on Cancer (IARC) (ref IEC 14–02), Lyon, France, as well as the local ethics committees of the study centers. All participants provided written informed consent for data collection and storage as well as individual follow-up.

The UK Biobank study was approved by the Northwest Multi-Centre Research Ethics Committee (reference for UK Biobank is 16/NW/0274) and all participants provided written informed consent to participate in the UK Biobank study.

Role of funders

The funders had no role in the study design, data collection, data analysis, interpretation or writing of this report.

Results

The mean age (SD) of the study participants (68% women) at baseline in EPIC was 51 (7.4) years. In UK Biobank, the mean age of the study participants (49% women) at baseline was 55 (7.5) years. Further baseline characteristics are shown in Table S2.

Environmental models

After a median follow-up of 5.3 years (IQR: 4.0 – 9.0) and 8.8 years (IQR: 5.1 – 11.1), 66,360 (27.0%) and 25,429 (57.5%) of the individuals experienced BMI and WHR gain, respectively.

After the selection procedure, BMI and WHR gain models included, respectively, 14 and 10 socio-demographic, lifestyle, and dietary predictors. Both models included sex, country, BMI/WHR at baseline, level of education, smoking status, physical activity, consumption of condiments and sauces, and meat and meat products. The BMI gain model further included age at baseline, alcohol intake, and

Under review

consumption of cake and biscuits, egg and egg products, fish and shellfish, and processed culinary ingredients (NOVA 2) such as table sugar, oils, and salt. The WHR gain model additionally selected consumption of fat and potatoes. Beta estimates of associations of the selected predictors with BMI and WHR gain including and excluding country are presented in Table S3 and Table S4.

The AUC in the validation sample for BMI gain was 0.687 (95% CI:0.679-0.696) (Fig. 1 and Table S5). Estimates were similar in men and women (Table S5) and by BMI category (Table S6). The predictive ability of the model decreased after removing country (AUC:0.642, 95% CI:0.634-0.651). In contrast, the model performed better in southern (AUC:0.774, 95% CI:0.758-0.791) than in northern European regions (AUC:0.649, 95% CI:0.638-0.659) (Table S5). For WHR gain, the AUC was 0.752 (95% CI:0.738-0.766) for the overall population, being similar by sex (Fig. 1 and Table S5). Removing country from the model only marginally affected the predictive ability (AUC:0.741, 95% CI:0.727-0.755).The AUC was higher in southern (AUC:0.766, 95% CI:0.750-0.782) than in northern European regions (AUC:0.719, 95% CI:0.690-0.747) (Table S5).

Polygenic risk scores

The geographic distribution of the PRS for BMI and PC2 (short, high WHR) showed higher mean values in southern than northern European countries (Fig. 2). In contrast, the geographic distribution of PRS for WHR, PC1 (overall adiposity), and PC3 (tall, high WHR) presented higher mean values in northern rather than in southern European countries (Fig. 2). All patterns were consistently replicated in the 1000 Genomes sample (Fig. 2).

After a median follow-up of 5.16 years (IQR:3.58–6.95) and 8.82 years (IQR:5.38–11.18), 6,619 (22.1%) and 3,503 (54.3%) of the individuals experienced BMI and WHR gain, respectively.

All PRSs were positively associated with BMI and WHR gain except PC3 PRS that showed an inverse association with BMI gain (Fig. 3 and Table S7). Associations between PRS of PC2 and PC3 and WHR gain were less robust (Fig. 3 and Table S7). Results were consistent in UK Biobank, by sex, European region, age (threshold at 55 years), and after further adjustments (Fig. 3 and Table S7-S9).

For BMI and WHR gain, PRSs showed null predictive ability (Fig. 1 and Table S10). Similar results were observed by European regions and by sex (Table S10). PRS for BMI and PC1 showed a stronger predictive ability for BMI gain in early adulthood (~20 years old) ($AUC_{PRS\ BMI}$:0.618, 95% CI:0.606-0.631; $AUC_{PRS\ PC1}$:0.601, 95% CI:0.589-0.613) (Table S10). When environmental and PRSs were combined, the predictive ability did not improve for either BMI or WHR gain (Fig. 1 and Table S11). Additionally, individuals' environmental model scores and PRSs were not correlated (Table S12).

Under review

Discussion

In this longitudinal study across eight European countries, we developed and validated environmental prediction models of BMI and WHR gain over a period of 5-years at mid-late adulthood. We combined an environmental prediction model with genetic factors by adding PRSs for BMI, WHR, and 3 body shapes phenotypes. We found that the environmental model achieved a remarkable predictive ability, which could help to risk-stratify middle-aged men and women for adiposity gain. Adding the PRSs for BMI, WHR, or three body shape phenotypes did not improve the predictive ability of the environmental models. In addition to our main findings, we reported differences in the European genetic distribution of these anthropometric traits showing that individuals from northern countries are genetically more susceptible to higher adiposity than from southern European countries when height is not relevant for the trait.

A high-performance adiposity gain prediction model is key to identify individuals at high risk of obesity and, consequently, at high risk of numerous comorbidities and health outcomes. Previous work did not attain sufficient predictive ability (AUC=0.57),[14] or was restricted to a particular country,[15] challenging the evaluation of its transferability across Europe. Our work adds insights in the usefulness of genetics for adiposity gain prediction models, suggests new relevant environmental predictors, and provides a validated model applicable to European individuals. The improvement in adiposity gain prediction in our study (AUC=0.69 vs AUC=0.57) was not due to the addition of a PRS of adiposity related anthropometric traits, but is rather explained by a larger number of candidate predictors (40 vs 21 items) and a larger sample size (245,699 vs 53,758), which may contribute to a more precise characterization of the distinct patterns that lead to adiposity gain, regardless the different dietary patterns across European countries.[35] Main differences between predictors included a more refined characterization of diet and the inclusion of country which improved the predictive ability of the BMI gain model ($AUC_{without\ country}$=0.64). To avoid individuals that experienced normal weight fluctuations[36] being classified as cases and to give a clinical meaning to our analysis[19], we set a threshold of BMI gain at ≥5% than BMI at baseline. Previous studies used a 10% of weight gain threshold (almost two SD of gain phenotypes) which makes the comparison between models less straightforward.[14,15]

WHR, a proxy for body fat distribution, is thought to be superior to BMI in predicting cardiometabolic risk.[37] Accurately predicting WHR gain may therefore also be of importance. Our WHR gain model performed better (AUC=0.75) than a previous model for central adiposity gain (proxied by WC adjusted on BMI) among German individuals (AUC=0.70),[15] however, the improved performance of our model is likely explained by differences in study population and design, but not by adding PRS for WHR gain.

Under review

A recent study concluded that PRSs performed poorly in individual risk prediction after assessing 926 PRSs for 310 diseases.[38] Although our results are in line with this study as we showed that none of the PRSs of adiposity related traits improved the predictive ability of our models, the BMI and PC1 PRSs presented a higher predictive ability for 5-years BMI gain in early adulthood. Therefore, our analysis suggests that the genetic background could have a higher effect on early rather than mid-late adulthood and the PRSs usefulness may be lifetime dependent. This is supported by a twin pairs study which indicated that the role of genetic factors becomes relatively less important with aging, whereas environmental effects become stronger.[39] Whether the joint contribution of environmental and genetic factors improves the prediction of adiposity gain in early adulthood remains as a question mark and should be further investigated.

The PRSs of BMI, WHR, and three body shape phenotypes were also used to investigate the geographic distribution of genetic predisposition to adiposity across European regions. A previous study depicted genetic patterns for height and BMI showing higher predisposition in northern than southern European countries and an inverse trend, respectively. These contradictory patterns were explained by the process of natural selection on genetic variants for height that are also used to predict BMI.[12] Accordingly, our study showed higher genetic predispositions for a higher BMI and higher values of PC2 (short, centrally obese) in southern as compared to northern countries, as height is negatively driving these traits. Our study also reported the distribution of genetically predicted WHR and PC1 which presented higher values in northern than southern countries. The genetic analysis of PC1 identified genetic variants not previously associated with BMI which led to a different genetic characterization of adiposity.[5] Therefore, the genetic components of WHR and PC1 could better characterize adiposity regional differences than the BMI genetic component.

The main strength of this work is that our prediction models were developed and validated in a large sample from diverse European countries, broadly representing European regions. The results of our analysis need to be interpreted with the following limitations. First, although standardized protocols to measure anthropometric traits were applied in the different EPIC centers, some of the measurements were self-reported. However, the accuracy of these anthropometric measures was improved by using prediction equations.[18] Second, time to achieve BMI and WHR gain was estimated assuming linearity through lifetime as only two measurement points in mid-late adulthood were available for this work. Prior research in a subgroup of EPIC participants suggested that weight gain over an 8-year follow-up period can be well approximated linearly at a population level.[40] Finally, although previous research has shown that weight gain may depend on cultural background,[41,42] no information about ethnicity of the study participants was available. To account for it, we used level of education as a proxy of socio-economic position as it has been shown to explain part of the potential weight change differences between ethnicities.[43] Additionally, EPIC participants showing extreme genetic differences have been removed from our study sample.

Under review

Our environmental prediction models for BMI and WHR gain may be useful to discriminate individuals at high risk of adiposity gain within a period of 5 years at mid-late adulthood. While genetic factors were not relevant at this stage of life, better predictive performance of genetic factors has been observed in early adulthood. These findings suggest a more important role of genetics in early-adulthood adiposity gain and highlight the importance of preventing adiposity gain through modifiable environmental factors in mid-late adulthood.

Under review

Data sharing

EPIC data are available for investigators who seek to answer important questions on health and disease in the context of research projects that are consistent with the legal and ethical standard practices of IARC/WHO and the EPIC centres. The primary responsibility for accessing the data belongs to IARC and the EPIC centres. For information on how to submit an application for gaining access to EPIC data and/or biospecimens, please follow the instructions at https://epic.iarc.fr/access/. The UK Biobank resource is available to bona fide researchers for health-related research in the public interest. All researchers who wish to access the research resource must register with UK Biobank by completing the registration form in the Access Management System (AMS-https://bbams.ndph.ox.ac.uk/ams/). The UK Biobank data can be provided by UK Biobank Limited pending scientific review and a completed material transfer agreement.

Summary statistics concerning the anthropometric traits used to derive the PRSs are open access and can be found in https://zenodo.org/records/1251813#.XCLJ7vZKhE4 and in GWAS Catalog (waiting for publication).

Acknowledgements

The authors thank all EPIC participants and staff for their outstanding contribution to the study. UKB is an open access resource. Bona fide researchers can apply to use the UKB dataset by registering and applying at http://ukbiobank.ac.uk/register-apply/. This research has been conducted using the UKB Resource under Application Number 55870 and we express our gratitude to the participants and those involved in building the resource.

Declaration of interests

The authors declare no competing interests.

Contributors

Conceptualisation: R.C.-T., formal analysis: L.P.-N and R.C.-T., funding acquisition: H.B., H.F., and R.C.-T., investigation: L.P.-N and R.C.-T., methodology: L.P.-N and R.C.-T., resources: A.A, H.F., and R.C.-T., supervision: N.D., M.J.G., H.F., and R.C.-T., validation: L.P.-N and R.C.-T., visualisation: L.P.-N and R.C.-T., writing – original draft: L.P.-N and R.C.-T., and writing– review & editing: All authors.

IARC disclaimer

Where authors are identified as personnel of the International Agency for Research on Cancer/World Health Organisation, the authors alone are responsible for the views expressed in this article and they do not necessarily represent the decisions, policy, or views of the International Agency for Research on Cancer/World Health Organisation.

Under review

Funding

This work was supported by the French National Cancer Institute (INCA_N°2019-176) 1220 and the German Research Foundation (BA 5459/2-1). R.C.T. was supported by the Miguel Servet Program CP21/00058, funded by the Instituto de Salud Carlos III and co-funded by the European Union.
The coordination of EPIC-Europe is financially supported by International Agency for Research on Cancer (IARC) and also by the Department of Epidemiology and Biostatistics, School of Public Health, Imperial College London which has additional infrastructure support provided by the NIHR Imperial Biomedical Research Centre (BRC).
The national cohorts are supported by: Danish Cancer Society (Denmark);Ligue Nationale Contre le Cancer, Institut Gustave Roussy, Mutuelle Générale de l'Education Nationale (MGEN), Institut National de la Santé et de la Recherche Médicale (INSERM), French National Research Agency (ANR, reference ANR-10-COHO-0006), French Ministry for Higher Education (subsidy 2102918823, 2103236497, and 2103586016) (France); German Cancer Aid, German Cancer Research Center (DKFZ), German Institute of Human Nutrition Potsdam-Rehbruecke (DIfE), Federal Ministry of Education and Research (BMBF) (Germany); Associazione Italiana per la Ricerca sul Cancro-AIRC-Italy, Italian Ministry of Health, Italian Ministry of University and Research (MUR), Compagnia di San Paolo (Italy); "Europe against Cancer" Programme of the European Commission (DG SANCO); Dutch Ministry of Public Health, Welfare and Sports (VWS), the Netherlands Organisation for Health Research and Development (ZonMW), World Cancer Research Fund (WCRF), (The Netherlands); UiT The Arctic University of Norway; Health Research Fund (FIS) - Instituto de Salud Carlos III (ISCIII), Regional Governments of Andalucía, Asturias, Basque Country, Murcia and Navarra, and the Catalan Institute of Oncology - ICO (Spain); Swedish Cancer Society, Swedish Research Council and County Councils of Skåne and Västerbotten (Sweden); Cancer Research UK (C864/A14136 to EPIC-Norfolk; C8221/A29017 to EPIC-Oxford), Medical Research Council (MR/N003284/1, MC-UU_12015/1 and MC_UU_00006/1 to EPIC-Norfolk; MR/Y013662/1 to EPICOxford) (United Kingdom).

Under review

References

[1] Lobstein T, Brinsden H, Neveux M, Cavalcanti OB, Barquera S, Baur L, et al. World Obesity Atlas 2022. World Obesity Federation 2022 2022:289.

[2] World Health Organization. Fact Sheet: Obesity and overweight. World Health Organization 2024. https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight (accessed June 3, 2024).

[3] Pulit SL, Stoneman C, Morris AP, Wood AR, Glastonbury CA, Tyrrell J, et al. Meta-Analysis of genome-wide association studies for body fat distribution in 694 649 individuals of European ancestry. Hum Mol Genet 2019;28. https://doi.org/10.1093/hmg/ddy327.

[4] Locke AE, Kahali B, Berndt SI, Justice AE, Pers TH, Day FR, et al. Genetic studies of body mass index yield new insights for obesity biology. Nature 2015;518. https://doi.org/10.1038/nature14177.

[5] Peruchet-Noray L, Sedlmeier AM, Dimou N, Baurecht H, Fervers B, Fontvieille E, et al. Tissue-specific genetic variation suggests distinct molecular pathways between body shape phenotypes and colorectal cancer. Sci Adv 2024;10:eadj1987. https://doi.org/10.1126/sciadv.adj1987.

[6] Timpson NJ, Greenwood CMT, Soranzo N, Lawson DJ, Richards JB. Genetic architecture: The shape of the genetic contribution to human traits and disease. Nat Rev Genet 2018;19. https://doi.org/10.1038/nrg.2017.101.

[7] Mars N, Koskela JT, Ripatti P, Kiiskinen TTJ, Havulinna AS, Lindbohm J V., et al. Polygenic and clinical risk scores and their impact on age at onset and prediction of cardiometabolic diseases and common cancers. Nat Med 2020;26. https://doi.org/10.1038/s41591-020-0800-0.

[8] Abraham G, Havulinna AS, Bhalala OG, Byars SG, De Livera AM, Yetukuri L, et al. Genomic prediction of coronary heart disease. Eur Heart J 2016;37. https://doi.org/10.1093/eurheartj/ehw450.

[9] Khera A V., Chaffin M, Aragam KG, Haas ME, Roselli C, Choi SH, et al. Genome-wide polygenic scores for common diseases identify individuals with risk equivalent to monogenic mutations. Nat Genet 2018;50. https://doi.org/10.1038/s41588-018-0183-z.

[10] Mavaddat N, Michailidou K, Dennis J, Lush M, Fachal L, Lee A, et al. Polygenic Risk Scores for Prediction of Breast Cancer and Breast Cancer Subtypes. Am J Hum Genet 2019;104. https://doi.org/10.1016/j.ajhg.2018.11.002.

[11] Seibert TM, Fan CC, Wang Y, Zuber V, Karunamuni R, Parsons JK, et al. Polygenic hazard score to guide screening for aggressive prostate cancer: Development and validation in large scale cohorts. BMJ (Online) 2018;360. https://doi.org/10.1136/bmj.j5757.

[12] Robinson MR, Hemani G, Medina-Gomez C, Mezzavilla M, Esko T, Shakhbazov K, et al. Population genetic differentiation of height and body mass index across Europe. Nat Genet 2015;47. https://doi.org/10.1038/ng.3401.

[13] Vilhjálmsson BJ, Yang J, Finucane HK, Gusev A, Lindström S, Ripke S, et al. Modeling Linkage Disequilibrium Increases Accuracy of Polygenic Risk Scores. Am J Hum Genet 2015;97. https://doi.org/10.1016/j.ajhg.2015.09.001.

Under review

[14] Steffen A, Sørensen TIA, Knüppel S, Travier N, Sánchez MJ, Huerta JM, et al. Development and Validation of a Risk Score Predicting Substantial Weight Gain over 5 Years in Middle-Aged European Men and Women. PLoS One 2013;8. https://doi.org/10.1371/journal.pone.0067429.

[15] Bachlechner U, Boeing H, Haftenberger M, Schienkiewitz A, Scheidt-Nave C, Vogt S, et al. Predicting risk of substantial weight gain in German adults-A multi-center cohort approach. Eur J Public Health 2017;27. https://doi.org/10.1093/eurpub/ckw216.

[16] Riboli E. The EPIC Project: rationale and study design. European Prospective Investigation into Cancer and Nutrition. Int J Epidemiol 1997;26. https://doi.org/10.1093/ije/26.suppl_1.s6.

[17] Riboli E, Hunt K, Slimani N, Ferrari P, Norat T, Fahey M, et al. European Prospective Investigation into Cancer and Nutrition (EPIC): study populations and data collection. Public Health Nutr 2002;5. https://doi.org/10.1079/phn2002394.

[18] Haftenberger M, Lahmann P, Panico S, Gonzalez C, Seidell J, Boeing H, et al. Overweight, obesity and fat distribution in 50- to 64-year-old participants in the European Prospective Investigation into Cancer and Nutrition (EPIC). Public Health Nutr 2002;5. https://doi.org/10.1079/phn2002396.

[19] Stevens J, Truesdale KP, McClain JE, Cai J. The definition of weight maintenance. Int J Obes 2006;30. https://doi.org/10.1038/sj.ijo.0803175.

[20] Sullivan LM, Massaro JM, D'Agostino RB. Presentation of multivariate data for clinical use: The Framingham Study risk score functions. Stat Med 2004;23. https://doi.org/10.1002/sim.1742.

[21] McLernon DJ, Giardiello D, Van Calster B, Wynants L, van Geloven N, van Smeden M, et al. Assessing Performance and Clinical Usefulness in Prediction Models with Survival Outcomes: Practical Guidance for Cox Proportional Hazards Models. Ann Intern Med 2023;176. https://doi.org/10.7326/M22-0844.

[22] Uno H, Cai T, Tian L, Wei LJ. Evaluating prediction rules for t-year survivors with censored regression models. J Am Stat Assoc 2007;102. https://doi.org/10.1198/016214507000000149.

[23] Hung H, Chiang CT. Optimal Composite Markers for Time-Dependent Receiver Operating Characteristic Curves with Censored Survival Data. Scandinavian Journal of Statistics 2010;37. https://doi.org/10.1111/j.1467-9469.2009.00683.x.

[24] Kamarudin AN, Cox T, Kolamunnage-Dona R. Time-dependent ROC curve analysis in medical research: Current methods and applications. BMC Med Res Methodol 2017;17. https://doi.org/10.1186/s12874-017-0332-6.

[25] Blanche P, Dartigues JF, Jacqmin-Gadda H. Estimating and comparing time-dependent areas under receiver operating characteristic curves for censored event times with competing risks. Stat Med 2013;32. https://doi.org/10.1002/sim.5958.

[26] Team RC. R: A language and environment for statistical computing v. 3.6. 1 (R Foundation for Statistical Computing, Vienna, Austria, 2019). Sci Rep 2021;11.

[27] RStudio Team. RStudio: Integrated Development Environment for R. RStudio, PBC, Boston, MA URL http://www.rstudio.com/. (2022). n.d.

Under review

[28] Sudlow C, Gallacher J, Allen N, Beral V, Burton P, Danesh J, et al. UK Biobank: An Open Access Resource for Identifying the Causes of a Wide Range of Complex Diseases of Middle and Old Age. PLoS Med 2015;12. https://doi.org/10.1371/journal.pmed.1001779.

[29] Bycroft C, Freeman C, Petkova D, Band G, Elliott LT, Sharp K, et al. The UK Biobank resource with deep phenotyping and genomic data. Nature 2018;562. https://doi.org/10.1038/s41586-018-0579-z.

[30] Privé F, Albiñana C, Arbel J, Pasaniuc B, Vilhjálmsson BJ. Inferring disease architecture and predictive ability with LDpred2-auto. The American Journal of Human Genetics 2023;110:2042–55. https://doi.org/https://doi.org/10.1016/j.ajhg.2023.10.010.

[31] Ried JS, Jeff JM, Chu AY, Bragg-Gresham JL, Van Dongen J, Huffman JE, et al. A principal component meta-analysis on multiple anthropometric traits identifies novel loci for body shape. Nat Commun 2016;7. https://doi.org/10.1038/ncomms13357.

[32] Sedlmeier AM, Viallon V, Ferrari P, Peruchet-Noray L, Fontvieille E, Amadou A, et al. Body shape phenotypes of multiple anthropometric traits and cancer risk: a multi-national cohort study. Br J Cancer 2022. https://doi.org/10.1038/s41416-022-02071-3.

[33] Auton A, Abecasis GR, Altshuler DM, Durbin RM, Bentley DR, Chakravarti A, et al. A global reference for human genetic variation. Nature 2015;526. https://doi.org/10.1038/nature15393.

[34] Romaguera D, Norat T, Vergnaud AC, Mouw T, May AM, Agudo A, et al. Mediterranean dietary patterns and prospective weight change in participants of the EPIC-PANACEA project. American Journal of Clinical Nutrition 2010;92. https://doi.org/10.3945/ajcn.2010.29482.

[35] Slimani N, Fahey M, Welch A, Wirfält E, Stripp C, Bergström E, et al. Diversity of dietary patterns observed in the European Prospective Investigation into Cancer and Nutrition (EPIC) project. Public Health Nutr 2002;5. https://doi.org/10.1079/phn2002407.

[36] Orsama AL, Mattila E, Ermes M, Van Gils M, Wansink B, Korhonen I. Weight rhythms: Weight increases during weekends and decreases during weekdays. Obes Facts 2014;7. https://doi.org/10.1159/000356147.

[37] Stefan N, Schulze MB. Metabolic health and cardiometabolic risk clusters: implications for prediction, prevention, and treatment. Lancet Diabetes Endocrinol 2023;11. https://doi.org/10.1016/S2213-8587(23)00086-4.

[38] Hingorani AD, Gratton J, Finan C, Schmidt AF, Patel R, Sofat R, et al. Performance of polygenic risk scores in screening, prediction, and risk stratification: secondary analysis of data in the Polygenic Score Catalog. BMJ Medicine 2023;2:e000554. https://doi.org/10.1136/bmjmed-2023-000554.

[39] Silventoinen K, Jelenkovic A, Sund R, Yokoyama Y, Hur YM, Cozen W, et al. Differences in genetic and environmental variation in adult BMI by sex, age, time period, and region: An individual-based pooled analysis of 40 twin cohorts. American Journal of Clinical Nutrition 2017;106. https://doi.org/10.3945/ajcn.117.153643.

[40] von Ruesten A, Steffen A, Floegel A, van der A DL, Masala G, Tjønneland A, et al. Trend in obesity prevalence in European adult cohort populations during follow-up since 1996 and their predictions to 2015. PLoS One 2011;6. https://doi.org/10.1371/journal.pone.0027455.

Under review

[41] Burke GL, Bild DE, Hilner JE, Folsom AR, Wagenknecht LE, Sidney S. Differences in weight gain in relation to race, gender, age and education in young adults: the CARDIA Study. Coronary Artery Risk Development in Young Adults. Ethn Health 1996;1.

[42] Tan MM, Bush T, Lovejoy JC, Javitz H, Torres AJ, Wassum K, et al. Race differences in predictors of weight gain among a community sample of smokers enrolled in a randomized controlled trial of a multiple behavior change intervention. Prev Med Rep 2021;21. https://doi.org/10.1016/j.pmedr.2020.101303.

[43] Chor D, Faerstein E, Kaplan GA, Lynch JW, Lopes CS. Association of weight change with ethnicity and life course socioeconomic position among Brazilian civil servants. Int J Epidemiol 2004;33. https://doi.org/10.1093/ije/dyg277.

Under review

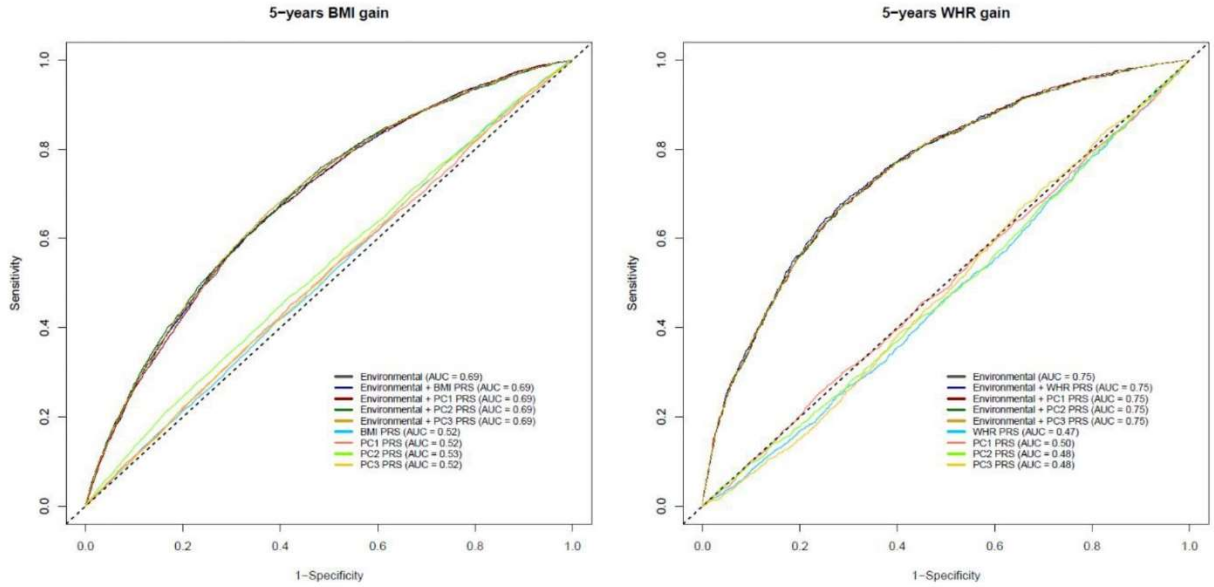


Fig. 1. Time-dependent Area Under the Curve (AUC) for the prediction of BMI and WHR gain in a period of 5 years for the environmental model, PRS of BMI, WHR, and body shape phenotypes (PC1-3), and environmental and PRS models combined. Environmental models for BMI and WHR gain were developed in 245,699 and 44,190 individuals, respectively. All models were validated in 29,953 for BMI gain and 6,456 for WHR gain. BMI, body mass index; PC, principal component; PRS, polygenic risk score; WHR, waist-to-hip ratio.

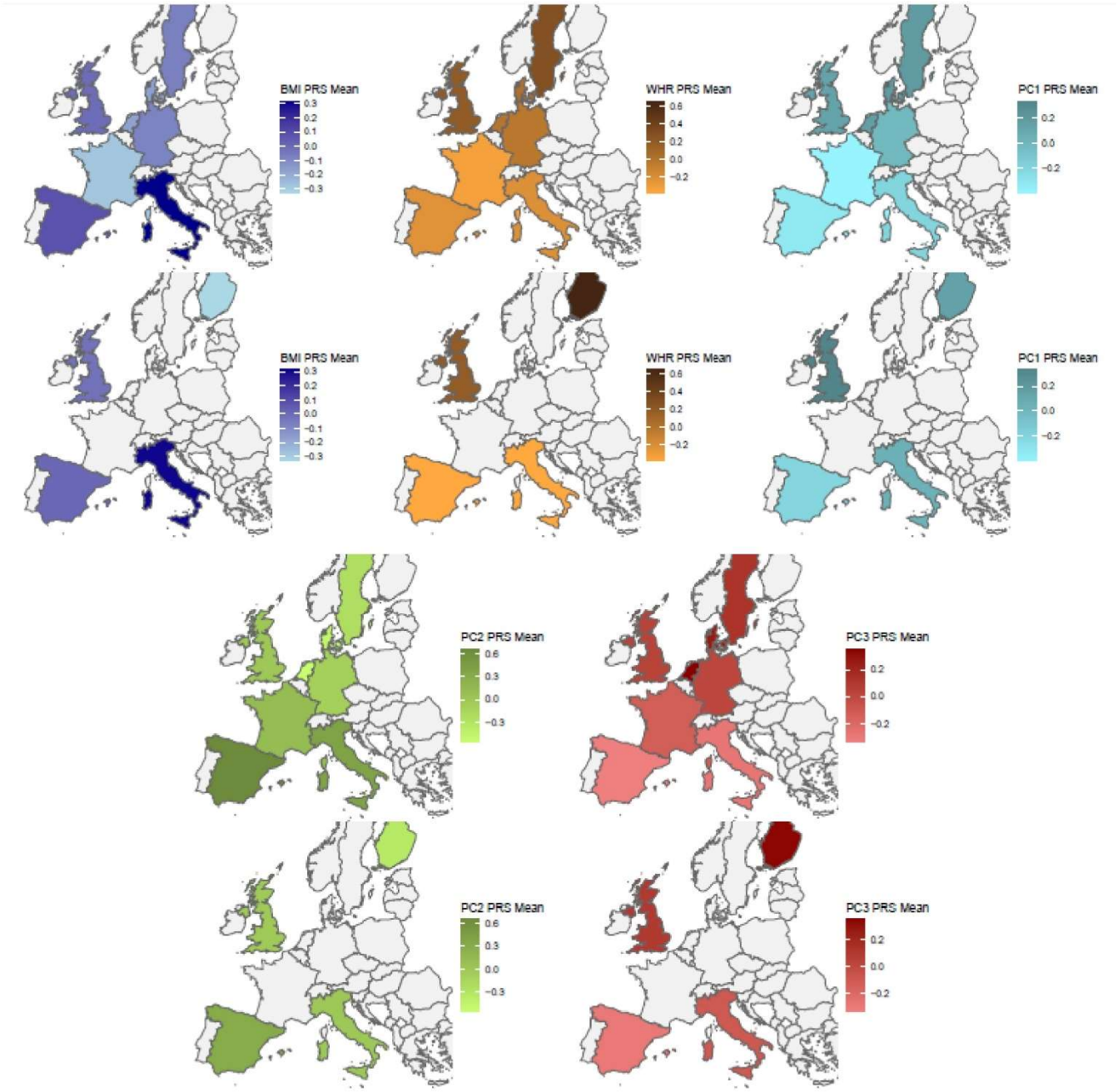


Fig. 2. Genetic predisposition by European country to BMI (dark blue), WHR (orange), PC1 (light blue), PC2 (green), and PC3 (red) in the EPIC cohort (top) and 1000 Genomes Project (bottom). PRS were developed in 29,953 and 396 EPIC and 1000 Genomes Project individuals, respectively. BMI, body mass index; PC, principal component; PRS, polygenic risk score; WHR, waist-to-hip ratio.

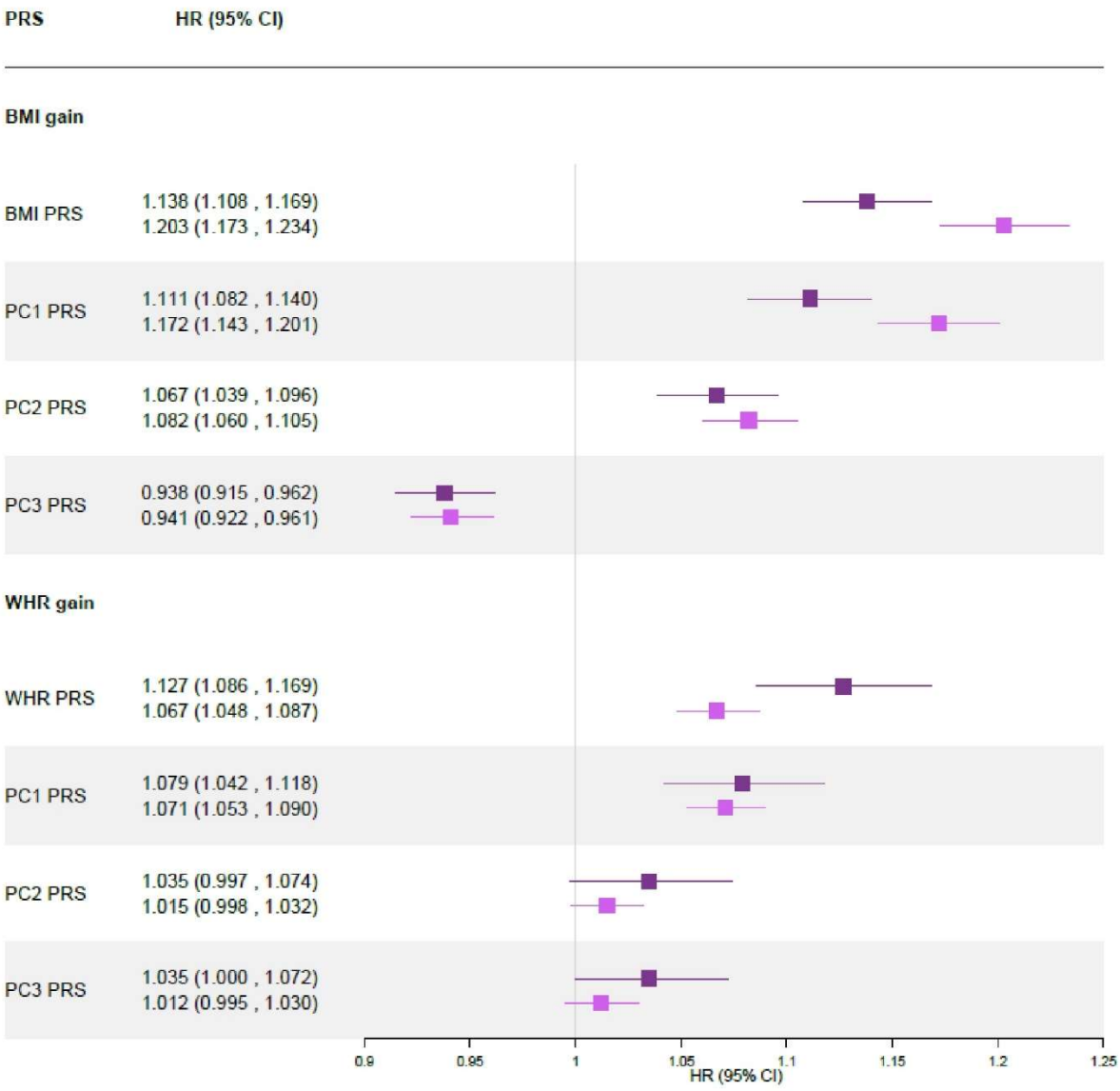


Fig. 3. Associations between the polygenic risk scores of BMI, WHR, and body shape phenotypes (PC1 – 3) and BMI and WHR gain in EPIC (dark purple) and UK Biobank (light purple). Associations were performed in 29,953 for BMI gain and 6,456 for WHR gain. BMI, body mass index; CI, confidence interval; HR, hazard ratio; PC, principal component; PRS, polygenic risk score; WHR, waist-to-hip ratio.

DISCUSSION

This thesis aimed to improve our understanding of the heterogeneous pathways via which adiposity modulates cancer outcome and inflammatory biomarkers through novel and holistic indicators, i.e., data-driven body shape phenotypes. These subtypes of adiposity may effectively complement traditional indicators like BMI. In this thesis, diverse methodological approaches and study designs were deployed (prospective cohort analysis, GWAS, functional analysis, PRS, prediction models, MR analysis) detailed in the results section. This thesis underscored the importance to embrace more nuanced adiposity indicators as complementary health determinants and provided insights into how variations in body shape phenotypes can influence cancer risk and inflammatory processes. Additionally, adiposity gain prediction models were refined and inform targeted prevention strategies, ultimately contributing to more personalized and effective healthcare interventions. These findings advocate for further studies on the integration of body shape phenotypes into personalized prevention strategies and clinical standard protocols.

1. MAIN FINDINGS AND INTERPRETATION

1.1. The body shape phenotypes

We derived body shape phenotypes through a PCA on BMI, height, HC, WC, weight, and WHR across two of the largest European cohorts: UK Biobank and EPIC. Body shape phenotypes were consistently built (i.e., similar loadings were attributed to the anthropometric variables) in all investigated populations, including different ancestries available in UK Biobank (i.e., Caucasians, Africans, Asians, and Chinese). These results were also comparable to the PCA loadings reported by Ried et al. from the GIANT consortium.[67] Additionally, the variance explained by the single anthropometric traits to the PCs were highly comparable across all these populations. Overall, these results highlight the transportability and robustness of the body shape phenotypes within diverse populations.

To achieve the first aim of this thesis, the biological basis of the body shape phenotypes were investigated particularly in Study I. The updated GWAS on 460,198 UK biobank participants further informed the genetic basis of body shape phenotypes. A total of 3,414 independent genetic variants were associated with four distinct body shape phenotypes, while the 23% of the tagged genetic regions were not previously linked to any of the six anthropometric traits that built the body shape phenotypes. In addition, only 59 genetic variants were shared between body shape phenotypes. Most relevant genes revealed potential implication of these body shape phenotypes and cancer hallmarks such as cell proliferation, DNA replication, and angiogenesis. A vast proportion of the identified variants were found in intronic and intergenic regions, suggesting a regulatory role in gene expression rather than direct involvement in biological processes through an altered protein structure or function.

Importantly, a substantial proportion of phenotype variability for the first two PCs was explained by the independent genetic variants. The PC1 genetic variants represented the 30.9% of the body shape phenotype characterizing overall adiposity variability; while the largest GWAS to date on BMI included ~700,000 individuals and identified close to one thousand genetic regions explaining the 6% of phenotype variability.[265] The highest loading for height was found in PC2 (tall and low WHR), with genetic variants capturing the 34.8% of phenotype variability. Similarly, the identified variants improved the variability explained obtained from the largest GWAS for height which explained 25% of the variability of the phenotype.[265]

In Study IV, PRSs of BMI, WHR, and three body shape phenotypes were derived to investigate the geographic distribution of genetic predisposition to adiposity across European regions. A previous study including 9,416 individuals from 14 European countries depicted genetic patterns for height and BMI and showed higher predisposition for height in northern than southern European countries, but an inverse trend for BMI. These opposite patterns were explained by the process of natural selection on genetic variants for height that are also used to predict BMI.[321] Accordingly, Study IV showed higher genetic predispositions for a higher BMI and higher values of PC2 (which was reverse, indicating short and centrally obese individuals) in southern as compared to northern countries, as height is negatively driving these traits. This study also reported the distribution of genetically predicted WHR and PC1 which presented higher values in northern than southern countries. The genetic analysis of PC1 presented in Study I identified genetic variants not previously associated with BMI which led to a different genetic characterization of adiposity. Therefore, the genetic components of WHR and PC1 could better characterize adiposity regional differences than the BMI genetic component. Overall, this thesis highlighted differences of the genetically predicted adiposity in Europe indicating that individuals from northern countries have a higher genetic predisposition to adiposity than from southern European countries.

A subsequent tissue expression analysis including 54 tissues from the GTEx consortium showed that the GWAS results of PC1 presented gene expression enrichment in tissues with high proportion of neural cells (brain and pituitary gland tissues); while GWAS results of PC2 and PC3 showed gene expression enrichment in tissues with high proportion of mesenchymal cells (nerve, blood vessel, and reproductive tissues of cervix, uterus, and ovary; and PC3 additionally in adipose, breast, and fallopian tube tissues) that describe distinct pathways via different adiposity distribution may be acting.[322]

Overall, these results highlighted the independence and importance of the genetic architectures across body shape phenotypes suggesting that overall and abdominal adiposity needs to be considered as different phenotypes with distinct molecular origin and metabolic consequences.

1.2. Body shape phenotypes and cancer risk

The second aim of this thesis (i.e., to investigate associations between body shape phenotypes and risk of major cancers such as colorectal and breast) was captured in Study I and II. These two cancers were prioritized for several reasons. First, colorectal and breast cancers show high incidences and poor survival rates becoming main public health concerns worldwide. Thus, it is of high importance to understand and investigate underlying risk factors to develop preventive strategies. Second, adiposity is associated with both cancers although some aspects of these associations are yet to be clarified. For instance, it is unclear how subtypes of adiposity are related to colorectal cancer and how they associate with breast cancer given their time-dependent complex relationship (e.g., adiposity is associated differently depending on lifetime). Third, the largest genetic data worldwide are available for overall colorectal and breast cancers (52,775 cases and 45,940 controls for colorectal cancer and 133,384 cases and 113,789 controls for breast cancer) which allows for well-powered genetic analysis, obtaining the most robust evidence possible.

For colorectal cancer, observational and MR analyses were performed to triangulate the results and achieve more solid evidence for causality. PC1 and PC3 were both robustly positively associated with overall colorectal cancer risk, its subsites (colon, distal colon, proximal colon, and rectal cancer), and among men and women. However, no evidence of association was found for PC2 and any of the outcomes included in the analysis.

To our knowledge, only one observational study investigated the associations between body shape phenotypes and colorectal cancer risk with similar results to Study I.[69] Additionally, the Study I results are in line with previous observational and MR analyses showing positive associations between BMI (normally used to assess overall adiposity), WC, and WHR (main trait driving PC3) and colorectal cancer.[183,184,323,324] The estimates between observational and MR analyses reported in Study I were more comparable than between other studies, where MR results showed higher estimates than the observational settings.[183,184,323,324] This could be explained by the specificities of both PC1 and PC3 over BMI and WHR, respectively, that also capture the contribution of other anthropometric traits. Some discrepancies were found in literature among the associations reported by sex.[183,184,323,324] Comparable to PC1, previous observational and MR analyses (using sex-specific genetic instruments for BMI) showed higher estimates among men than women which were in line with Study I.[183,184] However, other MR analyses showed controversial associations: stronger estimates among women than men.[323,324] Regarding PC3, the results from observational and MR analyses in Study I showed less agreement. The observational results found positive associations with both sexes and stronger positive estimates than previous literature using traditional adiposity indicators.[183] Although MR analysis for

WC/WHR and colorectal cancer were scarce, a previous study used sex-specific genetic variants to proxy WHR. Results from this study were in line with the results from Study I as WHR increased the risk of colorectal cancer among women while no association was found among men.[184] MR results from Study I highlighted that body shape phenotypes can assess adiposity-colorectal cancer association in a manner similar to sex-specific traditional adiposity indicators, without the need to construct sex-specific genetic body shape instruments. This allowed for a larger simple size to obtain the information concerning MR instruments, which translates to a more powerful analysis. Additionally, results of Study I suggested that overall adiposity may have different effects on colorectal cancer subsites; while variation was observed among sex for abdominal adiposity (PC3) on overall colorectal cancer. As far as PC2 is concern, results were also interesting. Observational analyses showed a null association between PC2 and colorectal cancer risk, while genetic analyses suggested a weak positive association that was not confirmed by sensitivity analyses. This contradicts previous positive associations between height and colorectal cancer, which may have been overestimated.[158,183,325] This could be explained by the non-adjustment for abdominal adiposity in these previous studies, which is further supported by the results obtained for PC3.

For breast cancer risk assessment, MR analyses were performed between the body shape phenotypes and the risk of overall breast cancer and five molecular subtypes (Luminal A, Luminal B, Luminal B/HER2-, HER2+, and Triple Negative). Results indicated that PC1 was inversely associated with overall breast cancer risk showing similar trends across breast cancer subtypes. Regarding PC2, robust and positive association was only observed with Luminal A subtype of breast cancer. However, positive associations with overall and breast cancer subtypes, other than HER2+, cannot be ruled out. Less conclusive results were obtained from the associations for PC3. Suggestive evidence was found for differences across breast cancer subtypes, indicating an inverse association with HER2+.

The relationship between adiposity (mainly proxied by BMI) and breast cancer has been widely studied although controversial results have been reported. Observational analyses showed positive associations for postmenopausal status and inverse or no associations for premenopausal status.[69,326–329] However, previous MR analyses showed an inverse association between BMI and breast cancer risk, independent of menopausal status.[135,153–156] Potential explanations of the differences between both approaches could be explained by recent findings pointing out that genetic instruments may likely reflect body fatness during early life periods rather than later adulthood resulting in this inverse association regardless the menopausal period of assessment. This was also supported by recent studies suggesting no additional effect of later life BMI once accounting for childhood BMI.[330] Similarly, other studies showed inverse associations between childhood and adolescence BMI and breast cancer risk among pre and postmenopausal women.[331–333] Thus, it is likely that the genetic instrument for PC1

in Study II is capturing adiposity in early stages of life and, therefore, depicting the inverse association with breast cancer risk. Results from Study IV (i.e., adiposity prediction model) also supported the genetic effect differences across lifetime and are further discussed below (see Section 1.4. Preventive strategies for adiposity gain and cancer burden: Prediction). On the other hand, genetic instruments for PC2 (tall individuals with low WHR) and PC3 (tall individuals with high WHR) showed positive, but not significant, associations with breast cancer overall and most of subtypes; except for PC2 and Luminal A subtype which was statistically significant. Height was the anthropometric trait mainly and positively defining PC2 and PC3, and results of Study II of a positive association are slightly weaker compared to previous literature analyzing height.[157,158] In addition, results regarding the relationship between WHR and breast cancer risk are still scarce. However, MR results performed in Study II suggested that WHR would not modify the potential relationship between height and breast cancer risk.[155,334] There may be additional explanations that may help interpret the findings of this thesis. The genetic instruments assessing body shape phenotypes and breast cancer risk were less powerful than the genetic instruments used to assess body shape phenotypes and colorectal cancer risk. The genetic instrument for body shape phenotypes in Study II was derived from the GWAS published by Ried et al.,[67] while the updated GWAS in UK Biobank (Study I) was used for colorectal cancer. The updated GWAS doubled the sample size compared to Ried et al.,[67] used more advanced methodologies (BOLT-LMM vs. PLINK), and found much more genetic variants associated with the body shape phenotypes.

1.3. Molecular pathways between body shape phenotypes and cancer: Inflammation

Potential molecular pathways mechanistically explaining adiposity-cancer associations involve inflammation.[90] The relationship between the body shape phenotypes and inflammatory biomarkers was further investigated in Study III. Additionally, and for comparison, Study III also explored the associations of inflammatory biomarkers with traditional indicators such as BMI, height, HC, WC, weight, and ratios as well as more complex indicators such as ABSI and HI. Regarding inflammatory biomarkers, Study III mainly focused on CRP as it was available in both EPIC and UK Biobank cohorts. Several other inflammatory biomarkers such as ILs, IL1ra, TNF-α, leptin, and adiponectin were also available for a subset of women in EPIC. This study included 17,943 and 426,223 participants from EPIC and UK Biobank and were meta-analysed. Results showed positive associations between PC1 and CRP in both sexes, comparable to other adiposity indicators such as BMI, WC, WHR, and ABSI. Similar patterns of PC1 and traditional adiposity indicators were also observed for positive associations with pro-inflammatory adipokines including IL6, I1ra, TNF-α, and leptin in women. PC2 was comparable to height and showed inverse associations with CRP, IL6, IL1ra, and leptin. Most interestingly, sex-specific associations were found between PC3 and CRP levels that were not comparable to any result from other adiposity indicator. While PC3 was inversely associated with CRP among women, positive

associations were found among men. The differential associations of PC3 with CRP by sex adds valuable phenotypical information beyond traditional adiposity indicators. Additionally, the findings on inflammatory biomarkers with PC2 and PC3 suggested that height mitigates the positive association between adiposity and CRP, especially in women. Differences between sexes may be due to women having a higher proportion of body fat than men, even when they score the same BMI.[335] Thus, it is not surprising that this physiological difference led to variations in CRP levels between sexes. Given that inflammation implicated in colorectal cancer development, Study III may further suggest that the height-colorectal cancer risk may be overestimated and requires further investigation.

Overall, Study III results highlighted the usefulness of body shape phenotypes to capture underlying biological subtilities leading to inflammatory pathways and go beyond traditional adiposity indicators.

1.4. Preventive strategies for adiposity gain and cancer burden: Prediction

Developing strategies to reduce the lifetime exposure of risk factors is crucial for cancer prevention and reduction of cancer burden, in addition to understand the potential molecular pathways that link risk factors such as adiposity and cancer development. One strategy was to build a prediction model to discriminate individuals at higher risk. Thus, this thesis aimed to develop and validate a prediction model for adiposity gain over a 5-year period at mid-late adulthood across eight European countries. Three different models were explored: environmental, genetic (based on PRSs for BMI, WHR, and 3 body shape phenotypes), and a combination of the two. Results showed a remarkable predictive ability for the environmental model that was not improved by the genetic factors. Thus, a model restricted to environmental factors (i.e., socio-demographic, anthropometric, lifestyle, and dietary predictors) proved to be useful and applicable to discriminate European men and women at higher risk of adiposity gain at mid-late adulthood.

The environmental prediction model presented in Study IV overcame previous adiposity gain models in its predictive ability (AUC=0.69 vs. 0.57)[113] and in population scope,[114] which make the model more generalizable across Europe. This improvement is mainly due to the finding of new relevant environmental predictors for adiposity gain such as more diverse food groups and the larger sample that could be included in the analysis. Both allowed to better characterize the patterns responsible of adiposity gain, despite the different dietary patterns across Europe.[336] However, it is important to highlight that the model do not defined cases (i.e., individuals classified as gaining weight) in an identical manner. Previous studies used a threshold of 10%[113,114] of weight gain while a ≥5% of BMI was used in Study IV. Although this threshold was chosen also to avoid individuals that experienced normal weight fluctuations[337] being classified as cases and to give a clinical meaning to this analysis[338], it entangles comparison between models. WHR gain was also assessed as a proxy of adiposity gain

given the relevance of body fat distribution on diseases development. WHR gain model also overcame previous literature in predictive ability (AUC=0.75 vs. 0.70)[114] although previous evidence was scarce, and differences could be attributed to study population and design.

PRSs from different adiposity indicators such as BMI, WHR, and three body shape phenotypes did not improve the prediction ability of environmental models. PRSs for BMI and WHR were selected because of their relevance in primary care, and for the body shape phenotypes because of the rich source of biological information shown in Study I. In line with these results, another study assessed 926 PRSs for 310 diseases and concluded that PRSs performed poorly in individual risk prediction.[339] On the contrary, Study IV results showed that BMI and PC1 PRSs presented higher predictive ability for 5-years BMI gain in early adulthood, highlighting that genetic background could have higher effect in this stage of life rather than mid-late adulthood. Several studies, including the Study II of this thesis, support the fact that genetics effect may be lifetime dependent.[280,339] First, a twin pairs study indicated that the role of genetic factors become relatively less important with aging, whereas environmental effects become stronger.[339] Additionally, a previous study found that a BMI-genetic score was positively and inversely associated with weight gain before and after reaching middle age, respectively.[280] Finally, Study II suggested that body shape PC1 genetic instrument reflected early life overall adiposity. In this thesis, it was not possible to assess the combined effects of environmental and genetic factors in early adulthood given the lack of environmental data in this life period. However, it may be of public health high interest to further assess this potential improved adiposity model, especially given the current increasing trend of obesity in young ages.[4]

2. STRENGTHS AND LIMITATIONS

2.1. Strengths: Data sources

The four studies included in this thesis used large-scale data from UK Biobank and EPIC combined with data from genetic consortia. Study I involved three data sources namely UK Biobank (to derive the body shape phenotypes, their observational associations with colorectal cancer, and perform the GWAS), GTEx (to perform tissue expression enrichment analysis and thus explore the genetic expression by tissues underlying the body shape phenotypes), and the GECCO consortium (to triangulate the observational associations through genetic analyses). Study II used data from the BCAC consortium to study genetic associations between the body shape phenotypes and overall breast cancer risk and subtypes. Study III used both UK biobank and EPIC to investigate the associations between traditional and complex adiposity indicators (including the body shape phenotypes) and CRP levels. The EPIC study was additionally used to indagate the same associations with further inflammatory biomarkers. In Study IV, adiposity gain prediction models were based on 8 European countries in EPIC and combined with PRSs trained in UK Biobank and tested in EPIC.

Using large datasets in epidemiological studies is crucial for several reasons. First, large datasets enhance the statistical power of a study to discover associations, if any. Second, large datasets provide greater generalizability of the findings. Third, large datasets improve the ability to control for confounding variables in observational analysis. In summary, the use of large datasets in epidemiological studies strengthens the study's reliability, generalizability, and depth of analysis, allowing to better understand underlying risk factors.

2.2. Strengths: Triangulation

Triangulation is important in epidemiological studies, significantly enhancing the strength and credibility of research findings. When multiple data sources and methodologies are accounted for that may help mitigate the inherent biases and limitations of any single method, as it provides a more comprehensive and complete view of the question under study. This holistic view is particularly valuable in epidemiology, specifically in adiposity research, given the existing complex interplay of biological, social, and environmental factors.

Triangulation of the evidence was applied in Studies I, III, and IV and indirectly in Study II. Study I used two large independent datasets: UK Biobank for the observational and GWAS analyses, and the colorectal cancer genetic consortia dataset for the MR approach. Additionally, it integrated different methodologies (i.e., observational and MR analysis) to strengthen the evidence of the associations between the body shape phenotypes and colorectal cancer risk. Similarly, Study II performed MR

analysis to triangulate previous observational studies[69] also assessing the association between the body shape phenotypes and breast cancer risk. In Study III, triangulation was applied through multiple datasets (UK Biobank and EPIC) in the associations of adiposity indicators and CRP levels. Finally, associations between PRSs of BMI, WHR, and three body shape phenotypes and BMI/WHR gain were assessed in both EPIC and UK Biobank in Study IV.

2.3. Strengths: Sensitivity analysis

We performed multiple sensitivity analyses to evaluate the influence of residual confounding and reverse causation bias in the observational setting and to assess the potential violation of the MR assumptions. In short, in Study I multiple sensitivity analyses were performed for the observational setting including the exclusion of the current and former smokers to address potential residual confounding by smoking, the two initial years of follow-up to control for reverse causation, and additionally fitted a crude model that included all the body shape phenotypes to understand the degree of confounding. For the MR analyses in Study I and II, sensitivity analyses included methodologies to check the potential violation of the second (i.e., the genetic variants are not associated with any potential confounder) and third (i.e., the genetic variants are associated with the outcome only through the exposure) MR assumptions.[252] The Cochran's Q test was employed to evaluate heterogeneity among causal effects derived from each of the selected variants.[340] MR-Egger regression was also implemented providing a statistical test for directional pleiotropy (intercept term different from zero).[257] The weighted median approach was performed as it allows for the violations of the second and the third assumptions when up 50% of the genetic variants are invalid (i.e., violation of one or more MR assumptions).[258,341] Both tests provide valid MR estimates in the presence of directional pleiotropy but suffer from reduced power.[257,342] Scatter plots depicted the genetic associations between body shape phenotypes and breast and colorectal cancer risk to visually examine the consistency of MR estimates and the potential associated bias. Although these were the main sensitivity analyses performed for the MR approaches, Study II also included searching in PhenoScanner[343,344] (available at http://www.phenoscanner.medschl.cam.ac.uk) and the GWAS catalog[255,256] (available at https://www.ebi.ac.uk/gwas/) to assess whether the genetic variants selected as genetic instruments were associated with other traits in previous GWASs,[252,255,343] examining funnel plots to detect potential bias, using leave-one genetic variant-out analysis to assess whether any association was driven by specific genetic variants, and performing MR-PRESSO method to identify and remove any outlying variants.[259] This last method regresses genetic variant-outcome on genetic variant-exposure and uses square of residuals to identify outliers. Finally, sensitivity analyses in Study III included further adjustment for menopausal status (pre or postmenopausal), use of menopausal hormonal treatment, and stratification by menopausal status among women as well as

exclusion of participants with cardiovascular diseases (myocardial infarction, stroke, or hypertension), and those with diabetes at baseline. Further sensitivity analysis included adjusting by ethnicity (white/mixed/Asian/black/ other/prefer not to answer) to account for the potential variation across ethnic groups, associations between obesity categories [Obesity class I (BMI 30 to <35 kg/m^2), obesity class II (BMI 35 to <40 kg/m^2), and Obesity class III (BMI ≥40 kg/m^2)], and analyses without adjusting for age, variable already included in the construction of the PCs.

Overall, the huge amount of sensitivity analyses performed across the studies included in this thesis highlights the high quality and robustness of the study designs and results.

2.4. Limitations: Body shape phenotypes assessment

This thesis showed that body shape phenotypes are of interest for adiposity subtypes measurement and further characterization. However, their interpretation is still not straightforward. Future studies should focus on categorizing the body shape phenotypes depending on their health risk, similarly to the BMI categories, to enhance interpretation and applicability in primary care.

Additionally, body shape phenotypes were derived in all cohorts based on one-point-in-time assessment that may not fully capture all the behaviour and changes of the six anthropometric traits that built the PCs over the life course. Also, it was not assessed how a cumulative high body shape exposure would refine the associations with cancer risk and inflammation.

2.5. Limitations: Methodology and study design

Although observational analyses were adjusted for major confounders, it is likely that results are slightly biased by unmeasured confounding. Addressing unmeasured confounding typically requires careful study design, such as randomization in RCTs, that attempt to account for these hidden variables. However, it remains a persistent issue, particularly in observational studies where not all relevant factors can be measured or controlled, complicating the interpretation of results and the determination of causality. This limitation has been addressed through triangulation using other methodologies (i.e., MR) that are less affected by this disadvantage. MR results should also be interpreted with their own limitations. First, the MR studies can slightly be biased because of uncontrolled confounding from family effects such as assortative mating, dynastic effects, and population structure.[345] Assortative mating, where individuals select partners with similar traits, can lead to increased genetic similarity within families, potentially biasing MR results by amplifying the genetic associations with traits or diseases. Dynastic effects, which involve the interplay of genetic inheritance and shared family environments across generations, can confound MR studies by making it difficult to disentangle genetic effects from environmental influences. Population structure, the

presence of subgroups within a population with distinct genetic backgrounds, can also introduce bias in MR by creating spurious associations if these subgroups are not properly accounted for. This bias was minimized by performing two-sample MR analyses in samples composed of European ancestry individuals although this may cause findings not to be generalizable to other ethnic groups (see 2.6. Limitations: Ancestry diversity).

Relevant for Study IV, time to achieve BMI and WHR gain was estimated assuming linearity through lifetime as only two measurement points in mid-late adulthood were available in EPIC. However, prior research in a subgroup of EPIC participants suggested that weight gain over an 8-year follow-up period can be well approximated linearly at a population level.[346]

2.6. Limitations: Ancestry diversity

Although the data used to perform the studies included in this thesis were large, most of the analyses performed were adjusted for ethnicity (observational analyses) or restricted to Caucasians (genetic analyses) to ensure plausibility of the results (e.g., minimizing bias from population stratification). Ancestry diversity is crucial in epidemiological association studies because it ensures that research findings are generalizable and relevant across different populations. Genetic variants and environmental exposures can vary significantly between populations, meaning that studies limited to a single ancestry group may miss critical associations or produce results that are not applicable to other groups. Moreover, embracing diversity in research supports the development of more inclusive and equitable healthcare interventions, particularly in the context of precision medicine, and helps to address health disparities by ensuring that all populations benefit from scientific advancements.

In this work, body shape phenotypes were calculated across different ancestries highlighting their transferability and comparability. However, not enough sample size of individuals from non-European ancestry was available for genetic analyses (i.e., GWAS, PRS, and MR) and no information on the ethnicity was collected at baseline in EPIC.

3. IMPLICATIONS, PUBLIC HEALTH MESSAGES, AND FUTURE DIRECTIONS

Body shape phenotypes showed to be a complementary and useful approach to characterize subtypes of adiposity providing more and subtle biological information than traditional indicators, as well as improving the identification and characterization of individuals with obesity. Additionally, body shape phenotypes were shown to be robust across different populations and sex which enhance their applicability. However, further research is needed to reduce the complexity on the interpretation of body shape phenotypes before their potential implementation in standard health protocols. Thus, it is important to stress that body shape phenotypes do not aim to replace traditional adiposity indicators rather to become a useful complement. Future studies should investigate their association with other diseases to assess their relevance as well as to identify high-risk categories of each body shape values to facilitate their clinical interpretation.

We provided strong evidence of the association between body shape phenotypes and risk of breast, colorectal, and inflammatory biomarkers status. However, mechanistic studies are needed to further understand the potential molecular pathways underlying these associations as well as mediation analyses to determine in which proportion the association between the body shape phenotypes and cancer undergoes through inflammation.

Although PRSs did not improve the prediction capacity of adiposity gain in adulthood, they showed to be associated with adiposity gain in early adulthood. PRSs can be used as risk stratification tools giving information of an individual's genetic predisposition to a certain disease. For obesity, which presents a complex relationship between genetics and environmental factors where lifetime is important, the knowledge of the genetic background could lead to stronger changes in individuals' lifestyle choices (e.g., physical activity, diet, smoking…) to balance the genetic predisposition to an obese status. However, this thesis provided evidence that genetics is not playing a vital role in adiposity gain, certainly not in middle to late adulthood. This strongly highlights the importance of continuing campaigning for a healthy lifestyle in both individual and global perspective. Additionally, the prediction model showed high prediction ability to discriminate individuals at high risk of adiposity gain and could be applied in clinical practice. Future work should attempt to refine this model finding new and relevant risk factors for adiposity gain such as circadian rhythms, microbiota, and blood biomarkers.

Overall, this work highlights the importance of investigating new adiposity indicators to prevent obesity and reduce cancer burden.

CONCLUSIONS

From the research conducted during this thesis we can conclude the following:

1. Body shape phenotypes were consistently derived in independent large cohorts showing their robustness across different populations.

2. Four distinct body shape phenotypes were associated with 3,414 independent genetic variants. Of these, 570 variants were not previously associated with any of the six single anthropometric traits that built the body shape phenotypes. Additionally, a very few of the genetic variants (59) were shared among them. This highlighted the independence within the genetic architectures of the body shape phenotypes.

3. The genetic distribution of adiposity indicated that individuals from northern European countries are genetically more susceptible to higher adiposity than individuals from southern European countries. Also, findings showed that the genetic predisposition to higher WHR and PC1 could better characterize geographical differences in adiposity than the BMI genetic determinants.

4. Genetic bases of body shape phenotypes presented differential enrichment regarding genetic expression patterns, with PC1 basis enriched in tissues with high proportion of neural cells and PC2-4 bases enriched in tissues with high proportion of mesenchymal cells.

5. Both PC1 and PC3 were positively associated with colorectal cancer, its subsites, and among men and women.

6. PC1 was inversely associated with overall breast cancer and subtypes, suggesting that genetic instruments may reflect adiposity during childhood/adolescence rather than during later adulthood.

7 A positive association between tall individuals with low WHR (PC2) and breast cancer was found although was only robust for breast cancer Luminal A subtype.

8 Positive associations between adiposity indicators and pro-inflammatory biomarkers were found and confirmed the role of adiposity in low-grade inflammation.

9 PC2 and PC3 were inversely associated with pro-inflammatory biomarkers in women suggesting that height could mitigate the impact of abdominal adiposity on inflammation.

10 PC3 showed interesting sex-specific associations with CRP being positively associated among men and inversely among women. These differential associations by sex were not captured by other central adiposity indicators emphasizing the usefulness of the body shape phenotypes.

11 An environmental model for adiposity gain was developed and validated, and it may be useful to discriminate individuals at high risk of adiposity gain within a period of 5 years at mid-late adulthood.

12 Genetic factors did not contribute to adiposity gain prediction at mid-late adulthood. However, better predictive performance of genetic factors was observed in early adulthood.

REFERENCES

1 Bays, H. E. *et al.* Obesity, adiposity, and dyslipidemia: A consensus statement from the National Lipid Association. *J Clin Lipidol* **7**, (2013).

2 Bray, G. A., Kim, K. K. & Wilding, J. P. H. Obesity: a chronic relapsing progressive disease process. A position statement of the World Obesity Federation. *Obesity Reviews* **18**, (2017).

3 Lobstein, T. *et al. World Obesity Atlas 2022*. *World Obesity Federation 2022* (2022).

4 Copenhagen: WHO Regional Office for Europe. *WHO European Regional Obesity Report 2022* (2022).

5 Nutrition and Food Safety (NFS). *The Double Burden of Malnutrition: Policy Briefing*. *World Health Organization* (2017).

6 Phelps, N. H. *et al.* Worldwide trends in underweight and obesity from 1990 to 2022: a pooled analysis of 3663 population-representative studies with 222 million children, adolescents, and adults. *The Lancet* **403**, (2024).

7 Barker, C. & Green, A. Opening the debate on DALYs. *Health Policy Plan* **11**, (1996).

8 World Health Organization. Obesity and overweight factsheet. https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight (2024).

9 Swinburn, B., Egger, G. & Raza, F. Dissecting obesogenic environments: The development and application of a framework for identifying and prioritizing environmental interventions for obesity. *Prev Med (Baltim)* **29**, (1999).

10 Swinburn, B. & Egger, G. Preventive strategies against weight gain and obesity. *Obesity Reviews* **3**, (2002).

11 Stokols, D., Grzywacz, J. G., McMahan, S. & Phillips, K. Increasing the health promotive capacity of human environments. *American Journal of Health Promotion* **18**, (2003).

12 Booth, S. L. *et al.* Environmental and societal factors affect food choice and physical activity: Rationale, influences, and leverage points. *Nutr Rev* **59**, (2001).

13 Lake, A. & Townshend, T. Obesogenic environments: Exploring the built and food environments. *Journal of The Royal Society for the Promotion of Health* **126**, (2006).

14 Popkin, B. M. Nutrition in transition: The changing global nutrition challenge. *Asia Pac J Clin Nutr* **10**, (2001).

15 Ezzati, M. *et al.* Rethinking the 'diseases of affluence' paradigm: Global patterns of nutritional risks in relation to economic development. *PLoS Med* **2**, (2005).

16 Davis, A., Valsecchi, C. & Fergusson, M. *Unfit for Purpose: How Car Use Fuels Climate Change and Obesity. Institute for European Environmental Policy* (2007).

17 Prentice, A. M. & Jebb, S. A. Obesity in Britain: Gluttony or sloth? *BMJ* **311**, (1995).

18 Samaras, K., Kelly, P. J., Chiano, M. N., Spector, T. D. & Campbell, L. V. Genetic and environmental influences on total-body and central abdominal fat: The effect of physical activity in female twins. *Ann Intern Med* **130**, (1999).

19 Chavez-Ugalde, Y. *et al.* Conceptualizing the commercial determinants of dietary behaviors associated with obesity: A systematic review using principles from critical interpretative synthesis. *Obes Sci Pract* **7**, (2021).

20 World Health Organization. The digital food environment factsheet. https://iris.who.int/handle/10665/342072 (2021).

21 Lauber, K., Rutter, H. & Gilmore, A. B. Big food and the World Health Organization: A qualitative study of industry attempts to influence global-level non-communicable disease policy. *BMJ Glob Health* **6**, (2021).

22 Hill, A. J. Developmental issues in attitudes to food and diet. *Proceedings of the Nutrition Society* **61**, (2002).

23 Handy, S. L., Boarnet, M. G., Ewing, R. & Killingsworth, R. E. How the built environment affects physical activity: Views from urban planning. *Am J Prev Med* **23**, (2002).

24 Howard Frumkin, Lawrence Frank & Richard Jackson. *Urban Sprawl and Public Health: Designing, Planning, and Building for Healthy Communities*. (Washington, DC, Island Press, 2004).

25 National Institute of Health. Overweight & Obesity Statistics. *Gastroenterology* **158**, (2021).

26 Apovian, C. M. Obesity: definition, comorbidities, causes, and burden. *Am J Manag Care* **22**, (2016).

27 Hu, F. *Obesity Epidemiology*. (Oxford University Press, 2008).

28 Cornier, M. A. *et al.* Assessing adiposity: A scientific statement from the american heart association. *Circulation* **124**, (2011).

29 Kim, C. H. Measurements of Adiposity and Body Composition. *The Korean Journal of Obesity* **25**, (2016).

30 Nutrition and Food Safety (NFS). *Physical Status: The Use of and Interpretation of Anthropometry, Report of a WHO Expert Committee*. *World Health Organization* (1995).

31 Browning, L. M. *et al.* Measuring abdominal adipose tissue: Comparison of simpler methods with MRI. *Obes Facts* **4**, (2011).

32 Sommer, I. *et al.* The performance of anthropometric tools to determine obesity: a systematic review and meta-analysis. *Sci Rep* **10**, (2020).

33 Gallagher, D. *et al.* How useful is body mass index for comparison of body fatness across age, sex, and ethnic groups? *Am J Epidemiol* **143**, (1996).

34 Ross, R. *et al.* Sex differences in lean and adipose tissue distribution by magnetic resonance imaging: Anthropometric relationships. *American Journal of Clinical Nutrition* **59**, (1994).

35 Forbes, G. B. The adult decline in lean body mass. *Hum Biol* **48**, (1976).

36 Rolland-Cachera, M. F. *et al.* Body mass index variations: Centiles from birth to 87 years. *Eur J Clin Nutr* **45**, (1991).

37 Swinburn, B. A., Craig, P. L., Daniel, R., Dent, D. P. D. & Strauss, B. J. G. Body composition differences between Polynesians and Caucasians assessed by bioelectrical impedance. *Int J Obes* **20**, (1996).

38 Deurenberg, P., Deurenberg-Yap, M. & Guricci, S. Asians are different from Caucasians and from each other in their body mass index/body fat per cent relationship. *Obesity Reviews* **3**, (2002).

39 Rush, E. C. *et al.* BMI, fat and muscle differences in urban women of five ethnicities from two countries. *Int J Obes* **31**, (2007).

40 Aloia, J. F., Vaswani, A., Mikhail, M. & Flaster, E. R. Body composition by dual-energy X-ray absorptiometry in black compared with white women. *Osteoporosis International* **10**, (1999).

41 Fernández, J. R. *et al.* Is percentage body fat differentially related to body mass index in Hispanic Americans, African Americans, and European Americans? *American Journal of Clinical Nutrition* **77**, (2003).

42 Barba, C. *et al.* Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. *The Lancet* **363**, (2004).

43 Stefan, N. & Schulze, M. B. Metabolic health and cardiometabolic risk clusters: implications for prediction, prevention, and treatment. *Lancet Diabetes Endocrinol* **11**, (2023).

44 Lee, C. M. Y., Huxley, R. R., Wildman, R. P. & Woodward, M. Indices of abdominal obesity are better discriminators of cardiovascular risk factors than BMI: a meta-analysis. *J Clin Epidemiol* **61**, (2008).

45 Han, T. S., Richmond, P., Avenell, A. & Lean, M. E. J. Waist circumference reduction and cardiovascular benefits during weight loss in women. *Int J Obes* **21**, (1997).

46 Wang, Y., Rimm, E. B., Stampfer, M. J., Willett, W. C. & Hu, F. B. Comparison of abdominal adiposity and overall obesity in predicting risk of type 2 diabetes among men. *American Journal of Clinical Nutrition* **81**, (2005).

47 Yusuf, S. *et al.* Obesity and the risk of myocardial infarction in 27 000 participants from 52 countries: A case-control study. *Lancet* **366**, (2005).

48 Schneider, H. J. *et al.* Accuracy of anthropometric indicators of obesity to predict cardiovascular risk. *Journal of Clinical Endocrinology and Metabolism* **92**, (2007).

49 Ross, R., Leger, L., Morris, D., De Guise, J. & Guardo, R. Quantification of adipose tissue by MRI: Relationship with anthropometric variables. *J Appl Physiol* **72**, (1992).

50 Pouliot, M. C. *et al.* Waist circumference and abdominal sagittal diameter: Best simple anthropometric indexes of abdominal visceral adipose tissue accumulation and related cardiovascular risk in men and women. *Am J Cardiol* **73**, (1994).

51 Nutrition and Food Safety (NFS). *Waist Circumference and Waist-Hip Ratio: Report of a WHO Expert Consultation*. *World Health Organization* (2011).

52 Ross, R. *et al.* Does the relationship between waist circumference, morbidity and mortality depend on measurement protocol for waist circumference? *Obesity Reviews* **9**, (2008).

53 World Health Organization. STEPwise approach to NCD risk factor surveillance (STEPS). https://www.who.int/teams/noncommunicable-diseases/surveillance/systems-tools/steps (2017).

54 Obesity: preventing and managing the global epidemic. Report of a WHO consultation. *World Health Organ Tech Rep Ser* **894**, (2000).

55 Townsend, N. & Scriven, A. *Public Health Mini-Guides: Obesity*. *Public Health Mini-Guides: Obesity* (Churchill Livingstone, 2014).

56 Harris, E. Study: Waist-to-Hip Ratio Might Predict Mortality Better Than BMI. *JAMA* **330**, (2023).

57 Schneider, H. J. Consider Body Height. *Dtsch Arztebl International* **107**, (2010).

58 Soto González, A. *et al.* Predictors of the metabolic syndrome and correlation with computed axial tomography. *Nutrition* **23**, (2007).

59 Ashwell, M. & Gibson, S. Waist-to-height ratio as an indicator of early health risk: Simpler and more predictive than using a matrix based on BMI and waist circumference. *BMJ Open* **6**, (2016).

60 Ashwell, M. & Hsieh, S. D. Six reasons why the waist-to-height ratio is a rapid and effective global indicator for health risks of obesity and how its use could simplify the international public health message on obesity. *Int J Food Sci Nutr* **56**, (2005).

61 Browning, L. M., Hsieh, S. D. & Ashwell, M. A systematic review of waist-to-height ratio as a screening tool for the prediction of cardiovascular disease and diabetes: 05 could be a suitable global boundary value. *Nutr Res Rev* **23**, (2010).

62 Krakauer, N. Y. & Krakauer, J. C. A new body shape index predicts mortality hazard independently of body mass index. *PLoS One* **7**, (2012).

63 Christakoudi, S. *et al.* A Body Shape Index (ABSI) achieves better mortality risk stratification than alternative indices of abdominal obesity: results from a large European cohort. *Sci Rep* **10**, (2020).

64 Shingleton, A. W. Allometry: The study of biological scaling. *Nature Education* **3**, (2010).

65 Klingenberg, C. P. Size, shape, and form: concepts of allometry in geometric morphometrics. *Dev Genes Evol* **226**, (2016).

66 Krakauer, N. Y. & Krakauer, J. C. An Anthropometric Risk Index Based on Combining Height, Weight, Waist, and Hip Measurements. *J Obes* **2016**, (2016).

67 Ried, J. S. *et al.* A principal component meta-analysis on multiple anthropometric traits identifies novel loci for body shape. *Nat Commun* **7**, (2016).

68 Greenacre, M. *et al.* Principal component analysis. *Nature Reviews Methods Primers* **2**, 100 (2022).

69 Sedlmeier, A. M. *et al.* Body shape phenotypes of multiple anthropometric traits and cancer risk: a multi-national cohort study. *Br J Cancer* **128**, (2023).

70 Ali, A. T., Hochfeld, W. E., Myburgh, R. & Pepper, M. S. Adipocyte and adipogenesis. *Eur J Cell Biol* **92**, (2013).

71 MacDougald, O. A. & Mandrup, S. Adipogenesis: Forces that tip the scales. *Trends in Endocrinology and Metabolism* **13**, (2002).

72 Tam, J. *et al.* Blockade of VEGFR2 and not VEGFR1 can limit diet-induced fat tissue expansion: Role of local versus bone marrow-derived endothelial cells. *PLoS One* **4**, (2009).

73 Fève, B. Adipogenesis: Cellular and molecular aspects. *Best Pract Res Clin Endocrinol Metab* **19**, (2005).

74 Camp, H. S., Ren, D. & Leff, T. Adipogenesis and fat-cell function in obesity and diabetes. *Trends Mol Med* **8**, (2002).

75 Rosen, E. D. & Spiegelman, B. M. Molecular regulation of adipogenesis. *Annu Rev Cell Dev Biol* **16**, (2000).

76 Cinti, S. The adipose organ: morphological perspectives of adipose tissues. *Proceedings of the Nutrition Society* **60**, (2001).

77 Wu, J. *et al.* Beige adipocytes are a distinct type of thermogenic fat cell in mouse and human. *Cell* **150**, (2012).

78 Liu, W. *et al.* A heterogeneous lineage origin underlies the phenotypic and molecular differences of white and beige adipocytes. *J Cell Sci* **126**, (2013).

79 Wang, W. & Seale, P. Control of brown and beige fat development. *Nat Rev Mol Cell Biol* **17**, (2016).

80 Fantuzzi, G. Adipose tissue, adipokines, and inflammation. *Journal of Allergy and Clinical Immunology* **115**, (2005).

81 Frayn, K. N., Karpe, F., Fielding, B. A., Macdonald, I. A. & Coppack, S. W. Integrative physiology of human adipose tissue. *Int J Obes* **27**, (2003).

82 Grant, R. W. & Dixit, V. D. Adipose tissue as an immunological organ. *Obesity* **23**, (2015).

83 Hotamisligil, G. S., Shargill, N. S. & Spiegelman, B. M. Adipose Expression of Tumor Necrosis Factor-α: Direct Role in Obesity-Linked Insulin Resistance. *Science* **259**, (1993).

84 Ouchi, N., Parker, J. L., Lugus, J. J. & Walsh, K. Adipokines in inflammation and metabolic disease. *Nat Rev Immunol* **11**, (2011).

85 Waki, H. & Tontonoz, P. Endocrine functions of adipose tissue. *Annu Rev Pathol* **2**, (2007).

86 Medzhitov, R. Origin and physiological roles of inflammation. *Nature* **454**, (2008).

87 Hotamisligil, G. S. Inflammation and metabolic disorders. *Nature* **444**, (2006).

88 Gregor, M. F. & Hotamisligil, G. S. Inflammatory mechanisms in obesity. *Annu Rev Immunol* **29**, (2011).

89 Bastard, J. P. *et al.* Recent advances in the relationship between obesity, inflammation, and insulin resistance. *Eur Cytokine Netw* **17**, (2006).

90 Renehan, A. G., Zwahlen, M. & Egger, M. Adiposity and cancer risk: New mechanistic insights from epidemiology. *Nat Rev Cancer* **15**, (2015).

91 Straczkowski, M. *et al.* Plasma interleukin-8 concentrations are increased in obese subjects and related to fat mass and tumor necrosis factor-α system. *Journal of Clinical Endocrinology and Metabolism* **87**, (2002).

92 Akdis, M. *et al.* Interleukins, from 1 to 37, and interferon-γ: Receptors, functions, and roles in diseases. *Journal of Allergy and Clinical Immunology* **127**, (2011).

93 Du Clos, T. W. Function of C-reactive protein. *Ann Med* **32**, (2000).

94 Harmancey, R., Wilson, C. R. & Taegtmeyer, H. Adaptation and maladaptation of the heart in obesity. *Hypertension* **52**, (2008).

95 Zhang, Y. *et al.* Positional cloning of the mouse obese gene and its human homologue. *Nature* **372**, (1994).

96 Idriss Haitham T. & Naismith James H. TNFα and the TNF receptor superfamily: Structure-function relationship(s) - Idriss - 2000 - Microscopy Research and Technique - Wiley Online Library. *Microsc Res Tech* **50**, (2000).

97 Zhang, H., Potter, B. J., Cao, J. M. & Zhang, C. Interferon-gamma induced adipose tissue inflammation is linked to endothelial dysfunction in type 2 diabetic mice. *Basic Res Cardiol* **106**, (2011).

98 Curat, C. A. *et al.* From Blood Monocytes to Adipose Tissue-Resident Macrophages: Induction of Diapedesis by Human Mature Adipocytes. *Diabetes* **53**, (2004).

99 Weisberg, S. P. *et al.* Obesity is associated with macrophage accumulation in adipose tissue. *Journal of Clinical Investigation* **112**, (2003).

100 Xu, H. *et al.* Chronic inflammation in fat plays a crucial role in the development of obesity-related insulin resistance. *Journal of Clinical Investigation* **112**, (2003).

101 Visser, M., Bouter, L. M., McQuillan, G. M., Wener, M. H. & Harris, T. B. Elevated C-reactive protein levels in overweight and obese adults. *J Am Med Assoc* **282**, (1999).

102 Festa, A. *et al.* The relation of body fat mass and distribution to markers of chronic inflammation. *Int J Obes* **25**, (2001).

103 Park, H. S., Park, J. Y. & Yu, R. Relationship of obesity and visceral adiposity with serum concentrations of CRP, TNF-α and IL-6. *Diabetes Res Clin Pract* **69**, (2005).

104 Murray, E. T. *et al.* Overweight across the life course and adipokines, inflammatory and endothelial markers at age 60-64 years: Evidence from the 1946 birth cohort. *Int J Obes* **39**, (2015).

105 Eswar, S., Rajagopalan, B., Ete, K. & Nageswara Rao Gattem, S. Serum Tumor Necrosis Factor Alpha (TNF-α) Levels in Obese and Overweight Adults: Correlations With Metabolic Syndrome and Inflammatory Markers. *Cureus* **16**, (2024).

106 Christakoudi, S., Riboli, E., Evangelou, E. & Tsilidis, K. K. Associations of body shape index (ABSI) and hip index with liver, metabolic, and inflammatory biomarkers in the UK Biobank cohort. *Sci Rep* **12**, (2022).

107 Cnop, M. *et al.* Relationship of adiponectin to body fat distribution, insulin sensitivity and plasma lipoproteins: Evidence for independent roles of age and sex. *Diabetologia* **46**, (2003).

108 Weyer, C. *et al.* Hypoadiponectinemia in obesity and type 2 diabetes: Close association with insulin resistance and hyperinsulinemia. *Journal of Clinical Endocrinology and Metabolism* **86**, (2001).

109 Alonzo, T. A. Clinical Prediction Models: A Practical Approach to Development, Validation, and Updating: By Ewout W. Steyerberg. *Am J Epidemiol* **170**, (2009).

110 Han, K., Song, K. & Choi, B. W. How to develop, validate, and compare clinical prediction models involving radiological parameters: Study design and statistical methods. *Korean J Radiol* **17**, (2016).

111 Pepe, M. S., Janes, H., Longton, G., Leisenring, W. & Newcomb, P. Limitations of the odds ratio in gauging the performance of a diagnostic, prognostic, or screening marker. *Am J Epidemiol* **159**, (2004).

112 Florkowski, C. M. Sensitivity, specificity, receiver-operating characteristic (ROC) curves and likelihood ratios: communicating the performance of diagnostic tests. *Clin Biochem Rev* **29 Suppl 1**, (2008).

113 Steffen, A. *et al.* Development and Validation of a Risk Score Predicting Substantial Weight Gain over 5 Years in Middle-Aged European Men and Women. *PLoS One* **8**, (2013).

114 Bachlechner, U. *et al.* Predicting risk of substantial weight gain in German adults-A multi-center cohort approach. *Eur J Public Health* **27**, (2017).

115 World Health Organization. Cancer factsheet. https://www.who.int/news-room/fact-sheets/detail/cancer (2022).

116 National Cancer Institute. What Is Cancer? https://www.cancer.gov/about-cancer/understanding/what-is-cancer (2021).

117 Bray, F. *et al.* Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* **74**, (2024).

118 Ferlay, J. *et al.* Global Cancer Observatory: Cancer Today (version 1.1). *Lyon, France: International Agency for Research on Cancer.* https://gco.iarc.fr/today/ (2024).

119 World Health Organization. International Classification of Diseases, 11th Revision (ICD). https://www.who.int/standards/classifications/classification-of-diseases.

120 World Health Organization. International Classification of Diseases for Oncology, 3rd Edition (ICD-O-3). https://www.who.int/standards/classifications/other-classifications/international-classification-of-diseases-for-oncology.

121 Hanahan, D. & Weinberg, R. A. The hallmarks of cancer. *Cell* **100**, (2000).

122 Hanahan, D. & Weinberg, R. A. Hallmarks of Cancer: The Next Generation. *Cell* **144**, (2011).

123 Hanahan, D. Hallmarks of Cancer: New Dimensions. *Cancer Discov* **12**, (2022).

124 Arnold M, Lam F, Ervik M & Soerjomataram I. Cancer and Obesity: Global burden of cancer attributable to excess weight. *Lyon, France: International Agency for Research on Cancer* http://gco.iarc.fr/obesity (2015).

125 Arnold, M. *et al.* Global burden of cancer attributable to high body-mass index in 2012: A population-based study. *Lancet Oncol* **16**, (2015).

126 Brennan, P. & Davey-Smith, G. Identifying Novel Causes of Cancers to Enhance Cancer Prevention: New Strategies Are Needed. *J Natl Cancer Inst* **114**, (2022).

127 Lauby-Secretan, B. *et al.* Body Fatness and Cancer — Viewpoint of the IARC Working Group. *New England Journal of Medicine* **375**, (2016).

128 World Cancer Research Fund/American Institute for Cancer Research. *Continuous Update Project Expert Report 2018. Diet, Nutrition, Physical Activity and Cancer: A Global Perspective.*

129 Recalde, M. *et al.* Longitudinal body mass index and cancer risk: a cohort study of 2.6 million Catalan adults. *Nat Commun* **14**, (2023).

130 Lawlor, D. A., Tilling, K. & Smith, G. D. Triangulation in aetiological epidemiology. *Int J Epidemiol* **45**, (2016).

131 Porta, M. *A Dictionary of Epidemiology*. (Oxford University Press, 2016).

132 McNamee, R. Confounding and confounders. *Occup Environ Med* **60**, (2003).

133 Smith, G. D. & Ebrahim, S. Epidemiology - Is it time to call it a day? *Int J Epidemiol* **30**, (2001).

134 Fang, Z., Song, M., Lee, D. H. & Giovannucci, E. L. The Role of Mendelian Randomization Studies in Deciphering the Effect of Obesity on Cancer. *JNCI: Journal of the National Cancer Institute* **114**, (2022).

135 Larsson, S. C. & Burgess, S. Causal role of high body mass index in multiple chronic diseases: a systematic review and meta-analysis of Mendelian randomization studies. *BMC Med* **19**, (2021).

136 Calle, E. E. & Kaaks, R. Overweight, obesity and cancer: Epidemiological evidence and proposed mechanisms. *Nat Rev Cancer* **4**, (2004).

137 Khandekar, M. J., Cohen, P. & Spiegelman, B. M. Molecular mechanisms of cancer development in obesity. *Nat Rev Cancer* **11**, (2011).

138 Roberts, D. L., Dive, C. & Renehan, A. G. Biological mechanisms linking obesity and cancer risk: New perspectives. *Annu Rev Med* **61**, (2010).

139 Van Kruijsdijk, R. C. M., Van Der Wall, E. & Visseren, F. L. J. Obesity and cancer: The role of dysfunctional adipose tissue. *Cancer Epidemiology Biomarkers and Prevention* **18**, (2009).

140 Pollak, M. The insulin and insulin-like growth factor receptor family in neoplasia: An update. *Nat Rev Cancer* **12**, (2012).

141 Bray, G. A. The underlying basis for obesity: Relationship to cancer. *Journal of Nutrition* **132**, (2002).

142 Rose, D. P., Komninou, D. & Stephenson, G. D. Obesity, adipocytokines, and insulin resistance in breast cancer. *Obesity Reviews* **5**, (2004).

143 Dalamaga, M., Diakopoulos, K. N. & Mantzoros, C. S. The role of adiponectin in cancer: A review of current evidence. *Endocr Rev* **33**, (2012).

144 Landskron, G., De La Fuente, M., Thuwajit, P., Thuwajit, C. & Hermoso, M. A. Chronic inflammation and cytokines in the tumor microenvironment. *J Immunol Res* **2014**, (2014).

145 Menon G, Alkabban FM & Ferguson T. *Breast Cancer*. (StatPearls Publishing, Treasure Island (FL), 2024).

146 Feng, Y. *et al.* Breast cancer development and progression: Risk factors, cancer stem cells, signaling pathways, genomics, and molecular pathogenesis. *Genes Dis* **5**, (2018).

147 World Cancer Research Fund/American Institute for Cancer Research. *Continuous Update Project Expert Report 2018. Diet, Nutrition, Physical Activity and Breast Cancer.*

148 Rakha, E. A., Tse, G. M. & Quinn, C. M. An update on the pathological classification of breast cancer. *Histopathology* **82**, (2023).

149 Sonnenblick, A., Fumagalli, D., Sotiriou, C. & Piccart, M. Is the differentiation into molecular subtypes of breast cancer important for staging, local and systemic therapy, and follow up? *Cancer Treat Rev* **40**, (2014).

150 Orrantia-Borunda, E., Anchondo-Nuñez, P., Acuña-Aguilar, L. E., Gómez-Valles, F. O. & Ramírez-Valdespino, C. A. Subtypes of Breast Cancer. in *Breast Cancer* (Exon Publications, Brisbane (AU), 2022).

151 Eliyatkin, N., Yalcin, E., Zengel, B., Aktaş, S. & Vardar, E. Molecular Classification of Breast Carcinoma: From Traditional, Old-Fashioned Way to A New Age, and A New Way. *Journal of Breast Health* **11**, (2015).

152 Goldhirsch, A. *et al.* Strategies for subtypes-dealing with the diversity of breast cancer: Highlights of the St Gallen international expert consensus on the primary therapy of early breast cancer 2011. *Annals of Oncology* **22**, (2011).

153 Guo, Y. *et al.* Genetically Predicted Body Mass Index and Breast Cancer Risk: Mendelian Randomization Analyses of Data from 145,000 Women of European Descent. *PLoS Med* **13**, (2016).

154 Ooi, B. N. S. *et al.* The genetic interplay between body mass index, breast size and breast cancer risk: A Mendelian randomization analysis. *Int J Epidemiol* **48**, (2019).

155 Gao, C. *et al.* Mendelian randomization study of adiposity-related traits and risk of breast, ovarian, prostate, lung and colorectal cancer. *Int J Epidemiol* **45**, (2016).

156 Shu, X. *et al.* Associations of obesity and circulating insulin and glucose with breast cancer risk: A Mendelian randomization analysis. *Int J Epidemiol* **48**, (2019).

157 Zhang, B. *et al.* Height and breast cancer risk: Evidence from prospective studies and mendelian randomization. *J Natl Cancer Inst* **107**, (2015).

158 Lai, F. Y. *et al.* Adult height and risk of 50 diseases: A combined epidemiological and genetic analysis. *BMC Med* **16**, (2018).

159 Barker, D. J. P. & Thornburg, K. L. Placental programming of chronic diseases, cancer and lifespan: A review. *Placenta* **34**, (2013).

160 Rolland-Cachera, M. F. Rate of growth in early life: A predictor of later health? *Adv Exp Med Biol* **569**, (2005).

161 IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Personal Habits and Indoor Combustions. *IARC Monogr Eval Carcinog Risks Hum* **100E**, (2012).

162 Pieroth, R., Paver, S., Day, S. & Lammersfeld, C. Folate and Its Impact on Cancer Risk. *Curr Nutr Rep* **7**, (2018).

163 McTiernan, A. Mechanisms linking physical activity with cancer. *Nat Rev Cancer* **8**, (2008).

164 Friedenreich, C. M., Neilson, H. K. & Lynch, B. M. State of the epidemiological evidence on physical activity and cancer prevention. *Eur J Cancer* **46**, (2010).

165 Shiovitz, S. & Korde, L. A. Genetics of breast cancer: A topic in evolution. *Annals of Oncology* **26**, (2015).

166 Admoun, C. & Mayrovitz, H. N. The Etiology of Breast Cancer. in *Breast Cancer* (Exon Publications, Brisbane (AU), 2022).

167 Beral, V. *et al.* Familial breast cancer: Collaborative reanalysis of individual data from 52 epidemiological studies including 58 209 women with breast cancer and 101 986 women without the disease. *Lancet* **358**, (2001).

168 Hamajima, N. *et al.* Menarche, menopause, and breast cancer risk: Individual participant meta-analysis, including 118 964 women with breast cancer from 117 epidemiological studies. *Lancet Oncol* **13**, (2012).

169 Graham A. Colditz, Heather J. Baer & Tamimi Rulla M. Breast Cancer. in *Cancer Epidemiology and Prevention* (eds. David Schottenfeld & Joseph F. Fraumeni) (Oxford Academic, New York, 2006).

170 Russo, J., Moral, R., Balogh, G. A., Mailo, D. & Russo, I. H. The protective role of pregnancy in breast cancer. *Breast Cancer Research* **7**, (2005).

171 Britt, K., Ashworth, A. & Smalley, M. Pregnancy and the risk of breast cancer. *Endocr Relat Cancer* **14**, (2007).

172 Bernstein, L. Epidemiology of endocrine-related risk factors for breast cancer. *J Mammary Gland Biol Neoplasia* **7**, (2002).

173 Lambe, M. *et al.* Parity, age at first and last birth, and risk of breast cancer: A population-based study in Sweden. *Breast Cancer Res Treat* **38**, (1996).

174 Ma, H., Bernstein, L., Pike, M. C. & Ursin, G. Reproductive factors and breast cancer risk according to joint estrogen and progesterone receptor status: A meta-analysis of epidemiological studies. *Breast Cancer Research* **8**, (2006).

175 Beral, V., Bull, D., Doll, R., Peto, R. & Reeves, G. Breast cancer and breastfeeding: Collaborative reanalysis of individual data from 47 epidemiological studies in 30 countries, including 50 302 women with breast cancer and 96 973 women without the disease. *Lancet* **360**, (2002).

176 Greendale, G. A., Lee, N. P. & Arriola, E. R. The menopause. *Lancet* **353**, (1999).

177 Collaborative Group on Hormonal Factors in Breast Cancer. Type and timing of menopausal hormone therapy and breast cancer risk: individual participant meta-analysis of the worldwide epidemiological evidence. *The Lancet* **394**, (2019).

178 Baojun Duan *et al.* Colorectal Cancer: An Overview. in *Gastrointestinal Cancers* (Exon Publications, Brisbane (AU), 2022).

179 Dekker, E., Tanis, P. J., Vleugels, J. L. A., Kasi, P. M. & Wallace, M. B. Colorectal cancer. *The Lancet* **394**, (2019).

180 Humphries, A. & Wright, N. A. Colonic crypt organization and tumorigenesis. *Nat Rev Cancer* **8**, (2008).

181 Marcelle Meseeha & Maximos Attia. *Colon Polyps*. (StatPearls Publishing, Treasure Island (FL), 2024).

182 Fearon, E. R. Molecular genetics of colorectal cancer. *Annual Review of Pathology: Mechanisms of Disease* **6**, (2011).

183 World Cancer Research Fund/American Institute for Cancer Research. *Continuous Update Project Expert Report 2018. Diet, Nutrition, Physical Activity and Colorectal Cancer.*

184 Bull, C. J. *et al.* Adiposity, metabolites, and colorectal cancer risk: Mendelian randomization study. *BMC Med* **18**, (2020).

185 Gunnell, D. *et al.* Height, Leg Length, and Cancer Risk: A Systematic Review. *Epidemiol Rev* **23**, (2001).

186 Bray, I. *et al.* Associations of childhood and adulthood height and the components of height with insulin-like growth factor levels in adulthood: A 65-year follow-up of the Boyd Orr cohort. *Journal of Clinical Endocrinology and Metabolism* **91**, (2006).

187 Albanes, D. & Winick, M. Are cell number and cell proliferation risk factors for cancer? *J Natl Cancer Inst* **80**, (1988).

188 Rumgay, H. *et al.* Global burden of cancer in 2020 attributable to alcohol consumption: a population-based study. *Lancet Oncol* **22**, (2021).

189 Gunter, M. J. *et al.* Meeting report from the joint IARC-NCI international cancer seminar series: A focus on colorectal cancer. *Annals of Oncology* **30**, (2019).

190 Zhao, Z. *et al.* Red and processed meat consumption and colorectal cancer risk: A systematic review and meta-analysis. *Oncotarget* **8**, (2017).

191 Aune, D. *et al.* Dietary fibre, whole grains, and risk of colorectal cancer: Systematic review and dose-response meta-analysis of prospective studies. *BMJ* **343**, (2011).

192 Aune, D. *et al.* Dairy products and colorectal cancer risk: A systematic review and meta-analysis of cohort studies. *Annals of Oncology* **23**, (2012).

193 Vieira, A. R. *et al.* Foods and beverages and colorectal cancer risk: A systematic review and meta-analysis of cohort studies, an update of the evidence of the WCRF-AICR Continuous Update Project. *Annals of Oncology* **28**, (2017).

194 Murphy, N. *et al.* Consumption of dairy products and colorectal cancer in the European Prospective Investigation into Cancer and Nutrition (EPIC). *PLoS One* **8**, (2013).

195 Kim, H. *et al.* Total calcium, dairy foods and risk of colorectal cancer: A prospective cohort study of younger US women. *Int J Epidemiol* **52**, (2023).

196 Barrubés, L., Babio, N., Becerra-Tomás, N., Rosique-Esteban, N. & Salas-Salvadó, J. Association between Dairy Product Consumption and Colorectal Cancer Risk in Adults: A Systematic Review and Meta-Analysis of Epidemiologic Studies. *Advances in Nutrition* **10**, (2019).

197 Keum, N. N., Lee, D. H., Greenwood, D. C., Zhang, X. & Giovannucci, E. L. Calcium intake and colorectal adenoma risk: Dose-response meta-analysis of prospective observational studies. *Int J Cancer* **136**, (2015).

198 Bonovas, S., Fiorino, G., Lytras, T., Malesci, A. & Danese, S. Calcium supplementation for the prevention of colorectal adenomas: A systematic review and meta-analysis of randomized controlled trials. *World J Gastroenterol* **22**, (2016).

199 Diallo, A. *et al.* Red and processed meat intake and cancer risk: Results from the prospective NutriNet-Santé cohort study. *Int J Cancer* **142**, (2018).

200 Skog, K. I., Johansson, M. A. E. & Jägerstad, M. I. Carcinogenic heterocyclic amines in model systems and cooked foods: A review on formation, occurrence and intake. *Food and Chemical Toxicology* **36**, (1998).

201 Cross, A. J. & Sinha, R. Meat-related mutagens/carcinogens in the etiology of colorectal cancer. *Environ Mol Mutagen* **44**, (2004).

202 Xie, Y. *et al.* N-nitrosamines in processed meats: Exposure, formation and mitigation strategies. *J Agric Food Res* **13**, (2023).

203 Goldman, R. & Shields, P. G. Food mutagens. *Journal of Nutrition* **133**, (2003).

204 Cross, A. J., Pollock, J. R. A. & Bingham, S. A. Haem, not protein or inorganic iron, is responsible for endogenous intestinal N-nitrosation arising from red meat. *Cancer Res* **63**, (2003).

205 Slavin, J. L. Mechanisms for the Impact of Whole Grain Foods on Cancer Risk. *J Am Coll Nutr* **19**, (2000).

206 Bingham, S. A. Mechanisms and experimental and epidemiological evidence relating dietary fibre (non-starch polysaccharides) and starch to protection against large bowel cancer. *Proceedings of the Nutrition Society* **49**, (1990).

207 Pi-Sunyer, X. Do glycemic index, glycemic load, and fiber play a role in insulin sensitivity, disposition index, and type 2 diabetes? *Diabetes Care* **28**, (2005).

208 Kim, K. H., Tsao, R., Yang, R. & Cui, S. W. Phenolic acid profiles and antioxidant activities of wheat bran extracts and the effect of hydrolysis conditions. *Food Chem* **95**, (2006).

209 Celiberto, F. *et al.* Fibres and Colorectal Cancer: Clinical and Molecular Evidence. *Int J Mol Sci* **24**, (2023).

210 Norat, T. & Riboli, E. Dairy products and colorectal cancer. A review of possible mechanisms and epidemiological evidence. *Eur J Clin Nutr* **57**, (2003).

211 Guéguen, L. & Pointillart, A. The Bioavailability of Dietary Calcium. *J Am Coll Nutr* **19**, (2000).

212 Newmark, H. L., Wargovich, M. J. & Bruce, W. R. Colon cancer and dietary fat, phosphate, and calcium: A hypothesis. *J Natl Cancer Inst* **72**, (1984).

213 Fedirko, V. *et al.* Effects of vitamin D and calcium on proliferation and differentiation in normal colon mucosa: A randomized clinical trial. *Cancer Epidemiology Biomarkers and Prevention* **18**, (2009).

214 Llor, X. *et al.* K-ras Mutations in 1,2-Dimethylhydrazine-induced Colonic Tumors: Effects of Supplemental Dietary Calcium and Vitamin D Deficiency. *Cancer Res* **51**, (1991).

215 Pierre, F. H. F. *et al.* Calcium and α-tocopherol suppress cured-meat promotion of chemically induced colon carcinogenesis in rats and reduce associated biomarkers in human volunteers. *American Journal of Clinical Nutrition* **98**, (2013).

216 Murphy, N. *et al.* A Nested Case–Control Study of Metabolically Defined Body Size Phenotypes and Risk of Colorectal Cancer in the European Prospective Investigation into Cancer and Nutrition (EPIC). *PLoS Med* **13**, (2016).

217 Ma, J. *et al.* A prospective study of plasma C-peptide and colorectal cancer risk in men. *J Natl Cancer Inst* **96**, (2004).

218 Jenab, M. *et al.* Serum C-peptide, IGFBP-1 and IGFBP-2 and risk of colon and rectal cancers in the European prospective investigation into cancer and nutrition. *Int J Cancer* **121**, (2007).

219 Zhou, B. *et al.* C-reactive protein, interleukin-6 and the risk of colorectal cancer: a meta-analysis. *Cancer Causes and Control* **25**, (2014).

220 Quadrilatero, J. & Hoffman-Goetz, L. Physical activity and colon cancer: A systematic review of potential mechanisms. *Journal of Sports Medicine and Physical Fitness* **43**, (2003).

221 Ma, P., Yao, Y., Sun, W., Dai, S. & Zhou, C. Daily sedentary time and its association with risk for colorectal cancer in adults. *Medicine (United States)* **96**, (2017).

222 Botteri, E. *et al.* Smoking and Colorectal Cancer Risk, Overall and by Molecular Subtypes: A Meta-Analysis. *American Journal of Gastroenterology* **115**, (2020).

223 Gram, I. T., Park, S. Y., Wilkens, L. R., Haiman, C. A. & Le Marchand, L. Smoking-related risks of colorectal cancer by anatomical subsite and sex. *Am J Epidemiol* **189**, (2020).

224 Rodgman, A. & Perfetti, T. The Alphabetical Index to Components Identified in Tobacco, Tobacco Smoke, and Tobacco Substitute Smoke. in *The Chemical Components of Tobacco and Tobacco Smoke, Second Edition* (2013).

225 IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Tobacco smoke and involuntary smoking. *IARC Monogr Eval Carcinog Risks Hum* **83**, (2004).

226 Jasperson, K. W., Tuohy, T. M., Neklason, D. W. & Burt, R. W. Hereditary and Familial Colon Cancer. *Gastroenterology* **138**, (2010).

227 Hampel, H. *et al.* Feasibility of screening for Lynch syndrome among patients with colorectal cancer. *Journal of Clinical Oncology* **26**, (2008).

228 Stoffel, E. *et al.* Calculation of Risk of Colorectal and Endometrial Cancer Among Patients With Lynch Syndrome. *Gastroenterology* **137**, (2009).

229 Botstein, D. & Risch, N. Discovering genotypes underlying human phenotypes: Past successes for mendelian disease, future approaches for complex disease. *Nat Genet* **33**, (2003).

230 Uffelmann, E. *et al.* Genome-wide association studies. *Nature Reviews Methods Primers* **1**, (2021).

231 Visscher, P. M. *et al.* 10 Years of GWAS Discovery: Biology, Function, and Translation. *Am J Hum Genet* **101**, (2017).

232 Tam, V. *et al.* Benefits and limitations of genome-wide association studies. *Nat Rev Genet* **20**, (2019).

233 Craig Venter, J. *et al.* The sequence of the human genome. *Science* **291**, (2001).

234 Sachidanandam, R. *et al.* A map of human genome sequence variation containing 1.42 million single nucleotide polymorphisms. *Nature* **409**, (2001).

235 Manolio, T. A. *et al.* Finding the missing heritability of complex diseases. *Nature* **461**, (2009).

236 Hunter, D. J., Altshuler, D. & Rader, D. J. From Darwin's Finches to Canaries in the Coal Mine — Mining the Genome for New Biology. *New England Journal of Medicine* **358**, (2008).

237 Pearson, T. A. & Manolio, T. A. How to interpret a genome-wide association study. *JAMA* **299**, (2008).

238 Timpson, N. J., Greenwood, C. M. T., Soranzo, N., Lawson, D. J. & Richards, J. B. Genetic architecture: The shape of the genetic contribution to human traits and disease. *Nat Rev Genet* **19**, (2018).

239 Choi, S. W., Mak, T. S. H. & O'Reilly, P. F. Tutorial: a guide to performing polygenic risk score analyses. *Nat Protoc* **15**, (2020).

240 Márquez-Luna, C. *et al.* Multiethnic polygenic risk scores improve risk prediction in diverse populations. *Genet Epidemiol* **41**, (2017).

241 Vilhjálmsson, B. J. *et al.* Modeling Linkage Disequilibrium Increases Accuracy of Polygenic Risk Scores. *Am J Hum Genet* **97**, (2015).

242 Privé, F., Arbel, J. & Vilhjálmsson, B. J. LDpred2: Better, faster, stronger. *Bioinformatics* **36**, (2020).

243 Privé, F., Albiñana, C., Arbel, J., Pasaniuc, B. & Vilhjálmsson, B. J. Inferring disease architecture and predictive ability with LDpred2-auto. *The American Journal of Human Genetics* **110**, (2023).

244 Hariton, E. & Locascio, J. J. Randomised controlled trials – the gold standard for effectiveness research: Study design: randomised controlled trials. *BJOG* **125**, (2018).

245 Sibbald, B. & Roland, M. Understanding controlled trials: Why are randomised controlled trials important? *BMJ* **316**, (1998).

246 Glass, T. A., Goodman, S. N., Hernán, M. A. & Samet, J. M. Causal inference in public health. *Annu Rev Public Health* **34**, (2013).

247 Davey Smith, G. & Hemani, G. Mendelian randomization: genetic anchors for causal inference in epidemiological studies. *Hum Mol Genet* **23**, (2014).

248 Smith, G. D. & Ebrahim, S. 'Mendelian randomization': Can genetic epidemiology contribute to understanding environmental determinants of disease? *Int J Epidemiol* **32**, (2003).

249 Mendel, G. Experiments on Plant Hybridization. *Proceedings of the Natural History Society of Brünn* **IV**, (1866).

250 Lawlor, D. A. Commentary: Two-sample Mendelian randomization: Opportunities and challenges. *Int J Epidemiol* **45**, (2016).

251 Burgess, S. & Thompson, S. G. Bias in causal estimates from Mendelian randomization studies with weak instruments. *Stat Med* **30**, (2011).

252 Dimou, N. L. & Tsilidis, K. K. A primer in Mendelian Randomization methodology with a focus on utilizing published summary association data. *Methods in Molecular Biology* **1793**, (2018).

253 Sanderson, E. *et al.* Mendelian randomization. *Nature Reviews Methods Primers* **2**, (2022).

254 Zheng, J. *et al.* Recent Developments in Mendelian Randomization Studies. *Curr Epidemiol Rep* **4**, (2017).

255 MacArthur, J. *et al.* The new NHGRI-EBI Catalog of published genome-wide association studies (GWAS Catalog). *Nucleic Acids Res* **45**, (2017).

256 Sollis, E. *et al.* The NHGRI-EBI GWAS Catalog: knowledgebase and deposition resource. *Nucleic Acids Res* **51**, (2023).

257 Bowden, J., Smith, G. D. & Burgess, S. Mendelian randomization with invalid instruments: Effect estimation and bias detection through Egger regression. *Int J Epidemiol* **44**, (2015).

258 Bowden, J., Davey Smith, G., Haycock, P. C. & Burgess, S. Consistent Estimation in Mendelian Randomization with Some Invalid Instruments Using a Weighted Median Estimator. *Genet Epidemiol* **40**, (2016).

259 Verbanck, M., Chen, C. Y., Neale, B. & Do, R. Detection of widespread horizontal pleiotropy in causal relationships inferred from Mendelian randomization between complex traits and diseases. *Nat Genet* **50**, (2018).

260 Loos, R. J. F. & Yeo, G. S. H. The genetics of obesity: from discovery to biology. *Nat Rev Genet* **23**, (2022).

261 Frayling, T. M. *et al.* A common variant in the FTO gene is associated with body mass index and predisposes to childhood and adult obesity. *Science* **316**, (2007).

262 Scuteri, A. *et al.* Genome-wide association scan shows genetic variants in the FTO gene are associated with obesity-related traits. *PLoS Genet* **3**, (2007).

263 Speliotes, E. K. *et al.* Association analyses of 249,796 individuals reveal 18 new loci associated with body mass index. *Nat Genet* **42**, (2010).

264 Locke, A. E. *et al.* Genetic studies of body mass index yield new insights for obesity biology. *Nature* **518**, (2015).

265 Yengo, L. *et al.* Meta-analysis of genome-wide association studies for height and body mass index in ~700 000 individuals of European ancestry. *Hum Mol Genet* **27**, (2018).

266 Pulit, S. L. *et al.* Meta-Analysis of genome-wide association studies for body fat distribution in 694 649 individuals of European ancestry. *Hum Mol Genet* **28**, (2019).

267 Shungin, D. *et al.* New genetic loci link adipose and insulin biology to body fat distribution. *Nature* **518**, (2015).

268 Bradfield, J. P. *et al.* A genome-wide association meta-analysis identifies new childhood obesity loci. *Nat Genet* **44**, (2012).

269 Wheeler, E. *et al.* Genome-wide SNP and CNV analysis identifies common and low-frequency variants associated with severe early-onset obesity. *Nat Genet* **45**, (2013).

270 Meyre, D. *et al.* Genome-wide association study for early-onset and morbid adult obesity identifies three new risk loci in European populations. *Nat Genet* **41**, (2009).

271 Lu, Y. *et al.* New loci for body fat percentage reveal link between adiposity and cardiometabolic disease risk. *Nat Commun* **7**, (2016).

272 Hübel, C. *et al.* Genomics of body fat percentage may contribute to sex bias in anorexia nervosa. *American Journal of Medical Genetics, Part B: Neuropsychiatric Genetics* **180**, (2019).

273 Zillikens, M. C. *et al.* Large meta-analysis of genome-wide association studies identifies five loci for lean body mass. *Nat Commun* **8**, (2017).

274 Chu, A. Y. *et al.* Multiethnic genome-wide meta-analysis of ectopic fat depots identifies loci associated with adipocyte development and differentiation. *Nat Genet* **49**, (2017).

275 Kalantari, N., Doaei, S., Keshavarz-Mohammadi, N., Gholamalizadeh, M. & Pazan, N. Review of studies on the fat mass and obesity-associated (FTO) gene interactions with environmental factors affecting on obesity and its impact on lifestyle interventions. *ARYA Atheroscler* **12**, (2016).

276 Hendricks, A. E. *et al.* Rare Variant Analysis of Human and Rodent Obesity Genes in Individuals with Severe Childhood Obesity. *Sci Rep* **7**, (2017).

277 Turcot, V. *et al.* Protein-altering variants associated with body mass index implicate pathways that control energy intake and expenditure in obesity. *Nat Genet* **50**, (2018).

278 Emdin, C. A. *et al.* Analysis of predicted loss-of-function variants in UK Biobank identifies variants protective for disease. *Nat Commun* **9**, (2018).

279 Akbari, P. *et al.* Sequencing of 640,000 exomes identifies GPR75 variants associated with protection from obesity. *Science* **373**, (2021).

280 Silventoinen, K. *et al.* Differences in genetic and environmental variation in adult BMI by sex, age, time period, and region: an individual-based pooled analysis of 40 twin cohorts. *Am J Clin Nutr* **106**, (2017).

281 Elks, C. E. *et al.* Variability in the heritability of body mass index: A systematic review and meta-regression. *Front Endocrinol* **3**, (2012).

282 Rose, K. M., Newman, B., Mayer-Davis, E. J. & Selby, J. V. Genetic and behavioral determinants of waist-hip ratio and waist circumference in women twins. *Obes Res* **6**, (1998).

283 Henneman, P. *et al.* Prevalence and heritability of the metabolic syndrome and its individual components in a Dutch isolate: The Erasmus Rucphen Family study. *J Med Genet* **45**, (2008).

284 Robinson, M. R. *et al.* Genotype-covariate interaction effects and the heritability of adult body mass index. *Nat Genet* **49**, (2017).

285 Yang, J. *et al.* Genetic variance estimation with imputed variants finds negligible missing heritability for human height and body mass index. *Nat Genet* **47**, (2015).

286 Kutalik, Z., Whittaker, J., Waterworth, D., Beckmann, J. S. & Bergmann, S. Novel method to estimate the phenotypic variation explained by genome-wide association studies reveals large fraction of the missing heritability. *Genet Epidemiol* **35**, (2011).

287 Wood, A. R. *et al.* Defining the role of common variation in the genomic and biological architecture of adult human height. *Nat Genet* **46**, (2014).

288 Ghosh, S. & Bouchard, C. Convergence between biological, behavioural and genetic determinants of obesity. *Nat Rev Genet* **18**, (2017).

289 Finucane, H. K. *et al.* Partitioning heritability by functional annotation using genome-wide association summary statistics. *Nat Genet* **47**, (2015).

290 Winkler, T. W. *et al.* A joint view on genetic variants for adiposity differentiates subtypes with distinct metabolic implications. *Nat Commun* **9**, (2018).

291 Sudlow, C. *et al.* UK Biobank: An Open Access Resource for Identifying the Causes of a Wide Range of Complex Diseases of Middle and Old Age. *PLoS Med* **12**, (2015).

292 Riboli, E. The EPIC Project: rationale and study design. European Prospective Investigation into Cancer and Nutrition. *Int J Epidemiol* **26**, (1997).

293 Lonsdale, J. *et al.* The Genotype-Tissue Expression (GTEx) project. *Nat Genet* **45**, (2013).

294 Aguet, F. *et al.* The GTEx Consortium atlas of genetic regulatory effects across human tissues. *Science* **369**, (2020).

295 Zhang, H. *et al.* Genome-wide association study identifies 32 novel breast cancer susceptibility loci from overall and subtype-specific analyses. *Nat Genet* **52**, (2020).

296 Huyghe, J. R. *et al.* Discovery of common and rare genetic risk variants for colorectal cancer. *Nat Genet* **51**, (2019).

297 UK Biobank Coordinating Centre. UK Biobank: Protocol for a large-scale prospective epidemiological resource UK Biobank Coordinating Centre Stockport. *UKBB-PROT-09-06 (Main Phase)* **06**, (2007).

298 Elliott, P. & Peakman, T. C. The UK Biobank sample handling and storage protocol for the collection, processing and archiving of human blood and urine. *Int J Epidemiol* **37**, (2008).

299 Bycroft, C. *et al.* The UK Biobank resource with deep phenotyping and genomic data. *Nature* **562**, (2018).

300 Nielsen, J. & Wohlert, M. Sex chromosome abnormalities found among 34,910 newborn children: Results from a 13-year incidence study in Arhus, Denmark. *Birth Defects Orig Artic Ser* **26**, (1990).

301 McCarthy, S. *et al.* A reference panel of 64,976 haplotypes for genotype imputation. *Nat Genet* **48**, (2016).

302 Huang, J. *et al.* Improved imputation of low-frequency and rare variants using the UK10K haplotype reference panel. *Nat Commun* **6**, (2015).

303 Fry, D., Almond, R., Moffat, S., Gordon, M. & Singh, P. *UK Biobank Biomarker Project: Companion Document to Accompany Serum Biomarker Data*. https://biobank.ndph.ox.ac.uk/ukb/refer.cgi?id=1227 (2019).

304 Riboli, E. *et al.* European Prospective Investigation into Cancer and Nutrition (EPIC): study populations and data collection. *Public Health Nutr* **5**, (2002).

305 Haftenberger, M. *et al.* Overweight, obesity and fat distribution in 50- to 64-year-old participants in the European Prospective Investigation into Cancer and Nutrition (EPIC). *Public Health Nutr* **5**, (2002).

306 Spencer, E. A., Appleby, P. N., Davey, G. K. & Key, T. J. Validity of self-reported height and weight in 4808 EPIC–Oxford participants. *Public Health Nutr* **5**, (2002).

307 Spencer, E. A., Roddam, A. W. & Key, T. J. Accuracy of self-reported waist and hip measurements in 4492 EPIC–Oxford participants. *Public Health Nutr* **7**, (2004).

308 Auton, A. *et al.* A global reference for human genetic variation. *Nature* **526**, (2015).

309 Aleksandrova, K. *et al.* Total and high-molecular weight adiponectin and risk of colorectal cancer: The European prospective investigation into cancer and nutrition study. *Carcinogenesis* **33**, (2012).

310 Aleksandrova, K. *et al.* Leptin and soluble leptin receptor in risk of colorectal cancer in the European prospective investigation into cancer and nutrition cohort. *Cancer Res* **72**, (2012).

311 Aleksandrova, K. *et al.* Inflammatory and metabolic biomarkers and risk of liver and biliary tract cancer. *Hepatology* **60**, (2014).

312 Aleksandrova, K. *et al.* Circulating C-reactive protein concentrations and risks of colon and rectal cancer: A nested case-control study within the European prospective investigation into cancer and nutrition. *Am J Epidemiol* **172**, (2010).

313 Cust, A. E. *et al.* Plasma adiponectin levels and endometrial cancer risk in pre- and postmenopausal women. *Journal of Clinical Endocrinology and Metabolism* **92**, (2007).

314 Dossus, L. *et al.* Tumor necrosis factor (TNF)-α, soluble TNF receptors and endometrial cancer risk: The EPIC study. *Int J Cancer* **129**, (2011).

315 Dossus, L. *et al.* Adipokines and inflammation markers and risk of differentiated thyroid carcinoma: The EPIC study. *Int J Cancer* **142**, (2018).

316 Dossus, L. *et al.* Obesity, inflammatory markers, and endometrial cancer risk: A prospective case - control study. *Endocr Relat Cancer* **17**, (2010).

317 Grote, V. A. *et al.* Inflammation marker and risk of pancreatic cancer: A nested case-control study within the EPIC cohort. *Br J Cancer* **106**, (2012).

318 Grote, V. A. *et al.* The association of circulating adiponectin levels with pancreatic cancer risk: A study within the prospective EPIC cohort. *Int J Cancer* **130**, (2012).

319 Ose, J. *et al.* Inflammatory markers and risk of epithelial ovarian cancer by tumor subtypes: The EPIC cohort. *Cancer Epidemiology Biomarkers and Prevention* **24**, (2015).

320 Das, S. *et al.* Next-generation genotype imputation service and methods. *Nat Genet* **48**, (2016).

321 Robinson, M. R. *et al.* Population genetic differentiation of height and body mass index across Europe. *Nat Genet* **47**, (2015).

322 Breschi, A. *et al.* A limited set of transcriptional programs define major cell types. *Genome Res* **30**, (2020).

323 Thrift, A. P. *et al.* Mendelian randomization study of body mass index and colorectal cancer risk. *Cancer Epidemiology Biomarkers and Prevention* **24**, (2015).

324 Jarvis, D. *et al.* Mendelian randomisation analysis strongly implicates adiposity with risk of developing colorectal cancer. *Br J Cancer* **115**, (2016).

325 Khankari, N. K. *et al.* Association between Adult Height and Risk of Colorectal, Lung, and Prostate Cancer: Results from Meta-analyses of Prospective Studies and Mendelian Randomization Analyses. *PLoS Med* **13**, (2016).

326 Kabat, G. C. *et al.* Risk of breast, endometrial, colorectal, and renal cancers in postmenopausal women in association with a body shape index and other anthropometric measures. *Cancer Causes and Control* **26**, (2015).

327 Bhaskaran, K. *et al.* Body-mass index and risk of 22 specific cancers: a population-based cohort study of 5·24 million UK adults. *The Lancet* **384**, (2014).

328 Renehan, A. G., Tyson, M., Egger, M., Heller, R. F. & Zwahlen, M. Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. *The Lancet* **371**, (2008).

329 Liu, K. *et al.* Association between body mass index and breast cancer risk: Evidence based on a dose–response meta-analysis. *Cancer Manag Res* **10**, (2018).

330 Richardson, T. G., Sanderson, E., Elsworth, B., Tilling, K. & Smith, G. D. Use of genetic variation to separate the effects of early and later life adiposity on disease risk: Mendelian randomisation study. *The BMJ* **369**, (2020).

331 Baer, H. J., Tworoger, S. S., Hankinson, S. E. & Willett, W. C. Body fatness at young ages and risk of breast cancer throughout life. *Am J Epidemiol* **171**, (2010).

332 Baer, H. J. *et al.* Body fatness during childhood and adolescence and incidence of breast cancer in premenopausal women: A prospective cohort study. *Breast Cancer Research* **7**, (2005).

333 Yang, T. Y. O. *et al.* Body size in early life and the risk of postmenopausal breast cancer. *BMC Cancer* **22**, (2022).

334 Chen, G. C. *et al.* Central obesity and risks of pre- and postmenopausal breast cancer: a dose–response meta-analysis of prospective studies. *Obesity Reviews* **17**, (2016).

335 Power, M. L. & Schulkin, J. Sex differences in fat storage, fat metabolism, and the health risks from obesity: Possible evolutionary origins. *British Journal of Nutrition* **99**, (2008).

336 Slimani, N. *et al.* Diversity of dietary patterns observed in the European Prospective Investigation into Cancer and Nutrition (EPIC) project. *Public Health Nutr* **5**, (2002).

337 Orsama, A. L. *et al.* Weight rhythms: Weight increases during weekends and decreases during weekdays. *Obes Facts* **7**, (2014).

338 Stevens, J., Truesdale, K. P., McClain, J. E. & Cai, J. The definition of weight maintenance. *Int J Obes* **30**, (2006).

339 Hingorani, A. D. *et al.* Performance of polygenic risk scores in screening, prediction, and risk stratification: secondary analysis of data in the Polygenic Score Catalog. *BMJ Medicine* **2**, (2023).

340 Higgins, J. P. T., Thompson, S. G., Deeks, J. J. & Altman, D. G. Measuring inconsistency in meta-analyses. *Br Med J* **327**, (2003).

341 Pagoni, P., Dimou, N. L., Murphy, N. & Stergiakouli, E. Using Mendelian randomisation to assess causality in observational studies. *Evid Based Ment Health* **22**, (2019).

342 Bowden, J. *et al.* A framework for the investigation of pleiotropy in two-sample summary data Mendelian randomization. *Stat Med* **36**, (2017).

343 Staley, J. R. *et al.* PhenoScanner: A database of human genotype-phenotype associations. *Bioinformatics* **32**, (2016).

344 Kamat, M. A. *et al.* PhenoScanner V2: An expanded tool for searching human genotype-phenotype associations. *Bioinformatics* **35**, (2019).

345 Brumpton, B. *et al.* Avoiding dynastic, assortative mating, and population stratification biases in Mendelian randomization through within-family analyses. *Nat Commun* **11**, (2020).

346 von Ruesten, A. *et al.* Trend in obesity prevalence in European adult cohort populations during follow-up since 1996 and their predictions to 2015. *PLoS One* **6**, (2011).

ANNEXES

ANNEX I

SUPPLEMENTARY MATERIAL STUDY I

Tissue-specific genetic variation suggests distinct molecular pathways between body shape phenotypes and colorectal cancer

Laia Peruchet-Noray, Anja M. Sedlmeier, Niki Dimou, …,
Robert Carreras-Torres, Marc J. Gunter, Heinz Freisling

Sci. Adv. **10, eadj1987 (2024)**

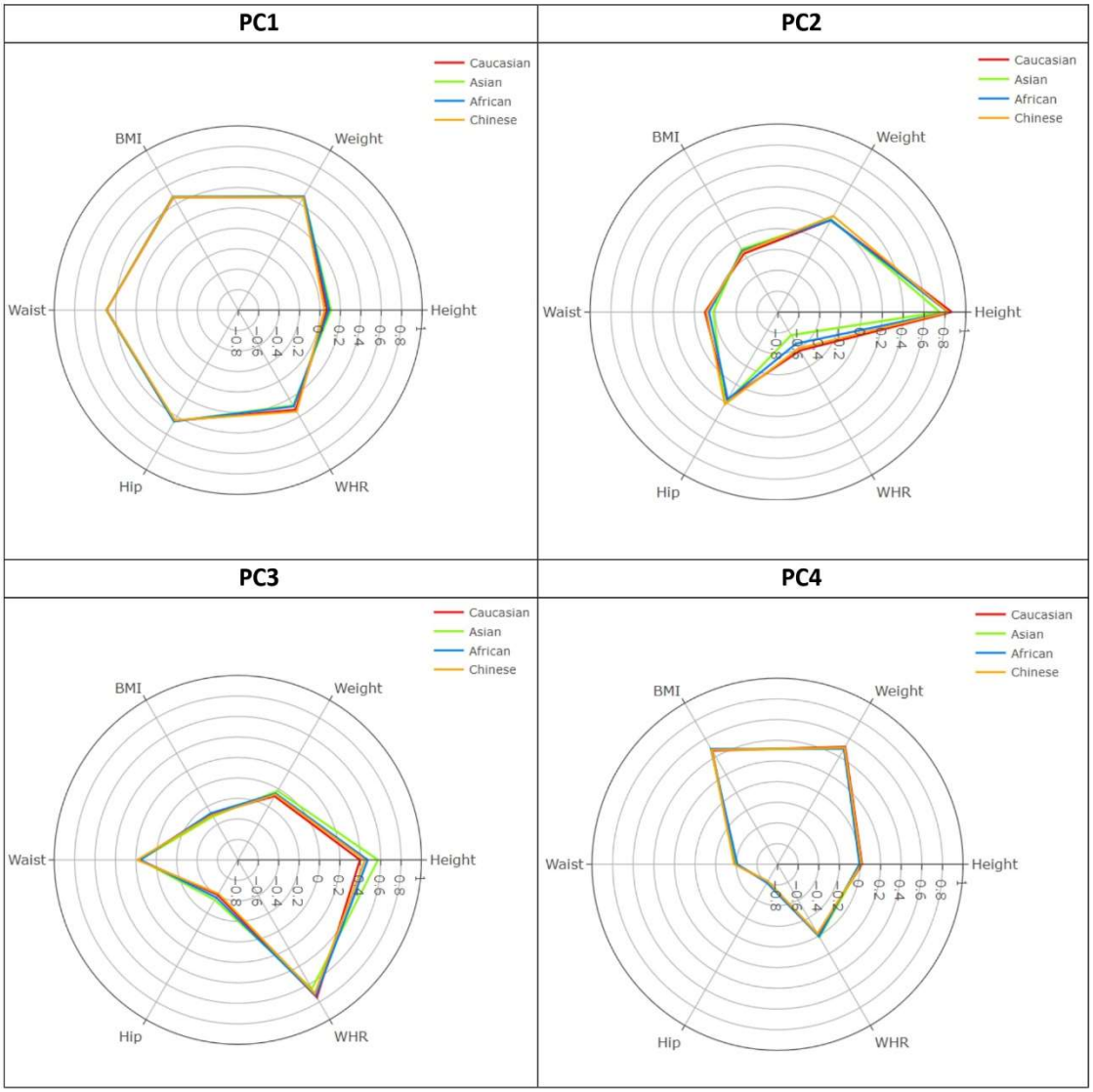


Figure S1. Body shape phenotypes (PC1 - 4) loadings by different ancestries available in UK Biobank (Caucasian in red, Asian in green, African in blue, and Chinese in orange). $N_{Caucasians}$ = *460,198,* $N_{African}$ = 7,269, N_{Asian} = 9,751 and $N_{Chinese}$ = 2,359. PC, principal component.

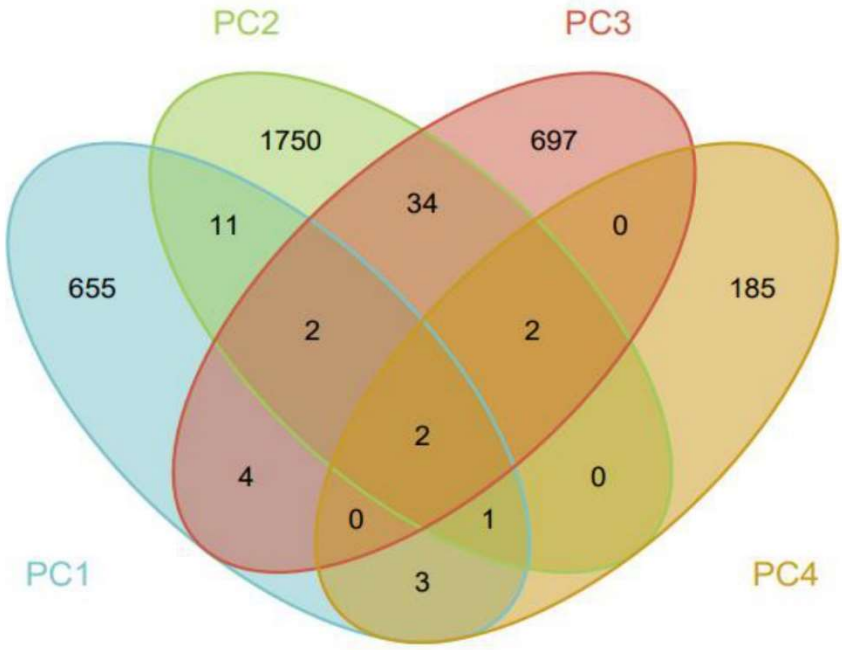


Figure S2. Venn diagram showing the number of genetic variants associated to each body shape phenotype (PC1 - 4) and the genetic variants they share. PC, principal component.

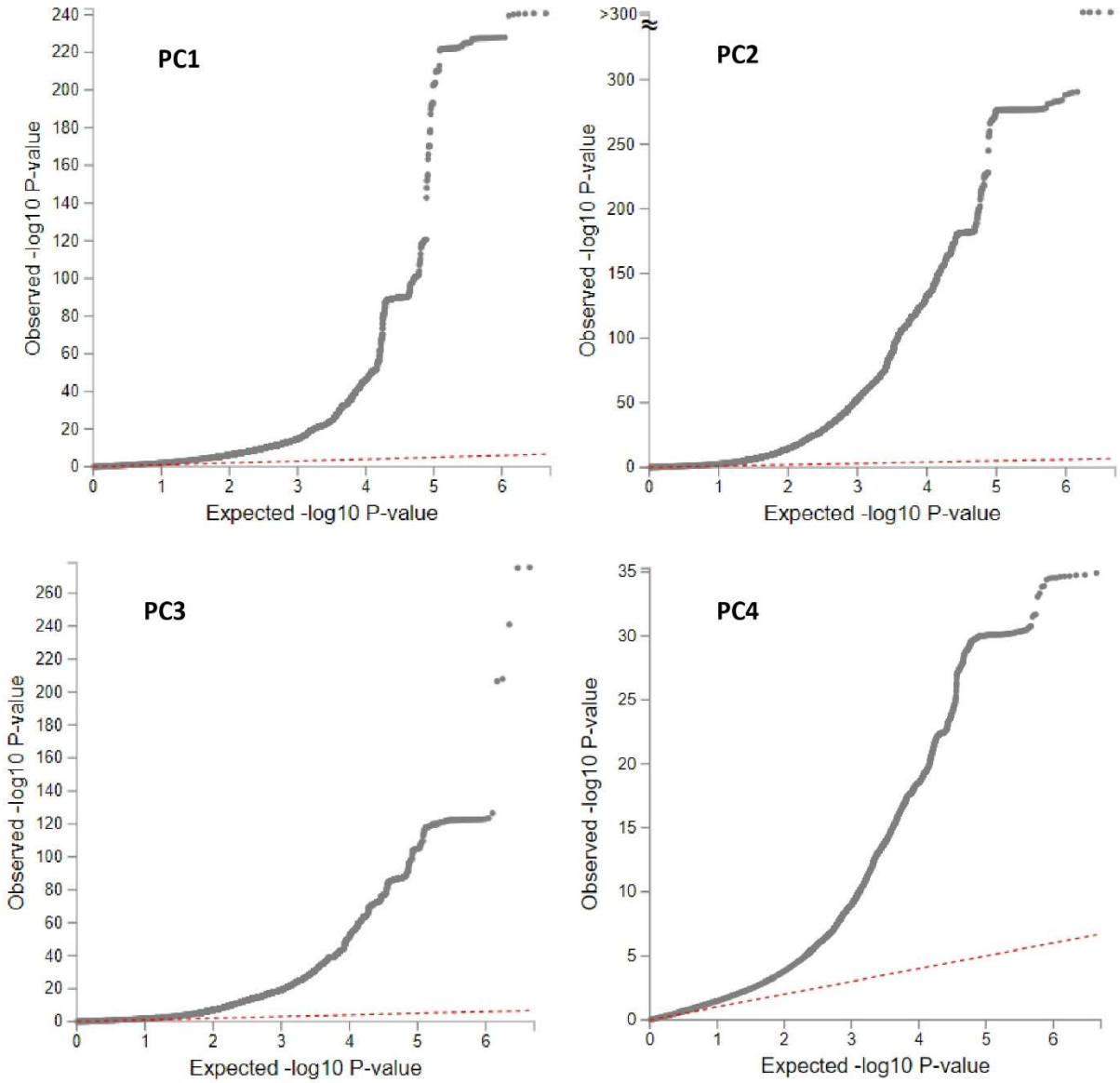


Figure S3. Q-Q plots of body shape phenotypes (PC1 - 4) genome-wide association study (GWAS) summary statistics. PC, principal component.

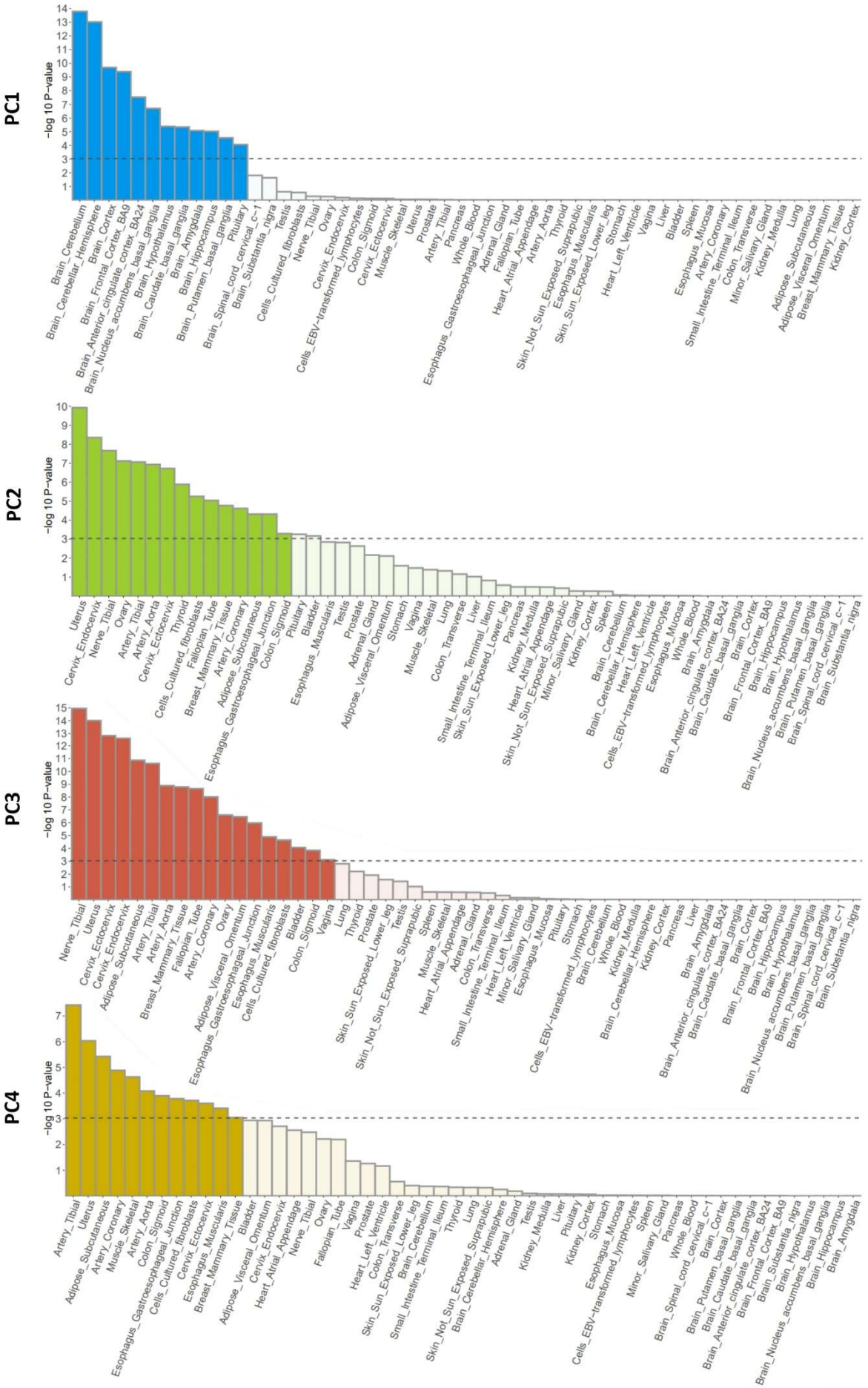


Figure S4. Specific tissue expression profile analysis for the four body shape phenotypes (PC1 - 4). Specific tissues reaching a p-value < 9.26×10^{-4}, after Bonferroni correction, are highlighted in darker colors. PC, principal component.

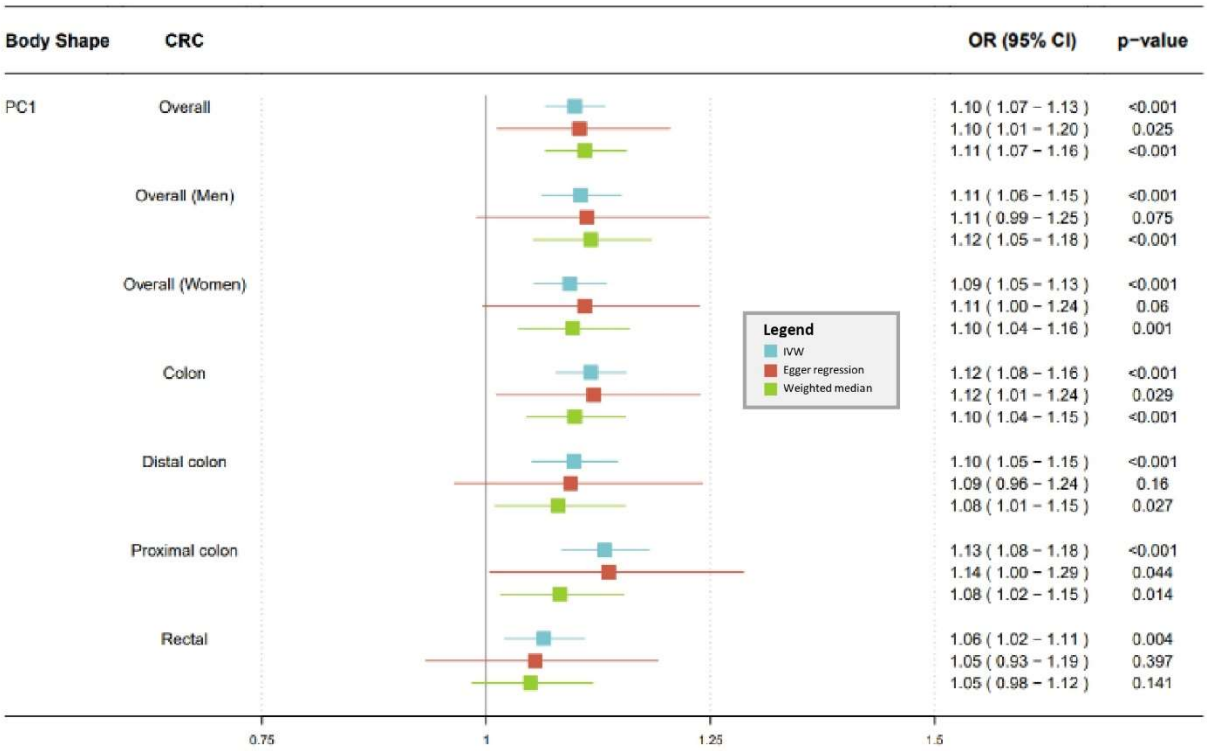


Figure S5. Mendelian randomization (MR) estimates between body shape phenotype PC1 and colorectal cancer (CRC) risk, by sex, and subsites using IVW (blue), MR Egger regression (red) and weighted median (green) MR approaches. CI, confidence interval; OR, odds ratio; PC, principal component.

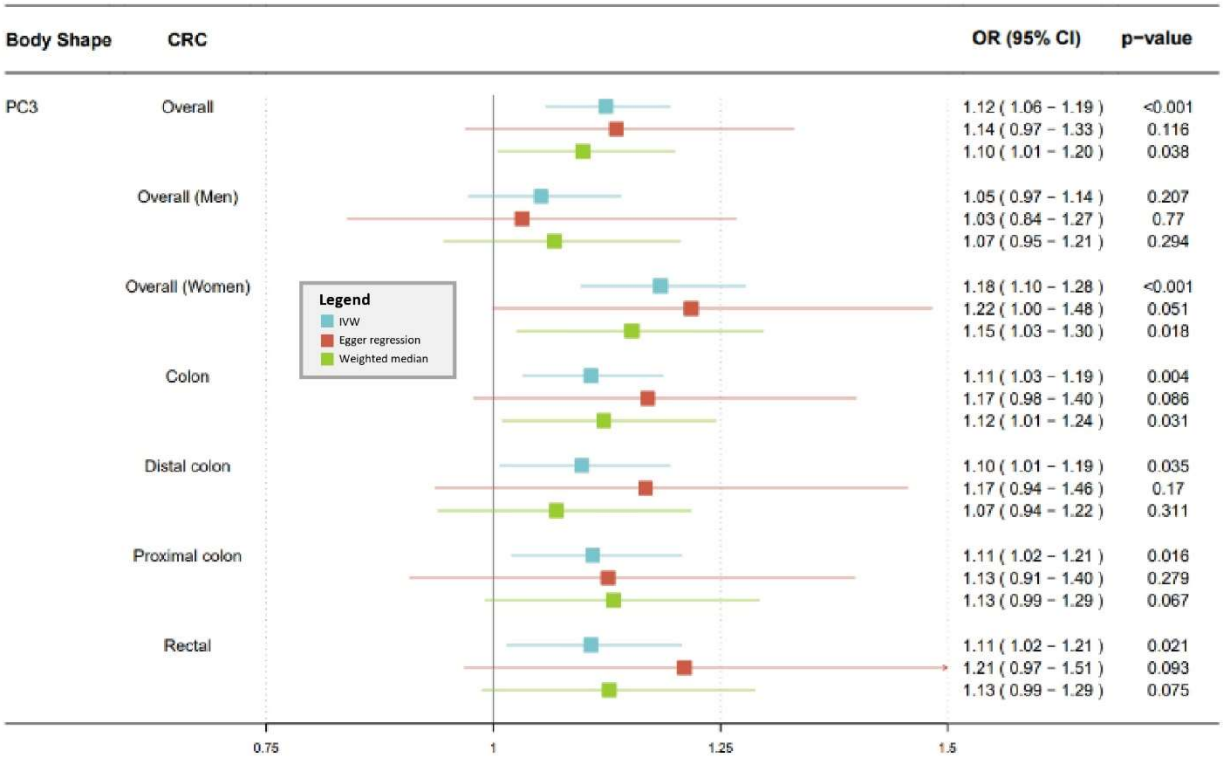


Figure S6. Mendelian randomization (MR) estimates between body shape phenotype PC3 and colorectal cancer (CRC) risk, by sex, and subsites using random-effects inverse-variance weighted (IVW) (blue), MR Egger regression (red) and weighted median (green) MR approaches. CI, confidence interval; OR, odds ratio; PC, principal component.

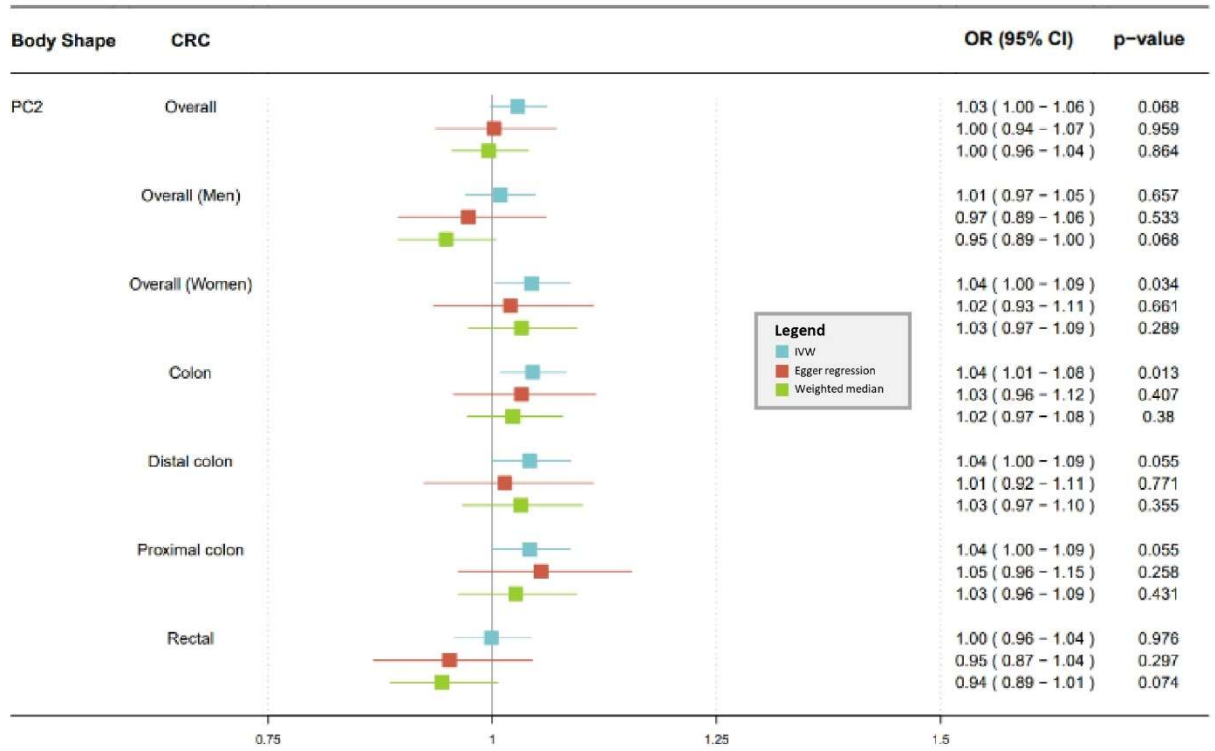


Figure S7. Mendelian randomization (MR) estimates between body shape phenotype PC2 and colorectal cancer (CRC) risk, by sex, and random-effects inverse-variance weighted (IVW) (blue), MR Egger regression (red) and weighted median (green) MR approaches. CI, confidence interval; OR, odds ratio; PC, principal component.

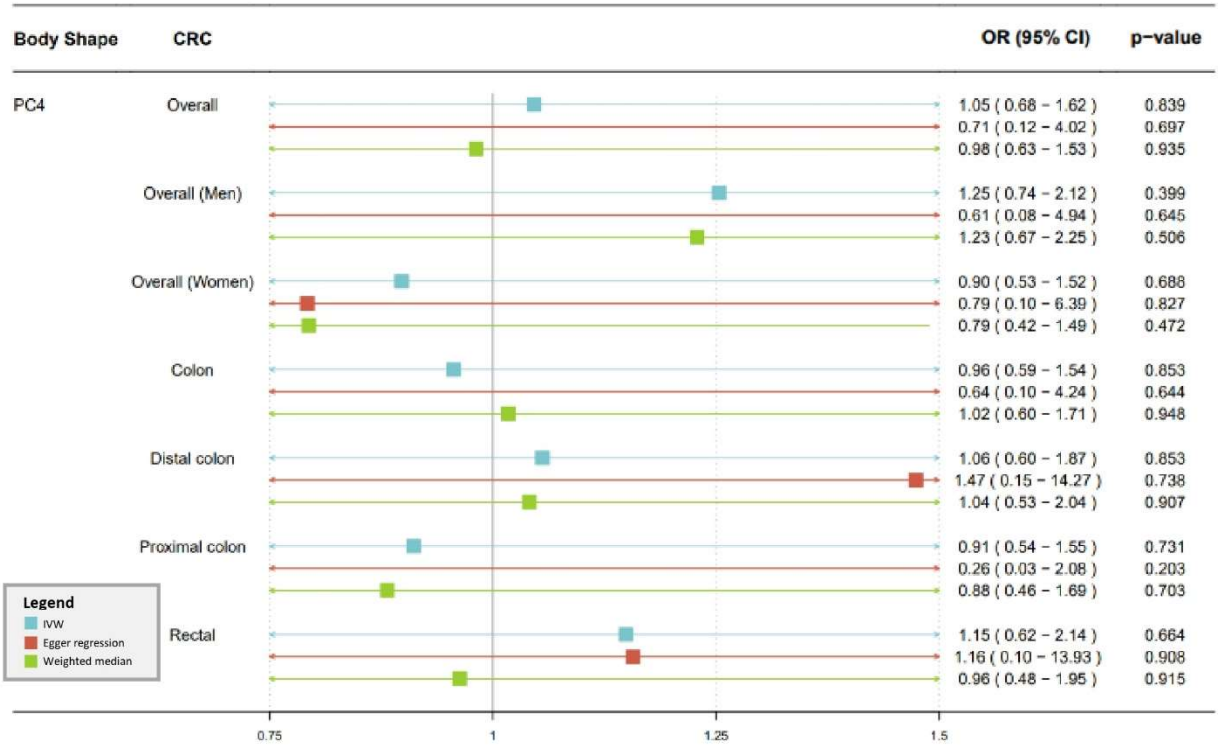


Figure S8. Mendelian randomization (MR) estimates between body shape phenotype PC4 and colorectal cancer (CRC) risk, by sex, and subsites random-effects inverse-variance weighted (IVW) (blue), MR Egger regression (red) and weighted median (green) MR approaches. CI, confidence interval; OR, odds ratio; PC, principal component.

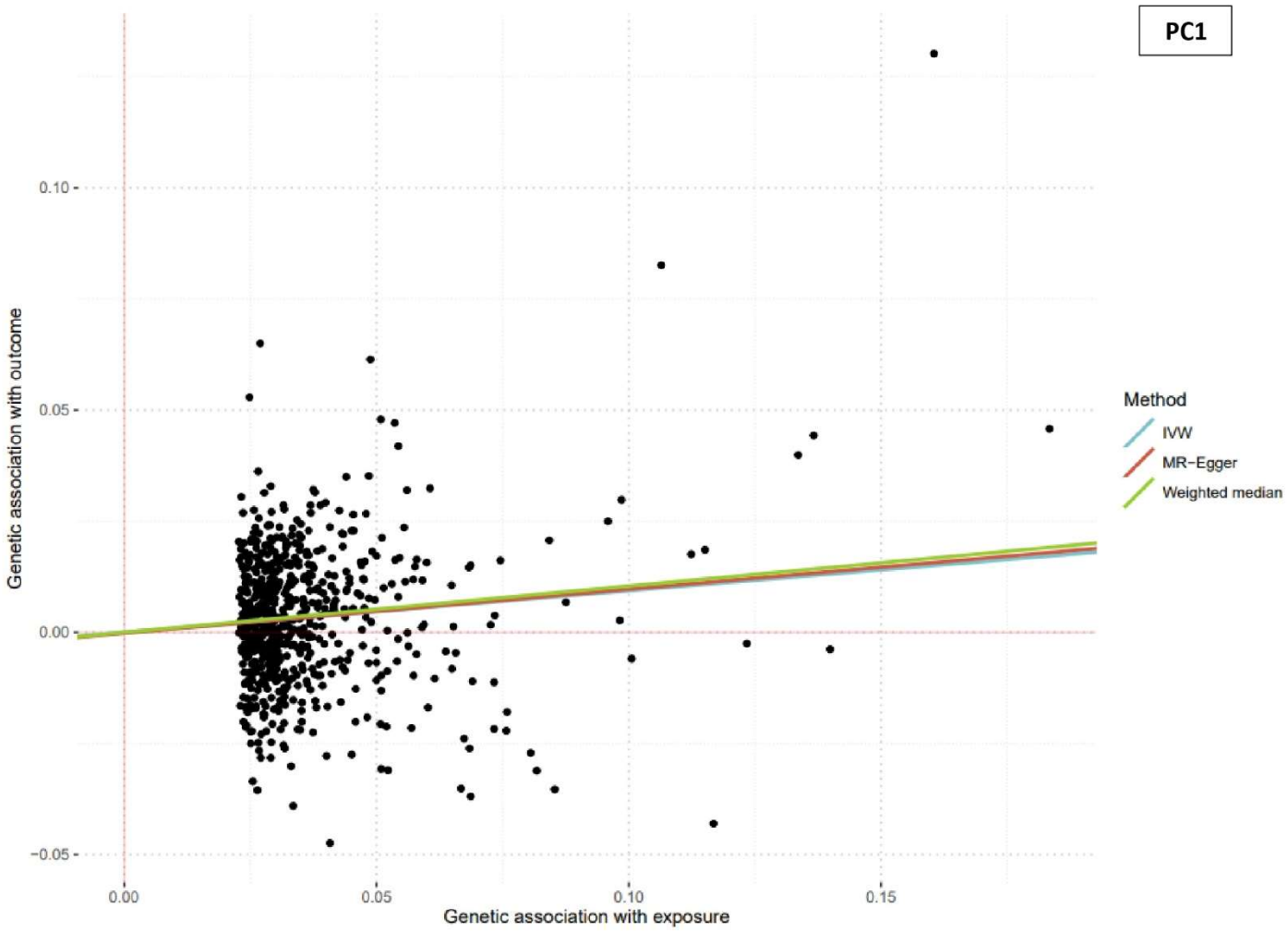


Figure S9. Scatter plot depicting the genetic associations of the body shape PC1 related instruments with the risk of overall colorectal cancer. PC, principal component.

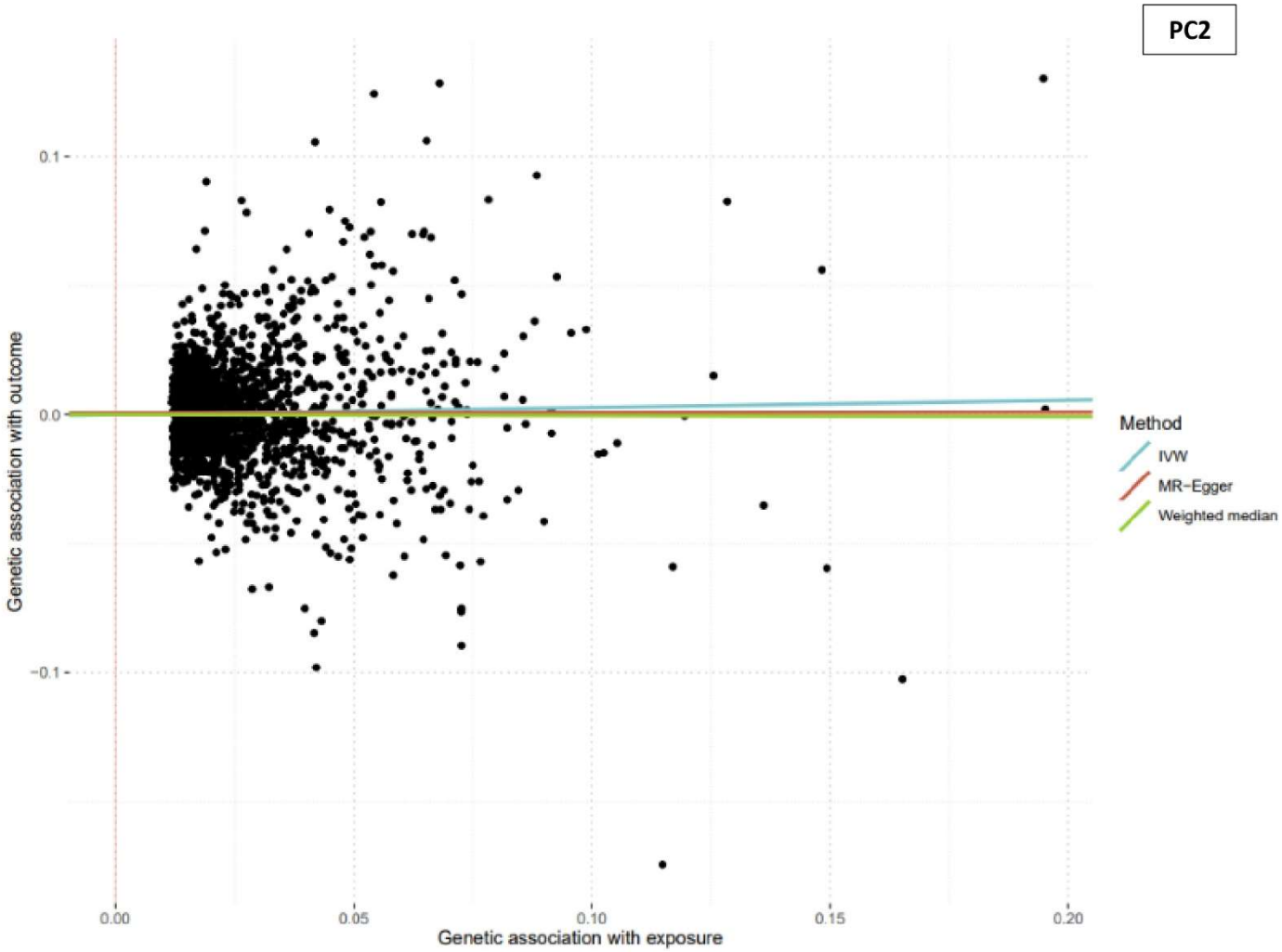


Figure S10. Scatter plot depicting the genetic associations of the body shape PC2 related instruments with the risk of overall colorectal cancer. PC, principal component.

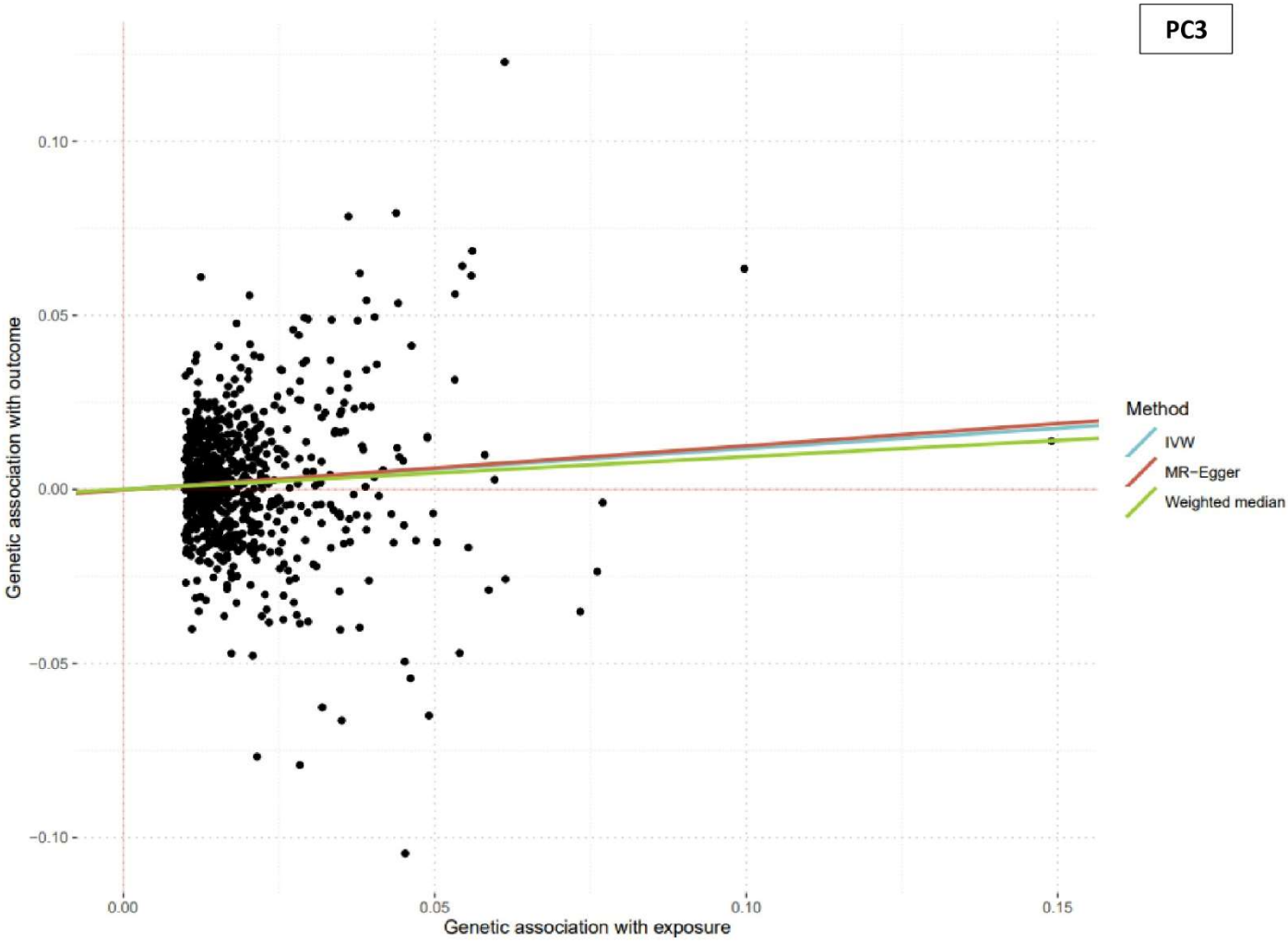


Figure S11. Scatter plot depicting the genetic associations of the body shape PC3 related instruments with the risk of overall colorectal cancer. PC, principal component.

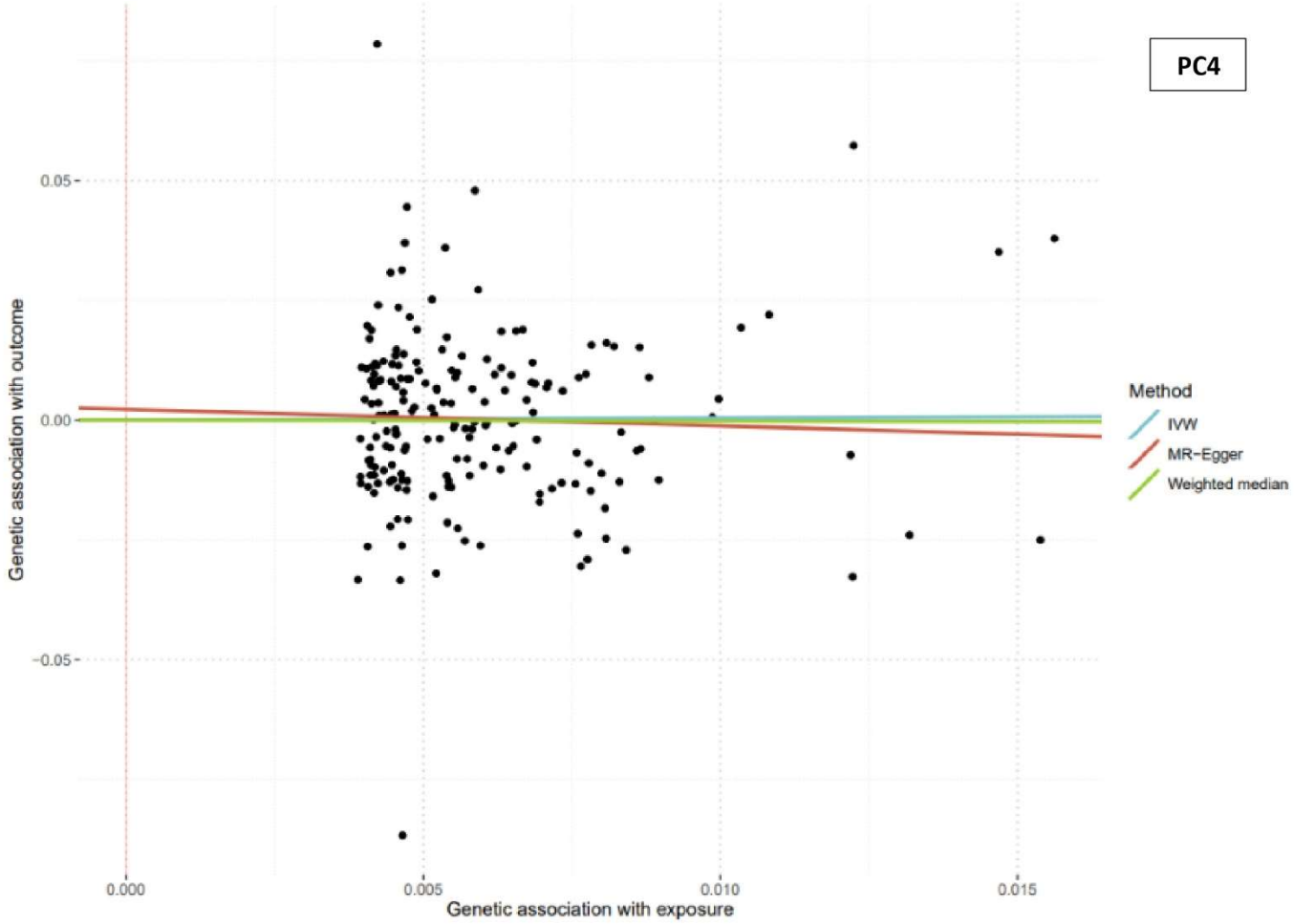


Figure S12. Scatter plot depicting the genetic associations of the body shape PC4 related instruments with the risk of overall colorectal cancer. PC, principal component.

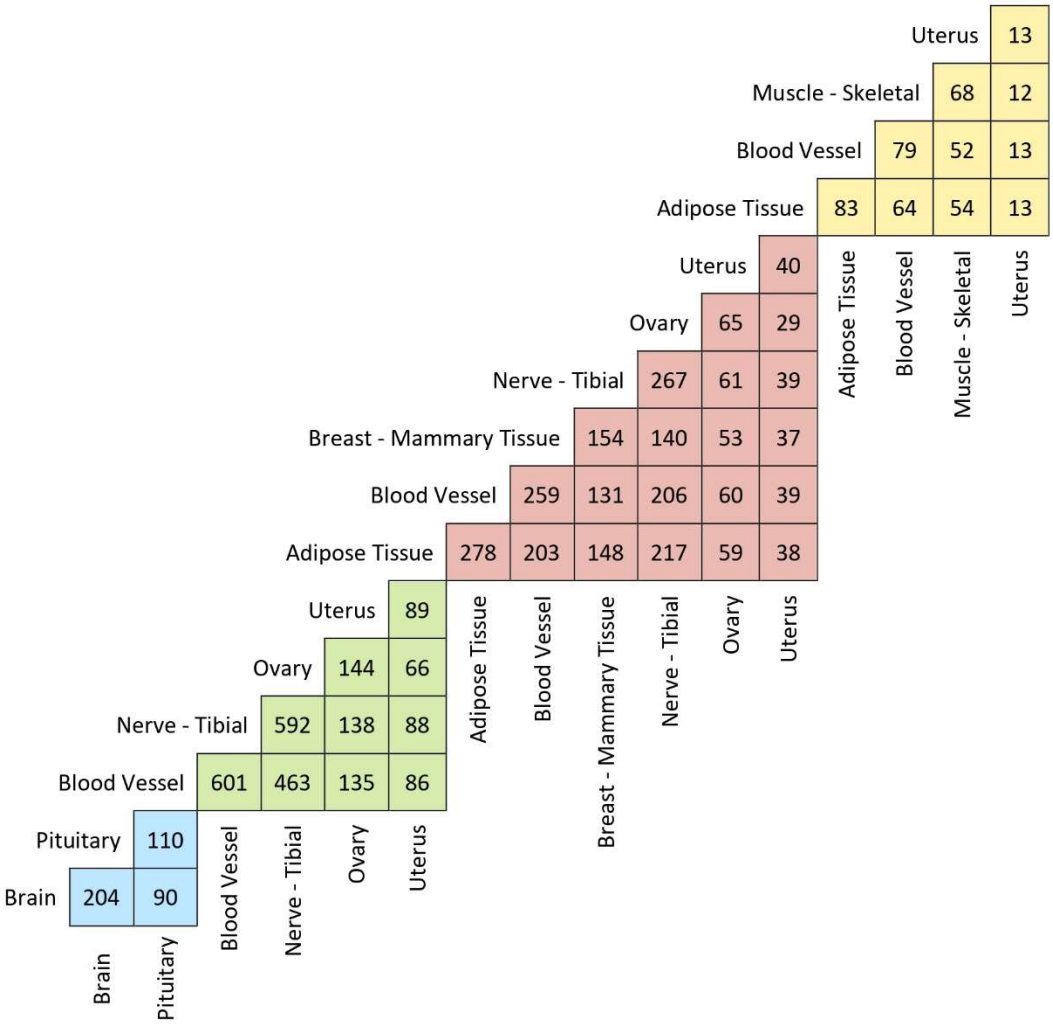


Figure S13. Number of genetic variants included in the tissue-specific MR analysis that are shared between tissues of each body shape phenotype (PC1 – 4). PC1 in blue, PC2 in green, PC3 in red, and PC4 in yellow.

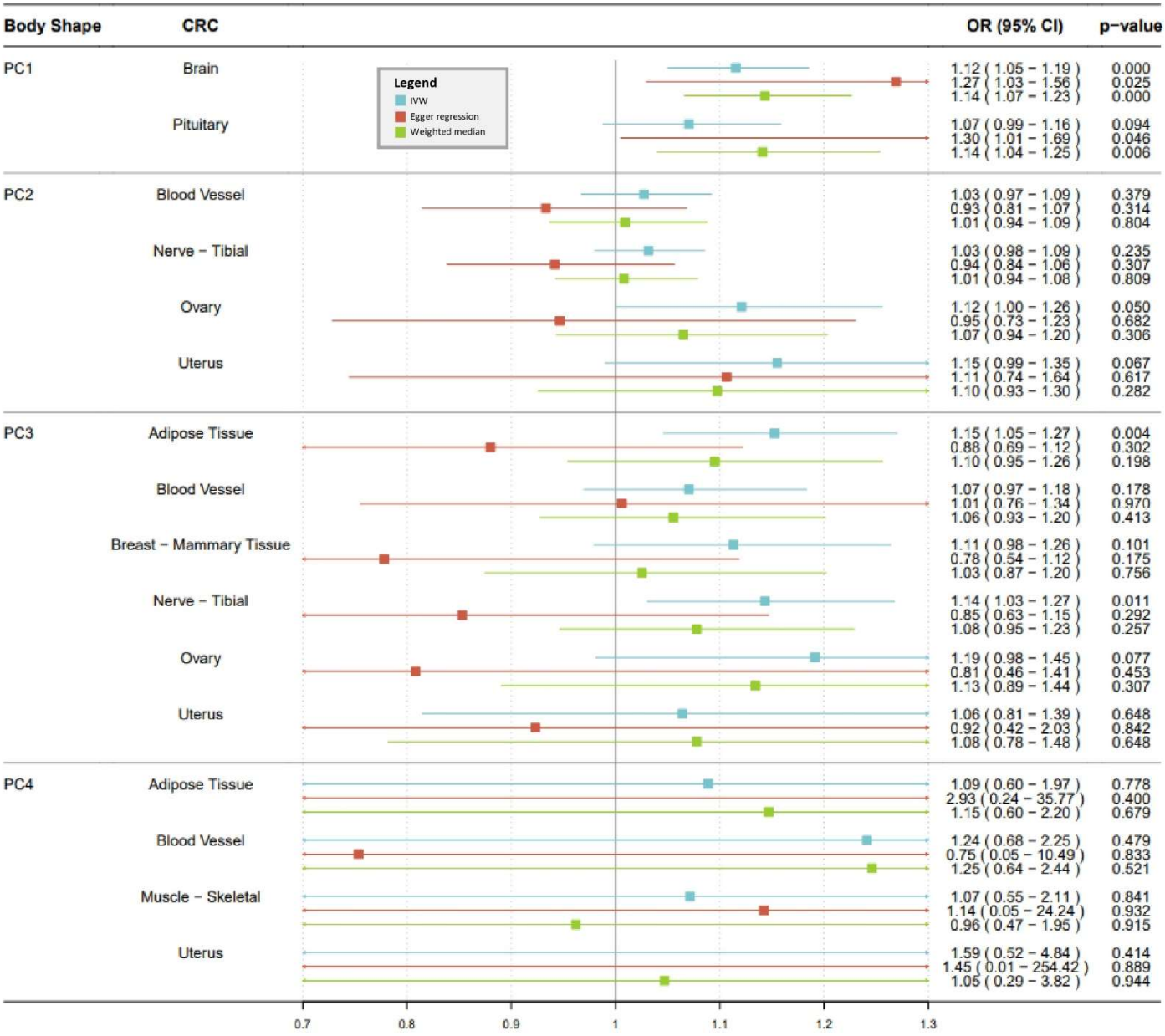


Figure S14. Mendelian randomization (MR) estimates between body shape phenotypes (PC1 - 4) grouped gene sets and overall colorectal cancer (CRC) risk using random-effects inverse-variance weighted (IVW) (blue), MR Egger regression (red) and weighted median (green) MR approaches. CI, confidence interval; OR, odds ratio; PC, principal component.

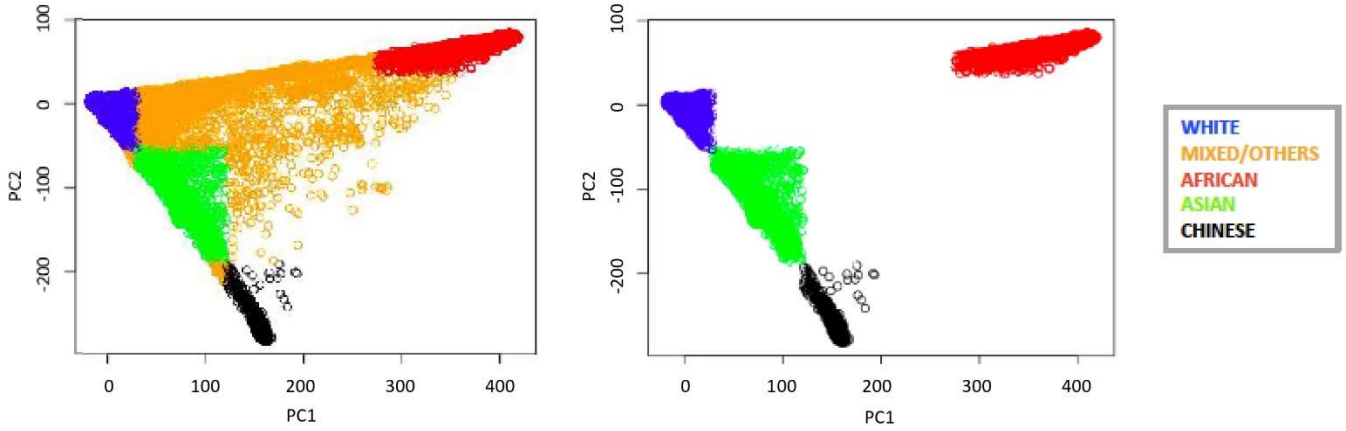


Figure S15. Clustering of individuals by ethnicity. Plot of genetic principal component (PC) 1 and PC2 for all the individuals included in the genetic analysis (n= 460,198). Based on self-reported information (White, other, mixed, or missing) and the clustering, 5 (White, mixed/others, African, Asian, and Chinese) and 4 (White, African, Asian, and Chinese) ethnic groups are represented in the left and right figures, respectively.

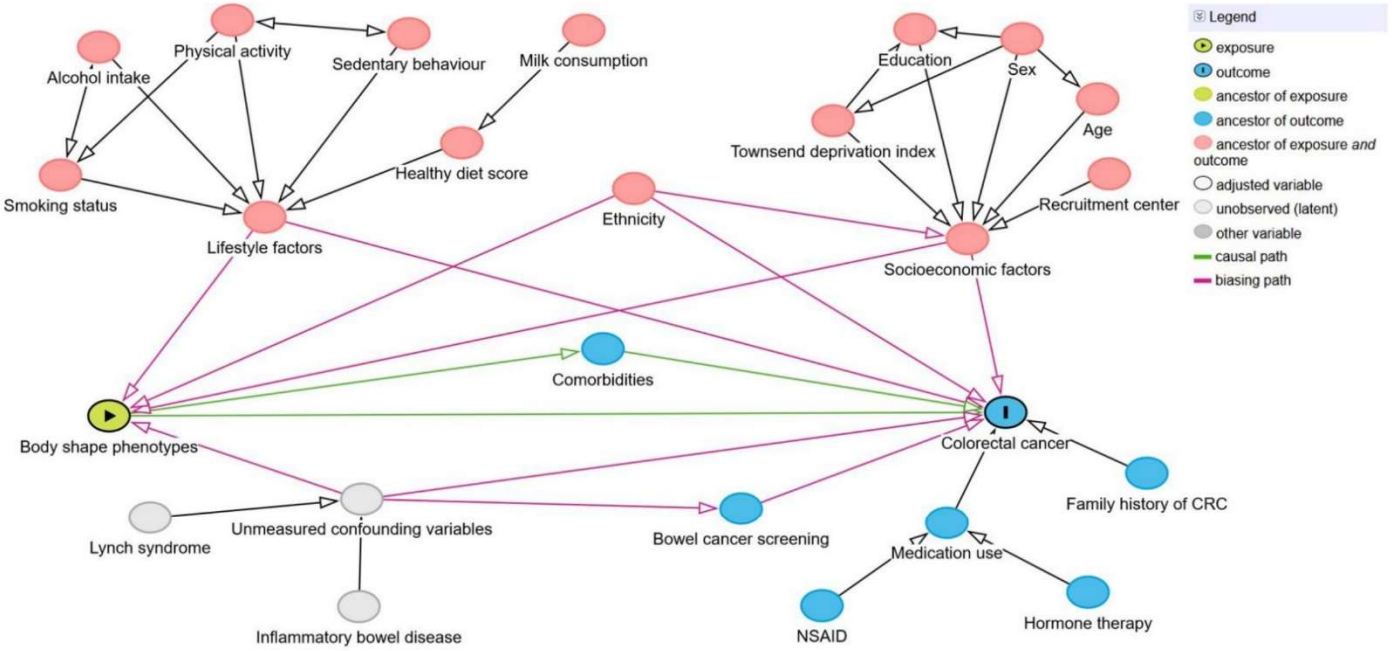


Figure S16. Extended directed acyclic graph (DAG) depicting the assumed causal relationship between body shape phenotypes and colorectal cancer risk with its confounding and mediating paths.
Socioeconomic factors: age, sex, recruitment center, the Townsend deprivation index, and education; ethnicity: White, Mixed, Asian/British Asian, Black/Black British, Chinese, other; lifestyle factors: tobacco smoking, physical activity, sedentary behavior, adherence to a healthy diet score, milk intake, alcohol intake frequency; medication use: nonsteroidal anti-inflammatory drugs (NSAID) and hormone therapy in postmenopausal women; bowel cancer screening, and family history of colorectal cancer (father and/or mother).

We did not adjust for comorbidities such as type 2 diabetes, because we assumed that in the pathway from body shapes to colorectal cancer this comorbidity would rather be a mediator than a confounder.

Unmeasured (known) confounders: inflammatory bowel syndrome and Lynch syndrome. Both phenotypes are difficult to diagnose clinically and data availability in the UK Biobank is therefore limited. However, as indicated in the DAG, we assumed that the confounding paths for both phenotypes are at least partly blocked by accounting for family history of colorectal cancer.

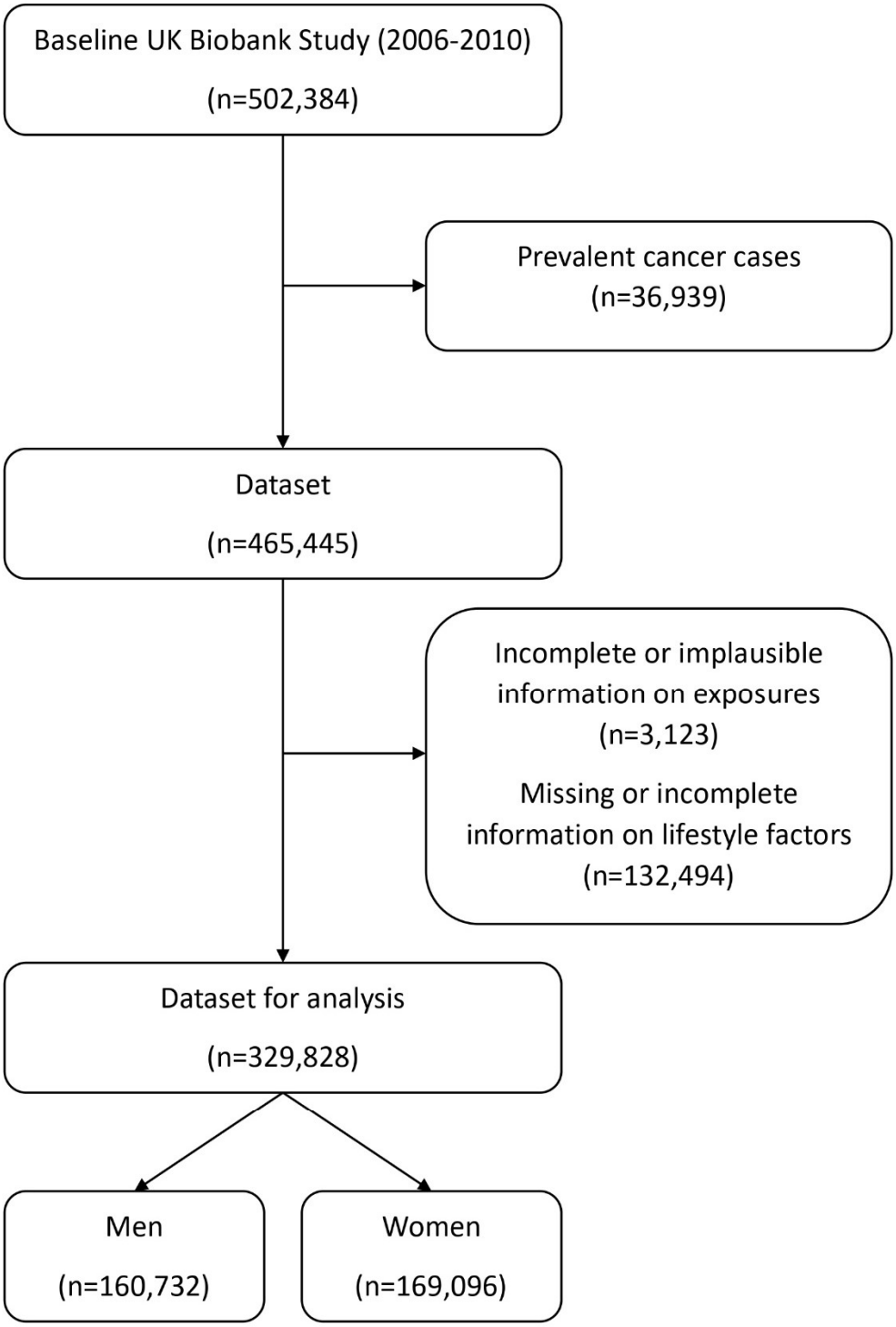


Figure S17. Flowchart of the UK Biobank study population.

Observational Analysis	PC1	PC2	PC3	PC4
Height	0.081	0.853	0.417	0.023
Weight	0.478	0.218	-0.078	0.509
BMI	0.471	-0.154	-0.288	0.471
HC	0.448	0.180	-0.404	-0.606
WC	0.488	-0.109	0.167	-0.388
WHR	0.323	-0.395	0.739	-0.020
Proportion of variance	0.662	0.194	0.123	0.020
Cumulative Proportion	0.662	0.856	0.979	0.999
Genetic Analysis	**PC1**	**PC2**	**PC3**	**PC4**
Height	0.072	0.865	0.399	0.020
Weight	0.478	0.217	-0.082	0.512
BMI	0.472	-0.152	-0.279	0.469
HC	0.448	0.172	-0.406	-0.604
WC	0.488	-0.101	0.168	-0.391
WHR	0.323	-0.376	0.751	-0.019
Proportion of variance	0.663	0.192	0.125	0.019
Cumulative Proportion	0.663	0.855	0.980	0.999

Table S1. Principal components (PC) loadings, proportion of variance and cumulative proportion for the individuals included in observational and genetic analyses. Sample size in observational analysis = 329,828 and in genetic analysis = 460,198 participants. BMI, body mass index; HC, hip circumference; WC, waist circumference; WHR, waist-to-hip ratio.

	PC1		PC2		PC3		PC4	
	Men	**Women**	**Men**	**Women**	**Men**	**Women**	**Men**	**Women**
Height	0.042	0.113	0.851	0.842	0.448	0.414	0.022	0.050
Weight	0.481	0.475	0.226	0.208	-0.086	-0.070	0.489	0.492
BMI	0.479	0.463	-0.106	-0.195	-0.272	-0.289	0.479	0.502
HC	0.457	0.440	0.181	0.197	-0.354	-0.444	-0.609	-0.584
WC	0.489	0.485	-0.110	-0.109	0.184	0.137	-0.399	-0.398
WHR	0.300	0.344	-0.410	0.398	0.747	0.724	0.028	-0.063

Table S2. Principal components (PC) loadings by sex (genetic analyses sample size). BMI, body mass index; HC, hip circumference; WC, waist circumference; WHR, waist-to-hip ratio.

	Men (n=160,732)					Women (n=169,096)				
	Q1	Q2	Q3	Q4	Q5	Q1	Q2	Q3	Q4	Q5
	Mean (SD) or %					Mean (SD) or %				
No. (%)	32,121 (20.0)	31,902 (19.8)	32,419 (20.2)	32,017 (19.9)	32,273 (20.1)	33,791 (20.0)	34,019 (20.1)	33,897 (20.0)	33,682 (19.9)	33,707 (19.9)
Age at recruitment (years)	56.5 (8.3)	56.5 (8.2)	56.4 (8.2)	56.4 (8.1)	56.0 (8.0)	55.1 (8.1)	55.3 (8.1)	56.0 (8.0)	56.2 (7.9)	55.6 (7.8)
Median follow-up time (years)	10.9	10.9	10.9	10.9	10.9	10.9	11.0	10.9	11.0	10.9
Anthropometric variables										
Weight (kg)	69.7 (5.7)	78.2 (4.3)	84.2 (4.4)	91.1 (4.9)	106.0 (11.5)	56.1 (4.6)	63.2 (3.9)	68.6 (4.2)	75.4 (4.9)	91.5 (12.0)
Height (cm)	173.6 (6.6)	175.2 (6.5)	176.1 (6.5)	177.0 (6.6)	178.0 (6.8)	161.5 (6.0)	162.8 (6.2)	163.1 (6.3)	163.2 (6.3)	163.5 (6.3)
Body mass index (kg/m^2)	23.2 (1.8)	25.5 (1.5)	27.2 (1.5)	29.1 (1.7)	33.5 (3.6)	21.5 (1.7)	23.9 (1.5)	25.8 (1.6)	28.3 (1.9)	34.3 (4.5)
Waist circumference (cm)	83.0 (4.7)	90.6 (3.1)	95.6 (3.1)	101.1 (3.4)	112.4 (8.2)	69.7 (3.8)	76.6 (3.1)	82.2 (3.4)	88.9 (4.1)	102.1 (8.8)
Hip circumference (cm)	95.5 (3.9)	99.8 (3.3)	102.6 (3.3)	105.8 (3.5)	113.0 (7.0)	92.5 (4.3)	97.7 (3.9)	101.3 (4.1)	105.9 (4.7)	117.1 (9.5)
Waist-to-hip ratio	0.9 (0.1)	0.9 (0.1)	0.9 (0.1)	1.0 (0.1)	1.0 (0.1)	0.8 (0.1)	0.8 (0.1)	0.8 (0.1)	0.8 (0.1)	0.9 (0.1)
Caucasian ethnicity (%)	94.2	95.0	95.7	96.2	96.5	95.7	96.1	95.7	95.0	93.9
Townsend deprivation index	-1.4 (3.1)	-1.6 (3.0)	-1.6 (2.90)	-1.6 (3.0)	-1.2 (3.1)	-1.5 (2.9)	-1.7 (2.9)	-1.7 (2.8)	-1.4 (2.9)	-0.9 (3.2)
Regular NSAID use (%)	21.4	25.1	27.2	30.7	36.3	20.1	22.4	24.8	27.5	32.1
Hormone replacement therapy (%)	0	0	0	0	0	32.8	35.2	37.7	39.0	36.0
Family history of CRC (%)	6.5	6.8	7.1	6.9	6.6	5.8	5.6	6.0	5.7	5.4
Bowel cancer screening (%)	31.6	32.2	32.5	32.5	31.1	28.1	28.1	29.5	29.9	28.9
Highest qualification (%)										
College/University degree	44.9	41.4	38.3	34.3	30.3	42.5	39.0	35.6	32.5	29.7
A-levels/AS-levels or equivalent	22.7	23.9	24.6	25.6	26.1	21.9	21.8	22.6	23.4	23.7
O-levels/GCSEs or equivalent	20.7	22.6	23.9	25.6	27.2	25.9	28.2	28.9	29.7	30.9
None (of the above)	11.8	12.1	13.2	14.5	16.4	9.8	11.0	12.9	14.5	15.6
MET (min/week)	3153.9 (2992.8)	2925.6 (2850.6)	2784.3 (2801.7)	2671.5 (2795.6)	2322.8 (2656.5)	2891.9 (2590.9)	2729.9 (2483.4)	2568.8 (2409.5)	2422.0 (2366.6)	2085.4 (2252.0)
Sedentary behavior (h/day)	4.5 (2.4)	4.9 (2.4)	5.2 (2.5)	5.5 (2.6)	6.1 (2.9)	3.8 (1.9)	4.0 (1.9)	4.3 (2.0)	4.6 (2.1)	5.0 (2.4)
Highest diet score (%)										
Lowest	0.3	0.2	0.3	0.3	0.4	0.0	0.0	0.1	0.1	0.1
Low	1.9	1.8	1.9	2.3	3.0	0.5	0.5	0.5	0.7	1.1
Low/medium	8.5	8.8	10.1	11.2	13.0	3.6	3.8	4.2	4.5	6.3
Medium	26.5	29.4	30.5	32.3	34.6	18.3	20.2	21.3	23.0	25.5
Medium/high	38.4	39.4	39.2	37.8	35.3	46.0	47.8	47.2	47.0	44.8
High	20.8	18.0	16.1	14.7	12.4	27.0	24.2	23.5	21.8	19.8
Highest	3.6	2.4	2.0	1.5	1.3	4.6	3.5	3.1	2.9	2.5
Milk intake >300ml/day (%)	74.1	75.0	73.3	72.9	70.8	68.8	71.8	73.4	72.5	70.7
Smoking status (%)										
Never	57.8	53.6	51.0	46.8	43.6	64.7	61.9	60.1	58.5	57.7
Previous	29.3	35.4	38.1	42.2	45.1	27.1	30.4	32.1	33.3	34.0
Current	12.9	11.0	10.9	11.0	11.3	8.3	7.8	7.8	8.2	8.4
Alcohol intake (%)										
Daily or almost daily	27.3	28.0	27.6	26.6	23.1	20.5	19.2	18.5	16.4	11.4
3-4 times per week	26.7	28.4	28.6	28.3	24.5	24.2	24.9	23.1	21.5	16.4
1-2 times per week	24.2	25.1	25.3	25.8	27.6	25.4	26.8	27.0	26.5	25.0
1-3 times per month	8.4	7.9	8.0	8.3	10.7	11.1	11.6	12.5	13.5	16.1
Special occasions only	7.0	5.8	5.6	6.0	8.0	11.0	10.9	12.0	14.0	20.0
Never	6.4	4.8	4.8	4.9	6.2	7.7	6.8	6.9	8.2	11.2

Table S3. Baseline characteristics of participants according to sex-specific quintiles of loadings of principal component 1 in the UK Biobank (observational analysis sample size). Sex-specific quintiles of loadings of principal component 1 were defined by their distribution (20th quantile, 40th quantile, 60th quantile, 80th quantile); for men: 20th quantile=-0.76, 40th quantile=-0.32, 60th quantile=0.10, 80th quantile=0.65; for women: 20th quantile=-0.91, 40th quantile=-0.45, 60th quantile=0.03, 80th quantile=0.71. CRC: colorectal cancer; NSAID: non-steroidal anti-inflammatory drug.

Complete case					
		PC1	PC2	PC3	PC4
	Cases (n)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
TOTAL (n=329,828)					
Colon	2443	**1.16 (1.11-1.21)**	0.97 (0.93-1.01)	**1.10 (1.06-1.14)**	0.99 (0.95-1.03)
Colon distal	966	**1.15 (1.07-1.23)**	0.97 (0.91-1.04)	**1.10 (1.03-1.17)**	0.96 (0.90-1.03)
Colon proximal	1370	**1.17 (1.11-1.24)**	0.97 (0.91-1.02)	**1.11 (1.05-1.17)**	1.00 (0.94-1.05)
Colorectal	3728	**1.13 (1.09-1.17)**	0.98 (0.94-1.01)	**1.09 (1.05-1.13)**	0.99 (0.96-1.03)
Rectum	1285	**1.07 (1.01-1.14)**	0.99 (0.93-1.04)	**1.07 (1.01-1.14)**	1.00 (0.95-1.06)
MEN (n=160,732)					
Colorectal	2239	**1.17 (1.11-1.23)**	0.97 (0.93-1.02)	**1.09 (1.04-1.15)**	0.98 (0.94-1.02)
WOMEN (n=169,096)					
Colorectal	1489	**1.09 (1.03-1.15)**	0.97 (0.92-1.03)	**1.08 (1.03-1.13)**	1.00 (0.94-1.05)
Never smokers					
TOTAL (n=183,679)					
Colon	1207	**1.16 (1.09-1.23)**	0.96 (0.91-1.02)	**1.11 (1.05-1.17)**	1.01 (0.96-1.07)
Colon distal	468	**1.12 (1.01-1.23)**	0.99 (0.90-1.09)	1.05 (0.96-1.15)	1.01 (0.92-1.11)
Colon proximal	683	**1.19 (1.10-1.29)**	0.94 (0.87-1.02)	**1.14 (1.06-1.23)**	1.00 (0.93-1.08)
Colorectal	1787	**1.13 (1.07-1.19)**	0.95 (0.90-1.00)	**1.09 (1.04-1.14)**	1.00 (0.95-1.05)
Rectum	580	1.08 (0.98-1.18)	0.93 (0.85-1.01)	1.06 (0.97-1.15)	0.96 (0.88-1.05)
MEN (n=81,263)					
Colorectal	949	**1.20 (1.11-1.29)**	0.91 (0.86-0.98)	**1.12 (1.04-1.20)**	0.97 (0.91-1.04)
WOMEN (n=102,416)					
Colorectal	838	1.07 (1.00-1.15)	0.98 (0.92-1.06)	1.07 (1.00-1.14)	1.00 (0.93-1.08)
Follow-up time > 2 years					
TOTAL (n=324,431)					
Colon	2087	**1.17 (1.12-1.23)**	0.97 (0.93-1.02)	**1.10 (1.05-1.15)**	1.00 (0.95-1.04)
Colon distal	802	**1.14 (1.06-1.23)**	0.96 (0.89-1.03)	**1.10 (1.02-1.18)**	0.97 (0.90-1.04)
Colon proximal	1206	**1.18 (1.11-1.26)**	0.97 (0.91-1.03)	**1.10 (1.04-1.17)**	1.02 (0.96-1.08)
Colorectal	3173	**1.14 (1.10-1.18)**	0.97 (0.94-1.01)	**1.09 (1.05-1.13)**	1.00 (0.97-1.04)
Rectum	1086	**1.08 (1.01-1.15)**	0.99 (0.93-1.05)	**1.07 (1.00-1.14)**	1.01 (0.95-1.08)
MEN (n=157,710)					
Colorectal	1875	**1.17 (1.11-1.23)**	0.98 (0.93-1.02)	**1.09 (1.03-1.15)**	0.98 (0.94-1.03)
WOMEN (n=166,721)					
Colorectal	1298	**1.11 (1.05-1.18)**	0.97 (0.91-1.03)	**1.08 (1.03-1.14)**	1.01 (0.96-1.07)
Crude model					
TOTAL (n=329,828)					
Colon	2443	**1.18 (1.13-1.23)**	0.98 (0.94-1.02)	**1.11 (1.06-1.15)**	0.99 (0.95-1.03)
Colon distal	966	**1.16 (1.09-1.24)**	0.98 (0.92-1.04)	**1.11 (1.04-1.18)**	0.96 (0.90-1.03)
Colon proximal	1370	**1.19 (1.12-1.25)**	0.98 (0.93-1.03)	**1.12 (1.06-1.18)**	0.99 (0.94-1.05)
Colorectal	3728	**1.14 (1.10-1.18)**	0.98 (0.95-1.02)	**1.10 (1.06-1.14)**	0.99 (0.96-1.02)
Rectum	1285	**1.07 (1.01-1.14)**	0.99 (0.94-1.05)	**1.09 (1.02-1.15)**	1.00 (0.95-1.06)
MEN (n=160,732)					
Colorectal	2239	**1.18 (1.13-1.24)**	0.98 (0.94-1.02)	**1.11 (1.05-1.16)**	0.97 (0.93-1.02)
WOMEN (n=169,096)					
Colorectal	1489	**1.10 (1.04-1.16)**	0.99 (0.93-1.04)	**1.08 (1.03-1.14)**	1.00 (0.95-1.05)

Table S4. Associations between body shape phenotypes (PC1 - 4) per 1 SD increment and colorectal cancer (CRC) incidence in the complete case dataset (n=329,828), in never smokers (n=183,679), after further excluding the initial 2 years of follow-up (n=324,431), and as a crude model (n=329,828). Hazard ratios per 1 SD increment in each PC from Cox proportional hazards regression using age as the underlying time metric. Stratified by sex, age in 5-year categories, and center. Adjusted for ethnicity, Townsend deprivation index, intake of non-steroidal anti-inflammatory drugs, education, smoking status, alcohol status and intake frequency, MET Min/week, sedentary behavior, healthy diet score, milk intake, hormone replacement therapy, family history of CRC, bowel cancer screening. All four principal components were mutually adjusted. Crude hazard ratios per 1 SD increment in each PC from Cox proportional hazards regression using age as the underlying time metric in the complete case dataset (n=329,828). Stratified by sex, age in 5-year categories, and center. All four principal components were mutually adjusted. Bold font indicates statistical significance (p-value < 0.05). PC, principal component.

Outcome	Exposure	Heterogeneity			Egger intercept		
		Cochran's Q	df	p-value	Estimate	95% CI	p-value
Overall	PC1	999.099	671	< 0.001	0.000	-0.003 , 0.003	0.898
	PC2	3043.754	1773	< 0.001	0.001	-0.001 , 0.002	0.382
	PC3	1139.40	733	< 0.001	0.000	-0.003 , 0.003	0.892
	PC4	450.8924	192	< 0.001	0.002	-0.007 , 0.012	0.649
Overall (Men)	PC1	894.842	671	< 0.001	0.000	-0.004 , 0.004	0.923
	PC2	2408.643	1773	< 0.001	0.001	-0.001 , 0.003	0.354
	PC3	960.500	733	< 0.001	0.000	-0.003 , 0.004	0.832
	PC4	326.4463	192	< 0.001	0.004	-0.007 , 0.016	0.487
Overall (Women)	PC1	778.338	671	0.003	-0.001	-0.004 , 0.003	0.764
	PC2	2587.901	1773	< 0.001	0.001	-0.001 , 0.003	0.554
	PC3	888.611	733	< 0.001	-0.001	-0.004 , 0.003	0.763
	PC4	325.8687	192	< 0.001	0.001	-0.011 , 0.012	0.903
Colon	PC1	950.152	671	< 0.001	0.000	-0.004 , 0.003	0.954
	PC2	2789.540	1773	< 0.001	0.000	-0.002 , 0.002	0.738
	PC3	1025.401	733	< 0.001	-0.001	-0.004 , 0.002	0.541
	PC4	373.7163	192	< 0.001	0.002	-0.008 , 0.013	0.668
Distal colon	PC1	866.015	671	< 0.001	0.000	-0.004 , 0.004	0.964
	PC2	2424.078	1773	< 0.001	0.001	-0.002 , 0.003	0.513
	PC3	919.797	733	< 0.001	-0.001	-0.005 , 0.003	0.550
	PC4	317.9822	192	< 0.001	-0.002	-0.014 , 0.011	0.766
Proximal colon	PC1	898.1401	671	< 0.001	0.000	-0.004 , 0.004	0.948
	PC2	2493.266	1773	< 0.001	0.000	-0.003 , 0.002	0.773
	PC3	936.479	733	< 0.001	0.000	-0.004 , 0.003	0.878
	PC4	289.055	192	< 0.001	0.007	-0.004 , 0.019	0.221
Rectal	PC1	803.636	671	< 0.001	0.000	-0.004 , 0.005	0.871
	PC2	2372.954	1773	< 0.001	0.001	-0.001 , 0.004	0.248
	PC3	921.793	733	< 0.001	-0.002	-0.006 , 0.002	0.392
	PC4	376.2022	192	< 0.001	0.000	-0.014 , 0.014	0.995

Table S5. Heterogeneity test and Egger intercept results for body shape phenotypes (PC1 - 4) and overall colorectal cancer risk, subsites and by sex. CI, confidence interval; PC, principal component.

PC	Tissue	Heterogeneity			Egger intercept		
		Cochran's Q	df	p-value	Estimate	95% CI	p-value
PC1	Brain	394.3695	203	< 0.001	-0.005	-0.012 , 0.003	0.207
	Pituitary	205.2431	109	< 0.001	-0.007	-0.017 , 0.002	0.118
PC2	Blood vessel	1169.7420	600	< 0.001	0.002	0.000 , 0.005	0.089
	Nerve - Tibial	1092.7574	591	< 0.001	0.003	-0.000 , 0.005	0.080
	Ovary	341.2845	143	< 0.001	0.005	-0.002 , 0.011	0.161
	Uterus	212.7641	88	< 0.001	0.001	-0.008 , 0.010	0.817
PC3	Adipose tissue	453.8644	277	< 0.001	0.005	0.001 , 0.010	0.018
	Blood Vessel	393.5795	258	< 0.001	0.001	-0.004 , 0.006	0.648
	Breast	241.6158	153	< 0.001	0.007	0.000 , 0.013	0.039
	Nerve - Tibial	440.7192	266	< 0.001	0.005	0.000 , 0.011	0.039
	Ovary	100.4234	64	0.0025	0.007	-0.002 , 0.017	0.145
	Uterus	67.2299	39	0.0033	0.003	-0.011 , 0.016	0.707
PC4	Adipose tissue	167.2578	82	< 0.001	-0.006	-0.020 , 0.008	0.425
	Blood Vessel	147.6044	78	< 0.001	0.003	-0.012 , 0.017	0.703
	Muscle	146.9878	67	< 0.001	0.000	-0.017 , 0.017	0.966
	Uterus	16.8309	12	0.1561	0.001	-0.030 , 0.031	0.971

Table S6. Heterogeneity test and Egger intercept results for body shape phenotypes (PC1 - 4) grouped gene sets and overall colorectal cancer risk. CI, confidence interval; PC, principal component.

	PC1				PC2			
	5th	95th	Difference	SD-unit difference	5th	95th	Difference	SD-unit difference
BMI (kg/m^2)	20.6	39.5	18.9	3.9	29.2	26.1	-3.1	-0.6
Weight (kg)	56.1	112.3	56.2	3.5	72.6	86.6	14.0	0.9
Height (cm)	165.0	168.7	3.7	0.4	157.4	181.8	24.4	2.7
WHR	0.8	0.9	0.1	1.0	0.9	0.8	-0.1	-1.0
WC (cm)	70.2	117.8	47.6	3.5	94.4	88.9	-5.5	-0.4
HC (cm)	90.2	125.8	35.6	3.9	100.1	107.5	7.4	0.8
	PC3				PC4			
	5th	95th	Difference	SD-unit difference	5th	95th	Difference	SD-unit difference
BMI (kg/m^2)	33.1	26.9	-6.2	-1.3	28.2	31.2	3.0	0.6
Weight (kg)	86.8	79.3	-7.5	-0.5	79.2	90.0	10.8	0.7
Height (cm)	161.8	171.3	9.5	1.0	168.1	169.4	1.3	0.1
WHR	0.8	1.0	0.2	2.0	0.9	0.9	0.0	0.0
WC (cm)	92.6	97.2	4.6	0.3	99.1	92.4	-6.7	-0.5
HC (cm)	116.4	99.9	-16.5	-1.8	111.3	102.5	-8.8	-1.0

Table S7. Mean values and the difference in standard deviation (SD) units of each anthropometric trait for study participants in the top and bottom 5% of each body shape phenotypes (PC1 - 4). 1 SD unit for BMI in the study population corresponded to 4.8 kg/m^2, weight = 15.9 kg, height = 9.2 cm, WHR = 0.1, WC = 13.5 cm, HC = 9.2 cm. For instance, the difference between 95th and 5th percentile in PC1 corresponds to 3.9 SD BMI-units difference (18.9 / 4.8 = 3.9). BMI, body mass index; HC, hip circumference; PC, principal component; WC, waist circumference; WHR, waist-to-hip ratio.

	Men	Women
PC1	0.015 (1.86)	-0.028 (2.08)
PC2	0.042 (1.09)	0.043 (1.03)
PC3	0.008 (0.76)	-0.001 (0.93)
PC4	0.003 (0.34)	0.002 (0.34)

Table S8. Mean and standard deviations of principal component (PC) scores for each body shape phenotypes (PC1 - 4) and by sex. PC, principal component.

General tissue	Specific tissue	Sample size
Adipose Tissue	Subcutaneous	581
	Visceral (Omentum)	469
Blood Vessel	Aorta	387
	Coronary	213
	Tibial	584
Brain	Amygdala	129
	Anterior cingulate cortex (BA24)	147
	Caudate (basal ganglia)	194
	Cerebellar Hemisphere	175
	Cerebellum	209
	Cortex	205
	Front Cortex (BA9)	175
	Hippocampus	165
	Hypothalamus	170
	Nucleus accumbens (basal ganglia)	202
	Putamen (basal ganglia)	170
	Spinal cord (cervical c-1)	126
	Substantia nigra	114
Breast - Mammary Tissue		396
Muscle - Skeletal		706
Nerve -Tibial		532
Ovary		167
Pituitary		237
Uterus		129

Table S9. GTEx data sample sizes by specific tissue.

Body shape	General tissue	Specific tissue	Num. genetic variants
PC1	Brain	Amygdala	40
		Anterior cingulate cortex (BA24)	55
		Caudate (basal ganglia)	87
		Cerebellar Hemisphere	113
		Cerebellum	135
		Cortex	105
		Front Cortex (BA9)	89
		Hippocampus	58
		Hypothalamus	56
		Nucleus accumbens (basal ganglia)	84
		Putamen (basal ganglia)	74
		Spinal cord (cervical c-1)	47
		Substantia nigra	30
	Pituitary		110
PC2	Blood Vessel	Aorta	418
		Coronary	181
		Tibial	550
	Nerve-Tibial		592
	Ovary		144
	Uterus		89
PC3	Adipose Tissue	Subcutaneous	258
		Visceral (Omentum)	180
	Blood Vessel	Aorta	181
		Coronary	75
		Tibial	231
	Breast – Mammary Tissue		154
	Nerve-Tibial		267
	Ovary		65
	Uterus		40
PC4	Adipose Tissue	Subcutaneous	79
		Visceral (Omentum)	55
	Blood Vessel	Aorta	54
		Coronary	28
		Tibial	73
	Muscle – Skeletal		68
	Uterus		13

Table S10. Genetic variants mapped in each specific tissue included as genetic instruments in the specific-tissue MR analysis. PC, principal component.

Summary statistics for the genetic association with body shape PC1

rsid	CHR	BP	GENPOS	ALLELE1	ALLELE0	A1FREQ	INFO	CHISQ_LINREG	P_LINREG	BETA	SE	CHISQ_BOLT_LMM_INF	pval
rs10749659	1	151033979	0	C	T	0.227435	0.996126	39.6929	3.00E-10	0.031006	0.00492265	39.6728	3.00E-10
rs10799782	1	23313923	0	T	A	0.165728	0.995792	47.9125	4.50E-12	0.0388902	0.00554472	49.1951	2.30E-12
rs10803149	1	243818286	0	A	T	0.131435	0.990097	41.2469	1.30E-10	0.0390655	0.00613792	40.5084	2.00E-10
rs10915840	1	225668524	0	G	A	0.725842	0.988667	32.5465	1.20E-08	0.0266276	0.00465001	32.791	1.00E-08
rs1108548	1	218634787	0	A	G	0.723235	0.992477	39.6541	3.00E-10	-0.0290489	0.00462237	39.4937	3.30E-10
rs11165493	1	96274928	0	G	A	0.656738	0.98478	43.1903	5.00E-11	-0.0288559	0.00436789	43.6441	3.90E-11
rs11165643	1	96924097	0	C	T	0.408975	0.998087	73.859	8.40E-18	-0.0360364	0.00418798	74.0414	7.60E-18
rs11205303	1	149906413	0	T	C	0.593201	1	33.0193	9.10E-09	-0.0239331	0.00420308	32.4236	1.20E-08
rs11208659	1	65979280	0	T	C	0.917466	0.993169	45.1789	1.80E-11	-0.0499514	0.00750084	44.348	2.70E-11
rs113658831	1	210097016	0	C	G	0.837754	0.999716	47.6096	5.20E-12	-0.0385564	0.00558469	47.6644	5.10E-12
rs11555079	1	41493749	0	G	A	0.780281	0.999287	37.3853	9.70E-10	-0.0309167	0.00497179	38.6688	5.00E-10
rs115866895	1	1592638	0	A	G	0.736492	0.98279	60.6082	7.00E-15	0.0366564	0.00471078	60.5501	7.20E-15
rs116715046	1	111355258	0	C	T	0.951421	0.992924	38.8357	4.60E-10	0.060621	0.0095999	39.8762	2.70E-10
rs1167311	1	49996959	0	G	A	0.318818	0.981126	84.6112	3.60E-20	0.0410857	0.00445046	85.2258	2.70E-20
rs12031634	1	34584393	0	G	A	0.703041	0.989901	43.3095	4.70E-11	0.0300896	0.00452875	44.1446	3.00E-11
rs12032291	1	32129041	0	A	G	0.585925	0.998245	31.4132	2.10E-08	0.0238142	0.00418243	32.4201	1.20E-08
rs12046439	1	107536799	0	T	C	0.754417	0.965482	34.9649	3.40E-09	-0.0287168	0.00487719	34.6685	3.90E-09
rs1205593	1	11252716	0	T	C	0.240566	0.996309	33.0703	8.90E-09	0.0279524	0.00482707	33.533	7.00E-09
rs12072739	1	98315893	0	A	G	0.775455	1	52.1397	5.20E-13	-0.0354323	0.00494628	51.3147	7.90E-13
rs12128526	1	7723957	0	G	A	0.541772	1	41.1552	1.40E-10	-0.026471	0.00413731	40.9358	1.60E-10
rs12131794	1	219766226	0	C	A	0.708277	0.996198	32.0651	1.50E-08	-0.0262086	0.00453786	33.3568	7.70E-09
rs12134553	1	1796717	0	A	C	0.555787	0.990002	39.655	3.00E-10	0.0263115	0.00416613	39.8865	2.70E-10
rs12140153	1	62579891	0	G	T	0.905305	0.949526	86.4486	1.40E-20	0.0683028	0.00721604	89.5939	2.90E-21
rs12562344	1	174257396	0	A	G	0.889401	0.998725	36.0272	1.90E-09	-0.0395731	0.00657029	36.2769	1.70E-09
rs1318408	1	11925781	0	A	G	0.880678	0.993411	36.1323	1.80E-09	-0.0389151	0.00637104	37.3092	1.00E-09
rs13303360	1	203488344	0	G	A	0.829215	0.988593	29.811	4.80E-08	-0.0316489	0.00551526	32.9294	9.60E-09
rs17014332	1	209520450	0	T	C	0.789623	0.998102	37.417	9.50E-10	-0.0315716	0.0050542	39.0199	4.20E-10
rs17531363	1	107977075	0	A	C	0.702669	0.986708	42.5312	7.00E-11	0.029876	0.00453184	43.4606	4.30E-11
rs1778830	1	156489974	0	G	A	0.637873	0.991782	33.5147	7.10E-09	-0.0257628	0.00429974	35.9006	2.10E-09
rs183315407	1	46201427	0	G	A	0.959656	0.991408	35.0408	3.20E-09	0.0615353	0.0105041	34.3189	4.70E-09
rs189727255	1	33775350	0	G	A	0.684893	0.989183	57.9974	2.60E-14	0.0336775	0.00445416	57.1673	4.00E-14
rs1937800	1	80792560	0	C	T	0.699928	0.99796	39.8681	2.70E-10	-0.0291235	0.00449272	42.0212	9.00E-11
rs197374	1	112289983	0	C	T	0.61956	0.998592	54.4188	1.60E-13	-0.0316866	0.00423913	55.8724	7.70E-14
rs2030342	1	97388226	0	C	T	0.443444	0.993846	30.4422	3.40E-08	-0.0234346	0.0041529	31.8428	1.70E-08
rs2678204	1	201800511	0	T	G	0.659206	0.995691	94.3148	2.70E-22	-0.0426359	0.00436059	95.6006	1.40E-22
rs284227	1	82379446	0	C	T	0.243289	0.995433	40.3168	2.20E-10	0.0308163	0.00480392	41.15	1.40E-10
rs34517439	1	78450517	0	C	A	0.877645	0.972235	185.995	2.40E-42	-0.0875441	0.00637101	188.816	5.80E-43
rs3737992	1	33234128	0	G	A	0.831195	0.999129	64.9296	7.80E-16	0.0436629	0.00549639	63.1058	2.00E-15
rs3766823	1	32197257	0	G	A	0.828286	1	45.2641	1.70E-11	-0.0376864	0.00546299	47.5894	5.30E-12
rs3789586	1	51054322	0	C	T	0.846857	0.996505	33.4298	7.40E-09	-0.0324712	0.00572577	32.161	1.40E-08
rs3814333	1	184007119	0	C	T	0.685137	0.990011	30.8436	2.80E-08	-0.0249077	0.00446313	31.145	2.40E-08
rs41279738	1	110082551	0	T	G	0.973917	0.988925	91.0934	1.40E-21	-0.123395	0.0129785	90.3961	1.90E-21
rs4520444	1	197141988	0	G	T	0.696164	0.996434	30.4167	3.50E-08	0.0245907	0.00448766	30.0263	4.30E-08
rs4648450	1	2723214	0	C	A	0.533384	0.984985	47.2796	6.20E-12	0.0289412	0.00415286	48.5667	3.20E-12
rs4660586	1	42407229	0	C	T	0.260935	0.993915	50.4448	1.20E-12	0.0333462	0.0047033	50.2675	1.30E-12
rs543874	1	177889480	0	A	G	0.794436	1	358.639	5.60E-80	-0.098199	0.00510567	369.921	1.90E-82
rs61765650	1	72753112	0	A	G	0.808573	0.999641	117.463	2.30E-27	0.0572985	0.00523867	119.631	7.60E-28
rs61777072	1	77988959	0	G	C	0.889465	0.991198	48.9298	2.70E-12	0.0459007	0.00659846	48.3898	3.50E-12
rs61779331	1	39970928	0	C	A	0.771735	0.995907	72.0193	2.10E-17	-0.0416648	0.0049129	71.922	2.20E-17
rs61813324	1	156049877	0	C	T	0.8642	0.96847	77.4149	1.40E-18	-0.0535988	0.00610635	77.0454	1.70E-18
rs630602	1	54728864	0	G	C	0.393162	0.989788	31.4715	2.00E-08	-0.0234838	0.0042402	30.6734	3.10E-08
rs6577585	1	6715440	0	G	A	0.658808	0.999094	37.4339	9.50E-10	-0.0261055	0.00434795	36.0492	1.90E-09
rs6604866	1	74992546	0	G	C	0.434496	0.998978	53.9666	2.00E-13	0.0303728	0.00415335	53.4779	2.60E-13
rs6669341	1	47678458	0	A	G	0.417375	1	58.1764	2.40E-14	0.0323498	0.00417797	59.9532	9.70E-15
rs6676899	1	242972908	0	G	A	0.661778	0.97807	30.6578	3.10E-08	-0.0242157	0.00440565	30.2116	3.90E-08
rs72697933	1	115625081	0	T	C	0.940885	0.991031	31.5596	1.90E-08	0.0496667	0.00877208	32.0572	1.50E-08
rs7519259	1	66434743	0	G	A	0.470957	0.991962	58.4326	2.10E-14	-0.0308747	0.0041443	55.5013	9.30E-14
rs7549358	1	115252609	0	G	C	0.356296	0.999159	38.9042	4.50E-10	0.0267932	0.0043044	38.7457	4.80E-10
rs76798800	1	154994978	0	G	T	0.733694	0.996349	53.3636	2.80E-13	-0.0340252	0.00467203	53.0382	3.30E-13
rs77560793	1	175001179	0	G	A	0.969475	0.985289	44.0236	3.20E-11	0.0805581	0.0120598	44.621	2.40E-11
rs815163	1	190294726	0	T	C	0.436944	0.999231	65.3872	6.20E-16	0.0334907	0.00415401	64.9999	7.50E-16
rs10175266	2	36784987	0	A	G	0.631345	0.998901	52.7896	3.70E-13	-0.0308954	0.00426453	52.4861	4.30E-13
rs10184537	2	50742025	0	C	T	0.660922	0.995004	39.5124	3.30E-10	0.0274429	0.00435412	39.7246	2.90E-10
rs10192894	2	62838936	0	A	G	0.56083	1	31.2962	2.20E-08	-0.023284	0.00414571	31.5441	1.90E-08
rs10201053	2	172889558	0	A	G	0.700486	0.997366	44.6968	2.30E-11	0.0302285	0.00450009	45.1222	1.90E-11
rs10490530	2	155158909	0	A	G	0.860708	0.994689	38.734	4.90E-10	-0.0369879	0.00595898	38.528	5.40E-10
rs10803762	2	161105876	0	G	A	0.322274	0.99214	37.5661	8.80E-10	-0.0272136	0.00442198	37.8738	7.50E-10
rs10932200	2	208387685	0	A	C	0.555456	0.997691	35.4875	2.60E-09	-0.0244915	0.00414551	34.904	3.50E-09
rs114964326	2	146015229	0	G	A	0.970979	0.979683	35.3837	2.70E-09	0.0757448	0.0123642	37.5296	9.00E-10
rs116713089	2	33359565	0	G	A	0.929273	1	35.5817	2.40E-09	0.0471471	0.008018	34.5762	4.10E-09
rs11900820	2	143983040	0	G	A	0.454994	0.998568	37.966	7.20E-10	0.0262612	0.00413553	40.3243	2.20E-10
rs12478299	2	193811641	0	T	C	0.748098	0.993247	33.964	5.60E-09	0.0274524	0.00475413	33.3441	7.70E-09
rs1263599	2	207941850	0	C	T	0.805222	0.987581	33.0852	8.80E-09	-0.0298414	0.00522756	32.5867	1.10E-08
rs13002767	2	60285450	0	T	A	0.754879	0.986202	35.491	2.60E-09	-0.0288076	0.00480376	35.9626	2.00E-09
rs13009450	2	37045086	0	C	T	0.35189	0.998069	29.9203	4.50E-08	-0.0236137	0.00431188	29.9914	4.30E-08
rs13395380	2	105590490	0	G	A	0.73688	0.998609	33.9888	5.50E-09	0.0272119	0.0046739	33.8968	5.80E-09
rs13427822	2	213414265	0	A	G	0.728505	0.976431	45.555	1.50E-11	0.0307754	0.00468035	43.2366	4.90E-11
rs13429686	2	105925165	0	A	G	0.87273	0.999485	36.8276	1.30E-09	-0.0372432	0.0061645	36.5003	1.50E-09
rs151252883	2	228998026	0	T	G	0.658166	0.999205	56.2459	6.40E-14	-0.0329162	0.00433733	57.5935	3.20E-14
rs1526612	2	76551482	0	A	T	0.0973828	0.995419	34.2259	4.90E-09	0.0412262	0.0069517	35.1695	3.00E-09
rs1609303	2	181567556	0	T	A	0.36848	0.991514	67.0845	2.60E-16	-0.0349637	0.00428357	66.6228	3.30E-16
rs1704191	2	200816393	0	C	A	0.364266	0.998324	34.1522	5.10E-09	-0.0250272	0.00427826	34.2207	4.90E-09
rs1728918	2	27635463	0	A	G	0.2782	0.981749	39.0999	4.00E-10	-0.0291697	0.00462817	39.7233	2.90E-10

rs1840126	2	236896765	0	A	C	0.436762	0.99842	31.4939	2.00E-08	0.023698	0.00415052	32.5999	1.10E-08
rs1861410	2	58933591	0	C	T	0.44455	0.992227	106.935	4.60E-25	0.0432804	0.00415143	108.69	1.90E-25
rs2091378	2	6145081	0	C	G	0.625779	0.993295	41.9877	9.20E-11	0.028505	0.00426141	44.7442	2.20E-11
rs2317011	2	236821648	0	C	T	0.21645	0.973573	34.4312	4.40E-09	0.0302217	0.00505976	35.6762	2.30E-09
rs2433733	2	230816703	0	G	A	0.321814	0.998196	55.5274	9.20E-14	0.0330238	0.00441055	56.062	7.00E-14
rs2685233	2	444923	0	T	G	0.711783	0.986386	40.3041	2.20E-10	-0.0289103	0.00457469	39.9375	2.60E-10
rs28414958	2	145622871	0	G	A	0.929873	0.995881	34.0018	5.50E-09	-0.0480587	0.00807349	35.4341	2.60E-09
rs2861690	2	67838685	0	C	G	0.610744	0.996968	67.4531	2.20E-16	0.0344388	0.00421417	66.7838	3.00E-16
rs308911	2	86855977	0	A	G	0.285603	0.994622	35.5658	2.50E-09	0.0271584	0.00456249	35.4329	2.60E-09
rs34234296	2	175166636	0	G	A	0.607306	0.975719	40.8171	1.70E-10	0.0273023	0.00426106	41.0546	1.50E-10
rs34847111	2	133524156	0	C	T	0.746303	0.986743	44.5861	2.40E-11	-0.031525	0.00476231	43.8202	3.60E-11
rs3791675	2	56111309	0	C	T	0.766032	1	32.2183	1.40E-08	0.0277685	0.00485239	32.7486	1.00E-08
rs3811514	2	228883721	0	T	C	0.514747	1	33.5061	7.10E-09	0.0234854	0.00411385	32.5912	1.10E-08
rs3900422	2	15038900	0	T	C	0.465352	0.998914	36.4378	1.60E-09	-0.0250358	0.00411522	37.0115	1.20E-09
rs4233727	2	28977244	0	T	C	0.326259	0.996415	36.5223	1.50E-09	0.0270674	0.00439115	37.9958	7.10E-10
rs4284873	2	69663305	0	G	A	0.587913	0.997254	39.0443	4.10E-10	0.0261597	0.00417939	39.1776	3.90E-10
rs4482463	2	205375909	0	C	A	0.0767614	0.99029	70.546	4.50E-17	0.0652562	0.0077571	70.7694	4.00E-17
rs4668314	2	171631258	0	G	T	0.389486	0.99212	30.931	2.70E-08	0.023179	0.0042353	29.9516	4.40E-08
rs4673553	2	211608379	0	T	G	0.551415	0.99302	48.8141	2.80E-12	-0.0282518	0.00414678	46.4161	9.60E-12
rs4851283	2	100894802	0	C	G	0.315324	0.983681	71.743	2.50E-17	0.0379202	0.00445776	72.3613	1.80E-17
rs534388650	2	25025038	0	A	G	0.980359	0.902039	33.0071	9.20E-09	-0.0879516	0.0155895	31.8291	1.70E-08
rs62106258	2	417167	0	T	C	0.951416	1	362.967	6.40E-81	0.183371	0.00955983	367.924	5.30E-82
rs62137973	2	54323609	0	C	T	0.612817	0.997435	30.929	2.70E-08	0.0235867	0.00422756	31.1283	2.40E-08
rs6543913	2	35437986	0	C	G	0.439537	0.997594	38.7776	4.70E-10	0.0261694	0.00414766	39.8091	2.80E-10
rs6711584	2	104421692	0	G	A	0.54827	0.987889	38.3166	6.00E-10	-0.0258598	0.00414978	38.8329	4.60E-10
rs6713781	2	40291940	0	G	C	0.598718	0.979136	35.3639	2.70E-09	0.0249542	0.00423711	34.6854	3.90E-09
rs6717591	2	206074790	0	T	C	0.383065	0.998945	30.7056	3.00E-08	0.0235385	0.00423708	30.862	2.80E-08
rs6722337	2	212033327	0	G	C	0.300991	0.988357	44.0948	3.10E-11	0.0289697	0.00451057	41.2501	1.30E-10
rs6733972	2	203652838	0	T	C	0.516748	0.989231	39.178	3.90E-10	-0.0251764	0.00414515	36.8898	1.20E-09
rs6739755	2	59330227	0	A	G	0.396892	0.995351	88.4255	5.30E-21	0.0404801	0.00421363	92.2933	7.50E-22
rs6749422	2	25150011	0	C	G	0.513727	0.996607	116.239	4.20E-27	-0.0438166	0.00411788	113.222	1.90E-26
rs6751993	2	635864	0	A	G	0.172448	0.971818	408.632	7.30E-91	-0.112374	0.00551835	414.68	3.50E-92
rs6755639	2	113981810	0	A	G	0.484867	0.999197	30.7346	3.00E-08	-0.023202	0.00410796	31.9006	1.60E-08
rs72803075	2	56603118	0	C	G	0.710119	0.981163	30.6231	3.10E-08	-0.0257805	0.00456577	31.8825	1.60E-08
rs72810068	2	25505793	0	T	C	0.689744	0.989193	47.2644	6.20E-12	-0.0307058	0.00446391	47.3161	6.00E-12
rs72847098	2	142810801	0	T	C	0.849967	0.990699	30.2657	3.80E-08	-0.0321126	0.00578538	30.8097	2.80E-08
rs73985439	2	212299249	0	A	C	0.692803	0.993984	40.6988	1.80E-10	-0.0292019	0.00447056	42.6676	6.50E-11
rs7573672	2	59155105	0	G	A	0.719348	0.995379	40.8709	1.60E-10	0.0295966	0.00458004	41.7585	1.00E-10
rs778094	2	147903802	0	G	A	0.42326	0.996989	54.0492	2.00E-13	0.030805	0.00417212	54.5166	1.50E-13
rs892513	2	198905874	0	C	T	0.818687	0.995147	37.8904	7.50E-10	0.032863	0.00535589	37.6489	8.50E-10
rs935166	2	26949366	0	G	A	0.492853	0.996261	65.7233	5.20E-16	0.0333626	0.00411702	65.6681	5.30E-16
rs9636391	2	50201110	0	A	G	0.162076	0.994568	41.2436	1.30E-10	0.0353846	0.00558733	40.1071	2.40E-10
rs10935143	3	134665159	0	G	A	0.551953	0.996497	33.5007	7.10E-09	0.0235244	0.00415503	32.0545	1.50E-08
rs111768603	3	42329113	0	G	T	0.890187	0.995825	45.9343	1.20E-11	0.044633	0.00659342	45.8238	1.30E-11
rs114547690	3	88100210	0	A	G	0.116102	0.997157	59.8535	1.00E-14	-0.0485026	0.00643673	56.7806	4.90E-14
rs11707955	3	41308348	0	T	C	0.528066	0.983521	51.01	9.20E-13	-0.029387	0.00415378	50.0521	1.50E-12
rs13081434	3	173662533	0	T	G	0.736158	1	35.5519	2.50E-09	0.0279359	0.00467239	35.7477	2.20E-09
rs13322435	3	156795468	0	A	G	0.596182	0.991687	36.4149	1.60E-09	0.0260816	0.00423125	37.9955	7.10E-10
rs1436347	3	104612394	0	C	T	0.41709	0.999163	41.4862	1.20E-10	-0.026487	0.00418003	40.152	2.30E-10
rs1471740	3	136328270	0	T	C	0.259449	0.995733	61.9741	3.50E-15	-0.0372541	0.00470893	62.5899	2.50E-15
rs1568488	3	153657951	0	G	C	0.404761	0.984716	60.9323	5.90E-15	-0.0316955	0.00423433	56.0304	7.10E-14
rs1584324	3	15833653	0	C	T	0.322401	0.998651	33.911	5.80E-09	0.0260982	0.00440554	35.0931	3.10E-09
rs17639546	3	61251635	0	G	A	0.851408	0.995828	59.1686	1.40E-14	0.0446563	0.00579681	59.3453	1.30E-14
rs1801282	3	12393125	0	C	G	0.880088	1	46.9288	7.40E-12	-0.042439	0.00633018	44.9469	2.00E-11
rs1857883	3	30052399	0	G	A	0.454795	0.99146	33.6234	6.70E-09	-0.0240574	0.00415197	33.573	6.90E-09
rs2016469	3	108023965	0	G	A	0.628204	0.9841	36.7103	1.40E-09	-0.0258304	0.00429776	36.1226	1.90E-09
rs2034768	3	93986371	0	A	G	0.48776	0.997984	84.748	3.40E-20	0.0369336	0.0041192	80.3927	3.10E-19
rs2035936	3	141298124	0	G	T	0.944237	0.971149	45.75	1.30E-11	-0.0589941	0.0091127	41.9105	9.60E-11
rs2569993	3	12926096	0	T	C	0.679976	0.992194	44.8021	2.20E-11	-0.0291579	0.00443121	43.2982	4.70E-11
rs33503	3	42427957	0	G	A	0.193842	1	39.4622	3.30E-10	0.03189	0.00521337	37.4173	9.50E-10
rs34373881	3	20432033	0	G	A	0.724021	0.99328	35.0215	3.30E-09	0.0277771	0.0046224	36.111	1.90E-09
rs376422625	3	131620699	0	T	C	0.727133	0.986661	95.0869	1.80E-22	-0.0453499	0.00466206	94.6232	2.30E-22
rs3851998	3	131876605	0	C	G	0.256927	0.990558	29.09	6.90E-08	0.0260641	0.00473898	30.2492	3.80E-08
rs3911063	3	85906928	0	T	C	0.677723	0.994436	73.3993	1.10E-17	0.037407	0.0044178	71.6958	2.50E-17
rs3914188	3	184010048	0	G	C	0.266647	1	46.4108	9.60E-12	0.0325976	0.00466542	48.819	2.80E-12
rs4017425	3	44028764	0	C	T	0.529989	0.994363	37.8482	7.60E-10	0.0257728	0.004134	38.8669	4.50E-10
rs4123668	3	82629523	0	T	C	0.597016	0.994571	47.8867	4.50E-12	-0.0290794	0.00420574	47.8065	4.70E-12
rs556464	3	173113680	0	C	G	0.471652	0.99539	54.8491	1.30E-13	-0.0298379	0.00413746	52.008	5.50E-13
rs557951	3	62713263	0	T	G	0.687269	0.99265	44.6191	2.40E-11	-0.0291137	0.00445458	42.7151	6.30E-11
rs61604727	3	70558473	0	T	C	0.792913	0.988241	37.1927	1.10E-09	-0.0311531	0.00511335	37.1185	1.10E-09
rs62243489	3	62482927	0	T	G	0.74098	0.989202	46.0183	1.20E-11	0.0323969	0.00472566	46.9982	7.10E-12
rs62246311	3	9498143	0	G	A	0.897573	0.998871	54.0444	2.00E-13	-0.0499913	0.00679301	54.1581	1.80E-13
rs6550961	3	25378486	0	G	A	0.833054	0.991614	36.2427	1.70E-09	0.0331882	0.00554586	35.812	2.20E-09
rs6766472	3	80651423	0	A	C	0.703068	0.994116	31.0442	2.50E-08	-0.0251095	0.00452285	30.8213	2.80E-08
rs6779368	3	185298868	0	A	G	0.653986	0.997462	31.5797	1.90E-08	0.0246122	0.00433844	32.1834	1.40E-08
rs6790206	3	161434707	0	A	G	0.459287	0.999928	41.8802	9.70E-11	-0.0270364	0.00412219	43.0172	5.40E-11
rs6795703	3	49930215	0	C	T	0.484145	0.99869	167.848	2.20E-38	-0.0530427	0.00412587	165.28	7.90E-38
rs724016	3	141105570	0	A	G	0.556035	1	101.096	8.80E-24	-0.0417111	0.00414785	101.125	8.60E-24
rs72906474	3	47817007	0	G	T	0.416563	0.974837	38.5756	5.30E-10	0.0261146	0.00422638	38.1794	6.50E-10
rs73015259	3	10017529	0	G	A	0.900925	0.996863	39.8847	2.70E-10	-0.0429301	0.00690733	38.6282	5.10E-10
rs73175572	3	185490184	0	A	G	0.888333	0.977974	30.5953	3.20E-08	-0.0368086	0.00661364	30.9754	2.60E-08
rs7372674	3	196149165	0	C	A	0.642536	0.99893	50.8087	1.00E-12	-0.0306658	0.00429937	50.8746	9.80E-13
rs7619139	3	25110415	0	T	A	0.410936	0.992517	58.1945	2.40E-14	-0.0323795	0.00419787	59.4953	1.20E-14
rs7628129	3	85095897	0	T	C	0.467828	0.990859	58.0464	2.60E-14	-0.0314525	0.004139	57.7456	3.00E-14
rs8192675	3	170724883	0	T	C	0.71181	1	76.2329	2.50E-18	-0.0393026	0.00454411	74.8073	5.20E-18
rs838209	3	176352763	0	A	G	0.66647	0.994973	30.7198	3.00E-08	-0.0242839	0.00437547	30.8028	2.90E-08

rs869400	3	185826740	0	T	G	0.18516	0.994015	92.7473	5.90E-22	-0.0519737	0.00531679	95.5582	1.40E-22
rs9814758	3	123062657	0	T	G	0.643753	0.989193	31.9359	1.60E-08	0.0249991	0.00432519	33.4072	7.50E-09
rs9816089	3	35599288	0	G	A	0.683945	0.992544	52.5958	4.10E-13	-0.0324735	0.00444497	53.3728	2.80E-13
rs9819699	3	148712656	0	A	G	0.645245	0.99484	30.1833	3.90E-08	-0.0244813	0.0043191	32.1279	1.40E-08
rs9852062	3	45373442	0	T	A	0.443625	0.989984	35.2062	3.00E-09	0.0241343	0.00416352	33.6008	6.80E-09
rs9861232	3	35005099	0	A	G	0.849012	0.993228	29.7555	4.90E-08	-0.0318741	0.00577253	30.4889	3.40E-08
rs10938398	4	45186139	0	G	A	0.56616	0.995763	181.996	1.80E-41	-0.0561215	0.00418071	180.201	4.40E-41
rs113079574	4	147354089	0	C	T	0.807718	0.988427	28.9048	7.60E-08	0.0287828	0.00527314	29.7938	4.80E-08
rs115462510	4	68454077	0	T	C	0.74308	0.973486	31.7718	1.70E-08	0.026514	0.00479396	30.5888	3.20E-08
rs11731255	4	6495698	0	A	G	0.526283	0.998595	36.8235	1.30E-09	-0.0252177	0.00413782	37.1423	1.10E-09
rs11735892	4	113320989	0	G	A	0.656063	0.985322	28.8138	8.00E-08	-0.0240547	0.00437864	30.1801	3.90E-08
rs12186148	4	139750074	0	G	C	0.570213	0.982514	32.1507	1.40E-08	-0.0244731	0.00420826	33.82	6.00E-09
rs1296328	4	137083193	0	A	C	0.44053	0.991395	74.37	6.50E-18	0.0362919	0.00418237	75.2962	4.10E-18
rs13107325	4	103188709	0	C	T	0.925028	1	69.3336	8.30E-17	-0.0649416	0.00785941	68.2756	1.40E-16
rs1346841	4	65651730	0	G	A	0.595463	0.990864	35.0171	3.30E-09	0.0248722	0.0042283	34.6018	4.00E-09
rs148636479	4	164359678	0	A	T	0.971373	0.879115	34.4403	4.40E-09	0.0758817	0.0132025	33.0339	9.10E-09
rs2051559	4	3298800	0	T	C	0.867294	0.99306	33.8457	6.00E-09	-0.0361438	0.00611052	34.9875	3.30E-09
rs2192527	4	18329824	0	A	G	0.535095	0.997785	63.7713	1.40E-15	-0.0332169	0.00415483	63.9165	1.30E-15
rs2318543	4	67803263	0	A	G	0.217054	0.992435	34.3315	4.60E-09	0.0295445	0.00502888	34.5153	4.20E-09
rs2322459	4	20260028	0	T	G	0.683413	0.994386	40.4199	2.00E-10	0.0278907	0.00445361	39.2188	3.80E-10
rs3113509	4	52932825	0	C	T	0.267891	0.993739	40.8525	1.60E-10	0.0302094	0.00467842	41.6954	1.10E-10
rs34656389	4	96153214	0	A	G	0.632535	0.996517	35.1412	3.10E-09	-0.0249099	0.00429088	33.7017	6.40E-09
rs34811474	4	25408838	0	G	A	0.76873	1	78.4754	8.10E-19	0.0433881	0.00490214	78.3375	8.70E-19
rs4148155	4	89054667	0	A	G	0.886416	0.999792	40.1238	2.40E-10	0.0411373	0.00650515	39.9905	2.60E-10
rs4240326	4	145839264	0	A	G	0.449993	0.999748	69.2799	8.50E-17	0.0348733	0.00415338	70.4987	4.60E-17
rs4292295	4	95021973	0	C	T	0.546589	0.98896	31.1991	2.30E-08	0.0235257	0.00417438	31.7616	1.70E-08
rs4398538	4	130724740	0	T	C	0.356899	0.992973	41.8239	1.00E-10	0.0280943	0.00432621	42.1718	8.40E-11
rs4596205	4	31012310	0	C	T	0.651168	0.991485	41.1351	1.40E-10	-0.0287521	0.00434696	43.7491	3.70E-11
rs537508	4	171042158	0	G	C	0.581424	0.989025	29.479	5.70E-08	-0.0230819	0.00421254	30.0231	4.30E-08
rs55981540	4	38860856	0	T	C	0.510786	0.997254	32.0367	1.50E-08	-0.0231085	0.00415077	30.9944	2.60E-08
rs56337234	4	1784403	0	C	T	0.506623	0.999122	30.6937	3.00E-08	-0.0227029	0.00413282	30.1766	3.90E-08
rs57800857	4	140863365	0	A	C	0.63489	0.988545	42.762	6.20E-11	0.0281212	0.00431793	42.4148	7.40E-11
rs6536575	4	162091639	0	T	C	0.480984	0.996164	42.3323	7.70E-11	-0.0263298	0.00413941	40.4591	2.00E-10
rs6821305	4	122713863	0	A	C	0.600899	0.996817	40.7302	1.70E-10	-0.0272712	0.00422146	41.7332	1.00E-10
rs6822996	4	119080617	0	C	G	0.810116	0.999739	29.4129	5.80E-08	0.0288712	0.00526056	30.1208	4.10E-08
rs6831020	4	55500226	0	C	A	0.706441	1	42.0797	8.80E-11	0.0290574	0.00453258	41.0981	1.40E-10
rs6844172	4	82189748	0	T	A	0.736788	0.993077	31.0267	2.50E-08	-0.0261648	0.00471065	30.8514	2.80E-08
rs6849518	4	20120274	0	C	T	0.87568	0.997345	60.8015	6.30E-15	-0.0481671	0.00626723	59.0678	1.50E-14
rs73213484	4	28489339	0	A	T	0.859133	0.996075	61.9118	3.60E-15	0.0467897	0.0059496	61.8479	3.70E-15
rs73234116	4	18778872	0	A	G	0.926122	0.976735	35.6607	2.30E-09	0.0491842	0.00798541	37.9365	7.30E-10
rs7674623	4	80794681	0	C	T	0.802764	0.987913	31.7624	1.70E-08	-0.0295358	0.00521642	32.0591	1.50E-08
rs7683836	4	180167906	0	G	A	0.442675	0.993983	31.7477	1.80E-08	0.0238505	0.00417353	32.6578	1.10E-08
rs10057678	5	236760	0	C	A	0.859485	0.973547	39.8989	2.70E-10	-0.0383428	0.00602585	40.4884	2.00E-10
rs11134999	5	176163794	0	C	T	0.684805	0.978165	32.6117	1.10E-08	0.0260342	0.00449132	33.6002	6.80E-09
rs11745618	5	105773821	0	A	G	0.4338	0.994472	37.9789	7.20E-10	-0.0256275	0.00417519	37.6758	8.40E-10
rs11951885	5	86727566	0	T	C	0.977231	0.98247	51.888	5.90E-13	-0.100578	0.0139431	52.0338	5.50E-13
rs13160735	5	144485978	0	G	A	0.677316	0.989774	33.2824	8.00E-09	-0.0257132	0.00443507	33.6134	6.70E-09
rs13163306	5	136571959	0	G	A	0.53373	0.997292	30.4324	3.50E-08	0.0229901	0.00414046	30.8308	2.80E-08
rs13355315	5	111225001	0	C	A	0.329414	0.995106	32.1182	1.50E-08	0.0246983	0.00439861	31.5286	2.00E-08
rs1363695	5	130378027	0	C	T	0.774015	0.983026	51.6035	6.80E-13	0.0355567	0.0049781	51.0169	9.20E-13
rs139218003	5	50954977	0	G	T	0.967418	0.997716	33.6431	6.60E-09	-0.0684368	0.0116484	34.518	4.20E-09
rs1459190	5	64070962	0	G	A	0.480398	0.98285	33.2124	8.30E-09	0.0240223	0.00417252	33.1461	8.50E-09
rs146728296	5	63940502	0	A	T	0.472776	0.99106	30.8987	2.70E-08	-0.0228821	0.00414658	30.4518	3.40E-08
rs1477290	5	87988934	0	T	C	0.863447	0.982214	111.525	4.50E-26	-0.0636966	0.00606639	110.249	8.60E-26
rs1582931	5	122657199	0	G	A	0.526972	0.982454	78.3041	8.80E-19	0.0372655	0.00416986	79.8676	4.00E-19
rs181372398	5	88097336	0	G	A	0.988602	0.903721	33.2381	8.20E-09	-0.118269	0.0204791	33.352	7.70E-09
rs2009416	5	92415111	0	C	T	0.64207	0.999035	43.678	3.90E-11	0.0284429	0.00431087	43.5327	4.20E-11
rs2130737	5	119321279	0	C	T	0.469263	0.995864	48.802	2.80E-12	0.0291412	0.00414433	49.4431	2.00E-12
rs2133561	5	139086651	0	A	T	0.388339	0.979123	66.4405	3.60E-16	0.0347372	0.00428178	65.8173	4.90E-16
rs2307111	5	75003678	0	T	C	0.6055	1	200.394	1.70E-45	0.0599582	0.00422999	200.918	1.30E-45
rs249612	5	66200783	0	C	T	0.28084	0.992302	44.8561	2.10E-11	-0.0305014	0.00460726	43.8282	3.60E-11
rs254024	5	103944020	0	G	T	0.562106	0.999158	52.0766	5.30E-13	-0.0304528	0.00415597	53.6921	2.30E-13
rs2546109	5	112162299	0	C	A	0.342398	0.982957	42.1399	8.50E-11	0.0283444	0.0043832	41.8168	1.00E-10
rs258762	5	142652057	0	T	A	0.414141	0.983871	37.4297	9.50E-10	-0.0253905	0.00422395	36.133	1.80E-09
rs261980	5	95844797	0	A	T	0.630285	0.99637	29.4757	5.70E-08	-0.0237738	0.00427874	30.872	2.80E-08
rs2964005	5	153214011	0	G	C	0.544061	0.996926	46.0569	1.10E-11	0.0281871	0.00414579	46.226	1.10E-11
rs329124	5	133865452	0	A	G	0.579525	0.996061	51.0898	8.80E-13	0.0297798	0.00418816	50.5589	1.20E-12
rs35689253	5	76597887	0	G	A	0.505605	0.995008	33.1122	8.70E-09	0.0242113	0.00413407	34.2989	4.70E-09
rs35727810	5	106377791	0	A	G	0.747417	0.995489	30.9461	2.70E-08	0.026811	0.00475867	31.7434	1.80E-08
rs365352	5	77401152	0	G	A	0.75544	0.998864	50.568	1.20E-12	0.0342501	0.00479573	51.0053	9.20E-13
rs3756668	5	67596088	0	G	A	0.540537	1	47.1357	6.60E-12	0.0287899	0.00414362	48.2749	3.70E-12
rs3943933	5	63020327	0	T	A	0.51914	0.999482	40.922	1.60E-10	-0.0265673	0.00413254	41.3295	1.30E-10
rs40071	5	107496102	0	T	C	0.820596	0.991752	54.8348	1.30E-13	0.0401034	0.00539414	55.2735	1.00E-13
rs4382197	5	88803179	0	C	T	0.632543	0.999628	32.234	1.40E-08	-0.0247524	0.00428492	33.3695	7.60E-09
rs4594820	5	27169910	0	T	G	0.716312	0.996911	30.1599	4.00E-08	0.0254094	0.00458432	30.7214	3.00E-08
rs59893724	5	80830788	0	A	G	0.756259	0.997428	56.4815	5.70E-14	0.0357243	0.00481202	55.1152	1.10E-13
rs6235	5	95728898	0	C	G	0.731867	1	61.0129	5.70E-15	-0.036692	0.00465577	62.1099	3.20E-15
rs6594967	5	115710803	0	T	C	0.675449	0.99607	32.3613	1.30E-08	0.0253129	0.0044094	32.9551	9.40E-09
rs6879208	5	152195529	0	C	A	0.892334	0.994709	29.6109	5.30E-08	-0.0366162	0.00668141	30.0339	4.20E-08
rs6899218	5	178988608	0	T	A	0.48707	0.993157	34.5889	4.10E-09	-0.0245485	0.00414479	35.0789	3.20E-09
rs698147	5	3513485	0	A	G	0.456341	0.994917	37.767	8.00E-10	0.0254581	0.00415104	37.6131	8.60E-10
rs71627577	5	43125795	0	A	G	0.889082	0.96169	31.1761	2.40E-08	0.0378288	0.00669865	31.8912	1.60E-08
rs72767253	5	51090842	0	C	A	0.957826	1	29.9554	4.40E-08	0.0563169	0.010282	30.0003	4.30E-08
rs7442885	5	87682877	0	C	G	0.786801	0.994821	108.795	1.80E-25	0.0522765	0.00506519	106.518	5.70E-25
rs7715256	5	153537893	0	G	T	0.427336	0.999683	48.3082	3.60E-12	0.029255	0.00416881	49.2468	2.30E-12
rs779655	5	170495158	0	G	C	0.271196	0.999407	55.6903	8.50E-14	-0.0343707	0.00464118	54.8428	1.30E-13

rs10949584	6	19129663	0	G	A	0.787891	0.990566	31.0732	2.50E-08	-0.0284006	0.00507099	31.3667	2.10E-08
rs11242730	6	2030663	0	G	T	0.759536	0.991312	41.9179	9.50E-11	-0.0309389	0.00484303	40.8108	1.70E-10
rs1159974	6	126090277	0	T	C	0.475025	1	51.5401	7.00E-13	-0.0295683	0.00413199	51.2076	8.30E-13
rs11968025	6	152168974	0	T	G	0.543404	0.987529	34.2351	4.90E-09	-0.024207	0.00416376	33.7994	6.10E-09
rs12198505	6	35409909	0	T	C	0.961857	0.961512	38.1485	6.60E-10	0.0673635	0.0109712	37.7002	8.20E-10
rs13210756	6	163009030	0	T	A	0.87163	0.963854	40.9861	1.50E-10	0.0399289	0.00628676	40.3387	2.10E-10
rs13340461	6	41924278	0	C	T	0.725443	0.993322	46.5755	8.80E-12	-0.0316588	0.00463697	46.6145	8.60E-12
rs139938004	6	31770134	0	G	A	0.95775	0.998864	45.4265	1.60E-11	0.0690306	0.0102543	45.3179	1.70E-11
rs156126	6	104810083	0	T	C	0.196853	0.994089	42.7653	6.20E-11	-0.0345922	0.00519651	44.3131	2.80E-11
rs2253310	6	108888593	0	C	G	0.373209	0.997162	104.557	1.50E-24	-0.0439983	0.00426732	106.307	6.30E-25
rs2357760	6	120213880	0	G	A	0.320472	0.994625	33.5241	7.00E-09	-0.0260066	0.00442918	34.4764	4.30E-09
rs240764	6	100953148	0	G	A	0.532504	0.987101	31.5008	2.00E-08	-0.0229973	0.0041621	30.5302	3.30E-08
rs2474896	6	51760527	0	C	T	0.45307	0.98415	79.55	4.70E-19	-0.0371181	0.00417431	79.068	6.00E-19
rs2478879	6	51152988	0	G	A	0.398115	0.989002	46.5418	9.00E-12	-0.029097	0.00424183	47.0534	6.90E-12
rs2744938	6	34552110	0	A	G	0.852559	0.999349	213.099	2.90E-48	-0.0853212	0.00580809	215.798	7.50E-49
rs2781668	6	131897278	0	C	T	0.834235	0.997136	32.8184	1.00E-08	-0.0320142	0.00555689	33.1911	8.40E-09
rs2875762	6	124925032	0	G	C	0.757523	0.990837	45.8426	1.30E-11	-0.0330163	0.00483728	46.586	8.80E-12
rs3130048	6	31613739	0	T	C	0.720401	1	97.0706	6.70E-23	-0.0450621	0.00459074	96.3516	9.60E-23
rs314279	6	105402083	0	C	A	0.115802	0.991907	31.3245	2.20E-08	0.0365369	0.00646038	31.9851	1.60E-08
rs33966734	6	41903798	0	C	A	0.98637	0.97389	33.9448	5.70E-09	0.106425	0.0180307	34.8384	3.60E-09
rs34045288	6	40369081	0	C	T	0.66505	0.999114	120.252	5.60E-28	-0.0476805	0.00437326	118.87	1.10E-27
rs41271299	6	19839415	0	C	T	0.948626	1	52.3499	4.60E-13	-0.0686514	0.00934531	53.9649	2.00E-13
rs4142412	6	34418892	0	G	A	0.223655	0.989034	88.0257	6.50E-21	0.04624	0.00498047	86.1975	1.60E-20
rs4467770	6	12086826	0	G	A	0.268941	0.989921	55.4289	9.70E-14	-0.0351184	0.0046731	56.4751	5.70E-14
rs4709744	6	164103661	0	T	C	0.694363	0.993275	31.0673	2.50E-08	-0.0248402	0.00448752	30.6406	3.10E-08
rs567230078	6	43588227	0	T	A	0.9731	0.998043	33.3402	7.70E-09	0.0726284	0.0127709	32.342	1.30E-08
rs62396185	6	26180634	0	G	C	0.740117	0.996828	141.655	1.20E-32	0.0560308	0.00471374	141.293	1.40E-32
rs62413414	6	80310375	0	C	T	0.848183	1	34.1482	5.10E-09	-0.0334896	0.00574486	33.983	5.60E-09
rs6456739	6	26604140	0	T	C	0.440731	1	62.0987	3.30E-15	-0.0327795	0.00415294	62.3008	2.90E-15
rs6909668	6	19724989	0	T	C	0.586586	0.983569	39.3694	3.50E-10	0.026912	0.0042229	40.6136	1.90E-10
rs6938973	6	98421721	0	T	C	0.398843	0.999353	57.5633	3.30E-14	-0.0315673	0.00421826	56.0026	7.20E-14
rs72892910	6	50816887	0	G	T	0.827848	0.995388	177.946	1.40E-40	-0.0732991	0.00547933	178.954	8.20E-41
rs765874	6	143185557	0	T	A	0.51039	0.997659	48.7628	2.90E-12	0.0286911	0.0041296	48.27	3.70E-12
rs77346201	6	90325025	0	G	C	0.950148	0.992946	31.4794	2.00E-08	-0.0545812	0.00950442	32.9788	9.30E-09
rs7740107	6	130374461	0	T	A	0.263999	0.998539	55.8675	7.80E-14	0.0352025	0.00467855	56.6142	5.30E-14
rs7760082	6	21919387	0	G	A	0.329752	0.996243	29.2607	6.30E-08	0.0240472	0.00438927	30.0154	4.30E-08
rs7761673	6	70357368	0	T	A	0.780121	0.99407	33.3362	7.80E-09	0.0285886	0.00499514	32.7559	1.00E-08
rs9257280	6	28833507	0	C	T	0.773665	0.999625	31.3233	2.20E-08	0.0275867	0.00493646	31.2297	2.30E-08
rs9277990	6	33308607	0	A	G	0.813615	0.996593	81.6938	1.60E-19	-0.0473015	0.00529799	79.7129	4.30E-19
rs9294260	6	83433228	0	G	A	0.523456	0.987597	58.1999	2.40E-14	-0.0322365	0.00415506	60.1924	8.60E-15
rs9321191	6	130165691	0	T	C	0.800928	0.998476	33.4728	7.20E-09	0.0293612	0.00516925	32.2622	1.30E-08
rs9370243	6	53789830	0	G	T	0.917898	0.994896	30.2241	3.80E-08	-0.0412294	0.00752476	30.0213	4.30E-08
rs9372414	6	97764299	0	C	T	0.652378	0.99425	46.096	1.10E-11	0.0298738	0.00434475	47.2772	6.20E-12
rs9463511	6	13178259	0	G	A	0.704791	0.999475	40.5005	2.00E-10	0.0293227	0.00452818	41.9336	9.40E-11
rs9478496	6	154333183	0	T	C	0.835695	0.992609	46.5638	8.90E-12	-0.0382589	0.00558825	46.872	7.60E-12
rs9496567	6	100602753	0	G	A	0.756841	0.994684	33.4523	7.30E-09	-0.0279961	0.00482444	33.6744	6.50E-09
rs10236214	7	150668070	0	C	T	0.358398	0.989853	77.5714	1.30E-18	-0.038621	0.00433892	79.2289	5.50E-19
rs10269774	7	92253972	0	G	A	0.673927	0.998874	65.188	6.80E-16	-0.0357615	0.00441873	65.4993	5.80E-16
rs1182199	7	2862542	0	C	A	0.695201	0.998804	67.7762	1.80E-16	0.036944	0.00449729	67.4816	2.10E-16
rs12333960	7	113472031	0	C	A	0.392624	0.99425	34.9117	3.40E-09	0.0252231	0.00424898	35.2393	2.90E-09
rs12375196	7	103416541	0	C	A	0.575774	0.988693	71.3466	3.00E-17	-0.0352995	0.00421281	70.209	5.30E-17
rs17132130	7	2108036	0	G	C	0.779231	0.9953	43.414	4.40E-11	0.0327759	0.00500307	42.9179	5.70E-11
rs1840660	7	114352615	0	G	A	0.610544	0.985424	38.3677	5.90E-10	-0.0269114	0.00427624	39.6048	3.10E-10
rs1852006	7	77829768	0	G	A	0.643072	1	39.8556	2.70E-10	0.0275277	0.00431727	40.6558	1.80E-10
rs215669	7	32378979	0	G	A	0.387599	0.994134	45.8694	1.30E-11	0.0295099	0.0042687	47.7909	4.70E-12
rs2272168	7	99102777	0	G	C	0.848134	0.995745	38.071	6.80E-10	0.0356476	0.00577832	38.059	6.90E-10
rs2289379	7	44804225	0	C	T	0.604226	0.990517	45.4823	1.50E-11	0.0279245	0.00424839	43.2038	4.90E-11
rs2396625	7	113028634	0	T	A	0.578042	0.985129	58.3835	2.20E-14	0.0323223	0.00421581	58.7816	1.80E-14
rs28452470	7	121957582	0	T	A	0.631197	0.99054	58.7898	1.80E-14	-0.0331571	0.00430278	59.3821	1.30E-14
rs34748838	7	130459242	0	C	T	0.511058	0.997304	34.6211	4.00E-09	-0.0244344	0.0041443	34.7615	3.70E-09
rs3800851	7	39417327	0	A	G	0.699254	0.977036	45.3234	1.70E-11	0.0302873	0.00455685	44.1767	3.00E-11
rs3807566	7	50564204	0	G	T	0.561411	0.994616	52.4432	4.40E-13	0.0303895	0.00417972	52.8632	3.60E-13
rs4577845	7	71647996	0	A	G	0.330316	0.996318	51.1463	8.60E-13	-0.0313982	0.00440639	50.7742	1.00E-12
rs4718964	7	70038969	0	G	T	0.586654	0.992974	48.297	3.70E-12	-0.0290602	0.00421607	47.5096	5.50E-12
rs4722398	7	3125220	0	C	T	0.86383	1	38.2821	6.10E-10	-0.0375845	0.00602142	38.96	4.30E-10
rs58862095	7	75081418	0	C	T	0.58035	0.99524	99.9503	1.60E-23	0.0415642	0.00420385	97.7561	4.70E-23
rs7780752	7	93241640	0	T	C	0.639329	0.998939	35.3993	2.70E-09	-0.0256284	0.00430339	35.4666	2.60E-09
rs7787384	7	76631727	0	G	A	0.176019	0.964542	72.7121	1.50E-17	0.047388	0.00553604	73.272	1.10E-17
rs7805441	7	78121458	0	C	T	0.498397	0.988033	31.8271	1.70E-08	-0.0227502	0.00416569	29.8261	4.70E-08
rs7810870	7	133581473	0	C	G	0.86587	0.99249	38.3421	5.90E-10	0.0371747	0.00609283	37.2268	1.10E-09
rs866279	7	6451481	0	A	G	0.882013	0.997814	39.7422	2.90E-10	-0.0403013	0.00642348	39.3638	3.50E-10
rs10113297	8	60654640	0	T	A	0.273446	0.993769	35.5183	2.50E-09	-0.0277811	0.0046513	35.6739	2.30E-09
rs1106761	8	142619234	0	G	A	0.615155	0.976038	43.9056	3.40E-11	-0.0284765	0.00430526	43.7497	3.70E-11
rs117176448	8	27261138	0	C	G	0.903897	1	47.7738	4.80E-12	-0.0484398	0.00701197	47.7225	4.90E-12
rs11779446	8	23388326	0	A	G	0.838816	0.991495	49.2787	2.20E-12	0.0386222	0.0056422	46.8573	7.60E-12
rs11780222	8	67205241	0	A	C	0.741378	0.991208	38.1388	6.60E-10	0.0293642	0.00473927	38.3896	5.80E-10
rs1252201	8	85469413	0	A	G	0.139745	0.980169	31.5725	1.90E-08	-0.0334311	0.00602313	30.8074	2.80E-08
rs12680342	8	95359638	0	T	G	0.770933	0.999326	45.8223	1.30E-11	0.0330066	0.00491593	45.0807	1.90E-11
rs12681792	8	62054463	0	C	A	0.807132	0.991067	29.4785	5.70E-08	-0.0290383	0.00526496	30.4195	3.50E-08
rs13264909	8	64702385	0	A	T	0.571169	0.995265	42.3601	7.60E-11	0.0279504	0.00418452	44.6154	2.40E-11
rs1483585	8	116555841	0	C	T	0.446427	0.99278	48.3819	3.50E-12	0.0293073	0.0041805	49.1467	2.40E-12
rs1559900	8	14207321	0	C	T	0.71397	1	41.4191	1.20E-10	-0.0295502	0.00457403	41.7371	1.00E-10
rs200119412	8	77224420	0	T	C	0.442485	0.988437	76.0599	2.80E-18	-0.0360458	0.00419046	73.992	7.80E-18
rs2725371	8	30854033	0	A	G	0.303811	0.990836	66.9349	2.80E-16	0.0366377	0.00451269	65.915	4.70E-16
rs2736202	8	116792426	0	C	T	0.240603	0.998157	75.7348	3.20E-18	-0.0418993	0.00484295	74.8505	5.10E-18
rs2919389	8	32588901	0	C	T	0.598801	0.987045	30.5409	3.30E-08	-0.0232495	0.0042419	30.0405	4.20E-08

rs2954021	8	126482077	0	A	G	0.49517	0.999631	37.2857	1.00E-09	-0.0259943	0.00413776	39.4663	3.30E-10
rs2980238	8	76314655	0	A	T	0.181627	0.991262	46.5448	9.00E-12	-0.0364146	0.00539651	45.533	1.50E-11
rs35957544	8	73440371	0	G	T	0.42504	0.997723	110.066	9.50E-26	0.0437922	0.00419256	109.102	1.50E-25
rs36061954	8	38329650	0	C	T	0.601108	0.997664	33.3066	7.90E-09	-0.024429	0.00422189	33.4809	7.20E-09
rs4072917	8	143300279	0	G	A	0.525577	0.990984	48.275	3.70E-12	-0.0288348	0.00415799	48.0913	4.10E-12
rs55675081	8	135582032	0	C	A	0.581506	0.994284	30.9219	2.70E-08	0.0237063	0.00419619	31.9167	1.60E-08
rs59104534	8	25666169	0	C	T	0.700912	0.99126	36.9444	1.20E-09	-0.0280007	0.00453488	38.1248	6.60E-10
rs72656010	8	57122215	0	T	C	0.867862	0.992891	41.0443	1.50E-10	0.039671	0.0061297	41.8859	9.70E-11
rs72673947	8	118884379	0	A	G	0.893281	0.986838	38.8131	4.70E-10	-0.0415524	0.00673834	38.0265	7.00E-10
rs7460093	8	144876159	0	G	A	0.46814	0.985434	36.6014	1.40E-09	-0.0247525	0.00418221	35.029	3.20E-09
rs7821259	8	85081619	0	T	G	0.26507	0.99552	29.024	7.10E-08	-0.0260211	0.00469995	30.6525	3.10E-08
rs7826312	8	32400115	0	T	C	0.40684	0.988577	29.4066	5.90E-08	-0.023119	0.00423088	29.8591	4.60E-08
rs7841468	8	68195769	0	T	C	0.717024	0.999158	34.1374	5.10E-09	-0.0276092	0.00459283	36.1365	1.80E-09
rs78565420	8	85703065	0	C	T	0.947794	0.963049	37.5484	8.90E-10	-0.0579581	0.00948817	37.3132	1.00E-09
rs814418	8	9936753	0	C	T	0.910774	0.995288	39.4404	3.40E-10	-0.0458586	0.0072618	39.8798	2.70E-10
rs10118701	9	103061366	0	A	G	0.679074	1	61.3389	4.80E-15	-0.0345877	0.00443805	60.7377	6.50E-15
rs1019240	9	122957315	0	A	T	0.35683	0.991476	39.8578	2.70E-10	-0.0276353	0.00433782	40.5868	1.90E-10
rs10756713	9	15880555	0	A	G	0.557531	0.990247	65.8011	5.00E-16	0.0342511	0.00419086	66.7948	3.00E-16
rs10760277	9	126093999	0	C	T	0.614712	0.992887	30.4995	3.30E-08	-0.0236075	0.00426705	30.6087	3.20E-08
rs10820852	9	94186973	0	C	A	0.724397	0.995276	42.033	9.00E-11	0.0302485	0.00464539	42.3997	7.40E-11
rs10821196	9	96433396	0	G	A	0.317054	0.98675	41.4141	1.20E-10	0.0289653	0.00448295	41.7472	1.00E-10
rs113132247	9	131026108	0	G	A	0.84711	0.991115	40.6619	1.80E-10	-0.0368398	0.00577455	40.7003	1.80E-10
rs1230692	9	126667393	0	G	A	0.879835	0.96761	34.9661	3.40E-09	-0.0383508	0.00648139	35.0116	3.30E-09
rs1327805	9	120896164	0	A	T	0.179356	0.993166	36.3999	1.60E-09	-0.032933	0.00541583	36.977	1.20E-09
rs1360201	9	73796450	0	C	T	0.518268	0.998985	34.736	3.80E-09	-0.0243899	0.00414155	34.6812	3.90E-09
rs139887373	9	122654933	0	T	A	0.901723	0.962878	34.0343	5.40E-09	-0.0407767	0.00709504	33.0305	9.10E-09
rs1411432	9	16728532	0	A	C	0.81409	0.991992	43.651	3.90E-11	-0.0348217	0.00534207	42.4894	7.10E-11
rs1475535	9	92212610	0	T	A	0.501813	0.995291	38.4666	5.60E-10	-0.0252931	0.00415668	37.0263	1.20E-09
rs1619442	9	81348300	0	T	C	0.14028	1	35.0068	3.30E-09	0.0352101	0.00595795	34.9254	3.40E-09
rs16916303	9	30823761	0	A	G	0.880531	0.977765	30.0552	4.20E-08	0.035217	0.00645152	29.7975	4.80E-08
rs17770336	9	28414625	0	C	T	0.676561	0.999747	115.444	6.30E-27	-0.0479387	0.00442365	117.438	2.30E-27
rs1934102	9	23228275	0	G	A	0.653179	0.974628	41.1385	1.40E-10	0.0279347	0.00440575	40.2019	2.30E-10
rs324534	9	9046080	0	T	G	0.685916	0.993759	32.0662	1.50E-08	0.0256528	0.0044743	32.8715	9.80E-09
rs34478611	9	35753898	0	G	A	0.757477	0.998229	30.6542	3.10E-08	-0.0270547	0.00483144	31.3569	2.10E-08
rs397776	9	101480921	0	G	A	0.243035	0.999752	31.6759	1.80E-08	0.0270906	0.00482943	31.4663	2.00E-08
rs4989244	9	102100348	0	G	A	0.56652	0.997522	38.5473	5.30E-10	0.0258608	0.00418533	38.1789	6.50E-10
rs6477694	9	111932342	0	C	T	0.352234	0.992013	44.3323	2.80E-11	0.0285218	0.0043525	42.9413	5.60E-11
rs6478538	9	124627012	0	A	G	0.32323	0.998957	35.1786	3.00E-09	0.0267318	0.00442965	36.4181	1.60E-09
rs6559820	9	87187401	0	G	A	0.938639	0.995782	34.7762	3.70E-09	-0.0509227	0.00863609	34.7687	3.70E-09
rs6597653	9	133788465	0	G	C	0.602765	0.990195	45.6808	1.40E-11	-0.0291324	0.00425003	46.9859	7.10E-12
rs7027304	9	129408290	0	C	T	0.346964	0.9888	38.4066	5.70E-10	-0.027378	0.00437069	39.2376	3.80E-10
rs7034554	9	37081301	0	A	G	0.62632	0.999051	43.1852	5.00E-11	0.0280079	0.00427691	42.8844	5.80E-11
rs7038943	9	120377178	0	T	C	0.661487	1	31.3323	2.20E-08	0.0250587	0.00437529	32.8021	1.00E-08
rs7046483	9	14777395	0	G	A	0.391414	0.992728	37.3676	9.80E-10	0.0257842	0.00425617	36.7001	1.40E-09
rs7047221	9	10158586	0	C	T	0.716741	0.99683	34.1437	5.10E-09	-0.0266079	0.00459895	33.4737	7.20E-09
rs7874154	9	27777012	0	T	C	0.505734	0.992514	42.0691	8.80E-11	-0.026922	0.00415887	41.9047	9.60E-11
rs10510025	10	118650996	0	C	T	0.753231	0.993388	51.3723	7.60E-13	-0.0343671	0.00480909	51.0693	8.90E-13
rs10764256	10	20905269	0	C	T	0.772343	0.994293	33.0629	8.90E-09	0.0284417	0.00495103	33.0006	9.20E-09
rs10823885	10	53674590	0	T	A	0.584574	0.999229	31.8581	1.70E-08	-0.0237023	0.00420617	31.7547	1.70E-08
rs10824211	10	76363107	0	C	T	0.860922	0.988647	36.5729	1.50E-09	-0.0363869	0.00600132	36.7618	1.30E-09
rs10883553	10	102635475	0	C	A	0.554085	1	48.7576	2.90E-12	-0.0288624	0.00416621	47.9935	4.30E-12
rs10887571	10	88030441	0	C	T	0.551058	0.979945	46.0265	1.20E-11	-0.0287581	0.00419616	46.9695	7.20E-12
rs10995427	10	64842838	0	G	A	0.63814	0.987289	31.1004	2.50E-08	0.0242099	0.00433458	31.1955	2.30E-08
rs11001963	10	78760959	0	C	T	0.418475	0.984358	31.9294	1.60E-08	-0.0243907	0.00422405	33.3418	7.70E-09
rs11012732	10	21830104	0	A	G	0.668718	0.997097	104.478	1.60E-24	-0.0453892	0.00440283	106.277	6.40E-25
rs11196657	10	115976570	0	T	C	0.763487	0.998773	45.3458	1.70E-11	-0.0331751	0.0048705	46.3955	9.70E-12
rs11199266	10	122061612	0	A	G	0.639302	0.992728	40.2606	2.20E-10	-0.0274701	0.00431923	40.4491	2.00E-10
rs11200595	10	124142629	0	T	C	0.529142	0.997779	34.3797	4.50E-09	-0.0239565	0.0041445	33.412	7.50E-09
rs113585475	10	33985434	0	C	T	0.900694	0.974611	40.9466	1.60E-10	0.0451001	0.00700698	41.428	1.20E-10
rs11594905	10	77659733	0	G	A	0.863638	1	31.3796	2.10E-08	-0.0346699	0.00602497	33.1126	8.70E-09
rs12765002	10	104635348	0	C	T	0.774971	0.998346	56.8566	4.70E-14	-0.0374649	0.00495839	57.0909	4.20E-14
rs17399739	10	87490850	0	A	G	0.931024	0.995634	47.2965	6.10E-12	-0.0569199	0.00817786	48.445	3.40E-12
rs2002023	10	76848524	0	C	T	0.591796	0.99714	33.6844	6.50E-09	-0.0243212	0.0042138	33.3137	7.80E-09
rs2172131	10	133978962	0	T	C	0.421012	1	48.2412	3.80E-12	0.0292336	0.00419234	48.624	3.10E-12
rs2297146	10	27382236	0	C	T	0.885504	0.99924	30.6127	3.20E-08	-0.0356553	0.0064988	30.101	4.10E-08
rs2356375	10	16751118	0	G	A	0.312589	0.994838	47.8447	4.60E-12	-0.0310079	0.00447933	47.9202	4.40E-12
rs2439823	10	99778226	0	A	G	0.454101	0.992434	87.9663	6.70E-21	-0.039275	0.00416652	88.8559	4.20E-21
rs2489654	10	34914875	0	C	T	0.637134	0.999783	32.5333	1.20E-08	-0.0247945	0.00430758	33.1317	8.60E-09
rs2542615	10	131128952	0	C	T	0.342035	0.978855	38.1624	6.50E-10	0.0272043	0.0043986	38.2511	6.20E-10
rs2802372	10	81047575	0	A	C	0.564665	0.989739	34.3866	4.50E-09	-0.0248216	0.00419774	34.9645	3.40E-09
rs2933451	10	66626611	0	C	A	0.328448	0.992657	31.6081	1.90E-08	0.0249004	0.00441891	31.7529	1.80E-08
rs35972789	10	75519691	0	C	A	0.962601	1	39.5163	3.30E-10	0.068676	0.0108887	39.7794	2.80E-10
rs3781396	10	126725553	0	C	G	0.675206	0.998167	43.4662	4.30E-11	-0.0293247	0.00441669	44.0832	3.10E-11
rs41310284	10	102447647	0	C	A	0.898688	0.983828	52.118	5.20E-13	0.0499917	0.00690131	52.4725	4.40E-13
rs4575195	10	114765747	0	C	A	0.68724	0.995719	42.1895	8.30E-11	0.0289843	0.00446534	42.1324	8.50E-11
rs7070670	10	61842645	0	C	T	0.671761	0.984754	34.6359	4.00E-09	0.0262526	0.00443534	35.0341	3.20E-09
rs71495048	10	34013633	0	C	T	0.916212	1	39.5106	3.30E-10	-0.0474793	0.00746792	40.4213	2.00E-10
rs7913496	10	10257277	0	C	T	0.179445	0.996819	32.2657	1.30E-08	0.0306622	0.00539486	32.3032	1.30E-08
rs79780963	10	104952499	0	C	T	0.922797	0.998609	42.7016	6.40E-11	-0.0508473	0.00774036	43.1532	5.10E-11
rs845084	10	125220036	0	G	A	0.741733	0.991228	41.2183	1.40E-10	-0.0300682	0.00474371	40.1772	2.30E-10
rs1038377	11	72337586	0	C	T	0.30978	0.989337	34.4793	4.30E-09	0.026176	0.00449355	33.9334	5.70E-09
rs10734398	11	28583215	0	T	G	0.320574	0.994515	34.5708	4.10E-09	-0.0258229	0.0044385	33.8484	6.00E-09
rs10796827	11	69444266	0	C	G	0.466586	0.987129	39.4178	3.40E-10	0.0262152	0.00417348	39.4556	3.40E-10
rs10835498	11	29258947	0	G	A	0.568966	0.994841	44.7622	2.20E-11	-0.0277465	0.00418455	43.9664	3.30E-11
rs10838193	11	43898020	0	G	A	0.675591	0.978882	33.6795	6.50E-09	0.0261436	0.00446743	34.2464	4.90E-09
rs10894605	11	132654027	0	A	G	0.576423	0.993809	40.377	2.10E-10	-0.0264968	0.00419408	39.9129	2.70E-10

rs10896012	11	65278461	0	T	C	0.782556	0.997115	67.649	2.00E-16	-0.0411077	0.00502631	66.8878	2.90E-16
rs11030016	11	27487992	0	C	T	0.259508	0.992773	46.2879	1.00E-11	-0.0317019	0.00473135	44.8953	2.10E-11
rs11042030	11	8690718	0	T	C	0.723875	0.995003	71.7573	2.40E-17	0.0397934	0.00463652	73.6608	9.30E-18
rs11234234	11	84613381	0	T	A	0.476317	0.986866	44.9595	2.00E-11	0.0282044	0.00417082	45.7288	1.40E-11
rs11512674	11	133743134	0	C	T	0.8996	0.96678	32.3008	1.30E-08	0.0394189	0.00699119	31.7912	1.70E-08
rs117353933	11	50344221	0	G	A	0.921128	1	32.2587	1.30E-08	-0.044297	0.00767263	33.3319	7.80E-09
rs12279433	11	116748221	0	G	T	0.939568	0.99772	39.3654	3.50E-10	-0.054265	0.00868859	39.0068	4.20E-10
rs12287076	11	47606865	0	G	C	0.292963	0.990837	104.714	1.40E-24	-0.0468363	0.00455893	105.545	9.30E-25
rs12364470	11	134601012	0	T	G	0.835075	1	52.4252	4.50E-13	-0.0393115	0.00556946	49.8211	1.70E-12
rs142808910	11	65836003	0	G	C	0.972092	0.975444	41.0832	1.50E-10	-0.0817788	0.0126847	41.5643	1.10E-10
rs2658797	11	93212254	0	C	T	0.518219	1	34.1693	5.10E-09	0.0245182	0.00413457	35.1655	3.00E-09
rs286508	11	85228358	0	A	G	0.864927	0.999248	36.3574	1.60E-09	0.0364789	0.00604631	36.4001	1.60E-09
rs28711392	11	13349559	0	T	C	0.632709	0.981882	37.3722	9.80E-10	0.0267408	0.00432597	38.2105	6.40E-10
rs35099456	11	66649527	0	G	C	0.936954	0.976505	72.0384	2.10E-17	0.0734587	0.00860751	72.8335	1.40E-17
rs3802858	11	115078492	0	T	C	0.572534	1	50.1274	1.40E-12	0.0296851	0.0041765	50.5186	1.20E-12
rs4755713	11	43532201	0	C	T	0.387939	0.995458	39.4956	3.30E-10	0.0269517	0.00425005	40.2146	2.30E-10
rs477895	11	64048912	0	C	T	0.163145	1	39.9016	2.70E-10	-0.0350056	0.00559093	39.2018	3.80E-10
rs567056	11	30435051	0	G	T	0.616373	0.992617	68.0894	1.60E-16	-0.0349836	0.00426257	67.3575	2.30E-16
rs61888762	11	27709630	0	C	G	0.680502	0.999394	186.884	1.50E-42	-0.0602025	0.00443382	184.363	5.40E-42
rs61903695	11	89922417	0	A	G	0.744686	0.99922	37.5439	8.90E-10	-0.0289319	0.00474563	37.1679	1.10E-09
rs643499	11	121938945	0	T	C	0.60223	0.992985	29.8783	4.60E-08	-0.0231751	0.00424035	29.8702	4.60E-08
rs6597975	11	838842	0	C	G	0.455562	0.986803	36.115	1.90E-09	-0.0250245	0.00417738	35.8858	2.10E-09
rs719802	11	113234679	0	T	C	0.385454	1	41.0935	1.50E-10	0.0267137	0.00424239	39.6503	3.00E-10
rs7925100	11	118941596	0	G	A	0.603615	0.999767	56.4683	5.70E-14	-0.0319449	0.00422573	57.1479	4.00E-14
rs7925748	11	131449439	0	A	G	0.589121	0.99533	31.3695	2.10E-08	-0.0235168	0.00420934	31.2126	2.30E-08
rs7930043	11	133183937	0	C	T	0.537413	0.985679	29.4564	5.70E-08	0.0228266	0.00416655	30.0144	4.30E-08
rs7933085	11	130796248	0	A	G	0.492171	0.989531	43.73	3.80E-11	-0.0272827	0.00415771	43.0594	5.30E-11
rs7948120	11	28763321	0	C	T	0.739524	0.989112	35.8166	2.20E-09	0.0280471	0.0047375	35.0492	3.20E-09
rs7950748	11	122762432	0	A	T	0.750813	0.984873	36.9089	1.20E-09	-0.0294334	0.00481855	37.3118	1.00E-09
rs79686965	11	46020909	0	A	G	0.983725	0.947446	32.5904	1.10E-08	-0.0958568	0.0167975	32.5653	1.20E-08
rs9783304	11	43660255	0	G	T	0.310631	0.999745	98.617	3.10E-23	0.0440203	0.00447248	96.8745	7.40E-23
rs10744146	12	17212881	0	G	A	0.486035	0.996441	39.4074	3.40E-10	0.0258728	0.00414506	38.9605	4.30E-10
rs10777858	12	97792745	0	G	T	0.471839	1	35.3833	2.70E-09	0.0244488	0.00414131	34.8531	3.60E-09
rs10842240	12	24060075	0	G	C	0.883808	0.99729	32.7548	1.00E-08	-0.0372721	0.00646546	33.233	8.20E-09
rs11056876	12	16472759	0	A	G	0.795052	0.988274	34.5461	4.20E-09	-0.0302739	0.00514335	34.6454	4.00E-09
rs11109097	12	97928437	0	C	T	0.303132	0.989376	31.0576	2.50E-08	0.025198	0.00451863	31.0971	2.50E-08
rs11113445	12	108088682	0	A	G	0.60868	0.999069	35.64	2.40E-09	-0.0253681	0.00423154	35.94	2.00E-09
rs1458156	12	41887940	0	C	T	0.511826	0.994547	64.5807	9.30E-16	-0.0335924	0.00414109	65.8041	5.00E-16
rs1480474	12	66326943	0	A	G	0.583449	0.994678	44.0867	3.10E-11	0.0276823	0.00420815	43.2734	4.80E-11
rs2013002	12	112200150	0	T	C	0.414635	0.987785	40.3792	2.10E-10	-0.0269475	0.00422705	40.6408	1.80E-10
rs2018749	12	122472503	0	G	T	0.77654	0.989718	45.7624	1.30E 11	0.0335083	0.00498016	45.2707	1.70E 11
rs2374731	12	108285600	0	C	T	0.755134	0.983767	45.3919	1.60E-11	0.0328842	0.00484556	46.056	1.10E-11
rs2712667	12	99588917	0	G	C	0.355482	0.993962	31.638	1.90E-08	0.0243152	0.00433546	31.4547	2.00E-08
rs3759094	12	56497903	0	C	T	0.662448	0.994422	59.5834	1.20E-14	0.033832	0.00437852	59.7036	1.10E-14
rs376237598	12	122587758	0	T	G	0.505366	0.979701	69.6137	7.20E-17	-0.0348729	0.00417722	69.695	6.90E-17
rs3764002	12	108618630	0	C	T	0.738063	1	30.709	3.00E-08	0.0263938	0.00470144	31.5167	2.00E-08
rs4759073	12	54653258	0	G	A	0.589576	0.999026	33.2233	8.20E-09	0.0238791	0.0042051	32.2465	1.40E-08
rs4842681	12	90133588	0	C	G	0.278671	0.991655	48.7502	2.90E-12	-0.0325976	0.00462121	49.7578	1.70E-12
rs55726687	12	991306	0	G	A	0.789635	0.997122	87.6217	7.90E-21	-0.0470417	0.00507312	85.9836	1.80E-20
rs6489159	12	123112806	0	G	A	0.261077	1	103.114	3.20E-24	-0.0475631	0.00470645	102.13	5.20E-24
rs6606686	12	110903380	0	G	C	0.319731	0.999469	43.2567	4.80E-11	0.0294303	0.00443427	44.0499	3.20E-11
rs704061	12	89771903	0	T	C	0.545523	0.996582	79.4082	5.10E-19	-0.0369169	0.0041536	78.9955	6.20E-19
rs7132908	12	50263148	0	G	A	0.615095	1	191.839	1.30E-43	-0.0590958	0.00425545	192.851	7.60E-44
rs7138383	12	103724090	0	G	A	0.745856	0.995624	58.9779	1.60E-14	0.0367748	0.00475534	59.8048	1.00E-14
rs7308788	12	19240689	0	G	A	0.301543	0.989736	30.2574	3.80E-08	-0.0256048	0.00453255	31.9123	1.60E-08
rs75412871	12	121709430	0	C	T	0.948104	0.995211	29.4407	5.80E-08	0.0509314	0.00933146	29.79	4.80E-08
rs76406609	12	114446456	0	C	T	0.932445	0.994133	39.4873	3.30E-10	0.0521144	0.00826119	39.7952	2.80E-10
rs76895963	12	4384844	0	T	G	0.979213	0.82244	99.4124	2.10E-23	-0.160483	0.0159869	100.77	1.00E-23
rs76929617	12	120867798	0	A	G	0.960966	0.994293	62.273	3.00E-15	0.0842389	0.0106985	61.9985	3.40E-15
rs77289077	12	121669268	0	C	T	0.874435	0.997775	30.774	2.90E-08	-0.0349334	0.00623954	31.3457	2.20E-08
rs7962636	12	116450006	0	T	C	0.351481	0.993608	44.0607	3.20E-11	0.0289021	0.00434287	44.2899	2.80E-11
rs7975187	12	60964108	0	A	G	0.786414	0.998162	35.9258	2.00E-09	-0.0304001	0.00505001	36.238	1.70E-09
rs900448	12	133404805	0	C	G	0.691417	0.998374	59.8612	1.00E-14	-0.0345234	0.00448053	59.37	1.30E-14
rs924817	12	91223470	0	T	G	0.631072	0.998296	34.6834	3.90E-09	0.0250865	0.00429116	34.1768	5.00E-09
rs9805009	12	118405172	0	C	G	0.711643	0.996404	31.5147	2.00E-08	0.0253504	0.00457536	30.6987	3.00E-08
rs116394958	13	86477072	0	C	T	0.725389	0.994773	36.0121	2.00E-09	-0.0279585	0.00465644	36.0511	1.90E-09
rs11841902	13	67492419	0	T	C	0.666123	0.992371	37.2571	1.00E-09	0.0272089	0.00441241	38.0252	7.00E-10
rs11842871	13	31042452	0	G	T	0.739249	0.996499	30.2398	3.80E-08	0.0261284	0.0047313	30.4976	3.30E-08
rs1218822	13	28011963	0	G	A	0.338242	0.999111	55.655	8.60E-14	-0.0326041	0.00438492	55.2868	1.00E-13
rs12872889	13	28674628	0	T	C	0.769169	0.973599	35.677	2.30E-09	-0.0296391	0.00498004	35.4213	2.70E-09
rs12877270	13	97047020	0	G	A	0.558758	0.982287	55.9599	7.40E-14	-0.0319283	0.00420769	57.579	3.20E-14
rs1336486	13	40784814	0	T	G	0.671203	0.994898	51.514	7.10E-13	-0.0318586	0.0044152	52.0658	5.40E-13
rs1886480	13	78489084	0	A	G	0.379456	0.997851	29.5112	5.60E-08	-0.0235203	0.00427459	30.2759	3.70E-08
rs1886558	13	111982615	0	A	G	0.392211	0.981529	41.4519	1.20E-10	0.0276421	0.00428387	41.636	1.10E-10
rs2121058	13	58627256	0	T	C	0.772401	0.99894	71.4204	2.90E-17	0.0418826	0.00494657	71.6902	2.50E-17
rs4435118	13	65480476	0	G	A	0.238625	0.998524	38.128	6.60E-10	-0.0293936	0.00486156	36.5556	1.50E-09
rs4477562	13	54104968	0	C	T	0.871279	0.982686	86.8219	1.20E-20	-0.0579192	0.00623771	86.2174	1.60E-20
rs484455	13	109835686	0	G	A	0.519154	0.991193	32.4635	1.20E-08	0.0237991	0.00415759	32.767	1.00E-08
rs56399737	13	33381721	0	C	T	0.550521	0.990985	35.0312	3.20E-09	0.0248942	0.00417928	35.4809	2.60E-09
rs6561766	13	54691484	0	A	G	0.118209	0.973397	41.4256	1.20E-10	0.0415124	0.00651076	40.6531	1.80E-10
rs722122	13	59399034	0	C	A	0.239576	0.992988	49.2339	2.30E-12	0.0347577	0.00487656	50.8012	1.00E-12
rs7982447	13	54453811	0	T	C	0.793734	0.993308	49.3502	2.10E-12	-0.0361618	0.00514124	49.4726	2.00E-12
rs9515446	13	112217108	0	A	G	0.551806	1	40.6799	1.80E-10	-0.0265947	0.00416741	40.7247	1.80E-10
rs9530843	13	79563749	0	A	C	0.550982	0.992791	40.6095	1.90E-10	0.0270957	0.00418442	41.9305	9.50E-11
rs9540493	13	66205704	0	A	G	0.454946	0.991447	30.1279	4.00E-08	0.0231748	0.00418333	30.6893	3.00E-08
rs9554237	13	28642942	0	C	G	0.814488	0.992642	31.4877	2.00E-08	-0.0302409	0.00534335	32.0304	1.50E-08

rs9556979	13	99241507	0	T	G	0.677232	0.978262	39.1638	3.90E-10	-0.0281656	0.00447678	39.5828	3.10E-10
rs9594689	13	42737268	0	T	G	0.625968	0.985432	35.939	2.00E-09	0.0258158	0.00431456	35.8014	2.20E-09
rs10139547	14	88390504	0	G	A	0.737763	1	33.9175	5.80E-09	-0.0273974	0.00470804	33.8639	5.90E-09
rs10145154	14	79939525	0	C	T	0.777794	0.997232	123.464	1.10E-28	-0.0556888	0.00499202	124.447	6.70E-29
rs11160601	14	101186641	0	C	T	0.907811	0.982419	44.6367	2.40E-11	-0.0484935	0.00721606	45.1614	1.80E-11
rs112971866	14	82812346	0	T	G	0.834122	0.994051	30.0566	4.20E-08	-0.0305022	0.00558551	29.8221	4.70E-08
rs11627567	14	103851775	0	C	T	0.784813	0.994658	34.8103	3.60E-09	0.0300603	0.00505843	35.3147	2.80E-09
rs1188158	14	56453962	0	C	T	0.450299	0.992064	32.6101	1.10E-08	-0.0237746	0.00418271	32.308	1.30E-08
rs1268403	14	21976476	0	T	C	0.795031	0.993767	37.0017	1.20E-09	0.0316897	0.00514765	37.8982	7.50E-10
rs12880358	14	101158809	0	C	G	0.905808	0.997972	36.4042	1.60E-09	-0.0433085	0.00709684	37.2406	1.00E-09
rs12885458	14	47303114	0	T	G	0.491295	0.997367	60.8413	6.20E-15	0.0325133	0.00415116	61.3455	4.80E-15
rs17115183	14	30137407	0	C	T	0.595796	0.993053	31.0507	2.50E-08	-0.0236937	0.00424039	31.2215	2.30E-08
rs17256211	14	23754580	0	A	G	0.351157	0.990048	47.3723	5.90E-12	-0.0296809	0.00436323	46.2742	1.00E-11
rs1955695	14	61021891	0	A	G	0.376267	0.997897	37.0262	1.20E-09	0.0260458	0.00428367	36.9695	1.20E-09
rs217672	14	62361021	0	A	C	0.728259	0.995442	45.7381	1.40E-11	-0.0316472	0.00467123	45.8996	1.20E-11
rs3803286	14	103246470	0	A	G	0.332918	0.998068	63.7144	1.40E-15	0.0351885	0.0043922	64.1858	1.10E-15
rs4082793	14	99700080	0	C	T	0.573438	0.994203	55.3114	1.00E-13	0.0313405	0.00420045	55.6699	8.60E-14
rs4517716	14	83013876	0	C	G	0.805889	1	35.6643	2.30E-09	-0.0306591	0.00524244	34.2019	5.00E-09
rs60163294	14	91674388	0	G	A	0.762924	0.989343	35.836	2.10E-09	0.0290422	0.00489377	35.2185	2.90E-09
rs6575340	14	94023972	0	G	A	0.363962	0.994477	80.9056	2.40E-19	-0.0387802	0.00431541	80.7561	2.60E-19
rs7159203	14	102303637	0	C	T	0.925608	0.991949	36.8541	1.30E-09	0.0487857	0.00792355	37.9093	7.40E-10
rs72681698	14	51207741	0	T	C	0.989228	1	33.4215	7.40E-09	0.116784	0.0200689	33.8624	5.90E-09
rs8011566	14	42939471	0	T	A	0.574282	0.995185	36.0996	1.90E-09	-0.025492	0.00420256	36.7944	1.30E-09
rs8013377	14	25934244	0	A	C	0.730739	0.999121	89.4727	3.10E-21	0.0447209	0.00467636	91.4547	1.10E-21
rs8016504	14	33308021	0	C	A	0.455831	0.984075	47.1713	6.50E-12	-0.0286832	0.00419199	46.8181	7.80E-12
rs9788550	14	29681138	0	G	C	0.752037	0.99178	77.0273	1.70E-18	0.0427481	0.00481627	78.7793	6.90E-19
rs10153031	15	67987293	0	T	G	0.3978	0.987778	113.624	1.60E-26	-0.0454751	0.00426362	113.76	1.50E-26
rs11636611	15	36391965	0	C	T	0.497107	0.998721	36.4935	1.50E-09	-0.0249009	0.00415529	35.9108	2.10E-09
rs11855017	15	42096146	0	C	A	0.818311	0.996317	31.0148	2.60E-08	-0.0305993	0.00538599	32.2769	1.30E-08
rs11856579	15	78012688	0	G	A	0.732469	0.99337	38.5426	5.40E-10	0.0293265	0.00469235	39.0609	4.10E-10
rs142592509	15	73782922	0	G	C	0.919056	0.957008	32.4345	1.20E-08	0.0439884	0.00775633	32.1635	1.40E-08
rs1657930	15	57120989	0	G	A	0.195634	1	30.2816	3.70E-08	0.0288509	0.00523444	30.3793	3.60E-08
rs17302219	15	59474067	0	G	A	0.769001	0.992017	33.3768	7.60E-09	-0.0288493	0.00494327	34.0598	5.30E-09
rs2290573	15	75129594	0	G	A	0.438529	0.980691	32.8095	1.00E-08	-0.0242505	0.00422467	32.9501	9.50E-09
rs2570237	15	52128880	0	T	C	0.535759	0.997848	50.1094	1.50E-12	0.0297697	0.00417025	50.9593	9.40E-13
rs34994596	15	80991447	0	T	C	0.702834	1	53.2989	2.90E-13	0.033059	0.00453813	53.0671	3.20E-13
rs4125566	15	85086958	0	T	C	0.76911	0.986892	45.6497	1.40E-11	0.03388	0.00495983	46.661	8.40E-12
rs530742363	15	89399167	0	C	T	0.323308	0.994132	29.4216	5.80E-08	0.0243963	0.00444803	30.0823	4.10E-08
rs57488047	15	79403002	0	T	C	0.531697	0.9861	50.5372	1.20E-12	0.0300309	0.00418657	51.4539	7.30E-13
rs61494430	15	53097493	0	C	G	0.771016	0.974047	34.5618	4.10E-09	-0.0293876	0.00500146	34.5252	4.20E-09
rs6598540	15	99230191	0	A	G	0.722984	0.99699	42.4206	7.40E-11	0.029862	0.00463715	41.47	1.20E-10
rs7171864	15	73227249	0	G	A	0.34008	0.9899	53.498	2.60E-13	-0.0320177	0.00440309	52.877	3.60E-13
rs7181498	15	95271404	0	T	C	0.354371	0.997847	39.5564	3.20E-10	0.0273026	0.0043446	39.492	3.30E-10
rs7183417	15	46586088	0	C	T	0.566653	0.996709	36.7134	1.40E-09	-0.025142	0.00419584	35.9057	2.10E-09
rs72749772	15	62367013	0	T	C	0.981334	0.989969	40.0761	2.40E-10	0.0985807	0.0154036	40.9581	1.60E-10
rs7498044	15	92573639	0	G	A	0.782055	0.980252	39.7788	2.80E-10	0.0324232	0.00507617	40.7981	1.70E-10
rs76095247	15	66593468	0	A	C	0.759059	0.991875	31.0743	2.50E-08	0.0272913	0.00486726	31.4397	2.10E-08
rs8024137	15	35837297	0	A	T	0.152078	0.993531	29.6996	5.00E-08	-0.0317591	0.00579995	29.9839	4.40E-08
rs10852374	16	15187804	0	G	C	0.243228	0.980958	33.1617	8.50E-09	0.0283192	0.004865	33.8841	5.80E-09
rs11150461	16	82448195	0	C	G	0.271974	0.992345	36.0628	1.90E-09	0.0285144	0.00467839	37.148	1.10E-09
rs12596053	16	4946794	0	A	C	0.428804	0.99545	71.5055	2.80E-17	0.035164	0.00418732	70.5219	4.60E-17
rs12926506	16	81722413	0	C	T	0.830137	0.985026	30.4173	3.50E-08	0.0304845	0.00555852	30.0775	4.20E-08
rs13329943	16	24733751	0	C	T	0.267859	0.993616	87.6004	8.00E-21	-0.0441288	0.00468131	88.8609	4.20E-21
rs1421085	16	53800954	0	T	C	0.596423	1	1096.5	1.90E-240	-0.139892	0.0042157	1101.16	1.90E-241
rs17819063	16	53873428	0	G	A	0.889284	0.950377	35.4052	2.70E-09	0.0401111	0.00675715	35.2373	2.90E-09
rs2319849	16	64717191	0	C	G	0.858013	0.958774	30.046	4.20E-08	0.0338503	0.00606057	31.1959	2.30E-08
rs25849	16	2265071	0	C	G	0.711382	0.992595	41.2496	1.30E-10	-0.0291411	0.00458214	40.4458	2.00E-10
rs3102352	16	89381305	0	C	G	0.125669	0.96548	33.5108	7.10E-09	0.0356924	0.00636357	31.4595	2.00E-08
rs34898535	16	31025641	0	C	T	0.622723	0.997302	142.657	7.00E-33	0.0510813	0.00427159	143.003	5.90E-33
rs369754041	16	53732186	0	G	T	0.873136	0.967455	59.2432	1.40E-14	-0.0489479	0.00631607	60.0584	9.20E-15
rs3814883	16	29994922	0	C	T	0.516405	0.991598	200.416	1.70E-45	-0.0594384	0.0041528	204.857	1.80E-46
rs4432271	16	20245283	0	C	T	0.131173	0.967482	33.716	6.40E-09	-0.0354858	0.0062269	32.4762	1.20E-08
rs4780885	16	20380004	0	G	C	0.501806	0.996871	60.4419	7.60E-15	0.0323426	0.00414124	60.9943	5.70E-15
rs55637757	16	89535888	0	C	T	0.868847	0.972529	31.3246	2.20E-08	0.0355707	0.00622617	32.6395	1.10E-08
rs55862211	16	69988812	0	A	C	0.60152	0.979684	31.2261	2.30E-08	-0.0244647	0.0042739	32.7666	1.00E-08
rs71385734	16	2160503	0	T	G	0.830556	0.987741	106.318	6.30E-25	0.057614	0.00554777	107.85	2.90E-25
rs7201895	16	407723	0	G	A	0.645718	0.987098	56.8224	4.80E-14	0.0325049	0.00434989	55.8394	7.90E-14
rs7206608	16	82872628	0	C	G	0.678051	0.996822	33.8834	5.90E-09	-0.0256972	0.00444398	33.4369	7.40E-09
rs7498665	16	28883241	0	A	G	0.599098	1	233.236	1.20E-52	-0.0648707	0.00422747	235.471	3.80E-53
rs7498798	16	73097029	0	G	A	0.357096	0.993273	48.7361	2.90E-12	0.0301371	0.00433758	48.2735	3.70E-12
rs803973	16	25660607	0	G	A	0.399556	0.993338	37.1246	1.10E-09	-0.0257705	0.00423181	37.0846	1.10E-09
rs8054079	16	19975407	0	C	T	0.858716	0.973751	69.6235	7.20E-17	0.050915	0.0060196	71.5412	2.70E-17
rs8055786	16	76702763	0	C	T	0.820074	0.995105	31.851	1.70E-08	-0.0310696	0.0054111	32.9686	9.40E-09
rs8062638	16	9720130	0	C	A	0.694234	0.990654	39.3968	3.50E-10	0.0288676	0.00450053	41.1427	1.40E-10
rs837346	16	9413353	0	C	T	0.503332	0.988738	34.8903	3.50E-09	-0.0245475	0.00416345	34.7622	3.70E-09
rs862320	16	69651866	0	C	T	0.589898	0.996511	81.6865	1.60E-19	0.0392594	0.00422279	86.4348	1.40E-20
rs879620	16	4015729	0	C	T	0.38603	0.994264	141.699	1.10E-32	-0.0514322	0.00426102	145.694	1.50E-33
rs9921705	16	71988220	0	G	A	0.776051	0.998157	40.3006	2.20E-10	0.0320371	0.0049735	41.4938	1.20E-10
rs1000940	17	5283252	0	A	G	0.698666	0.998715	36.9513	1.20E-09	-0.0275451	0.00454036	36.8051	1.30E-09
rs11150745	17	78757626	0	A	G	0.681691	0.995096	86.8024	1.20E-20	0.041762	0.00446976	87.2958	9.30E-21
rs113866544	17	46270606	0	T	C	0.932105	0.997015	80.2257	3.30E-19	-0.0745605	0.0082756	81.1742	2.10E-19
rs11653367	17	44191483	0	A	G	0.671337	0.98768	55.2119	1.10E-13	0.0333635	0.00444992	56.2132	6.50E-14
rs11655587	17	47140794	0	C	T	0.63857	0.993067	52.6013	4.10E-13	0.0314887	0.00434359	52.5549	4.20E-13
rs11658134	17	76739141	0	G	A	0.48733	0.993878	30.2689	3.80E-08	0.0235893	0.0041713	31.9808	1.60E-08
rs12945575	17	40713071	0	C	T	0.75148	0.996402	28.4254	9.70E-08	-0.026679	0.00482024	30.6338	3.10E-08
rs12952442	17	15895247	0	G	T	0.429965	0.998453	31.9528	1.60E-08	-0.0237556	0.00420399	31.9307	1.60E-08

rs17744603	17	52926401	0	C	G	0.831078	0.987811	37.8992	7.40E-10	-0.0350565	0.00557993	39.4711	3.30E-10
rs1914888	17	21267541	0	A	G	0.509942	0.993922	30.8945	2.70E-08	0.0230801	0.0041742	30.5723	3.20E-08
rs2242449	17	7095507	0	C	T	0.574537	0.983456	44.8776	2.10E-11	-0.0281494	0.00423783	44.1214	3.10E-11
rs2306593	17	34866546	0	C	T	0.511817	0.99664	69.7887	6.60E-17	0.0349933	0.00416856	70.4686	4.70E-17
rs34675417	17	28079167	0	A	G	0.744204	0.99033	34.7589	3.70E-09	-0.028413	0.00478935	35.195	3.00E-09
rs349792	17	39261560	0	T	A	0.309304	0.990781	39.0035	4.20E-10	0.0283288	0.00452081	39.2666	3.70E-10
rs35867081	17	79047278	0	A	G	0.487601	0.988195	49.5659	1.90E-12	0.0296777	0.00417967	50.4168	1.20E-12
rs4473241	17	42281282	0	G	T	0.71431	0.991768	31.69	1.80E-08	-0.0260001	0.0046259	31.5906	1.90E-08
rs4790292	17	1824305	0	C	A	0.845811	0.993444	90.4926	1.90E-21	0.0540704	0.00578062	87.4925	8.50E-21
rs55931203	17	65854602	0	C	T	0.812935	0.979292	101.403	7.50E-24	-0.0543032	0.00539002	101.501	7.10E-24
rs7211567	17	31460899	0	C	T	0.784343	1	40.23	2.30E-10	0.0317466	0.00504732	39.5615	3.20E-10
rs7213767	17	35054784	0	G	A	0.296248	0.985052	31.746	1.80E-08	-0.0256996	0.0045876	31.3822	2.10E-08
rs7223535	17	29211667	0	G	A	0.729564	0.99916	55.6154	8.80E-14	0.0351601	0.00468048	56.4312	5.80E-14
rs7226064	17	32237258	0	A	G	0.570443	0.992918	35.9195	2.10E-09	0.0257735	0.00421579	37.3757	9.70E-10
rs75438860	17	9801828	0	T	C	0.736787	1	32.8555	9.90E-09	-0.0265643	0.00472365	31.6259	1.90E-08
rs78378222	17	7571752	0	T	G	0.987631	0.957678	48.3709	3.50E-12	-0.133575	0.0192205	48.2967	3.70E-12
rs8074454	17	3981148	0	G	C	0.673349	0.999206	38.8566	4.60E-10	-0.0275214	0.00443642	38.4836	5.50E-10
rs936393	17	73847613	0	A	G	0.812735	0.993362	32.4031	1.30E-08	-0.030416	0.00534867	32.338	1.30E-08
rs11873305	18	58049192	0	A	C	0.961073	0.991033	159.494	1.50E-36	0.13665	0.0107832	160.594	8.40E-37
rs1547874	18	22159869	0	T	C	0.808836	0.992366	46.9561	7.30E-12	0.0360005	0.00530591	46.0358	1.20E-11
rs16941871	18	1676816	0	C	T	0.343375	0.990652	30.8571	2.80E-08	0.0241856	0.00438895	30.3662	3.60E-08
rs1788808	18	21090023	0	A	G	0.504846	0.996996	143.503	4.60E-33	0.0500231	0.00416233	144.434	2.90E-33
rs1834144	18	40744790	0	C	A	0.626486	0.99584	53.6224	2.40E-13	0.032093	0.00430378	55.6061	8.90E-14
rs1941697	18	31251276	0	G	A	0.550545	1	30.7969	2.90E-08	-0.0232388	0.00417011	31.055	2.50E-08
rs1942834	18	63315068	0	C	G	0.315707	0.99598	46.6901	8.30E-12	0.0307205	0.00447398	47.1486	6.60E-12
rs35761930	18	13182325	0	A	T	0.814922	0.978868	35.4281	2.60E-09	-0.0325356	0.00538755	36.4699	1.60E-09
rs58243949	18	52509833	0	C	T	0.766429	0.993955	37.0215	1.20E-09	-0.0300104	0.00492514	37.1284	1.10E-09
rs6567160	18	57829135	0	T	C	0.767543	0.998838	548.691	2.40E-121	-0.115098	0.00491175	549.112	2.00E-121
rs7230240	18	42597978	0	C	T	0.705368	0.99894	34.386	4.50E-09	0.0263106	0.00454949	33.4455	7.30E-09
rs7237783	18	39605066	0	A	G	0.879169	0.998745	36.9405	1.20E-09	-0.0386589	0.00638163	36.6974	1.40E-09
rs7239114	18	45921214	0	G	A	0.458044	0.985989	33.3061	7.90E-09	-0.0246602	0.00419429	34.5683	4.10E-09
rs7243357	18	56883319	0	T	G	0.822811	0.991938	39.4081	3.40E-10	0.0347543	0.0054564	40.5701	1.90E-10
rs76519884	18	41014155	0	T	C	0.958205	1	30.0417	4.20E-08	-0.0573466	0.0103623	30.6271	3.10E-08
rs784257	18	53397199	0	T	C	0.187535	0.98958	45.4911	1.50E-11	-0.0361353	0.00534217	45.754	1.30E-11
rs8084481	18	2680649	0	G	C	0.773938	0.998916	32.1891	1.40E-08	0.0281325	0.00497116	32.0259	1.50E-08
rs8088123	18	58100400	0	C	A	0.928592	0.987251	44.0157	3.30E-11	0.0536937	0.00810009	43.9407	3.40E-11
rs8089514	18	69224478	0	T	A	0.631386	0.976307	36.081	1.90E-09	-0.0259943	0.00434949	35.7173	2.30E-09
rs8097672	18	1839601	0	A	T	0.854861	0.986259	48.5895	3.20E-12	-0.0410714	0.00592051	48.124	4.00E-12
rs8098777	18	58190893	0	C	T	0.575033	0.994712	36.2495	1.70E-09	0.0258453	0.00421246	37.6436	8.50E-10
rs9948863	18	57968382	0	A	G	0.473788	0.994544	47.2262	6.30E-12	-0.0288439	0.00416632	47.9296	4.40E-12
rs10423928	19	46182304	0	T	A	0.805692	1	153.223	3.40E-35	0.0657038	0.00529902	153.741	2.60E-35
rs10424665	19	32895631	0	A	C	0.829371	0.995919	30.5086	3.30E-08	0.0309673	0.0055878	30.7131	3.00E-08
rs12974458	19	1866115	0	C	T	0.45634	0.989492	57.5848	3.20E-14	-0.0323243	0.00423229	58.3321	2.20E-14
rs12986231	19	18469017	0	T	C	0.731876	0.978345	62.1142	3.20E-15	0.0379571	0.00478477	62.931	2.10E-15
rs148108087	19	51781455	0	G	A	0.945116	0.908627	31.9699	1.60E-08	0.054316	0.00967697	31.5048	2.00E-08
rs243260	19	4363170	0	G	T	0.450023	1	34.2994	4.70E-09	-0.0250763	0.00421518	35.3911	2.70E-09
rs29941	19	34309532	0	A	G	0.326403	1	34.8823	3.50E-09	-0.0267836	0.00448808	35.6136	2.40E-09
rs350832	19	4069426	0	G	A	0.228379	0.990927	40.1423	2.40E-10	-0.031818	0.00503222	39.9784	2.60E-10
rs3760647	19	10735530	0	A	G	0.262595	0.994612	35.2709	2.90E-09	0.0281644	0.00478547	34.6378	4.00E-09
rs3810291	19	47569003	0	G	A	0.32372	1	133.134	8.40E-31	-0.052127	0.00448343	135.178	3.00E-31
rs4545921	19	49646006	0	A	G	0.400894	0.996813	35.5996	2.40E-09	0.0255613	0.00429329	35.4474	2.60E-09
rs55714539	19	18207397	0	A	C	0.656839	0.983204	72.3909	1.80E-17	-0.0378902	0.00445236	72.4221	1.70E-17
rs57894940	19	30293462	0	G	A	0.668619	0.994219	93.6992	3.70E-22	-0.0431548	0.00447494	92.9999	5.20E-22
rs62621197	19	8670147	0	C	T	0.963285	0.930027	33.7258	6.30E-09	0.0667614	0.0115837	33.2166	8.20E-09
rs6857	19	45392254	0	C	T	0.828513	0.996182	74.1994	7.10E-18	0.047915	0.0055808	73.714	9.00E-18
rs7412	19	45412079	0	C	T	0.919513	1	45.0588	1.90E-11	-0.0508016	0.00772188	43.2822	4.70E-11
rs744385	19	1947776	0	T	C	0.170372	0.996439	44.9382	2.00E-11	-0.0380848	0.00559718	46.2984	1.00E-11
rs8112818	19	18812785	0	A	G	0.599548	0.993578	72.4331	1.70E-17	0.0365435	0.00429516	72.3872	1.80E-17
rs1022753	20	53484855	0	C	T	0.235081	0.992653	30.581	3.20E-08	0.0274456	0.00491343	31.2015	2.30E-08
rs1056441	20	62370349	0	T	C	0.32525	0.997239	35.3921	2.70E-09	-0.0264248	0.00443652	35.4764	2.60E-09
rs16996657	20	15816236	0	T	C	0.871849	0.994853	37.7821	7.90E-10	-0.0383506	0.00623471	37.8366	7.70E-10
rs2151447	20	12702515	0	C	T	0.652006	0.99123	30.1443	4.00E-08	0.0243984	0.00437935	31.0388	2.50E-08
rs2889898	20	34646798	0	T	C	0.815257	0.989338	60.1089	9.00E-15	-0.0407622	0.00538522	57.2939	3.80E-14
rs35679975	20	51194941	0	T	C	0.80754	0.992052	109.938	1.00E-25	0.05547	0.00528686	110.083	9.40E-26
rs453329	20	25440593	0	G	A	0.56042	0.998223	43.1302	5.10E-11	-0.0271373	0.00419024	41.9428	9.40E-11
rs6010786	20	61544714	0	T	C	0.499453	0.999288	33.8669	5.90E-09	0.0240188	0.00416072	33.3246	7.80E-09
rs6030803	20	41986507	0	T	C	0.87428	0.989112	33	9.20E-09	0.0361524	0.00629156	33.0185	9.10E-09
rs62228193	20	50393979	0	G	A	0.655462	0.987969	30.9162	2.70E-08	0.0246216	0.00439985	31.3153	2.20E-08
rs761795	20	12413671	0	C	T	0.457181	0.998313	32.2191	1.40E-08	0.0235083	0.00417618	31.6874	1.80E-08
rs8356	20	43536455	0	C	T	0.731178	0.999054	33.236	8.20E-09	-0.0275118	0.00468457	34.4905	4.30E-09
rs947088	20	17171373	0	G	T	0.282705	0.992422	30.8739	2.80E-08	-0.0256665	0.00463089	30.7188	3.00E-08
rs11701433	21	40296411	0	C	T	0.329954	0.991685	51.2393	8.20E-13	-0.031877	0.00444191	51.501	7.20E-13
rs76040172	21	46488959	0	G	A	0.94582	0.988845	62.3674	2.90E-15	0.0733013	0.00924967	62.8016	2.30E-15
rs11704728	22	18130209	0	C	T	0.80298	0.990473	36.8135	1.30E-09	-0.0318188	0.00528651	36.2268	1.80E-09
rs1569497	22	39665395	0	A	G	0.559174	1	30.2352	3.80E-08	-0.0233563	0.00421485	30.7074	3.00E-08
rs28489620	22	41804716	0	G	A	0.709022	0.982294	45.776	1.30E-11	0.0316762	0.00464453	46.5139	9.10E-12
rs28722029	22	40611012	0	G	A	0.676596	0.993378	35.9064	2.10E-09	0.0267783	0.00449084	35.5557	2.50E-09
rs4680	22	19951271	0	G	A	0.484144	1	33.0613	8.90E-09	-0.0240965	0.00419369	33.0153	9.10E-09
rs5771118	22	50714289	0	T	C	0.258832	0.986674	30.305	3.70E-08	-0.0263884	0.00480415	30.1713	4.00E-08

Summary statistics for the genetic association with body shape PC2

rsid	CHR	BP	GENPOS	ALLELE1	ALLELE0	A1FREQ	INFO	CHISQ_LINREG	P_LINREG	BETA	SE	CHISQ_BOLT_LMM_INF	pval
rs2710889	1	958953	0	A	G	0.627381	0.990845	42.3832	7.50E-11	-0.0155336	0.00223906	48.1299	4.00E-12
rs1892289	1	1374834	0	A	G	0.786229	0.962721	36.3571	1.60E-09	-0.0161232	0.00267805	36.2464	1.70E-09
rs28401288	1	1574709	0	T	G	0.28954	0.975262	29.3063	6.20E-08	0.0132059	0.00240735	30.0925	4.10E-08
rs262649	1	2093746	0	G	T	0.728953	0.998172	93.2745	4.60E-22	-0.0234423	0.00242403	93.5245	4.00E-22
rs12743493	1	2224836	0	G	A	0.630355	0.981252	61.1193	5.40E-15	-0.0173764	0.00225478	59.3895	1.30E-14
rs2742690	1	2987268	0	C	A	0.791634	0.978606	32.6331	1.10E-08	0.0154268	0.0026849	33.0135	9.20E-09
rs7522354	1	6893053	0	G	A	0.826071	0.997806	43.0601	5.30E-11	-0.018647	0.00284656	42.9117	5.70E-11
rs12128234	1	8170219	0	T	C	0.185543	0.996672	52.372	4.60E-13	0.0204487	0.00277947	54.126	1.90E-13
rs11581328	1	8507773	0	G	A	0.790171	0.966726	71.8514	2.30E-17	-0.0226598	0.00269194	70.8568	3.80E-17
rs2311050	1	9334328	0	C	T	0.751445	0.967414	126.91	1.90E-29	0.0289655	0.00253896	130.152	3.80E-30
rs112541935	1	9342003	0	G	A	0.950085	0.948696	69.2676	8.60E-17	-0.0432925	0.00507736	72.7025	1.50E-17
rs7541338	1	9529832	0	G	A	0.447506	0.98203	32.3169	1.30E-08	0.0124458	0.00218639	32.4034	1.30E-08
rs11121522	1	10208768	0	T	C	0.89915	0.993337	105.871	7.90E-25	-0.0362249	0.00359337	101.627	6.70E-24
rs747124	1	10640933	0	C	G	0.554457	0.978009	39.0163	4.20E-10	0.0129205	0.00219173	34.7523	3.70E-09
rs6674994	1	11239515	0	T	C	0.259431	0.999484	83.8343	5.40E-20	0.0223828	0.00246118	82.7071	9.50E-20
rs6661012	1	16499913	0	C	T	0.653388	0.986027	42.6356	6.60E-11	-0.0144786	0.00227737	40.4189	2.00E-10
rs9435731	1	17306029	0	C	A	0.480372	1	350.638	3.10E-78	-0.0401305	0.0021571	346.105	3.00E-77
rs12730973	1	19709918	0	A	G	0.452841	0.996444	109.815	1.10E-25	-0.0230231	0.00217082	112.481	2.80E-26
rs12407400	1	19964620	0	G	A	0.761756	0.991207	83.3392	6.90E-20	-0.0233153	0.0025438	84.0073	4.90E-20
rs12743070	1	21573371	0	C	G	0.628035	0.987616	119.014	1.00E-27	-0.0244687	0.00224084	119.234	9.30E-28
rs213051	1	21621536	0	T	G	0.700039	1	33.8382	6.00E-09	-0.0133129	0.00235235	32.029	1.50E-08
rs1531829	1	21953304	0	G	A	0.642328	0.994856	30.9622	2.60E-08	-0.0123073	0.00225543	29.7764	4.80E-08
rs7543136	1	22472451	0	C	T	0.278989	0.989204	127.753	1.30E-29	0.0274574	0.00241328	129.451	5.40E-30
rs60999980	1	22493090	0	G	A	0.911413	0.950139	78.0828	9.90E-19	0.0332872	0.00388789	73.3034	1.10E-17
rs79891104	1	23430650	0	C	T	0.821516	0.997899	121.092	3.60E-28	0.0315678	0.0028148	125.775	3.40E-29
rs7523614	1	25196480	0	C	A	0.633345	0.974377	40.4096	2.10E-10	-0.0146916	0.00226355	42.1269	8.60E-11
rs7518779	1	25393004	0	G	A	0.591406	0.994095	65.4383	6.00E-16	-0.0174942	0.0021971	63.3996	1.70E-15
rs35431118	1	25800790	0	C	T	0.568004	0.997748	33.8811	5.90E-09	0.0123652	0.00217523	32.3137	1.30E-08
rs112262100	1	26433730	0	G	A	0.825275	0.999093	117.856	1.90E-27	-0.0309931	0.00283766	119.291	9.00E-28
rs2219320	1	26803430	0	T	C	0.746258	0.998268	126.426	2.50E-29	0.02855	0.00247536	133.026	8.90E-31
rs116705330	1	26965830	0	A	C	0.958024	0.911567	37.1818	1.10E-09	-0.0337891	0.00562878	36.035	1.90E-09
rs114165349	1	27021913	0	G	C	0.976803	0.985746	31.8633	1.70E-08	-0.0418605	0.00720889	33.7188	6.40E-09
rs567347869	1	27145540	0	A	G	0.973412	0.902224	30.6619	3.10E-08	0.0391472	0.00705743	30.7687	2.90E-08
rs1149040	1	31192304	0	G	T	0.525155	0.998558	36.3122	1.70E-09	0.0134265	0.00215786	38.7149	4.90E-10
rs6425704	1	31571777	0	G	A	0.667161	0.978303	43.1838	5.00E-11	-0.0148788	0.00231034	41.4749	1.20E-10
rs2292989	1	32135773	0	A	G	0.641756	0.994318	64.8409	8.10E-16	0.0182945	0.00225265	65.9563	4.60E-16
rs10914504	1	32393560	0	C	T	0.867364	0.997048	112.523	2.70E-26	-0.0336173	0.00318042	111.727	4.10E-26
rs55745410	1	33802817	0	A	G	0.645346	0.98896	39.5181	3.30E-10	0.014693	0.00226639	42.0292	9.00E-11
rs11263857	1	36588402	0	G	A	0.89654	0.979976	32.3435	1.30E-08	0.0197215	0.00357797	30.3814	3.50E-08
rs12116935	1	36789546	0	A	G	0.613871	1	58.6442	1.90E-14	0.0172793	0.00221233	61.0028	5.70E-15
rs115947878	1	37969794	0	G	C	0.915788	0.990987	64.8577	8.10E-16	0.0312175	0.00390348	63.9575	1.30E-15
rs61776719	1	38461319	0	C	A	0.445545	1	114.958	8.00E-27	0.0229614	0.00216773	112.198	3.20E-26
rs140753094	1	40641118	0	C	A	0.875229	0.995263	39.7149	2.90E-10	-0.0206928	0.00327102	40.0195	2.50E-10
rs1846158	1	40781038	0	G	A	0.831014	0.998037	83.6767	5.80E-20	0.0264704	0.00287758	84.6185	3.60E-20
rs4660493	1	41410502	0	A	G	0.651975	0.970334	31.7287	1.80E-08	-0.013266	0.00229841	33.3139	7.80E-09
rs369056255	1	41435867	0	T	C	0.97809	0.8937	29.4903	5.60E-08	0.0427004	0.00779796	29.9848	4.40E-08
rs2885697	1	41544279	0	G	T	0.335266	0.999895	257.549	5.90E-58	0.0365212	0.00228179	256.176	1.20E-57
rs2147904	1	42371414	0	T	C	0.434269	0.995497	31.6511	1.80E-08	0.0126138	0.00217828	33.5322	7.00E-09
rs2782641	1	44013355	0	G	A	0.386514	0.991824	73.3646	1.10E-17	0.0193514	0.0022235	75.7443	3.20E-18
rs184502689	1	45502217	0	C	T	0.979178	0.968808	47.532	5.40E-12	-0.0522411	0.00767456	46.3359	1.00E-11
rs2088956	1	45520908	0	T	C	0.158335	0.999824	31.7178	1.80E-08	-0.0165384	0.00295306	31.3647	2.10E-08
rs2991976	1	46048489	0	C	T	0.299533	0.999724	78.6605	7.40E-19	0.0213156	0.00235326	82.0459	1.30E-19
rs564914	1	47915233	0	A	T	0.587635	0.992796	89.9264	2.50E-21	-0.0209813	0.00219661	91.2348	1.30E-21
rs72904749	1	51367420	0	C	T	0.910453	0.999749	211.799	5.60E-48	-0.0555497	0.00377313	216.751	4.60E-49
rs17401875	1	52632627	0	A	T	0.885986	0.95271	49.1416	2.40E-12	-0.0242016	0.0034737	48.5405	3.20E-12
rs1288369	1	53575575	0	C	T	0.540707	1	31.252	2.30E-08	-0.0123079	0.0021606	32.4504	1.20E-08
rs17387330	1	54119578	0	G	A	0.676764	0.994693	81.0497	2.20E-19	-0.0214891	0.00231065	86.4903	1.40E-20
rs12083684	1	54891393	0	T	C	0.485127	0.992733	63.1647	1.90E-15	0.0173645	0.00216243	64.4823	9.70E-16
rs1811666	1	54956262	0	C	G	0.914959	0.962254	55.468	9.50E-14	0.0292457	0.00393926	55.118	1.10E-13
rs9436515	1	56120519	0	C	T	0.640953	0.994055	38.6732	5.00E-10	0.014107	0.0022518	39.2473	3.70E-10
rs778418	1	56644685	0	A	G	0.777508	0.998864	98.0881	4.00E-23	-0.0260438	0.00259365	100.829	1.00E-23
rs4072369	1	62505044	0	T	A	0.727375	0.989751	35.5939	2.40E-09	-0.0144374	0.00243674	35.1045	3.10E-09
rs71647469	1	65366509	0	C	T	0.987445	0.9185	40.1091	2.40E-10	-0.0652921	0.0100988	41.8006	1.00E-10
rs3008858	1	67390416	0	G	C	0.263756	1	75.2516	4.10E-18	-0.0217245	0.00244566	78.9061	6.50E-19
rs17090778	1	71531596	0	A	G	0.814082	0.997933	36.2246	1.80E-09	-0.0166907	0.00277983	36.0504	1.90E-09
rs34517439	1	78450517	0	C	A	0.877645	0.972235	194.662	3.10E-44	-0.0469726	0.00333633	198.222	5.10E-45
rs11801146	1	85915374	0	C	T	0.782376	0.999635	45.255	1.70E-11	0.0177208	0.00261414	45.9527	1.20E-11
rs1962482	1	86313536	0	G	T	0.832204	0.994594	44.4866	2.60E-11	0.0191262	0.00289306	43.7062	3.80E-11
rs385437	1	86822231	0	A	G	0.86467	0.999402	35.6402	2.40E-09	-0.0178728	0.00314893	32.2153	1.40E-08
rs4411112	1	88607616	0	A	G	0.10161	1	36.5917	1.50E-09	0.0214876	0.00356357	36.3587	1.60E-09
rs10922478	1	89144053	0	A	G	0.435035	0.999467	127.647	1.30E-29	-0.0244483	0.00217172	126.733	2.10E-29
rs12122664	1	91220615	0	A	C	0.683706	0.993263	44.6188	2.40E-11	0.0153154	0.00232495	43.3939	4.50E-11
rs284176	1	92223976	0	A	G	0.321703	0.984424	38.4333	5.70E-10	0.0147147	0.00232566	40.032	2.50E-10
rs113190075	1	93000332	0	C	A	0.204838	0.992669	135.682	2.30E-31	-0.0310844	0.00267549	134.983	3.30E-31
rs945631	1	93426167	0	G	A	0.958669	0.978969	48.7661	2.90E-12	-0.0393724	0.00548021	51.6167	6.70E-13
rs115615989	1	93715278	0	A	G	0.983973	0.966967	66.5414	3.40E-16	-0.0714204	0.00872337	67.031	2.70E-16
rs59304985	1	103270077	0	T	A	0.791551	0.98998	40.5531	1.90E-10	-0.0166399	0.00266622	38.9503	4.30E-10
rs2061708	1	103417203	0	G	C	0.4109	0.994885	225.07	7.10E-51	0.0329484	0.00219815	224.674	8.60E-51
rs34931959	1	110394303	0	A	G	0.600154	0.989526	37.0692	1.10E-09	-0.0135128	0.00221182	37.3242	1.00E-09
rs10857961	1	113082153	0	C	A	0.795164	0.999211	46.2182	1.10E-11	0.018313	0.00267071	47.0179	7.00E-12

rs17038164	1	118862669	0	T	C	0.743173	1	245.443	2.60E-55	0.0380841	0.0024721	237.33	1.50E-53
rs77247079	1	119159903	0	T	A	0.958311	0.943666	34.0466	5.40E-09	0.0313545	0.00555892	31.8141	1.70E-08
rs12129705	1	120191044	0	A	T	0.872425	0.963409	117.337	2.40E-27	0.034792	0.00329294	111.633	4.30E-26
rs611160	1	144894611	0	T	C	0.372097	1	36.5197	1.50E-09	0.0142268	0.00223729	40.436	2.00E-10
rs11576360	1	146740576	0	G	A	0.126105	0.999674	69.6706	7.00E-17	-0.0274816	0.00324733	71.6196	2.60E-17
rs12133943	1	147095081	0	C	G	0.902798	0.995216	34.8862	3.50E-09	-0.0211411	0.00365321	33.4891	7.20E-09
rs11205303	1	149906413	0	T	C	0.593201	1	513.631	1.00E-113	-0.0503216	0.0022007	522.863	1.00E-115
rs138309741	1	150512792	0	C	A	0.960208	0.968635	56.7103	5.00E-14	-0.04215	0.00560161	56.62	5.30E-14
rs10305739	1	150789953	0	T	A	0.948082	0.955587	52.9127	3.50E-13	0.0367171	0.00496946	54.5909	1.50E-13
rs6688113	1	151060527	0	G	A	0.977044	1	92.3812	7.10E-22	-0.068572	0.00720635	90.5446	1.80E-21
rs35485741	1	151241909	0	G	C	0.886313	0.996537	92.3407	7.30E-22	0.0335254	0.00340741	96.8049	7.70E-23
rs72698179	1	154522394	0	C	A	0.970937	0.934395	41.7068	1.10E-10	-0.0417208	0.00664376	39.4346	3.40E-10
rs61811895	1	154976137	0	G	T	0.827016	1	31.2541	2.30E-08	0.0160291	0.00285769	31.4623	2.00E-08
rs76798800	1	154994978	0	G	T	0.733694	0.996349	134.446	4.40E-31	-0.0279371	0.00244624	130.426	3.30E-30
rs505058	1	156106185	0	T	C	0.935136	1	57.3301	3.70E-14	-0.0335638	0.00437765	58.7842	1.80E-14
rs4657451	1	165492327	0	G	A	0.265645	0.992592	57.3795	3.60E-14	0.0186354	0.00245119	57.7997	2.90E-14
rs191746	1	165513116	0	T	C	0.0330885	0.996586	29.7304	5.00E-08	-0.0332844	0.00604161	30.3512	3.60E-08
rs76839558	1	170691131	0	T	G	0.853648	0.989805	106.531	5.60E-25	-0.0312367	0.00306667	103.752	2.30E-24
rs235860	1	171598212	0	C	T	0.741591	0.999032	27.0532	2.00E-07	-0.0136852	0.0024642	30.8428	2.80E-08
rs114780788	1	171894757	0	G	T	0.928397	0.978686	65.3708	6.20E-16	-0.0346859	0.00423186	67.1806	2.50E-16
rs4394690	1	172166210	0	G	C	0.689049	0.999842	361.489	1.30E-80	-0.0443379	0.00233193	361.509	1.30E-80
rs10489284	1	172367062	0	A	G	0.843849	0.99511	74.4349	6.30E-18	0.0259645	0.00297876	75.9783	2.90E-18
rs28680958	1	173848808	0	G	A	0.783084	0.998965	48.5319	3.20E-12	-0.0188996	0.00261834	52.1019	5.30E-13
rs76224110	1	176210729	0	T	G	0.933899	0.976959	53.4705	2.60E-13	-0.0324562	0.00439244	54.5988	1.50E-13
rs376317256	1	176276512	0	G	T	0.986259	0.767338	83.0441	8.00E-20	0.0969671	0.0105748	84.0819	4.70E-20
rs4233168	1	176500060	0	A	T	0.0810182	0.967932	71.6569	2.60E-17	0.0346361	0.00401911	74.2672	6.80E-18
rs1044299	1	176811873	0	C	T	0.454236	0.99631	223.443	1.60E-50	-0.0327705	0.00217532	226.945	2.80E-51
rs1534957	1	176821057	0	G	A	0.790581	0.999841	33.7228	6.40E-09	0.0148544	0.0026491	31.4423	2.10E-08
rs4652215	1	176925602	0	C	T	0.964947	0.982033	37.7583	8.00E-10	-0.0357235	0.00591287	36.5016	1.50E-09
rs10913299	1	177189898	0	G	T	0.666335	0.998559	39.8902	2.70E-10	-0.0144514	0.00228951	39.8413	2.80E-10
rs1609829	1	180909061	0	T	C	0.296769	0.984724	65.6564	5.40E-16	0.0192788	0.0023789	65.676	5.30E-16
rs2093985	1	183094322	0	C	T	0.43055	0.999909	57.2489	3.80E-14	0.0169787	0.00217619	60.8715	6.10E-15
rs2491445	1	183765337	0	C	T	0.196963	0.997812	30.0638	4.20E-08	-0.0148573	0.00271585	29.9273	4.50E-08
rs10797922	1	183894775	0	T	G	0.687768	0.996879	37.809	7.80E-10	-0.014209	0.00233048	37.1738	1.10E-09
rs1926872	1	184018475	0	T	C	0.653199	0.999282	376.032	9.10E-84	-0.0436045	0.00226829	369.543	2.40E-82
rs34985078	1	184054014	0	C	T	0.947917	0.965182	65.0829	7.20E-16	0.0401216	0.00494451	65.8428	4.90E-16
rs2821307	1	200043726	0	T	G	0.505983	0.996697	41.6703	1.10E-10	-0.0142439	0.00216093	43.4486	4.40E-11
rs12130750	1	200208417	0	T	C	0.590314	0.993242	46.4135	9.60E-12	-0.0155133	0.00220341	49.5696	1.90E-12
rs10920617	1	203318622	0	G	A	0.948714	0.996458	31.3957	2.10E-08	0.0269876	0.00490504	30.2722	3.80E-08
rs10900520	1	203780591	0	A	G	0.723839	1	31.5863	1.90E-08	-0.0140623	0.00241371	33.9424	5.70E-09
rs10900446	1	205062361	0	G	A	0.616927	0.998852	42.447	7.30E-11	0.014152	0.00222352	40.5088	2.00E-10
rs823114	1	205719532	0	G	A	0.452546	0.999155	74.855	5.10E-18	0.0184471	0.00216686	72.4766	1.70E-17
rs2993548	1	212217131	0	C	G	0.986144	0.987791	49.1782	2.30E-12	-0.0662277	0.00928711	50.8532	1.00E-12
rs10863937	1	212259964	0	A	C	0.588096	0.996442	60.5707	7.10E-15	0.0177276	0.00219397	65.2891	6.50E-16
rs12757404	1	214629616	0	A	G	0.604036	0.999671	76.3631	2.40E-18	0.0186889	0.00220303	71.9655	2.20E-17
rs3790731	1	217795891	0	T	A	0.602352	0.99855	28.7057	8.40E-08	-0.0121719	0.00220831	30.3807	3.60E-08
rs1417488	1	218523730	0	C	T	0.7455	0.987549	91.3144	1.20E-21	-0.0247042	0.00249232	98.251	3.70E-23
rs11466399	1	218591623	0	G	A	0.713484	0.995557	226.955	2.80E-51	-0.0363054	0.0023916	230.444	4.80E-52
rs559008623	1	218706189	0	A	C	0.983786	0.962828	59.3036	1.40E-14	-0.0680855	0.00871373	61.0521	5.60E-15
rs28459747	1	218763810	0	A	G	0.882115	0.975399	55.4145	9.80E-14	-0.025462	0.0033891	56.444	5.80E-14
rs183448601	1	218845863	0	G	T	0.885072	0.9964	39.4595	3.30E-10	-0.0219954	0.00338517	42.2186	8.20E-11
rs72742475	1	218879783	0	C	T	0.977674	1	50.1458	1.40E-12	-0.051987	0.00729719	50.7549	1.00E-12
rs2378005	1	218944148	0	G	A	0.643967	0.997101	65.7163	5.20E-16	0.0186486	0.00225563	68.3531	1.40E-16
rs2820446	1	219748818	0	C	G	0.702331	0.999783	114.595	9.70E-27	-0.0257134	0.00235898	118.815	1.10E-27
rs1890295	1	219933998	0	C	T	0.861952	0.997678	44.2789	2.80E-11	0.0210341	0.00313096	45.133	1.80E-11
rs2378436	1	221237584	0	G	A	0.440531	0.992907	52.563	4.20E-13	0.0163058	0.0021783	56.0341	7.10E-14
rs12723052	1	222771954	0	C	T	0.93944	0.963946	32.0118	1.50E-08	0.0267088	0.0046123	33.5332	7.00E-09
rs10916606	1	224570425	0	C	T	0.211953	0.994883	64.7204	8.60E-16	-0.0209115	0.00264724	62.4001	2.80E-15
rs1929865	1	227250459	0	A	G	0.0241963	0.982795	31.3562	2.10E-08	0.0392598	0.00708497	30.7058	3.00E-08
rs11588850	1	227927242	0	A	G	0.829575	0.992929	226.172	4.10E-51	0.0434941	0.00288258	227.666	1.90E-51
rs3820623	1	228107262	0	G	A	0.803547	0.993098	36.2183	1.80E-09	0.0169345	0.00272436	38.6382	5.10E-10
rs189043356	1	228161888	0	G	A	0.97279	0.940618	45.5865	1.50E-11	-0.0461314	0.0068394	45.4943	1.50E-11
rs2803841	1	235506853	0	G	A	0.644141	0.99749	58.2667	2.30E-14	0.0172534	0.00225569	58.5042	2.00E-14
rs2994328	1	243649330	0	G	A	0.776975	0.993798	64.9859	7.50E-16	-0.020855	0.00260232	64.2247	1.10E-15
rs80116665	1	244122296	0	G	A	0.932783	1	38.7692	4.80E-10	-0.0257338	0.00431065	35.6388	2.40E-09
rs397719	2	204870	0	T	G	0.150441	0.993138	47.83	4.60E-12	-0.0212117	0.00302189	49.2713	2.20E-12
rs150606467	2	1568378	0	G	A	0.960011	0.956977	53.019	3.30E-13	-0.0406714	0.00561975	52.3776	4.60E-13
rs66753271	2	1642790	0	T	C	0.920123	0.992417	32.8493	1.00E-08	-0.023313	0.00398647	34.1994	5.00E-09
rs6726887	2	1749257	0	A	G	0.728871	0.980941	44.7038	2.30E-11	-0.0161438	0.00244617	43.5549	4.10E-11
rs3922853	2	5830599	0	C	A	0.825966	1	53.5908	2.50E-13	0.0205705	0.00283682	52.5807	4.10E-13
rs10211501	2	6539705	0	C	G	0.310633	0.994672	38.5536	5.30E-10	-0.0145645	0.00233685	38.8441	4.60E-10
rs10171807	2	10201383	0	A	C	0.442322	0.990711	134.504	4.20E-31	0.0247246	0.00218074	128.543	8.50E-30
rs72771625	2	10400557	0	A	T	0.905914	0.991621	32.5933	1.10E-08	0.0220671	0.00371151	35.3501	2.80E-09
rs79735096	2	12175692	0	G	C	0.880462	0.998794	27.6802	1.40E-07	-0.0182277	0.00332193	30.108	4.10E-08
rs12621634	2	16121533	0	T	C	0.890943	0.992338	41.5978	1.10E-10	0.0227209	0.00346973	42.8806	5.80E-11
rs7589862	2	19613195	0	C	T	0.856972	0.992916	39.9689	2.60E-10	0.0197935	0.00308564	41.1486	1.40E-10
rs6732272	2	20042817	0	C	T	0.583173	0.998674	42.7749	6.10E-11	0.014032	0.00218427	41.2689	1.30E-10
rs52826764	2	20205541	0	C	T	0.970426	1	114.128	1.20E-26	0.0688419	0.00636145	117.11	2.70E-27
rs907868	2	20371167	0	C	T	0.525175	0.997737	61.2959	4.90E-15	-0.0166518	0.00216086	59.3843	1.30E-14
rs145225702	2	20617424	0	C	T	0.980043	0.950881	41.0025	1.50E-10	-0.0497991	0.00789792	39.7574	2.90E-10
rs12713004	2	23896049	0	A	G	0.274462	0.997566	241.421	1.90E-54	-0.0377141	0.00241712	243.451	7.00E-55
rs3795945	2	23920632	0	C	G	0.267127	0.998846	53.9626	2.00E-13	-0.0180994	0.00243466	55.2652	1.10E-13
rs75060829	2	25013941	0	A	C	0.930833	0.998806	51.5982	6.80E-13	0.0314169	0.00424491	54.776	1.40E-13

rs754536	2	25176200	0	C	T	0.506509	0.997752	289.082	7.90E-65	-0.0374476	0.00215726	301.332	1.70E-67
rs11693908	2	25348546	0	G	A	0.875566	0.956138	67.797	1.80E-16	0.026827	0.00333299	64.7852	8.40E-16
rs146839318	2	25468470	0	T	C	0.9825	0.940789	31.2404	2.30E-08	-0.0496351	0.00845401	34.4709	4.30E-09
rs12479314	2	25580305	0	G	C	0.95017	0.96881	55.7623	8.20E-14	-0.0376133	0.00502782	55.9659	7.40E-14
rs33994557	2	25973060	0	C	T	0.945699	1	52.3361	4.70E-13	0.0333268	0.00475145	49.1965	2.30E-12
rs1260326	2	27730940	0	T	C	0.395418	1	95.2509	1.70E-22	-0.0214256	0.00220343	94.5517	2.40E-22
rs4666067	2	28608504	0	C	T	0.551715	0.982055	59.3283	1.30E-14	0.0167558	0.00218418	58.8506	1.70E-14
rs1153122	2	32533457	0	T	C	0.303748	0.98876	50.3215	1.30E-12	-0.0157251	0.00235497	44.588	2.40E-11
rs111737248	2	33278875	0	G	A	0.98413	0.953064	40.6995	1.80E-10	-0.0566619	0.00881956	41.2751	1.30E-10
rs445151	2	33297412	0	C	T	0.22656	0.996271	40.4487	2.00E-10	-0.0164982	0.00257561	41.0309	1.50E-10
rs1545552	2	33360338	0	A	G	0.291573	0.994558	182.859	1.20E-41	-0.0326126	0.0023802	187.733	9.90E-43
rs6743685	2	33389595	0	A	C	0.477115	0.996382	88.8346	4.30E-21	-0.0206246	0.00215915	91.2445	1.30E-21
rs13430745	2	33568353	0	C	T	0.821071	0.969906	77.7355	1.20E-18	0.0252776	0.00285403	78.4431	8.20E-19
rs6543726	2	33845642	0	G	A	0.844483	0.992894	31.5466	1.90E-08	0.0162743	0.00298296	29.7651	4.90E-08
rs3821150	2	36795233	0	G	A	0.689593	0.99525	104.531	1.50E-24	0.0240027	0.00233107	106.025	7.30E-25
rs9678172	2	37720997	0	C	T	0.612134	0.988595	31.3796	2.10E-08	0.0126396	0.00222383	32.3045	1.30E-08
rs17511102	2	37960613	0	A	T	0.910678	1	94.8936	2.00E-22	-0.0367634	0.00378333	94.4237	2.50E-22
rs17038846	2	37995590	0	T	C	0.892786	0.959738	77.681	1.20E-18	0.0311276	0.0035569	76.5855	2.10E-18
rs10202845	2	42575820	0	A	G	0.886712	0.977733	71.1432	3.30E-17	0.0298991	0.00343508	75.7605	3.20E-18
rs3953604	2	43426753	0	G	C	0.477595	0.99559	33.6435	6.60E-09	-0.0126809	0.00216007	34.4638	4.30E-09
rs138958276	2	44042787	0	G	A	0.956951	0.97405	56.6302	5.30E-14	-0.0387525	0.00537443	51.9918	5.60E-13
rs7593987	2	44393532	0	A	G	0.191381	0.995656	131.851	1.60E-30	0.0317148	0.00274247	133.733	6.20E-31
rs343935	2	44991100	0	T	C	0.840754	0.99126	66.6495	3.20E-16	-0.024512	0.00296109	68.526	1.30E-16
rs4953375	2	46654484	0	T	A	0.489593	0.983013	50.1813	1.40E-12	-0.0160447	0.00217403	54.4668	1.60E-13
rs1109380	2	46924490	0	G	T	0.625423	0.997335	93.2874	4.50E-22	-0.0218	0.00222674	95.8457	1.20E-22
rs2436772	2	47283557	0	G	A	0.790511	1	50.6965	1.10E-12	-0.0186569	0.0026479	49.6451	1.80E-12
rs62138802	2	48530981	0	A	G	0.832468	0.99277	45.9538	1.20E-11	0.0190364	0.00289183	43.3337	4.60E-11
rs76493569	2	48601305	0	A	G	0.962656	0.98326	36.8856	1.30E-09	-0.0323309	0.0057262	31.879	1.60E-08
rs805445	2	54175440	0	T	C	0.868292	0.99397	42.8507	5.90E-11	0.0206755	0.00319574	41.8571	9.80E-11
rs10153704	2	54699421	0	A	C	0.955825	0.985657	43.3896	4.50E-11	-0.0361985	0.00527591	47.0745	6.80E-12
rs72799594	2	55640071	0	G	A	0.952175	0.955274	64.7838	8.40E-16	0.0411794	0.00516405	63.5884	1.50E-15
rs11125594	2	55975995	0	C	G	0.870982	0.964302	53.9995	2.00E-13	0.0236531	0.00327281	52.2317	4.90E-13
rs41393947	2	56011517	0	G	A	0.857585	0.987295	146.445	1.00E-33	-0.0382369	0.00310181	151.962	6.50E-35
rs59985551	2	56106928	0	C	T	0.774234	0.998856	753.969	5.50E-166	0.0705167	0.00257548	749.667	4.70E-165
rs76820952	2	56178882	0	T	C	0.951421	0.983828	139.366	3.70E-32	-0.0599645	0.00505214	140.876	1.70E-32
rs79920062	2	56259760	0	A	G	0.954378	0.971342	38.203	6.40E-10	-0.0317899	0.00523576	36.8656	1.30E-09
rs12466227	2	60148940	0	A	G	0.450748	0.995387	86.2861	1.60E-20	0.0196219	0.00217073	81.7096	1.60E-19
rs9309322	2	60441184	0	G	A	0.530485	1	46.1705	1.10E-11	0.0146339	0.00215642	46.0521	1.20E-11
rs10189857	2	60713235	0	A	G	0.567793	1	45.6066	1.40E-11	0.0145371	0.00217864	44.523	2.50E-11
rs10496091	2	61482261	0	G	A	0.719032	1	50.2394	1.40E-12	0.0170823	0.00239991	50.6644	1.10E-12
rs702883	2	65752085	0	A	G	0.649723	0.995533	55.5048	9.30E-14	-0.0177983	0.002265	61.7474	3.90E-15
rs678311	2	67671731	0	T	C	0.543099	0.985398	34.2456	4.90E-09	-0.0124471	0.00217819	32.6546	1.10E-08
rs80050140	2	68428541	0	C	T	0.919196	0.998226	72.0055	2.10E-17	0.0336344	0.00395995	72.1419	2.00E-17
rs112210761	2	69318443	0	C	G	0.751039	0.984537	52.094	5.30E-13	0.0178368	0.00251148	50.4402	1.20E-12
rs9989781	2	69377069	0	G	A	0.962262	0.96666	43.7029	3.80E-11	-0.0382485	0.00574142	44.3804	2.70E-11
rs7585767	2	70338344	0	A	G	0.510574	0.977358	66.5255	3.50E-16	0.0173131	0.00218063	63.0357	2.00E-15
rs17743415	2	71562503	0	T	C	0.433512	0.997646	246.371	1.60E-55	0.0337285	0.00217738	239.952	4.00E-54
rs2303597	2	71780821	0	T	C	0.293867	0.988983	79.5025	4.80E-19	0.0212752	0.0023785	80.0094	3.70E-19
rs17007417	2	72035671	0	T	C	0.142585	0.986971	47.5952	5.20E-12	0.020788	0.00310165	44.9201	2.10E-11
rs1079144	2	72366224	0	T	A	0.967218	0.913086	33.5762	6.90E-09	-0.0374909	0.00632425	35.1425	3.10E-09
rs12611708	2	73109017	0	A	C	0.107882	0.997378	31.7338	1.80E-08	0.0197464	0.00347777	32.2383	1.40E-08
rs114179578	2	85764582	0	G	A	0.988314	0.929928	30.831	2.80E-08	0.0583494	0.010392	31.5266	2.00E-08
rs72843872	2	85820027	0	A	G	0.694504	0.996298	84.7238	3.40E-20	-0.0216056	0.00234204	85.1025	2.80E-20
rs72842007	2	86025474	0	G	A	0.794047	0.965762	30.6513	3.10E-08	-0.0150632	0.00271277	30.8324	2.80E-08
rs7601115	2	86823608	0	T	C	0.532172	0.999628	29.1593	6.70E-08	-0.0118452	0.0021568	30.1623	4.00E-08
rs11681299	2	88901732	0	C	T	0.713094	0.99984	202.302	6.60E-46	-0.0342201	0.00237948	206.823	6.80E-47
rs2438709	2	97199694	0	A	G	0.220658	1	30.0534	4.20E-08	0.0144599	0.00259736	30.9931	2.60E-08
rs183743021	2	97283676	0	T	C	0.976191	0.957797	117.337	2.40E-27	0.0782802	0.00722073	117.528	2.20E-27
rs2278206	2	99172244	0	A	G	0.752122	1	36.5372	1.50E-09	0.0150183	0.00249388	36.2654	1.70E-09
rs4851300	2	100958804	0	C	A	0.651362	0.992881	35.4654	2.60E-09	-0.0134881	0.00226585	35.4355	2.60E-09
rs2140316	2	103098676	0	T	A	0.442172	0.9882	65.556	5.60E-16	-0.0178085	0.00218283	66.5601	3.40E-16
rs6739701	2	105132332	0	A	G	0.56726	0.989227	52.5943	4.10E-13	-0.0156326	0.00218693	51.0964	8.80E-13
rs6738207	2	105989716	0	G	A	0.599284	0.991811	57.1186	4.10E-14	-0.0163863	0.00220704	55.1243	1.10E-13
rs34795949	2	106711400	0	A	G	0.854401	0.994258	51.2086	8.30E-13	-0.0225183	0.00306537	53.9643	2.00E-13
rs73954925	2	111877174	0	C	G	0.936429	0.993603	47.9418	4.40E-12	0.031784	0.00442598	51.5702	6.90E-13
rs62161615	2	112061485	0	T	C	0.364415	0.968362	30.8276	2.80E-08	-0.0129675	0.0022828	32.2686	1.30E-08
rs200104212	2	112256611	0	G	C	0.790219	0.987107	47.2884	6.10E-12	-0.0183965	0.00266319	47.7161	4.90E-12
rs479305	2	119410052	0	T	C	0.741182	0.995557	33.9178	5.70E-09	0.0148952	0.00246295	36.5747	1.50E-09
rs13393992	2	121591328	0	C	T	0.838024	1	51.473	7.30E-13	0.0206042	0.00293024	49.4429	2.00E-12
rs4848645	2	121623691	0	C	G	0.830684	0.99386	98.3283	3.50E-23	0.0287709	0.00288254	99.6225	1.80E-23
rs6541743	2	121647802	0	G	A	0.620944	0.994806	39.0731	4.10E-10	-0.0139935	0.00222778	39.4552	3.40E-10
rs6430936	2	128007686	0	A	C	0.287954	1	37.612	8.60E-10	0.0147558	0.00238148	38.3911	5.80E-10
rs17262146	2	128958297	0	A	G	0.57754	0.994473	44.4513	2.60E-11	-0.0139925	0.00219183	40.7546	1.70E-10
rs6761931	2	136150512	0	A	G	0.925867	0.992728	34.5223	4.20E-09	0.0251095	0.00414468	36.7022	1.40E-09
rs1963394	2	141573427	0	G	T	0.452449	0.994209	35.5377	2.50E-09	-0.0123379	0.00217198	32.268	1.30E-08
rs17741562	2	148563066	0	T	C	0.799292	0.997008	52.43	4.50E-13	-0.0192592	0.00269796	50.9573	9.40E-13
rs72887152	2	156604025	0	T	A	0.833973	0.996676	56.2633	6.30E-14	-0.0204516	0.00290105	49.6984	1.80E-12
rs7425274	2	161203395	0	T	C	0.570814	0.997014	50.7264	1.10E-12	-0.0153766	0.00217816	49.8362	1.70E-12
rs4487103	2	165485978	0	G	C	0.384623	0.998134	43.7054	3.80E-11	0.0144169	0.00222503	41.9824	9.20E-11
rs355901	2	165639847	0	T	C	0.385861	0.989264	70.3919	4.90E-17	-0.0187121	0.00222704	70.5977	4.40E-17
rs2140046	2	169706079	0	T	C	0.636685	0.995714	158.842	2.00E-36	0.0283288	0.00224323	159.48	1.50E-36
rs58304328	2	170594803	0	C	G	0.873778	0.952841	28.4761	9.50E-08	-0.0182837	0.00332606	30.2184	3.90E-08
rs13385068	2	172047845	0	A	G	0.543173	0.981828	49.5866	1.90E-12	0.016011	0.00218521	53.6848	2.40E-13

rs12998320	2	172237268	0	C	G	0.70788	0.99217	87.4135	8.80E-21	-0.022048	0.00238002	85.8175	2.00E-20
rs55852614	2	172416869	0	T	C	0.752467	0.998601	139.224	3.90E-32	0.0297261	0.00249959	141.429	1.30E-32
rs76359852	2	174768849	0	A	T	0.812807	0.988604	62.4828	2.70E-15	0.022314	0.00277938	64.4555	9.90E-16
rs17400325	2	178565913	0	T	C	0.958568	1	109.261	1.40E-25	-0.055648	0.00540975	105.814	8.10E-25
rs71423581	2	179564694	0	G	A	0.97843	0.977432	32.7368	1.10E-08	-0.0424096	0.00749948	31.9791	1.60E-08
rs833152	2	183219101	0	C	A	0.427803	0.994136	33.1905	8.40E-09	0.0129015	0.0021822	34.9534	3.40E-09
rs1561369	2	183702964	0	G	A	0.880146	0.992073	58.5808	2.00E-14	-0.0263659	0.00332903	62.7262	2.40E-15
rs111688582	2	185362832	0	T	C	0.539534	0.981694	38.5525	5.30E-10	-0.0131933	0.0021846	36.4724	1.50E-09
rs11889872	2	188105155	0	T	C	0.505984	0.997511	76.8746	1.80E-18	-0.0191718	0.00216063	78.7341	7.10E-19
rs35917062	2	191660828	0	G	A	0.892822	1	57.4486	3.50E-14	0.0263493	0.00348235	57.2522	3.80E-14
rs6729346	2	199237818	0	C	T	0.786725	0.999219	32.5691	1.20E-08	0.0144414	0.00263213	30.1026	4.10E-08
rs1249093	2	199721062	0	A	G	0.536929	0.992765	34.8925	3.50E-09	0.0125772	0.00217353	33.484	7.20E-09
rs143794640	2	202234111	0	G	A	0.977906	0.99023	36.274	1.70E-09	-0.0430183	0.00736844	34.0843	5.30E-09
rs6435149	2	203271267	0	T	C	0.744228	0.997985	71.709	2.50E-17	0.0214333	0.00247436	75.033	4.60E-18
rs111737209	2	204298277	0	C	T	0.959529	0.985514	30.9833	2.60E-08	-0.0305409	0.0055074	30.7518	2.90E-08
rs1047891	2	211540507	0	C	A	0.684242	1	39.5892	3.10E-10	-0.0151134	0.00231792	42.5137	7.00E-11
rs7569142	2	213294557	0	C	T	0.601937	0.996561	36.7797	1.30E-09	-0.013985	0.00220545	40.2093	2.30E-10
rs76152268	2	216303813	0	T	C	0.984647	0.92052	63.8493	1.30E-15	0.0725321	0.00913746	63.0099	2.10E-15
rs7606034	2	216381241	0	A	G	0.345412	0.995153	28.6071	8.90E-08	0.0124089	0.00227311	29.8005	4.80E-08
rs7575757	2	216600284	0	C	A	0.180796	0.998796	48.2063	3.80E-12	-0.0199222	0.00280322	50.5082	1.20E-12
rs668844	2	217021602	0	C	A	0.517629	0.997186	33.3931	7.50E-09	-0.0126127	0.00215945	34.1136	5.20E-09
rs12477332	2	217492420	0	T	C	0.905632	0.995695	37.2172	1.10E-09	-0.0229552	0.00370108	38.4685	5.60E-10
rs4264545	2	217869089	0	T	G	0.760432	0.988739	58.9091	1.70E-14	-0.0192875	0.00254075	57.6271	3.20E-14
rs10205394	2	218150948	0	G	C	0.800002	0.993757	81.1866	2.10E-19	0.0237031	0.00270671	76.6883	2.00E-18
rs1478575	2	218278555	0	T	A	0.315455	0.99525	199.809	2.30E-45	-0.0330751	0.00232497	202.38	6.30E-46
rs934247	2	218598202	0	T	A	0.0256086	0.993577	83.4252	6.60E-20	-0.0620998	0.00684696	82.2592	1.20E-19
rs76018285	2	218608733	0	A	G	0.941591	0.908662	46.946	7.30E-12	-0.0326323	0.00482734	45.6962	1.40E-11
rs1870125	2	219187901	0	C	T	0.410049	0.999014	155.178	1.30E-35	-0.0270746	0.0021935	152.352	5.30E-35
rs6716635	2	219506257	0	G	A	0.430387	0.997379	181.149	2.70E-41	-0.0284231	0.00217996	169.998	7.40E-39
rs530210938	2	219631372	0	G	T	0.982117	0.82026	34.5662	4.10E-09	0.0525905	0.00898427	34.2648	4.80E-09
rs7558440	2	219729076	0	G	A	0.835294	0.989063	37.8219	7.80E-10	-0.0182478	0.0029236	38.9571	4.30E-10
rs16859483	2	219893421	0	G	A	0.976888	0.988466	34.9279	3.40E-09	-0.0444902	0.0072163	38.0101	7.00E-10
rs556441729	2	219969436	0	C	T	0.985486	0.970259	57.5183	3.30E-14	0.0664866	0.00913594	52.9617	3.40E-13
rs145296160	2	220004944	0	T	C	0.982933	0.905623	180.175	4.40E-41	0.117018	0.00873709	179.38	6.60E-41
rs74584209	2	220031800	0	C	T	0.969947	0.978383	80.4808	2.90E-19	-0.0568849	0.00637872	79.5293	4.80E-19
rs57703940	2	220190662	0	A	C	0.877661	0.998117	33.2563	8.10E-09	0.0192058	0.00329471	33.9807	5.60E-09
rs6711710	2	223956410	0	T	C	0.218624	0.992382	68.4763	1.30E-16	-0.0216267	0.00262335	67.9624	1.70E-16
rs10933046	2	225093291	0	C	A	0.346898	0.998422	84.1819	4.50E-20	-0.0207108	0.00226687	83.4715	6.50E-20
rs28432054	2	225545879	0	C	T	0.372453	0.998756	44.5039	2.50E-11	-0.0147993	0.00223149	43.9836	3.30E-11
rs113265459	2	225659728	0	G	A	0.981867	0.991549	44.1857	3.00E-11	-0.0529757	0.00812154	42.5478	6.90E-11
rs17246129	2	227259964	0	G	A	0.695704	0.993786	62.8646	2.20E-15	-0.018246	0.00235125	60.2192	8.50E-15
rs116376456	2	227326633	0	A	T	0.982857	0.97674	156.163	7.80E-36	0.105299	0.00839908	157.174	4.70E-36
rs80318152	2	227597345	0	G	A	0.953325	0.98382	31.691	1.80E-08	0.0301783	0.00515886	34.2201	4.90E-09
rs13015698	2	227700818	0	C	T	0.642908	1	29.6039	5.30E-08	-0.0123463	0.00225027	30.1028	4.10E-08
rs77001804	2	232290921	0	T	C	0.776768	0.976753	43.1201	5.10E-11	0.0179782	0.00262009	47.0826	6.80E-12
rs10202701	2	232328681	0	C	T	0.457814	0.994223	151.652	7.50E-35	-0.0266324	0.00217333	150.165	1.60E-34
rs4973022	2	232745518	0	G	A	0.249714	0.992093	34.5941	4.10E-09	-0.0144402	0.00249959	33.374	7.60E-09
rs5268	2	232790053	0	C	T	0.3659	0.981322	146.397	1.10E-33	-0.0279698	0.00225637	153.66	2.70E-35
rs59141578	2	232966003	0	C	T	0.979315	0.998666	117.699	2.00E-27	0.0821789	0.00757195	117.789	1.90E-27
rs901787	2	233088747	0	C	T	0.90326	0.995825	205.817	1.10E-46	0.0533713	0.00365425	213.314	2.60E-48
rs78198962	2	233094868	0	C	T	0.967669	1	250.743	1.80E-56	-0.0987172	0.0060919	262.591	4.70E-59
rs6437056	2	233097174	0	G	A	0.0897434	1	168.74	1.40E-38	0.0484306	0.00377339	164.731	1.00E-37
rs2139028	2	233163140	0	G	T	0.0160788	0.92964	34.1349	5.10E-09	0.0554507	0.00888996	38.9058	4.40E-10
rs11674608	2	233404294	0	C	G	0.643358	0.993995	49.4503	2.00E-12	0.0158845	0.00225417	49.6564	1.80E-12
rs283477	2	233649427	0	A	G	0.652928	0.999124	102.964	3.40E-24	0.0229259	0.00226779	102.199	5.00E-24
rs13408361	2	238382899	0	A	G	0.765121	0.997303	40.1368	2.40E-10	0.0153943	0.00254569	36.5684	1.50E-09
rs861072	2	239315688	0	C	T	0.24651	0.992951	32.5484	1.20E-08	0.0139446	0.00250776	30.92	2.70E-08
rs6431623	2	239674876	0	G	A	0.571128	0.985139	48.6133	3.10E-12	0.0151459	0.00219739	47.5086	5.50E-12
rs61277584	2	241774015	0	A	G	0.473647	0.996858	77.1877	1.60E-18	0.0190268	0.00216053	77.5556	1.30E-18
rs73110173	2	241982907	0	T	G	0.971571	0.989975	57.0994	4.10E-14	-0.0494331	0.00651946	57.4927	3.40E-14
rs11679356	2	242356894	0	C	T	0.799277	0.998231	60.7864	6.40E-15	0.0206436	0.00269457	58.694	1.80E-14
rs570235	2	242491353	0	I	C	0.408884	0.986318	131.453	2.00E-30	0.0247475	0.00220965	125.435	4.10E-29
rs2054872	3	4769176	0	C	A	0.839688	0.9926	34.1016	5.20E-09	-0.0174158	0.00296614	34.4749	4.30E-09
rs148193460	3	4910072	0	C	G	0.967288	0.90246	32.5176	1.20E-08	-0.0369508	0.00642538	33.0712	8.90E-09
rs4488814	3	10002400	0	T	C	0.753842	0.998421	45.2094	1.80E-11	-0.0167536	0.00252223	44.1214	3.10E-11
rs10433558	3	10183002	0	G	C	0.738327	0.971119	127.602	1.40E-29	0.0281975	0.00250685	126.521	2.40E-29
rs2616560	3	11656949	0	T	C	0.95207	0.996008	62.7548	2.30E-15	0.0422177	0.00509303	68.7128	1.10E-16
rs59447614	3	12302951	0	C	T	0.939085	0.989547	29.5519	5.40E-08	-0.0259299	0.0045644	32.2727	1.30E-08
rs6793957	3	12714156	0	G	A	0.253547	0.999303	34.6999	3.80E-09	-0.0147854	0.00249476	35.1245	3.10E-09
rs2597513	3	13555836	0	C	T	0.103371	1	133.667	6.50E-31	0.0418247	0.00356751	137.447	9.60E-32
rs2974401	3	13791475	0	A	T	0.718638	0.999136	67.1821	2.50E-16	-0.019518	0.00241238	65.4603	5.90E-16
rs112565405	3	14259894	0	A	G	0.970911	0.977831	67.1756	2.50E-16	0.0544161	0.00652799	69.4858	7.70E-17
rs13095528	3	14402962	0	A	G	0.562894	0.988575	36.7905	1.30E-09	0.0133633	0.00219793	36.9656	1.20E-09
rs3773486	3	15084880	0	T	A	0.747578	0.997849	33.0307	9.10E-09	-0.0139164	0.00250092	30.9639	2.60E-08
rs9826966	3	18737796	0	A	G	0.270684	0.99843	34.993	3.30E-09	0.0149443	0.00244416	37.3846	9.70E-10
rs73040019	3	23161678	0	T	C	0.841827	0.996689	43.9477	3.40E-11	-0.0194801	0.0029795	42.7463	6.20E-11
rs1349265	3	24159387	0	A	G	0.306289	0.987972	61.7038	4.00E-15	-0.0181398	0.00236351	58.9045	1.70E-14
rs35601156	3	24387022	0	T	A	0.809903	0.992137	30.5286	3.30E-08	-0.0156496	0.00277757	31.7452	1.80E-08
rs4417830	3	25034135	0	A	G	0.698791	0.979255	40.466	2.00E-10	-0.0149018	0.00239001	38.8757	4.50E-10
rs322701	3	25355041	0	A	T	0.764969	0.981748	35.7634	2.20E-09	-0.0149332	0.00258131	33.4675	7.20E-09
rs903346	3	27375517	0	G	C	0.32384	0.994601	36.3822	1.60E-09	0.0141427	0.00232678	36.9446	1.20E-09
rs6810039	3	33194990	0	C	A	0.600629	1	61.5265	4.40E-15	0.0168733	0.00221691	57.9303	2.70E-14
rs79495297	3	33535519	0	C	T	0.972651	0.993662	54.2063	1.80E-13	-0.0482484	0.00667544	52.2404	4.90E-13

rs56134614	3	33787533	0	C	A	0.962399	1	29.3153	6.20E-08	0.0316852	0.00569567	30.9473	2.70E-08
rs6762638	3	35833148	0	C	A	0.724254	0.999032	31.5573	1.90E-08	0.0136412	0.00243233	31.4528	2.00E-08
rs197769	3	37515916	0	G	A	0.43844	0.980746	34.9933	3.30E-09	0.0127462	0.00220504	33.4141	7.40E-09
rs9826470	3	38019428	0	C	T	0.751078	0.988786	85.4483	2.40E-20	-0.0236963	0.00252607	87.9981	6.60E-21
rs6781242	3	41300601	0	A	G	0.525168	0.978893	63.2475	1.80E-15	-0.0172901	0.00219617	61.9814	3.50E-15
rs3732858	3	43097765	0	G	A	0.83148	1	48.4735	3.30E-12	0.0197309	0.00290087	46.2635	1.00E-11
rs9844307	3	45609868	0	A	T	0.596236	0.987732	38.8553	4.60E-10	-0.0134433	0.00222933	36.3632	1.60E-09
rs724449	3	46935681	0	C	T	0.401297	0.999799	93.9714	3.20E-22	0.0210982	0.00221207	90.969	1.50E-21
rs111970477	3	47105581	0	A	G	0.97903	0.905092	35.8899	2.10E-09	0.0449226	0.00795316	31.9043	1.60E-08
rs142088257	3	47961738	0	G	A	0.987168	0.996738	43.4254	4.40E-11	-0.0630688	0.00964809	42.7313	6.30E-11
rs3172494	3	48731487	0	G	T	0.891244	0.988566	59.7573	1.10E-14	-0.0261061	0.00350568	55.4551	9.60E-14
rs55933602	3	50343600	0	C	T	0.896511	0.994757	63.1366	1.90E-15	0.0283341	0.00357432	62.8394	2.20E-15
rs35746825	3	51480941	0	G	A	0.953011	0.970598	131.721	1.70E-30	-0.0596536	0.00520906	131.146	2.30E-30
rs7642787	3	52075944	0	A	G	0.927408	0.956886	29.7847	4.80E-08	-0.0242089	0.00427698	32.0389	1.50E-08
rs145654156	3	52670617	0	A	C	0.963047	0.9926	41.1708	1.40E-10	0.0365554	0.00578355	39.9497	2.60E-10
rs2564924	3	53103155	0	C	T	0.44279	0.997669	291.297	2.60E-65	0.0377187	0.00218554	297.849	9.70E-67
rs793202	3	53511648	0	G	A	0.468796	0.991769	34.8749	3.50E-09	0.0131868	0.00218109	36.5535	1.50E-09
rs17321866	3	55041696	0	T	C	0.865516	0.990602	34.9495	3.40E-09	0.0186784	0.0031925	34.2309	4.90E-09
rs3913369	3	55481075	0	G	T	0.758572	0.99004	47.3323	6.00E-12	-0.0175417	0.00255011	47.318	6.00E-12
rs6762851	3	56686329	0	T	C	0.6428	0.999625	142.961	6.00E-33	0.027252	0.00226762	144.43	2.90E-33
rs6802104	3	58015300	0	C	T	0.372009	0.995561	117.605	2.10E-27	0.0238721	0.00225187	112.381	2.90E-26
rs9876744	3	58457630	0	G	T	0.659987	0.988858	33.9862	5.60E-09	-0.0132728	0.00230243	33.2314	8.20E-09
rs7621604	3	61557718	0	A	G	0.55475	0.993333	94.1118	3.00E-22	0.0206344	0.00218654	89.0566	3.80E-21
rs34182292	3	61578580	0	G	A	0.300093	0.990693	49.0697	2.50E-12	-0.0167807	0.00237963	49.7282	1.80E-12
rs251035	3	61978986	0	G	T	0.672265	0.991767	47.3385	6.00E-12	0.0159687	0.00232294	47.2565	6.20E-12
rs17066238	3	62160653	0	G	T	0.919951	0.995935	30.443	3.40E-08	-0.0222521	0.00400811	30.8222	2.80E-08
rs4132228	3	64708114	0	C	T	0.711402	1	72.3607	1.80E-17	-0.0207765	0.0023977	75.0855	4.50E-18
rs11131007	3	65198539	0	G	A	0.815089	0.972326	45.0554	1.90E-11	-0.0195324	0.0028342	47.4956	5.50E-12
rs35494829	3	67426281	0	T	C	0.885732	1	62.8366	2.20E-15	0.0270382	0.00341809	62.573	2.60E-15
rs11917652	3	71474135	0	T	C	0.442731	0.984486	38.3497	5.90E-10	-0.0133156	0.00220375	36.5085	1.50E-09
rs62245304	3	72383413	0	C	T	0.865771	0.974236	34.6258	4.00E-09	0.0184829	0.00322338	32.8789	9.80E-09
rs9809116	3	72397279	0	A	G	0.592178	0.985023	283.205	1.50E-63	0.0374419	0.00222547	283.057	1.60E-63
rs9823893	3	87315389	0	A	T	0.951524	0.978201	40.2235	2.30E-10	0.0319589	0.00510144	39.2463	3.70E-10
rs9825951	3	99269921	0	T	A	0.364265	0.981775	64.8067	8.30E-16	0.0177074	0.00227172	60.7576	6.50E-15
rs1461107	3	112824912	0	G	C	0.657638	0.986778	50.9385	9.50E-13	-0.0163857	0.00229871	50.8118	1.00E-12
rs55814436	3	112956865	0	C	T	0.793357	1	34.0126	5.50E-09	0.0153216	0.00267104	32.904	9.70E-09
rs11707275	3	114537043	0	T	G	0.953394	0.994791	54.3475	1.70E-13	-0.0375587	0.00515313	53.1226	3.10E-13
rs11715566	3	117562436	0	C	T	0.507001	0.998248	32.0752	1.50E-08	-0.0121959	0.00216582	31.709	1.80E-08
rs1716838	3	120106521	0	A	G	0.705273	0.994414	30.7778	2.90E-08	0.0132112	0.00237959	30.8234	2.80E-08
rs11720939	3	122964428	0	C	T	0.776995	0.991581	66.1677	4.10E-16	0.0215634	0.00261016	68.2499	1.40E-16
rs62267105	3	124645365	0	G	T	0.771792	0.989592	43.2107	4.90E-11	-0.0165798	0.00259347	40.8692	1.60E-10
rs34870876	3	128204877	0	C	G	0.938058	0.982391	51.5165	7.10E-13	-0.0323506	0.00452505	51.1113	8.70E-13
rs6762578	3	128992047	0	G	A	0.221808	0.992237	305.569	2.00E-68	-0.0457139	0.00261717	305.094	2.60E-68
rs2811462	3	129303436	0	T	G	0.771421	0.992438	169.328	1.00E-38	-0.0334963	0.0025864	167.727	2.30E-38
rs72628505	3	129398165	0	T	G	0.934033	0.96999	76.3781	2.30E-18	0.0390836	0.004425	78.0123	1.00E-18
rs4688801	3	130148760	0	A	G	0.919227	1	30.779	2.90E-08	-0.0216558	0.00397092	29.7418	4.90E-08
rs6776727	3	133981042	0	A	T	0.861626	0.99804	43.9264	3.40E-11	-0.0208431	0.00313531	44.1941	3.00E-11
rs13075185	3	134083063	0	C	T	0.649198	0.975868	40.0524	2.50E-10	-0.0146064	0.00229685	40.4408	2.00E-10
rs4245903	3	134317074	0	G	A	0.356755	0.998505	69.3865	8.10E-17	-0.0188645	0.00225922	69.7229	6.80E-17
rs35320690	3	135932494	0	T	C	0.724649	0.99786	148.26	4.20E-34	0.0294649	0.00242652	147.449	6.30E-34
rs1672936	3	138340590	0	A	G	0.454479	0.998156	55.361	1.00E-13	-0.0163841	0.00217605	56.6898	5.10E-14
rs6440003	3	141094209	0	G	A	0.556641	1	1538.51	0	-0.0855052	0.00217827	1540.85	0
rs73238075	3	141176845	0	A	G	0.986502	0.926959	60.5816	7.10E-15	0.0743982	0.00975505	58.1657	2.40E-14
rs77791416	3	141251799	0	A	G	0.980629	0.903186	37.2937	1.00E-09	0.0492515	0.00827192	35.4508	2.60E-09
rs114672208	3	141257640	0	A	G	0.971603	1	32.5788	1.10E-08	-0.0376969	0.00651347	33.4956	7.10E-09
rs73238087	3	141292466	0	G	A	0.989127	1	36.9728	1.20E-09	0.0622761	0.0104252	35.6842	2.30E-09
rs151099284	3	141337424	0	T	A	0.983651	0.867183	39.5876	3.10E-10	0.0554951	0.00916483	36.6657	1.40E-09
rs9837768	3	141847717	0	A	G	0.504934	0.998618	34.7741	3.70E-09	0.0125374	0.00216557	33.5174	7.10E-09
rs13327094	3	145764502	0	T	G	0.530355	0.989456	42.8774	5.80E-11	-0.0144393	0.00218037	43.8567	3.50E-11
rs1910466	3	147086268	0	T	C	0.501575	0.985882	76.3025	2.40E-18	0.0194057	0.00218012	79.231	5.50E-19
rs115396057	3	147870352	0	G	A	0.804354	0.974083	33.0462	9.00E-09	0.0165164	0.00276681	35.6347	2.40E-09
rs9855625	3	148842644	0	C	T	0.756931	0.988632	31.4079	2.10E-08	-0.0138766	0.00253556	29.9516	4.40E-08
rs1405895	3	153802823	0	C	T	0.256131	0.995405	36.7579	1.30E-09	-0.0157111	0.00248804	39.8748	2.70E-10
rs9834519	3	156379637	0	C	T	0.91874	0.973504	45.0061	2.00E-11	-0.027003	0.00401458	45.2424	1.70E-11
rs62276616	3	156382492	0	G	A	0.957113	0.982113	73.6967	9.10E-18	0.0460872	0.00539096	73.0851	1.20E-17
rs62274099	3	156810578	0	C	T	0.575246	0.985075	37.0532	1.10E-09	0.0134036	0.00220609	36.9147	1.20E-09
rs10936067	3	156905553	0	T	C	0.750768	0.997399	83.9736	5.00E-20	0.0227742	0.00250982	82.3375	1.10E-19
rs2693527	3	157991013	0	A	G	0.584138	0.999851	81.4175	1.80E-19	-0.0195202	0.00219578	79.0295	6.10E-19
rs62294340	3	169155476	0	G	A	0.61853	0.998341	45.1735	1.80E-11	-0.0151567	0.00223005	46.1934	1.10E-11
rs1997280	3	169238015	0	T	C	0.410192	0.992448	66.0874	4.30E-16	0.0180135	0.00220887	66.5054	3.50E-16
rs11718418	3	171771754	0	A	G	0.407534	0.995574	49.4621	2.00E-12	-0.0157212	0.00221052	50.5808	1.10E-12
rs7652177	3	171969077	0	C	G	0.495315	1	258.976	2.90E-58	-0.0352946	0.00216629	265.451	1.10E-59
rs35409041	3	172046841	0	G	T	0.989573	0.872763	32.8175	1.00E-08	-0.0662649	0.0114162	33.6918	6.50E-09
rs583269	3	172127777	0	T	C	0.533719	0.989234	263.018	3.80E-59	-0.0352122	0.00218314	260.149	1.60E-58
rs62282633	3	172266559	0	G	C	0.959382	0.970293	47.8803	4.50E-12	-0.0383246	0.00556276	47.4651	5.60E-12
rs11918587	3	178820666	0	C	T	0.928233	0.999021	31.5341	2.00E-08	0.0232852	0.00419648	30.7886	2.90E-08
rs35364893	3	181406433	0	A	G	0.85625	0.990747	28.5217	9.30E-08	-0.0170477	0.00309963	30.2492	3.80E-08
rs11545169	3	184020542	0	G	T	0.838568	1	65.2239	6.70E-16	0.0235494	0.00294511	63.9378	1.30E-15
rs6776312	3	185305480	0	C	A	0.656306	0.998289	50.8843	9.80E-13	0.0161705	0.00228177	50.2228	1.40E-12
rs138239478	3	185373312	0	T	C	0.981495	0.938323	75.5114	3.60E-18	0.0720355	0.00828617	75.5762	3.50E-18
rs2194411	3	185548663	0	G	A	0.871671	0.976742	437.073	4.70E-97	-0.0685534	0.00327512	438.131	2.80E-97
rs564696605	3	185613206	0	G	A	0.956947	0.941333	73.0272	1.30E-17	-0.0466065	0.00551196	71.4959	2.80E-17
rs7619337	3	187421567	0	C	T	0.66227	0.994173	43.775	3.70E-11	-0.0155728	0.00229303	46.1226	1.10E-11

rs61732778	3	187443314	0	G	A	0.928936	0.997529	150.281	1.50E-34	-0.0518391	0.00420816	151.751	7.20E-35
rs9290864	3	187505774	0	A	G	0.684494	0.982434	43.7897	3.70E-11	-0.0154287	0.00234854	43.1582	5.00E-11
rs726712	3	188273975	0	C	T	0.348296	0.999273	33.3776	7.60E-09	0.0132682	0.00227196	34.1054	5.20E-09
rs7650573	3	190896240	0	T	G	0.666019	0.982223	34.6283	4.00E-09	0.0138244	0.00231699	35.5997	2.40E-09
rs77060135	4	881327	0	A	G	0.887763	0.989559	36.1506	1.80E-09	-0.0210782	0.00346432	37.0194	1.20E-09
rs113289555	4	996998	0	G	T	0.766525	0.971688	121.069	3.70E-28	0.0289377	0.00260925	122.998	1.40E-28
rs11736125	4	1744939	0	C	T	0.658679	0.998034	151.092	1.00E-34	-0.028414	0.00229436	153.37	3.20E-35
rs142639234	4	1873888	0	A	G	0.945647	0.950284	43.0714	5.30E-11	-0.0322501	0.00492332	42.9087	5.70E-11
rs144351518	4	1893651	0	A	G	0.967362	0.924081	35.0472	3.20E-09	0.0374601	0.00636973	34.5856	4.10E-09
rs2187692	4	1983556	0	A	G	0.978778	1	55.8768	7.70E-14	0.0557109	0.00753672	54.6407	1.40E-13
rs116829201	4	3328004	0	C	T	0.976567	0.968866	32.5522	1.20E-08	-0.0419039	0.00730156	32.9365	9.50E-09
rs13108218	4	3443931	0	A	G	0.384401	0.983772	108.359	2.20E-25	-0.0236673	0.00225735	109.926	1.00E-25
rs2968669	4	4889866	0	C	G	0.474899	0.986951	39.7485	2.90E-10	-0.0138527	0.0021925	39.9199	2.60E-10
rs11722554	4	5016883	0	G	A	0.962089	1	32.4884	1.20E-08	0.0315959	0.00570489	30.6737	3.10E-08
rs35772786	4	7021211	0	T	G	0.494419	0.986816	65.9784	4.60E-16	-0.017169	0.00219215	61.3408	4.80E-15
rs4619890	4	7853160	0	G	A	0.498698	1	106.559	5.60E-25	-0.0226722	0.00217758	108.403	2.20E-25
rs10461079	4	8392724	0	G	A	0.706309	0.995458	40.3804	2.10E-10	0.015364	0.00239481	41.1592	1.40E-10
rs4621412	4	8605338	0	G	A	0.596576	0.989427	137.641	8.70E-32	0.0261453	0.00222885	137.603	8.90E-32
rs10939656	4	10014646	0	A	C	0.447256	0.995669	31.4388	2.10E-08	-0.0119769	0.00219173	29.8617	4.60E-08
rs13136927	4	10669522	0	A	C	0.447656	0.994598	34.7486	3.80E-09	-0.0131628	0.00219683	35.9009	2.10E-09
rs573890678	4	12486688	0	G	T	0.908784	0.938272	44.4215	2.60E-11	0.0263439	0.00391316	45.3215	1.70E-11
rs28783740	4	12911495	0	G	T	0.494585	0.996766	133.635	6.60E-31	0.0256445	0.002179	138.507	5.60E-32
rs223982	4	12967160	0	G	A	0.0647249	1	37.9825	7.10E-10	0.0273023	0.00442329	38.0984	6.70E-10
rs16888428	4	13264141	0	A	G	0.837362	0.987273	85.1337	2.80E-20	-0.0272484	0.00296286	84.5786	3.70E-20
rs6827090	4	13679527	0	G	A	0.796309	0.99512	38.0887	6.80E-10	-0.0168282	0.00270849	38.6033	5.20E-10
rs34869264	4	17640270	0	A	T	0.988218	0.971813	68.5095	1.30E-16	0.0856124	0.0102363	69.9495	6.10E-17
rs7673321	4	17957688	0	T	A	0.841419	0.999891	840.33	9.20E-185	0.0861081	0.00297807	836.024	7.90E-184
rs114192810	4	17969142	0	T	G	0.979692	0.978865	43.7076	3.80E-11	-0.0520481	0.00778637	44.6827	2.30E-11
rs76236231	4	18000776	0	G	A	0.976105	0.866338	61.9128	3.60E-15	-0.0604746	0.0076531	62.4411	2.70E-15
rs74537632	4	18020156	0	G	A	0.967466	0.971457	74.4286	6.30E-18	-0.0538882	0.00621963	75.0687	4.50E-18
rs6820982	4	18267556	0	C	T	0.98775	0.769633	31.7291	1.80E-08	0.0623045	0.011297	30.4167	3.50E-08
rs138278869	4	18309898	0	A	G	0.985857	0.931278	49.0176	2.50E-12	0.0652097	0.00958056	46.3279	1.00E-11
rs7658136	4	19312328	0	C	T	0.232061	0.994851	35.3861	2.70E-09	0.0156121	0.00258593	36.4493	1.60E-09
rs12510223	4	19891260	0	T	C	0.698772	0.984312	32.7727	1.00E-08	0.0135847	0.00239081	32.2856	1.30E-08
rs34811474	4	25408838	0	G	A	0.76873	1	53.2781	2.90E-13	-0.0193731	0.00258261	56.2702	6.30E-14
rs79131883	4	38644825	0	T	C	0.882352	1	67.8369	1.80E-16	0.0283589	0.00338337	70.2553	5.20E-17
rs7658917	4	39334387	0	T	C	0.544631	0.990255	64.4481	9.90E-16	-0.0172737	0.00219555	61.899	3.60E-15
rs794016	4	40051064	0	C	T	0.112639	1	68.1201	1.50E-16	-0.0286272	0.00343956	69.271	8.60E-17
rs963317	4	45129970	0	A	G	0.337126	0.999328	37.6386	8.50E-10	0.0138652	0.00230423	36.2079	1.80E-09
rs10018344	4	48498670	0	C	G	0.496811	0.997252	58.1155	2.50E-14	-0.0167567	0.00217818	59.182	1.40E-14
rs13115570	4	56387392	0	T	G	0.692075	0.998712	97.23	6.20E-23	-0.0242638	0.00235858	105.832	8.00E-25
rs73155600	4	56915061	0	C	A	0.72979	0.99767	34.7585	3.70E-09	0.0146338	0.0024517	35.627	2.40E-09
rs12645070	4	57770106	0	G	A	0.816695	0.99855	126.191	2.80E-29	-0.031485	0.00281517	125.083	4.90E-29
rs78862524	4	73171190	0	C	A	0.944931	0.947497	32.7815	1.00E-08	0.0282512	0.00489628	33.2919	7.90E-09
rs7697556	4	73515313	0	T	C	0.473916	1	236.602	2.20E-53	0.0336745	0.00218113	238.363	8.90E-54
rs112867328	4	81476986	0	C	T	0.982571	0.979781	114.123	1.20E-26	-0.0883988	0.00838585	111.122	5.60E-26
rs6816536	4	81746468	0	G	A	0.975648	1	38.8135	4.70E-10	0.0421663	0.00705549	35.7171	2.30E-09
rs1662835	4	82172449	0	T	C	0.69466	0.996478	341.898	2.50E-76	-0.0439883	0.00236838	344.964	5.30E-77
rs115757548	4	82322185	0	T	G	0.979877	0.983068	30.99	2.60E-08	0.0435786	0.00781303	31.1105	2.40E-08
rs10516757	4	86704797	0	A	G	0.875306	0.994533	49.0649	2.50E-12	0.0230622	0.00330111	48.807	2.80E-12
rs112415208	4	87313634	0	G	T	0.964367	0.987495	33.7368	6.30E-09	-0.0350241	0.00590607	35.167	3.00E-09
rs140557441	4	87659122	0	C	T	0.983985	0.97967	108.088	2.60E-25	0.0899457	0.00874907	105.691	8.60E-25
rs7656630	4	88173692	0	T	C	0.575994	0.996449	42.0557	8.90E-11	0.0147493	0.00220707	44.659	2.30E-11
rs1545735	4	88578487	0	T	C	0.481295	0.997173	89.7578	2.70E-21	0.0205238	0.00218508	88.2227	5.80E-21
rs9990702	4	88772316	0	T	C	0.337598	0.998528	55.1385	1.10E-13	0.0170915	0.00230235	55.1085	1.10E-13
rs17600719	4	100563999	0	G	A	0.839827	0.992382	75.4635	3.70E-18	-0.0258842	0.00297772	75.5619	3.50E-18
rs13131500	4	103385300	0	A	G	0.91248	0.968624	29.6295	5.20E-08	0.0213921	0.00391702	29.8261	4.70E-08
rs10026360	4	104374596	0	T	C	0.671897	1	56.3087	6.20E-14	-0.0168803	0.00231921	52.9762	3.40E-13
rs55729266	4	104573828	0	C	A	0.848601	0.998696	28.3422	1.00E-07	-0.0171595	0.00303785	31.9064	1.60E-08
rs139868653	4	105931075	0	C	T	0.977092	0.954258	103.32	2.90E-24	0.0747045	0.0074344	100.972	9.30E-24
rs2088483	4	106216367	0	T	C	0.609833	0.99342	228.968	1.00E-51	0.0336558	0.00223809	226.134	4.20E-51
rs1558172	4	109276830	0	G	A	0.635898	0.979541	48.0932	4.10E-12	0.0161119	0.00228849	49.567	1.90E-12
rs6836422	4	109423555	0	C	A	0.685101	0.974686	55.8286	7.90E-14	-0.0181762	0.00237554	58.544	2.00E-14
rs6827199	4	114896904	0	G	A	0.682466	0.993689	48.21	3.80E-12	-0.0164775	0.00234838	49.2318	2.30E-12
rs71608359	4	119204545	0	C	G	0.924443	0.998963	37.1945	1.10E-09	0.0250573	0.00412052	36.9797	1.20E-09
rs35579162	4	120710492	0	G	A	0.683705	0.992224	49.9818	1.60E-12	0.0164323	0.0023518	48.8196	2.80E-12
rs7666178	4	122578722	0	A	T	0.696467	0.996408	43.1561	5.10E-11	-0.0156602	0.00237036	43.6483	3.90E-11
rs6821305	4	122713863	0	A	C	0.600899	0.996817	90.0269	2.30E-21	-0.0208014	0.00222408	87.4749	8.50E-21
rs79429065	4	123587690	0	C	T	0.981712	0.965313	37.5955	8.70E-10	0.0499082	0.00825897	36.5168	1.50E-09
rs308435	4	123772018	0	C	A	0.845409	1	35.5964	2.40E-09	-0.0182006	0.00300874	36.5935	1.50E-09
rs11098677	4	123833516	0	G	T	0.212279	0.999399	97.5444	5.30E-23	0.0270435	0.00266342	103.098	3.20E-24
rs13141174	4	124932863	0	A	T	0.712772	0.998777	53.3178	2.80E-13	-0.0171803	0.00240723	50.9359	9.50E-13
rs35584094	4	126966882	0	G	A	0.688525	0.985204	50.1361	1.40E-12	0.0169309	0.00237178	50.9575	9.40E-13
rs10028489	4	140117993	0	G	A	0.451242	0.992099	31.2982	2.20E-08	0.0121322	0.00219477	30.5561	3.20E-08
rs809955	4	140874760	0	G	A	0.633799	0.997504	44.3796	2.70E-11	-0.0148438	0.00226362	43.0013	5.50E-11
rs300904	4	144239825	0	A	G	0.465928	0.992191	35.0782	3.20E-09	-0.012831	0.00219252	34.2476	4.90E-09
rs11721672	4	144426747	0	G	A	0.797859	0.996025	99.5921	1.90E-23	-0.0273974	0.00271605	101.752	6.30E-24
rs532589488	4	144979483	0	C	T	0.967683	0.852817	33.8953	5.80E-09	0.038854	0.00665979	34.0369	5.40E-09
rs2352767	4	145264890	0	C	A	0.941119	0.984695	67.5211	2.10E-16	0.0384768	0.00465898	68.205	1.50E-16
rs116338131	4	145357425	0	A	G	0.95841	0.997569	72.4729	1.70E-17	-0.0466939	0.00546957	72.8808	1.40E-17
rs2575572	4	145552729	0	T	C	0.508934	0.99852	400.176	5.00E-89	0.0431301	0.00217556	393.026	1.80E-87
rs7689420	4	145568352	0	T	C	0.168699	1	989.713	3.10E-217	-0.0915044	0.00290626	991.322	1.40E-217
rs149016704	4	145733581	0	T	G	0.986623	0.900822	48.0702	4.10E-12	-0.0693354	0.00996947	48.3689	3.50E-12

rs116662954	4	145982625	0	G	A	0.972601	1	129.591	5.00E-30	0.0766469	0.00666853	132.108	1.40E-30
rs36227682	4	146053033	0	T	A	0.965189	0.92204	116.801	3.20E-27	-0.0671013	0.00618705	117.624	2.10E-27
rs114734516	4	146127689	0	T	C	0.951281	0.997552	78.657	7.40E-19	0.0456125	0.0050757	80.7562	2.60E-19
rs13105189	4	146241836	0	A	C	0.923668	0.968341	52.3095	4.70E-13	0.0301189	0.00416853	52.205	5.00E-13
rs78806058	4	146656092	0	G	A	0.862756	0.99208	30.2165	3.90E-08	-0.017869	0.00317616	31.6516	1.80E-08
rs10000888	4	146809168	0	A	G	0.488747	0.99856	38.2834	6.10E-10	-0.0134644	0.0021795	38.1644	6.50E-10
rs34538686	4	149687379	0	C	T	0.795082	0.982535	34.3713	4.60E-09	-0.0159976	0.00272233	34.5327	4.20E-09
rs6825241	4	152543783	0	C	A	0.537133	0.998388	56.0353	7.10E-14	0.0166158	0.00218443	57.8582	2.80E-14
rs62337430	4	159994391	0	G	A	0.629714	0.999478	41.4844	1.20E-10	-0.0147934	0.0022531	43.1098	5.20E-11
rs72703414	4	184227430	0	A	G	0.934619	0.999769	79.5128	4.80E-19	0.0391148	0.00440775	78.7494	7.10E-19
rs60131767	4	186703959	0	G	A	0.525097	1	35.4833	2.60E-09	-0.013086	0.00217921	36.0593	1.90E-09
rs62345188	5	273143	0	A	G	0.831778	0.967949	53.8219	2.20E-13	-0.0214199	0.00295769	52.4479	4.40E-13
rs4702391	5	4066184	0	G	T	0.536248	0.998091	38.1978	6.40E-10	-0.0137547	0.00218333	39.6886	3.00E-10
rs274668	5	6711630	0	C	T	0.323929	0.993762	38.4639	5.60E-10	0.0145137	0.00232947	38.8189	4.70E-10
rs62348757	5	31533952	0	T	C	0.689306	0.996482	40.8619	1.60E-10	-0.0147798	0.00235204	39.4864	3.30E-10
rs10073495	5	32160713	0	T	C	0.364926	0.997588	28.2444	1.10E-07	-0.0124586	0.0022622	30.3302	3.60E-08
rs80285873	5	32699379	0	C	T	0.970462	0.830082	46.5603	8.90E-12	0.0473989	0.0070609	45.0627	1.90E-11
rs4421120	5	32763118	0	G	A	0.839434	0.997429	105.609	9.00E-25	-0.030612	0.00296631	106.5	5.70E-25
rs138394877	5	32782940	0	C	T	0.984713	0.996234	46.5994	8.70E-12	0.0612858	0.00888594	47.5678	5.30E-12
rs12656497	5	32831939	0	T	C	0.403596	0.997944	312.914	5.10E-70	0.0397023	0.00221757	320.536	1.10E-71
rs6867192	5	33010844	0	A	G	0.480475	0.998332	70.9879	3.60E-17	-0.0186721	0.00217541	73.6722	9.20E-18
rs116628330	5	33122151	0	T	C	0.956823	0.998592	36.8436	1.30E-09	0.0340639	0.00534659	40.5916	1.90E-10
rs6414859	5	33325863	0	T	C	0.236249	0.997339	123.263	1.20E-28	-0.0286605	0.00256678	124.678	6.00E-29
rs7731023	5	36181627	0	A	G	0.42477	1	52.3909	4.50E-13	-0.0157823	0.00219999	51.4637	7.30E-13
rs6899155	5	36786459	0	T	C	0.552098	0.989329	133.985	5.50E-31	0.0254036	0.00220147	133.157	8.40E-31
rs1818782	5	39424628	0	A	C	0.343464	0.989478	111.559	4.50E-26	-0.0241774	0.00230491	110.03	9.70E-26
rs59463904	5	42559473	0	T	C	0.940601	0.99048	66.3614	3.80E-16	0.0372835	0.00462651	64.942	7.70E-16
rs62372052	5	42724294	0	A	G	0.889579	1	158.618	2.30E-36	-0.0432538	0.00348498	154.045	2.30E-35
rs59255078	5	42960263	0	G	A	0.968852	0.996594	32.6487	1.10E-08	0.0359154	0.00627572	32.7517	1.00E-08
rs12055150	5	50418865	0	T	C	0.343247	0.990523	40.5152	2.00E-10	0.014383	0.00229937	39.1273	4.00E-10
rs111633992	5	52420011	0	T	C	0.768377	0.981036	30.5732	3.20E-08	0.0141786	0.00259995	29.7397	4.90E-08
rs62370473	5	52767121	0	G	A	0.791269	0.994149	73.1702	1.20E-17	0.0234809	0.00268304	76.5906	2.10E-18
rs114733527	5	52785902	0	C	T	0.987646	1	45.4258	1.60E-11	-0.0682466	0.00985552	47.9516	4.40E-12
rs11738691	5	54880229	0	G	T	0.338173	0.996675	168.14	1.90E-38	0.0302305	0.00230415	172.136	2.50E-39
rs192249	5	56197514	0	C	G	0.348218	0.996133	96.3022	9.90E-23	-0.0224686	0.00228783	96.4505	9.20E-23
rs4699935	5	58436444	0	G	A	0.321174	0.995964	56.2224	6.50E-14	0.0175209	0.00233312	56.3951	5.90E-14
rs36198109	5	60559156	0	G	A	0.615627	0.988463	34.5355	4.20E-09	0.0136539	0.00224998	36.8264	1.30E-09
rs264762	5	64384386	0	A	C	0.32836	0.999056	66.1932	4.10E-16	-0.0190025	0.00231443	67.4118	2.20E-16
rs2131591	5	64636129	0	T	A	0.819546	0.996411	36.4468	1.60E-09	-0.0167644	0.00283365	35.0011	3.30E-09
rs1490819	5	67099798	0	C	T	0.838016	0.988732	50.2602	1.30E-12	-0.020964	0.00296785	49.8957	1.60E-12
rs35745488	5	67183807	0	C	G	0.934075	0.972104	36.6877	1.40E-09	0.0268671	0.00445155	36.4267	1.60E-09
rs463133	5	67324323	0	T	C	0.903176	0.997568	47.4578	5.60E-12	-0.0254042	0.00368255	47.59	5.30E-12
rs9623	5	67597321	0	T	C	0.54107	0.999194	63.1063	2.00E-15	0.017369	0.00218366	63.2672	1.80E-15
rs62361857	5	72121964	0	C	T	0.827213	0.996274	46.3458	9.90E-12	0.0195493	0.00287755	46.1547	1.10E-11
rs34651	5	72144005	0	C	T	0.0812617	0.98407	90.3384	2.00E-21	0.0378446	0.00400756	89.176	3.60E-21
rs1978427	5	77430426	0	G	A	0.765654	0.997599	151.447	8.40E-35	0.0320742	0.00256582	156.265	7.40E-36
rs7712162	5	78945171	0	C	T	0.825906	0.997953	55.5128	9.30E-14	-0.0214767	0.00287215	55.9142	7.60E-14
rs9293822	5	79896291	0	G	A	0.345425	0.972882	29.2837	6.30E-08	0.0126991	0.00231954	29.9739	4.40E-08
rs55814810	5	82026431	0	A	G	0.59062	0.989814	36.1956	1.80E-09	-0.0134508	0.0022251	36.5423	1.50E-09
rs10037512	5	88354675	0	T	C	0.530319	1	132.638	1.10E-30	0.0249115	0.00218021	130.558	3.10E-30
rs7716447	5	88800331	0	A	G	0.639495	0.981425	53.0081	3.30E-13	0.0165921	0.00228783	52.5962	4.10E-13
rs1818351	5	90252077	0	T	C	0.293593	0.983429	28.1688	1.10E-07	0.013375	0.00240874	30.8326	2.80E-08
rs4489092	5	90420644	0	G	T	0.370704	0.98483	70.9538	3.70E-17	0.0188989	0.00227022	69.3004	8.50E-17
rs6235	5	95728898	0	C	G	0.731867	1	48.7462	2.90E-12	-0.0171966	0.00244962	49.2817	2.20E-12
rs56195293	5	107891473	0	G	A	0.771628	0.988873	34.2618	4.80E-09	0.0151529	0.00259903	33.9916	5.50E-09
rs13174528	5	108218583	0	A	G	0.916162	0.98813	68.3572	1.40E-16	0.0332305	0.00394168	71.074	3.40E-17
rs75421844	5	108220554	0	T	C	0.916315	0.989745	129.383	5.60E-30	-0.044914	0.00393472	130.297	3.50E-30
rs6867243	5	112100027	0	G	A	0.45868	0.99788	45.6068	1.40E-11	0.0148498	0.00217782	46.4945	9.20E-12
rs10075659	5	115065309	0	T	A	0.70133	0.994845	112.951	2.20E-26	-0.025022	0.00237984	110.547	7.40E-26
rs66926155	5	119864882	0	A	T	0.8814	0.997358	39.0046	4.20E-10	0.0206578	0.00336353	37.7205	8.20E-10
rs11241692	5	122727819	0	T	C	0.561332	0.998581	93.1391	4.90E-22	0.021026	0.00218808	92.339	7.30E-22
rs7717604	5	123989617	0	C	T	0.655965	0.999669	64.4864	9.70E-16	-0.018106	0.0022854	62.7653	2.30E-15
rs10063647	5	127371588	0	A	G	0.522321	0.995629	62.7581	2.30E-15	-0.017288	0.00217679	63.0746	2.00E-15
rs116302901	5	127802451	0	C	A	0.987264	1	70.9035	3.80E-17	-0.0821819	0.00968588	71.9903	2.20E-17
rs6866701	5	129069848	0	A	G	0.0761243	0.995746	103.674	2.40E-24	0.0417151	0.00410162	103.437	2.70E-24
rs7701414	5	131585958	0	A	G	0.539801	0.999622	271.86	4.50E-61	-0.0364276	0.00217959	279.326	1.10E-62
rs1476097	5	133837061	0	T	G	0.668402	0.982296	67.6916	1.90E-16	-0.0186796	0.00232642	64.4702	9.80E-16
rs31211	5	134363145	0	G	A	0.748975	0.998128	243.888	5.60E-55	0.0388865	0.00250505	240.97	2.40E-54
rs10040909	5	134515420	0	G	A	0.78299	0.999321	67.9523	1.70E-16	-0.0218995	0.00263318	69.1684	9.00E-17
rs7735408	5	137585341	0	G	A	0.21958	0.99519	52.0865	5.30E-13	0.0184873	0.00262924	49.4409	2.00E-12
rs2434576	5	138917674	0	A	G	0.707679	0.99562	115.889	5.00E-27	-0.0254966	0.00239498	113.334	1.80E-26
rs2569178	5	139992171	0	G	A	0.711618	0.996259	56.6099	5.30E-14	0.0181074	0.00240072	56.8894	4.60E-14
rs3749759	5	141041435	0	G	A	0.358423	0.9847	46.3344	1.00E-11	0.0153782	0.00228061	45.4685	1.60E-11
rs2434416	5	141789701	0	A	C	0.560749	0.994112	37.9955	7.10E-10	0.0139059	0.00219401	40.1716	2.30E-10
rs853168	5	142538764	0	G	C	0.752878	0.986919	35.965	2.00E-09	-0.0151485	0.00253461	35.7203	2.30E-09
rs11747997	5	142790752	0	A	C	0.671047	0.990573	60.0756	9.10E-15	-0.018028	0.00232212	60.2734	8.30E-15
rs4912945	5	143144557	0	A	T	0.576935	0.989218	47.0412	7.00E-12	-0.0150494	0.00220987	46.3768	9.80E-12
rs2277924	5	149324376	0	A	T	0.832476	0.981144	39.8184	2.80E-10	-0.0177672	0.00293322	36.6904	1.40E-09
rs10069931	5	156797005	0	C	T	0.671986	0.996995	40.8694	1.60E-10	0.0148928	0.00231495	41.3875	1.20E-10
rs4244425	5	158387892	0	A	G	0.583394	0.996349	38.7016	4.90E-10	0.0139132	0.00220811	39.7023	3.00E-10
rs1422669	5	158507655	0	T	C	0.571811	0.996733	36.2533	1.70E-09	0.0132879	0.00219529	36.6379	1.40E-09
rs35668185	5	168256455	0	T	C	0.792381	0.999243	210.683	9.70E-48	0.0392825	0.00267297	215.978	6.80E-49
rs4073717	5	170864021	0	G	T	0.798442	0.994201	183.474	8.50E-42	0.0369072	0.00271045	185.413	3.20E-42

rs142469471	5	170878247	0	G	A	0.950012	0.886822	36.1876	1.80E-09	-0.0326623	0.00529096	38.1087	6.70E-10
rs6892884	5	171015623	0	T	C	0.308378	1	90.2608	2.10E-21	-0.0222148	0.00235013	89.3511	3.30E-21
rs33852	5	171189571	0	A	G	0.677059	0.998041	157.928	3.20E-36	-0.0291845	0.00232193	157.982	3.10E-36
rs702101	5	171276393	0	G	A	0.40267	1	246.593	1.40E-55	-0.0353568	0.0022128	255.305	1.80E-57
rs6892217	5	171474120	0	C	T	0.39628	1	39.5211	3.20E-10	-0.014097	0.00222281	40.2205	2.30E-10
rs34013988	5	172197790	0	C	T	0.960864	0.997673	74.7626	5.30E-18	-0.0477611	0.00560215	72.6841	1.50E-17
rs116417701	5	172302688	0	C	T	0.988383	1	42.4413	7.30E-11	0.0645098	0.0101249	40.595	1.90E-10
rs3792819	5	172576296	0	A	G	0.914803	0.997974	36.8959	1.20E-09	-0.0233732	0.0038931	36.045	1.90E-09
rs67189644	5	172746465	0	A	C	0.965383	1	40.1711	2.30E-10	0.0373123	0.00594292	39.419	3.40E-10
rs62377261	5	172763348	0	T	A	0.652782	0.986769	29.7113	5.00E-08	0.0128392	0.00229404	31.3234	2.20E-08
rs7717113	5	172781401	0	A	G	0.754365	0.987421	72.0649	2.10E-17	-0.0217747	0.00254106	73.4301	1.00E-17
rs4867721	5	172983457	0	G	T	0.3981	0.997479	168.291	1.70E-38	0.0286562	0.00221981	166.65	4.00E-38
rs6556304	5	176586898	0	T	A	0.635878	0.977014	307.288	8.50E-69	-0.0400013	0.00228401	306.726	1.10E-68
rs78161830	5	176615083	0	A	G	0.976594	0.9893	112	3.60E-26	0.0772394	0.00722628	114.248	1.10E-26
rs17832583	5	177105020	0	C	T	0.58633	0.97726	39.5411	3.20E-10	-0.0137066	0.00222676	37.889	7.50E-10
rs3822593	5	178551299	0	T	G	0.416207	0.992794	52.0777	5.30E-13	0.0158248	0.00221175	51.1922	8.40E-13
rs466522	5	178687676	0	G	A	0.793738	0.976681	61.2753	5.00E-15	0.0211642	0.00271669	60.6905	6.70E-15
rs11748619	5	179727399	0	C	G	0.391724	0.998586	153.405	3.10E-35	-0.0278151	0.00222652	156.067	8.20E-36
rs382686	5	180629812	0	C	A	0.742311	0.997878	40.5623	1.90E-10	0.0152718	0.00249061	37.5982	8.70E-10
rs62390617	6	1623627	0	G	C	0.863928	0.969006	46.5024	9.20E-12	-0.0218804	0.00318674	47.143	6.60E-12
rs9392371	6	2190846	0	C	T	0.798235	0.992627	76.7851	1.90E-18	-0.023293	0.00268799	75.0927	4.50E-18
rs114690396	6	2415658	0	C	T	0.98762	0.969793	35.5077	2.50E-09	0.0578763	0.00986934	34.3895	4.50E-09
rs9504921	6	6762724	0	T	C	0.708477	0.99844	79.2072	5.60E-19	0.0214222	0.00236603	81.9757	1.40E-19
rs876122	6	6886297	0	A	G	0.121166	0.997455	122.057	2.20E-28	-0.0362618	0.00329472	121.133	3.60E-28
rs9379084	6	7231843	0	G	A	0.884383	0.942508	188.83	5.70E-43	0.0481324	0.00346451	193.015	7.00E-44
rs9505165	6	7327436	0	A	C	0.804083	0.983309	76.3725	2.30E-18	-0.0241502	0.00273041	78.232	9.20E-19
rs34867797	6	7657115	0	C	T	0.607895	0.99877	36.0571	1.90E-09	0.0125976	0.00220474	32.6482	1.10E-08
rs11243202	6	7719065	0	T	C	0.513624	0.989913	494.137	1.80E-109	-0.0480114	0.00216085	493.674	2.30E-109
rs13209685	6	7779729	0	G	T	0.840432	0.995568	137.286	1.00E-31	-0.0349266	0.00294015	141.115	1.50E-32
rs17605530	6	7780062	0	T	C	0.945919	1	31.3697	2.10E-08	0.0264279	0.00474977	30.9584	2.60E-08
rs267177	6	7828542	0	C	T	0.612406	0.988456	60.466	7.50E-15	-0.0168465	0.00222118	57.5243	3.30E-14
rs6916705	6	15027286	0	T	C	0.406615	1	35.7701	2.20E-09	0.0134044	0.00218617	37.5946	8.70E-10
rs11759978	6	15462871	0	C	T	0.86237	0.998925	49.6671	1.80E-12	0.0220287	0.00312097	49.8196	1.70E-12
rs1853655	6	18524374	0	T	C	0.672463	0.9919	37.4562	9.30E-10	-0.0140098	0.0022956	37.2453	1.00E-09
rs76643553	6	19804425	0	G	C	0.986991	0.903981	29.5396	5.50E-08	-0.0550417	0.00998305	30.3988	3.50E-08
rs41271299	6	19839415	0	C	T	0.948626	1	646.148	1.50E-142	-0.125571	0.00486884	665.159	1.10E-146
rs4134943	6	20483407	0	C	T	0.7982	1	35.0338	3.20E-09	-0.0161691	0.00267676	36.488	1.50E-09
rs1928175	6	22079485	0	G	A	0.439347	0.994089	45.58	1.50E-11	-0.0146799	0.0021702	45.7558	1.30E-11
rs7741044	6	23871293	0	T	C	0.687299	0.996551	29.7227	5.00E-08	0.0128395	0.00232271	30.5566	3.20E-08
rs77680150	6	25440592	0	T	G	0.988668	0.993948	30.7649	2.90E-08	-0.0558775	0.0101858	30.094	4.10E-08
rs7758716	6	25508629	0	T	G	0.580659	0.999352	51.7465	6.30E-13	0.0158198	0.00217652	52.8294	3.60E-13
rs62394491	6	25934106	0	C	T	0.963176	0.998781	44.2213	2.90E-11	0.0381951	0.00570498	44.8237	2.20E-11
rs9379832	6	26186200	0	A	G	0.744764	0.980367	563.56	1.40E-124	0.0604215	0.0024914	588.16	6.30E-130
rs138087738	6	26497347	0	A	C	0.98465	0.867881	40.4695	2.00E-10	0.0573024	0.0093754	37.3566	9.80E-10
rs3094575	6	29515802	0	T	C	0.241309	1	113.334	1.80E-26	-0.0269385	0.00251112	115.083	7.50E-27
rs543438530	6	29781965	0	C	G	0.989693	0.651904	50.2095	1.40E-12	0.0922777	0.0131707	49.0881	2.40E-12
rs2844747	6	30339593	0	T	C	0.421416	0.999946	44.2788	2.80E-11	-0.014712	0.00217473	45.7648	1.30E-11
rs116633440	6	30994470	0	C	G	0.987357	0.991345	139.694	3.10E-32	0.114803	0.00965274	141.45	1.30E-32
rs114198627	6	31195009	0	G	A	0.973831	1	38.258	6.20E-10	0.0431075	0.00672753	41.0576	1.50E-10
rs116212401	6	31214367	0	A	C	0.985436	0.846613	70.3639	4.90E-17	0.0816074	0.00978829	69.5098	7.60E-17
rs2523583	6	31327895	0	G	A	0.291843	0.998627	682.507	1.90E-150	0.0617344	0.00237203	677.355	2.50E-149
rs2229092	6	31540757	0	A	C	0.937944	1	149.589	2.10E-34	0.0552467	0.00445418	153.843	2.50E-35
rs41291790	6	31572664	0	G	A	0.989197	0.842523	39.1657	3.90E-10	0.0725758	0.0113194	41.109	1.40E-10
rs9270074	6	32554129	0	T	C	0.155599	1	177.739	1.50E-40	0.0401379	0.00298014	181.399	2.40E-41
rs41268942	6	32607126	0	A	G	0.796959	0.997659	84.8752	3.20E-20	0.0248877	0.0026785	86.3354	1.50E-20
rs4988888	6	32635197	0	T	C	0.747028	0.997336	141.983	9.80E-33	-0.0295402	0.00247894	142.001	9.70E-33
rs3135024	6	33047466	0	T	C	0.76104	0.999767	80.2205	3.30E-19	0.0226123	0.00251982	80.529	2.90E-19
rs7769838	6	33641956	0	T	C	0.290586	0.991983	124.178	7.70E-29	-0.0266939	0.00237416	126.417	2.50E-29
rs4713707	6	33839458	0	C	G	0.516042	0.97801	30.3717	3.60E-08	-0.0121589	0.00217705	31.1926	2.30E-08
rs1592269	6	34183057	0	G	A	0.0508511	0.991633	386.918	3.90E-86	0.095647	0.00490414	380.379	1.00E-84
rs115237838	6	34195616	0	G	A	0.973508	1	88.6297	4.80E-21	-0.0637234	0.00668682	90.8153	1.60E-21
rs112495680	6	34223098	0	A	G	0.866259	0.991617	109.281	1.40E-25	-0.0322202	0.00316727	103.488	2.60E-24
rs11968244	6	34409117	0	C	G	0.98985	0.859879	32.3693	1.30E-08	-0.0653436	0.0115669	31.9134	1.60E-08
rs11970421	6	34553163	0	C	T	0.925077	0.990219	114.13	1.20E-26	0.0443216	0.00410372	116.648	3.40E-27
rs112540634	6	34623905	0	C	T	0.863853	0.99872	506.234	4.20E-112	-0.0702571	0.00313106	503.498	1.60E-111
rs3734254	6	35395010	0	C	T	0.208964	0.996515	305.701	1.90E-68	-0.046737	0.00265214	310.548	1.70E-69
rs12525006	6	35417503	0	C	A	0.960803	1	48.1039	4.00E-12	-0.0396962	0.0055365	51.4075	7.50E-13
rs6923949	6	35496366	0	A	G	0.183201	0.996006	119.535	8.00E-28	-0.0308966	0.00277794	123.701	9.80E-29
rs58309506	6	36202743	0	G	T	0.907534	0.996769	31.154	2.40E-08	-0.0209882	0.00371871	31.8542	1.70E-08
rs4135240	6	36647680	0	T	C	0.668163	0.987593	40.488	2.00E-10	-0.0150974	0.00229964	43.1009	5.20E-11
rs72848059	6	36979875	0	A	G	0.895477	1	42.0812	8.80E-11	0.0231069	0.00350842	43.3771	4.50E-11
rs11755329	6	37368362	0	C	T	0.553837	0.977604	35.9158	2.10E-09	-0.0125765	0.00218677	33.076	8.90E-09
rs2815116	6	39187886	0	G	A	0.297596	0.988529	37.7529	8.00E-10	-0.0142209	0.00236691	36.0986	1.90E-09
rs13212930	6	41471389	0	T	A	0.95944	0.849285	79.4751	4.90E-19	-0.0543252	0.00591039	84.4829	3.90E-20
rs1319012	6	41852616	0	T	A	0.0741691	0.953062	245.859	2.10E-55	0.0651758	0.00420056	240.745	2.70E-54
rs33966734	6	41903798	0	C	A	0.98637	0.97389	187.856	9.30E-43	0.128377	0.00939388	186.759	1.60E-42
rs12662201	6	43131136	0	G	A	0.865543	0.997182	51.6071	6.80E-13	0.0231971	0.00315649	54.008	2.00E-13
rs62646255	6	43262303	0	T	C	0.606735	0.992627	107.56	3.40E-25	0.0226508	0.00220556	105.47	9.60E-25
rs998584	6	43757896	0	C	A	0.517209	0.994747	87.2434	9.60E-21	0.02069	0.00215519	92.1618	8.00E-22
rs573623	6	44562888	0	C	T	0.45948	0.997666	31.1655	2.40E-08	0.012102	0.00215977	31.3981	2.10E-08
rs1402599	6	44799657	0	A	G	0.271351	0.996491	116.314	4.10E-27	-0.0265611	0.00242143	120.323	5.40E-28
rs192155317	6	44951991	0	G	A	0.985464	0.956815	38.6871	5.00E-10	-0.0581127	0.00918886	39.9962	2.50E-10
rs9473132	6	47522357	0	G	A	0.309644	0.996286	92.5597	6.50E-22	-0.0222282	0.00232977	91.0291	1.40E-21

rs2067002	6	52371419	0	G	A	0.179338	0.993109	31.3419	2.20E-08	-0.0158432	0.00280876	31.8166	1.70E-08
rs2013674	6	56880459	0	C	T	0.844539	0.980862	39.1204	4.00E-10	0.0187083	0.00299085	39.1272	4.00E-10
rs701698	6	72179118	0	T	C	0.631482	0.998305	56.2619	6.30E-14	-0.0162253	0.00222703	53.0805	3.20E-13
rs28619506	6	76437598	0	C	T	0.469068	0.997133	155.216	1.30E-35	-0.0271918	0.00215576	159.102	1.80E-36
rs648831	6	80956208	0	C	T	0.47118	0.986277	182.045	1.70E-41	-0.0300806	0.00216767	192.57	8.70E-44
rs77104933	6	81061179	0	A	C	0.925486	0.998064	121.896	2.40E-28	-0.0439737	0.00409046	115.569	5.90E-27
rs1840332	6	81312758	0	C	T	0.473871	0.989518	34.285	4.80E-09	0.0127134	0.00216476	34.4908	4.30E-09
rs6906411	6	81913276	0	G	A	0.550614	0.983216	232.523	1.70E-52	0.033522	0.0021757	237.39	1.50E-53
rs146699049	6	81937504	0	T	A	0.976817	0.967163	48.9293	2.70E-12	0.0479522	0.00726342	43.5847	4.10E-11
rs34951006	6	82464180	0	G	T	0.862983	0.982799	73.5009	1.00E-17	-0.0259329	0.0031525	67.6693	1.90E-16
rs11751698	6	83708583	0	C	T	0.86024	0.995224	45.9545	1.20E-11	-0.0215409	0.00310701	48.0668	4.10E-12
rs61417237	6	84324159	0	G	A	0.6688	0.996806	43.4765	4.30E-11	-0.0149503	0.00228753	42.7136	6.30E-11
rs3857477	6	85993838	0	T	A	0.808671	0.997459	39.2564	3.70E-10	-0.0161005	0.00273691	34.6065	4.00E-09
rs13202806	6	86051820	0	G	A	0.94452	0.970683	28.2408	1.10E-07	-0.0262469	0.00477024	30.2743	3.80E-08
rs73752005	6	88092421	0	G	A	0.889721	0.996643	31.5919	1.90E-08	0.0187501	0.00343398	29.8134	4.80E-08
rs7747136	6	89826246	0	C	T	0.861975	0.98978	42.0104	9.10E-11	-0.0193642	0.00313311	38.1987	6.40E-10
rs7742854	6	98528143	0	C	T	0.606859	0.996121	43.3003	4.70E-11	-0.0142949	0.00220517	42.0224	9.00E-11
rs2894889	6	100161940	0	A	T	0.650718	0.996441	34.7969	3.70E-09	-0.0136779	0.00225421	36.8171	1.30E-09
rs732194	6	100626344	0	C	T	0.522478	0.99153	50.6238	1.10E-12	0.0154217	0.0021624	50.8622	9.90E-13
rs12198434	6	104727874	0	C	T	0.684077	0.997948	33.6451	6.60E-09	-0.0133186	0.00231288	33.1598	8.50E-09
rs9391254	6	105377347	0	C	T	0.679459	0.998808	440.947	6.70E-98	-0.0483842	0.00230243	441.604	4.80E-98
rs9398171	6	108983527	0	C	T	0.288746	0.996274	87.5575	8.20E-21	-0.0217986	0.00237302	84.3833	4.10E-20
rs2277113	6	109775436	0	T	C	0.590247	0.999735	118.405	1.40E-27	0.0238363	0.00218537	118.967	1.10E-27
rs500348	6	116716593	0	T	A	0.47088	0.996709	109.055	1.60E-25	-0.0227631	0.00215787	111.279	5.10E-26
rs544148	6	117466494	0	A	G	0.416527	0.994857	157.409	4.20E-36	-0.0275186	0.00218723	158.294	2.70E-36
rs389663	6	117868051	0	T	C	0.323524	0.995362	46.1338	1.10E-11	0.0154479	0.00230147	45.0536	1.90E-11
rs137910645	6	126504812	0	C	T	0.984045	0.88114	33.4221	7.40E-09	0.0517977	0.00913706	32.1373	1.40E-08
rs9388490	6	126704795	0	C	T	0.56081	0.995961	627.758	1.50E-138	-0.0546863	0.00217154	634.195	6.10E-140
rs142379782	6	127002531	0	A	G	0.980718	0.941243	33.6772	6.50E-09	0.0483614	0.00805702	36.0287	1.90E-09
rs2021356	6	127105087	0	G	A	0.564642	0.993151	66.9059	2.80E-16	-0.0177349	0.00217236	66.6491	3.20E-16
rs552047752	6	127171027	0	A	G	0.973336	0.99231	29.6807	5.10E-08	0.0377514	0.0066999	31.7489	1.80E-08
rs186296323	6	127189872	0	T	C	0.984953	0.962159	34.0537	5.40E-09	0.0535252	0.00898249	35.5078	2.50E-09
rs141783576	6	127439897	0	G	C	0.927627	0.965133	68.6577	1.20E-16	0.0363017	0.00422069	73.9754	7.90E-18
rs7774592	6	129823611	0	T	C	0.257867	0.997773	96.0376	1.10E-22	-0.0241589	0.00245956	96.4811	9.00E-23
rs138129054	6	130279289	0	G	A	0.972884	0.961189	33.3448	7.70E-09	-0.037759	0.00674117	31.374	2.10E-08
rs78271579	6	130313725	0	G	A	0.919796	1	63.7514	1.40E-15	0.0320385	0.00395753	65.5384	5.70E-16
rs7740107	6	130374461	0	T	A	0.263999	0.998539	510.621	4.60E-113	0.0545931	0.00243725	501.733	4.00E-111
rs4897447	6	130968384	0	G	T	0.905452	0.998599	29.597	5.30E-08	-0.0205725	0.00367411	31.3524	2.20E-08
rs13200945	6	131090082	0	G	A	0.950217	1	35.2927	2.80E-09	-0.028623	0.00494261	33.5365	7.00E-09
rs9321266	6	131316458	0	A	G	0.61306	0.997942	194.826	2.80E-44	-0.0312378	0.00221013	199.767	2.30E-45
rs7743622	6	132730372	0	C	G	0.432914	0.994236	34.761	3.70E-09	-0.0124736	0.00217494	32.8919	9.70E-09
rs211433	6	133610750	0	A	G	0.655409	0.999356	41.3323	1.30E-10	-0.0144508	0.00225942	40.9062	1.60E-10
rs212777	6	133795443	0	T	A	0.558592	0.997518	64.2304	1.10E-15	0.0174844	0.00216389	65.2882	6.50E-16
rs6935311	6	134911038	0	A	G	0.337936	1	33.3898	7.50E-09	0.0132676	0.00227371	34.0496	5.40E-09
rs72974722	6	139331419	0	A	C	0.819348	0.975158	41.5378	1.20E-10	0.0177896	0.00283226	39.4518	3.40E-10
rs4535566	6	140073706	0	T	A	0.771332	0.999718	51.5156	7.10E-13	0.0182272	0.00255782	50.7808	1.00E-12
rs13204703	6	140692862	0	T	C	0.752895	0.988899	62.7781	2.30E-15	-0.0196512	0.00250446	61.5677	4.30E-15
rs761522	6	142033527	0	T	C	0.5433	0.994836	34.3953	4.50E-09	-0.0127214	0.0021615	34.6386	4.00E-09
rs34574518	6	142406234	0	A	G	0.789617	0.997098	134.6	4.00E-31	0.030519	0.00264046	133.592	6.70E-31
rs9496369	6	142724918	0	C	T	0.714503	0.998693	639.714	3.90E-141	0.0607913	0.00238055	652.121	7.70E-144
rs117370777	6	142815094	0	G	A	0.97108	0.926143	40.5792	1.90E-10	-0.0419313	0.00666471	39.5835	3.10E-10
rs118113248	6	142893772	0	G	A	0.96053	0.921543	33.6333	6.70E-09	-0.0330096	0.00574671	32.9946	9.20E-09
rs13212496	6	143184083	0	T	C	0.69807	0.993775	33.6757	6.50E-09	0.0137372	0.00234905	34.199	5.00E-09
rs2328473	6	143638002	0	G	A	0.594459	0.995097	33.0258	9.10E-09	-0.0124205	0.00219127	32.1282	1.40E-08
rs2748501	6	146312258	0	G	A	0.560466	0.998064	53.1153	3.10E-13	0.0155251	0.00216916	51.2251	8.20E-13
rs6557136	6	151729237	0	T	G	0.717828	0.978759	54.5449	1.50E-13	-0.0179267	0.00241662	55.028	1.20E-13
rs3853252	6	152170247	0	G	A	0.544835	0.988318	269.324	1.60E-60	-0.0358882	0.00216891	273.791	1.70E-61
rs926779	6	152355920	0	G	A	0.725802	1	168.834	1.30E-38	-0.0319457	0.002409	175.853	3.90E-40
rs111550108	6	152461703	0	C	T	0.962007	0.992817	35.8876	2.10E-09	-0.034303	0.00563509	37.0564	1.10E-09
rs2813538	6	152521244	0	C	A	0.486431	0.997742	35.7176	2.30E-09	0.0134557	0.00214979	39.1761	3.90E-10
rs62428920	6	155550673	0	T	C	0.618093	0.989985	72.3306	1.80E-17	0.0198659	0.0022219	79.9402	3.90E-19
rs4242299	6	156586781	0	C	A	0.104819	0.9815	46.4376	9.50E-12	0.0244121	0.00354423	47.4421	5.70E-12
rs262827	6	158683646	0	A	T	0.663724	0.998761	71.4641	2.80E-17	-0.0196816	0.00227642	74.7509	5.30E-18
rs10455823	6	158929623	0	A	G	0.952589	0.985573	50.7007	1.10E-12	0.0373393	0.00509881	53.6284	2.40E-13
rs668871	6	160769811	0	C	T	0.529979	0.998393	201.059	1.20E-45	-0.0306284	0.00215417	202.157	7.10E-46
rs66930764	6	164103243	0	G	A	0.868587	0.995503	113.78	1.50E-26	-0.0346175	0.00318664	118.011	1.70E-27
rs11754057	6	166188779	0	A	G	0.611662	0.990573	29.1002	6.90E-08	0.0121165	0.00221477	29.9293	4.50E-08
rs9459531	6	166333799	0	A	G	0.522569	0.997778	96.6146	8.40E-23	0.0209784	0.00215325	94.9197	2.00E-22
rs6912533	6	166608849	0	C	T	0.339446	0.990339	61.9053	3.60E-15	0.018372	0.00228152	64.8429	8.10E-16
rs59888904	6	168726774	0	G	A	0.795802	0.979425	31.3615	2.10E-08	0.0152409	0.00269012	32.0981	1.50E-08
rs2763263	6	168814392	0	T	A	0.755224	0.983705	129.246	6.00E-30	0.0289592	0.00251931	132.132	1.40E-30
rs9364192	6	169343602	0	A	G	0.415845	0.993413	83.6239	6.00E-20	-0.0205071	0.00218621	87.988	6.60E-21
rs6605522	6	169656531	0	A	G	0.157241	1	45.9697	1.20E-11	-0.019561	0.00295084	43.9429	3.40E-11
rs150034256	7	2150009	0	G	A	0.976011	0.957173	34.1996	5.00E-09	-0.0435547	0.00725964	35.9949	2.00E-09
rs2023970	7	2519887	0	C	T	0.708917	0.995097	49.0783	2.50E-12	-0.0169355	0.0024003	49.7812	1.70E-12
rs2302342	7	2697881	0	G	T	0.86456	0.980845	30.598	3.20E-08	-0.0178472	0.00321119	30.8895	2.70E-08
rs11772886	7	2760259	0	G	C	0.928739	0.988747	52.822	3.70E-13	-0.0308037	0.00425451	52.4212	4.50E-13
rs798490	7	2801542	0	G	A	0.706124	0.998754	749.845	4.30E-165	0.065136	0.00238876	743.527	1.00E-163
rs56201904	7	5366062	0	G	A	0.887223	0.986677	57.1861	4.00E-14	0.0255205	0.00346251	54.3244	1.70E-13
rs12668141	7	7909537	0	A	C	0.564123	0.977993	32.0482	1.50E-08	0.0126449	0.00221774	32.5096	1.20E-08
rs10253861	7	8110475	0	G	A	0.447485	0.995669	122.547	1.80E-28	-0.0249677	0.00219164	129.784	4.60E-30
rs3779368	7	8215543	0	C	T	0.743659	0.967544	39.2993	3.60E-10	-0.016093	0.00252896	40.494	2.00E-10
rs11509137	7	12263799	0	T	C	0.58154	1	45.7432	1.30E-11	0.0152192	0.00220091	47.8165	4.70E-12

rs4721288	7	14019448	0	T	C	0.472359	0.994821	29.0417	7.10E-08	0.0123324	0.00218839	31.7574	1.70E-08
rs6980299	7	15715056	0	T	C	0.240193	0.99001	38.2258	6.30E-10	0.0155654	0.00256077	36.9469	1.20E-09
rs4484585	7	18718573	0	C	A	0.944903	0.995396	47.852	4.60E-12	0.0320871	0.0047762	45.1331	1.80E-11
rs73069039	7	18726079	0	A	G	0.98483	0.913846	30.3632	3.60E-08	-0.0507235	0.00930132	29.7393	4.90E-08
rs1178158	7	18785271	0	A	G	0.782477	0.986154	67.0485	2.60E-16	-0.0216315	0.0026547	66.3965	3.70E-16
rs2717350	7	19021073	0	A	G	0.215299	0.989703	36.0406	1.90E-09	-0.0164189	0.00266145	38.0587	6.90E-10
rs201945415	7	19230094	0	A	G	0.947856	0.980477	48.6287	3.10E-12	0.0343933	0.00493636	48.5439	3.20E-12
rs4509205	7	19616316	0	C	T	0.642974	0.982776	56.895	4.60E-14	-0.0173019	0.0022881	57.1797	4.00E-14
rs11978390	7	19649160	0	T	G	0.971564	0.98508	96.5642	8.60E-23	-0.0652182	0.00660416	97.5221	5.30E-23
rs3807949	7	20436519	0	A	T	0.515583	0.992776	128.956	6.90E-30	-0.024786	0.00218197	129.037	6.70E-30
rs3087888	7	23351080	0	C	G	0.929204	0.98839	55.5465	9.10E-14	0.0318225	0.00426629	55.6376	8.70E-14
rs34776209	7	23513093	0	C	T	0.75213	0.994537	280.937	4.70E-63	0.0421472	0.00252445	278.742	1.40E-62
rs34096175	7	23662428	0	A	G	0.965116	1	30.2395	3.80E-08	0.032976	0.00592895	30.9343	2.70E-08
rs6959005	7	23696342	0	G	C	0.244345	0.9959	43.07	5.30E-11	0.016483	0.00253819	42.1719	8.40E-11
rs4000777	7	24289027	0	G	C	0.737252	0.993039	32.7909	1.00E-08	0.0142375	0.0024769	33.0406	9.00E-09
rs2711117	7	24590069	0	T	A	0.774656	0.983817	36.7879	1.30E-09	-0.0160199	0.00262512	37.2408	1.00E-09
rs77622531	7	25804957	0	G	C	0.973696	0.998921	55.1905	1.10E-13	-0.0499716	0.00680278	53.9602	2.00E-13
rs1557779	7	27994758	0	T	C	0.0731744	0.98419	47.1488	6.60E-12	-0.0283919	0.00420704	45.5444	1.50E-11
rs506154	7	28202079	0	T	C	0.292949	0.999401	385.042	9.90E-86	0.0471069	0.00239101	388.155	2.10E-86
rs75658126	7	28720887	0	T	C	0.980176	0.979041	43.7877	3.70E-11	-0.0531243	0.00789301	45.3003	1.70E-11
rs62442203	7	28829253	0	G	C	0.596645	0.993427	158.491	2.40E-36	0.0282097	0.00222339	160.978	6.90E-37
rs148498571	7	28893108	0	C	T	0.987881	0.899007	38.0625	6.90E-10	-0.0690974	0.0104903	43.3854	4.50E-11
rs4988496	7	31008686	0	G	A	0.943159	1	37.288	1.00E-09	-0.0287181	0.00469377	37.4341	9.50E-10
rs142854193	7	33045510	0	C	T	0.976781	0.938121	46.2947	1.00E-11	-0.0518767	0.00745736	48.3922	3.50E-12
rs10281514	7	33153307	0	G	C	0.735541	0.97384	31.868	1.70E-08	0.0138396	0.00249804	30.6937	3.00E-08
rs315858	7	33920134	0	T	G	0.593124	0.991205	30.2571	3.80E-08	0.0123062	0.0022257	30.5711	3.20E-08
rs10257774	7	35229608	0	G	T	0.626505	0.980442	41.5895	1.10E-10	0.0147178	0.00227345	41.9097	9.60E-11
rs13237498	7	37975641	0	T	C	0.618986	0.992305	40.4738	2.00E-10	0.0142601	0.00225027	40.1583	2.30E-10
rs6956946	7	38110032	0	T	G	0.346544	0.998968	109.622	1.20E-25	-0.0245016	0.0022874	114.738	9.00E-27
rs139654893	7	42239557	0	A	G	0.934671	0.96103	44.4821	2.60E-11	-0.029624	0.00449215	43.4888	4.30E-11
rs140776140	7	44094935	0	C	T	0.944411	0.996334	35.9886	2.00E-09	-0.0291295	0.00475677	37.5009	9.10E-10
rs4724290	7	44196069	0	C	T	0.71771	0.986588	32.5009	1.20E-08	0.0140577	0.00242945	33.482	7.20E-09
rs879965	7	46049342	0	T	C	0.5572	0.999606	33.5244	7.00E-09	-0.0128785	0.00219478	34.4306	4.40E-09
rs117974146	7	46130120	0	C	A	0.983894	0.990887	68.2018	1.50E-16	0.0711933	0.00867817	67.3011	2.30E-16
rs1007358	7	46201355	0	A	G	0.786747	0.997433	95.6964	1.30E-22	-0.026127	0.00265693	96.6983	8.10E-23
rs35329760	7	46284490	0	G	A	0.940126	0.987371	68.9018	1.00E-16	0.03808	0.00461019	68.227	1.50E-16
rs723149	7	46577056	0	A	G	0.437064	1	137.904	7.70E-32	0.0261538	0.00219494	141.979	9.80E-33
rs71545965	7	47105208	0	T	C	0.878856	0.995622	35.5076	2.50E-09	0.0188813	0.00334154	31.928	1.60E-08
rs11555134	7	50659193	0	C	T	0.767196	0.984199	42.6942	6.40E-11	-0.0171068	0.00259506	43.4553	4.30E-11
rs7793921	7	56120881	0	G	A	0.310224	0.997104	72.4262	1.70E-17	-0.0201128	0.0023545	72.9708	1.30E-17
rs73148102	7	65438864	0	G	A	0.786076	0.993517	59.0936	1.50E-14	-0.0204956	0.0026611	59.3197	1.30E-14
rs78159548	7	67662295	0	C	A	0.809309	0.999161	39.3555	3.50E-10	-0.016666	0.00276836	36.2424	1.70E-09
rs4475377	7	69690408	0	A	G	0.786667	0.999197	34.0992	5.20E-09	0.0156243	0.00265823	34.5474	4.20E-09
rs7803932	7	70203673	0	G	A	0.828476	0.981019	37.5408	9.00E-10	-0.0180858	0.00291295	38.5485	5.30E-10
rs35493868	7	73039406	0	C	G	0.797516	0.996221	74.7108	5.40E-18	-0.0236076	0.00271228	75.759	3.20E-18
rs113946216	7	73303742	0	G	C	0.867304	0.977183	60.6313	6.90E-15	0.0246415	0.00324549	57.6467	3.10E-14
rs17855988	7	73474825	0	G	C	0.90145	0.965363	33.8851	5.80E-09	-0.0218778	0.0037098	34.7781	3.70E-09
rs113778748	7	73813883	0	G	C	0.96416	0.915516	31.2282	2.30E-08	-0.0336409	0.00610884	30.3262	3.70E-08
rs7796089	7	77512098	0	G	C	0.652318	0.999407	64.8716	8.00E-16	-0.018525	0.00228321	65.8301	4.90E-16
rs7783234	7	84621549	0	A	G	0.678529	0.996938	72.008	2.10E-17	0.0203001	0.0023349	75.5893	3.50E-18
rs55976025	7	87105176	0	G	C	0.890347	0.996774	40.4333	2.00E-10	-0.0226161	0.00349362	41.9068	9.60E-11
rs42039	7	92244422	0	C	T	0.755422	0.998318	696.393	1.80E-153	-0.0671785	0.00253668	701.343	1.50E-154
rs62466078	7	92468948	0	C	T	0.863133	0.998933	69.6059	7.20E-17	-0.0262709	0.00316985	68.6869	1.20E-16
rs34743807	7	92566685	0	A	G	0.883221	0.986672	148.381	3.90E-34	0.0409611	0.00341904	143.528	4.50E-33
rs11976540	7	92650552	0	C	T	0.754766	0.993033	58.2525	2.30E-14	-0.0192543	0.00254484	57.2444	3.80E-14
rs6976031	7	93088426	0	G	C	0.506562	0.996415	50.4252	1.20E-12	-0.0158226	0.00218406	52.4842	4.30E-13
rs42528	7	94049356	0	T	C	0.249923	0.995483	44.4318	2.60E-11	0.0171761	0.00252109	46.4163	9.60E-12
rs12704720	7	94106403	0	A	G	0.630651	0.997796	37.2382	1.00E-09	-0.0134546	0.00225786	35.5096	2.50E-09
rs73232633	7	96591668	0	A	G	0.9583	0.97595	43.1316	5.10E-11	0.0369326	0.00552717	44.6494	2.40E-11
rs45446698	7	99332948	0	T	G	0.957971	1	108.242	2.40E-25	-0.0568821	0.00542915	109.771	1.10E-25
rs117722415	7	100167156	0	G	A	0.969317	1	37.2866	1.00E-09	-0.0389734	0.00631377	38.103	6.70E-10
rs3757868	7	100482720	0	G	A	0.817189	0.998792	36.7927	1.30E-09	-0.0171669	0.00281485	37.1942	1.10E-09
rs35760677	7	100788382	0	G	T	0.567645	0.993262	50.4303	1.20E-12	-0.0151838	0.00220254	47.5238	5.40E-12
rs432002	7	101686485	0	T	C	0.172426	0.983327	41.1092	1.40E-10	-0.0188722	0.00290504	42.2026	8.20E-11
rs374409015	7	102111925	0	C	T	0.963321	0.946501	34.1904	5.00E-09	-0.0343651	0.00595848	33.2633	8.00E-09
rs6466484	7	114012911	0	A	C	0.601716	0.993116	57.4213	3.50E-14	0.016853	0.00223714	56.7499	4.90E-14
rs10228519	7	120799084	0	G	C	0.486071	0.998143	36.3561	1.60E-09	-0.0130583	0.00217943	35.8992	2.10E-09
rs1443749	7	121960438	0	C	T	0.634414	0.998696	42.4839	7.10E-11	-0.0148794	0.00225919	43.3775	4.50E-11
rs11556924	7	129663496	0	C	T	0.610853	1	41.5647	1.10E-10	-0.0140266	0.00223444	39.4067	3.40E-10
rs12533527	7	130626948	0	C	T	0.859711	0.982143	53.3589	2.80E-13	0.0230909	0.00316702	53.1593	3.10E-13
rs12707083	7	132804434	0	A	C	0.62817	0.990066	34.3335	4.60E-09	-0.0136834	0.00226378	36.536	1.50E-09
rs10155941	7	134422732	0	T	C	0.539339	0.998457	73.3527	1.10E-17	0.0186359	0.00218639	72.6516	1.50E-17
rs117297189	7	135115880	0	G	A	0.963463	0.967854	29.771	4.90E-08	0.0330716	0.00589306	31.4941	2.00E-08
rs11772708	7	135264737	0	A	G	0.826942	0.994042	108.335	2.30E-25	-0.0290716	0.00288798	101.333	7.80E-24
rs73160736	7	135394588	0	C	G	0.932022	0.991175	44.2251	2.90E-11	0.0284187	0.0043472	42.7354	6.30E-11
rs273945	7	137611566	0	A	C	0.421542	1	52.7773	3.70E-13	-0.0159742	0.00220733	52.3725	4.60E-13
rs199610373	7	139735856	0	A	G	0.817235	0.989741	97.0638	6.70E-23	-0.0282164	0.00283202	99.2683	2.20E-23
rs11972037	7	139815457	0	A	G	0.575986	0.995652	51.7404	6.30E-13	0.0153181	0.00220648	48.1959	3.90E-12
rs3829814	7	140426257	0	A	G	0.439311	0.974628	50.6389	1.10E-12	0.0160034	0.00222499	51.7333	6.40E-13
rs73158212	7	148383377	0	A	G	0.775714	0.97492	69.01	9.80E-17	0.0212219	0.00264425	64.411	1.00E-15
rs148190310	7	148564138	0	G	A	0.973748	0.975279	150.972	1.10E-34	-0.0845567	0.00689146	150.547	1.30E-34
rs822531	7	148629759	0	C	T	0.204755	0.984186	303.081	7.00E-68	-0.0475558	0.00271898	305.911	1.70E-68
rs6956736	7	148893472	0	G	C	0.253893	0.993007	45.7226	1.40E-11	0.0169097	0.00251045	45.3699	1.60E-11

rs6977081	7	150542515	0	G	T	0.666714	0.98358	132.62	1.10E-30	-0.0266965	0.00233127	131.136	2.30E-30
rs3918226	7	150690176	0	C	T	0.91878	0.970808	120.383	5.20E-28	0.0440761	0.00404647	118.646	1.30E-27
rs7792624	7	150968234	0	C	T	0.436467	0.985347	34.3048	4.70E-09	0.0128473	0.00221239	33.7208	6.40E-09
rs7350040	7	156170722	0	C	A	0.425631	0.98679	39.8984	2.70E-10	0.014043	0.00221701	40.1225	2.40E-10
rs4633074	8	4781874	0	G	A	0.480833	0.989934	34.1357	5.10E-09	0.0126521	0.00219847	33.1193	8.70E-09
rs113698072	8	8781000	0	G	T	0.943256	1	40.9828	1.50E-10	-0.0301493	0.00471672	40.8577	1.60E-10
rs7822154	8	12667111	0	G	A	0.795292	0.970494	41.6671	1.10E-10	0.0173012	0.00274777	39.6453	3.00E-10
rs59738387	8	13200212	0	G	A	0.789552	0.989111	63.124	1.90E-15	-0.0211512	0.00268667	61.9786	3.50E-15
rs76364830	8	13372120	0	G	A	0.936747	0.979492	111.243	5.20E-26	0.0486533	0.00452609	115.552	6.00E-27
rs7846369	8	13388296	0	C	T	0.938524	0.989227	50.6805	1.10E-12	0.0316196	0.00456989	47.8742	4.50E-12
rs11203927	8	17770036	0	G	A	0.316782	0.991345	34.1198	5.20E-09	0.0133343	0.00235757	31.9898	1.50E-08
rs4317590	8	19357642	0	A	G	0.52073	0.99391	47.6524	5.10E-12	-0.0149076	0.00219079	46.303	1.00E-11
rs286	8	19815256	0	A	T	0.913896	0.99519	46.7835	7.90E-12	-0.0258587	0.00390032	43.9556	3.40E-11
rs10866837	8	21861663	0	G	C	0.445842	0.992703	35.2861	2.80E-09	0.0128746	0.00220311	34.1505	5.10E-09
rs6558033	8	22251807	0	T	C	0.544572	0.997735	29.6555	5.20E-08	-0.0120748	0.00219062	30.3827	3.50E-08
rs4291276	8	23173591	0	A	G	0.234541	0.995294	140.977	1.60E-32	0.0305311	0.00258253	139.764	3.00E-32
rs73228208	8	23381769	0	G	A	0.774567	0.986519	122.349	1.90E-28	-0.029467	0.00262809	125.716	3.50E-29
rs8534	8	23432332	0	C	T	0.625349	0.987056	29.611	5.30E-08	-0.0125756	0.00227094	30.6652	3.10E-08
rs62501195	8	24041988	0	A	C	0.828873	0.966724	152.957	3.90E-35	0.0366874	0.00294526	155.162	1.30E-35
rs1506871	8	25314571	0	G	C	0.642923	0.997844	104.296	1.70E-24	0.0231916	0.00227923	103.534	2.60E-24
rs2053538	8	26399483	0	C	T	0.883614	0.996528	33.2675	8.00E-09	0.0199017	0.00340911	34.08	5.30E-09
rs554876	8	27506903	0	C	T	0.761091	0.998638	68.7359	1.10E-16	-0.0214342	0.00256212	69.9869	6.00E-17
rs3779639	8	30407991	0	G	A	0.507366	0.991933	60.3909	7.80E-15	-0.0165253	0.00219149	56.8619	4.70E-14
rs13282071	8	32492911	0	C	T	0.725283	0.980212	33.5231	7.00E-09	0.014369	0.00246725	33.9174	5.80E-09
rs62505473	8	38323765	0	C	G	0.593174	0.995956	43.5326	4.20E-11	0.014403	0.00222397	41.942	9.40E-11
rs147918758	8	41167562	0	C	G	0.611912	0.994731	37.1559	1.10E-09	0.0139963	0.00224852	38.7464	4.80E-10
rs10104817	8	49383858	0	A	G	0.756047	0.998128	69.2833	8.50E-17	-0.0215066	0.00254279	71.5355	2.70E-17
rs10089932	8	56866957	0	A	G	0.699399	1	35.5593	2.50E-09	0.0141224	0.00237937	35.2285	2.90E-09
rs139584477	8	57056704	0	G	A	0.987492	0.846849	35.0268	3.30E-09	-0.0637809	0.0106714	35.7222	2.30E-09
rs147888278	8	57099185	0	G	A	0.96659	0.989059	49.2476	2.30E-12	-0.0440203	0.00610396	52.0095	5.50E-13
rs72656010	8	57122215	0	T	C	0.867862	0.992891	471.212	1.70E-104	0.0705321	0.00323623	475.002	2.60E-105
rs78470252	8	57122827	0	G	A	0.976049	0.966689	48.8222	2.80E-12	0.0490993	0.00725677	45.7788	1.30E-11
rs62515433	8	57129291	0	A	T	0.778017	0.989588	394.728	7.70E-88	-0.0518923	0.00263741	387.123	3.50E-86
rs55701215	8	57667048	0	G	A	0.75528	0.999813	62.2088	3.10E-15	-0.0199627	0.00253959	61.7893	3.80E-15
rs73682817	8	58147316	0	C	T	0.909366	0.992009	31.5735	1.90E-08	-0.0212783	0.00381364	31.131	2.40E-08
rs12545525	8	60581812	0	T	A	0.867792	0.997194	71.8467	2.30E-17	-0.0270056	0.00323267	69.7884	6.60E-17
rs7836586	8	61655690	0	G	A	0.250924	0.999872	43.827	3.60E-11	-0.0164137	0.00251669	42.5358	6.90E-11
rs11557049	8	66692011	0	C	T	0.933799	1	30.5917	3.20E-08	0.0241602	0.00439244	30.2546	3.80E-08
rs150540391	8	67494885	0	C	T	0.986225	0.993719	60.3245	8.00E-15	0.0714117	0.0093866	57.8791	2.80E-14
rs62511285	8	68808450	0	G	C	0.879376	0.953474	37.8959	7.50E-10	0.0213537	0.00343516	38.6413	5.10E-10
rs831714	8	70136688	0	T	C	0.217159	0.999214	35.2221	2.90E-09	0.0160127	0.00265446	36.3896	1.60E-09
rs4492411	8	71980173	0	A	G	0.834569	0.978901	33.6753	6.50E-09	-0.0175934	0.00297178	35.0481	3.20E-09
rs1983532	8	75181108	0	A	C	0.673816	1	35.2301	2.90E-09	-0.0136316	0.00232712	34.3129	4.70E-09
rs75398276	8	75811566	0	G	A	0.740501	0.991156	82.5498	1.00E-19	-0.0227058	0.00249939	82.5285	1.00E-19
rs2956605	8	75883054	0	A	C	0.391437	0.984041	151.964	6.50E-35	0.0277707	0.00225	152.338	5.30E-35
rs118016106	8	75944111	0	G	A	0.975512	1	56.8187	4.80E-14	0.0525242	0.00706227	55.3135	1.00E-13
rs1531462	8	76752790	0	A	G	0.113484	0.992935	34.5968	4.10E-09	-0.0204926	0.0034543	35.1943	3.00E-09
rs10504628	8	77517422	0	A	G	0.958302	1	44.2015	3.00E-11	0.0359698	0.00545921	43.4126	4.40E-11
rs61729527	8	77761919	0	C	T	0.947932	1	41.7751	1.00E-10	0.0318032	0.00491739	41.8284	1.00E-10
rs4735766	8	78099782	0	G	T	0.714419	0.998878	266.6	6.20E-60	-0.0393641	0.0024168	265.289	1.20E-59
rs2129465	8	78776021	0	A	G	0.48604	0.998312	39.3044	3.60E-10	-0.0134222	0.00218583	37.7061	8.20E-10
rs11782610	8	87566158	0	A	G	0.252236	1	31.7927	1.70E-08	-0.0144205	0.00251293	32.9306	9.60E-09
rs68179213	8	92351635	0	G	T	0.94579	0.977773	32.0783	1.50E-08	0.0279892	0.0048683	33.0542	9.00E-09
rs6997004	8	96418497	0	A	G	0.83891	0.994523	56.3683	6.00E-14	0.0224584	0.00298119	56.7519	4.90E-14
rs79023150	8	99569792	0	A	C	0.892155	0.994509	35.5957	2.40E-09	0.02099	0.0035314	35.329	2.80E-09
rs1050969	8	103661730	0	T	C	0.982446	0.936719	34.5403	4.20E-09	-0.0496819	0.00857105	33.5992	6.80E-09
rs619227	8	109215100	0	C	A	0.570648	0.999167	38.5691	5.30E-10	-0.0132743	0.00220577	36.2163	1.80E-09
rs2721940	8	116636281	0	A	C	0.398152	0.997804	75.2657	4.10E-18	0.0192772	0.00223211	74.5857	5.80E-18
rs77249084	8	117572538	0	A	G	0.727762	0.990896	85.6718	2.10E-20	-0.0230216	0.0024627	87.3869	8.90E-21
rs72684290	8	120406650	0	T	C	0.973267	0.958461	42.8031	6.10E-11	-0.0441402	0.00690753	40.8341	1.70E-10
rs60869342	8	120456193	0	A	T	0.730489	0.972968	131.076	2.40E-30	0.0288698	0.00249317	134.086	5.20E-31
rs10283100	8	120596023	0	A	G	0.05556	1	70.7571	4.00E-17	-0.0409629	0.0047672	73.8335	8.50E-18
rs10089416	8	120778627	0	G	A	0.917621	0.999215	35.9373	2.00E-09	-0.0228869	0.0039685	33.2599	8.10E-09
rs1356747	8	121010856	0	A	C	0.0597811	1	32.5476	1.20E-08	-0.0263047	0.00460318	32.655	1.10E-08
rs11783086	8	123980448	0	T	C	0.645489	0.991042	73.6263	9.40E-18	-0.0199156	0.00229219	75.4889	3.70E-18
rs4870941	8	126498828	0	G	C	0.761995	0.971204	105.974	7.50E-25	0.0268935	0.00259852	107.113	4.20E-25
rs4551307	8	128599672	0	A	G	0.827036	1	48.6429	3.10E-12	0.0201357	0.00288653	48.661	3.00E-12
rs13274301	8	128988045	0	A	C	0.86935	1	49.1646	2.40E-12	0.0225568	0.00323715	48.5545	3.20E-12
rs35335041	8	129120060	0	T	C	0.863603	0.965415	49.6311	1.90E-12	0.0225099	0.00323632	48.3778	3.50E-12
rs1121948	8	129165056	0	A	G	0.798947	0.993255	101.398	7.50E-24	-0.027565	0.00273797	101.358	7.70E-24
rs6985031	8	130550637	0	T	C	0.617701	0.996078	59.1357	1.50E-14	0.0171865	0.00225278	58.2018	2.40E-14
rs4501553	8	130718314	0	G	A	0.676456	0.988556	32.526	1.20E-08	0.0136399	0.00234795	33.7478	6.30E-09
rs7816131	8	130719718	0	A	T	0.798382	0.996683	382.62	3.30E-85	0.053245	0.00272116	382.868	3.00E-85
rs62517707	8	131408202	0	G	A	0.819879	0.99326	50.6281	1.10E-12	-0.0205682	0.00285249	51.9931	5.60E-13
rs4537288	8	134610886	0	A	T	0.80053	0.999806	58.7145	1.80E-14	-0.0210451	0.00273037	59.4101	1.30E-14
rs28716235	8	135602976	0	A	C	0.628891	0.989323	274.445	1.20E-61	0.0374279	0.00226914	272.062	4.00E-61
rs2439810	8	135662661	0	G	A	0.805684	0.995849	58.677	1.90E-14	-0.0211338	0.0027577	58.7304	1.80E-14
rs2977474	8	141552183	0	C	T	0.876639	0.993608	42.9482	5.60E-11	-0.0219803	0.0033252	43.695	3.80E-11
rs151078229	8	144023755	0	A	G	0.557368	0.987626	46.0061	1.20E-11	0.0149232	0.00221197	45.5161	1.50E-11
rs11136278	8	144356057	0	A	G	0.240286	0.996202	102.014	5.50E-24	0.0257065	0.00255214	101.456	7.30E-24
rs9650469	8	144837330	0	G	C	0.407997	0.99304	67.8146	1.80E-16	-0.0182047	0.00222673	66.8391	2.90E-16
rs10866916	8	145006790	0	T	C	0.601384	0.996357	124.201	7.60E-29	0.0250772	0.00223276	126.145	2.90E-29
rs58626562	8	145502303	0	G	A	0.509874	1	35.4691	2.60E-09	0.0127308	0.00218121	34.0657	5.30E-09

rs62531538	9	600893	0	T	C	0.744237	0.993806	37.6539	8.40E-10	0.0152742	0.00251314	36.939	1.20E-09
rs10974438	9	4291928	0	A	C	0.648749	0.995405	33.402	7.50E-09	-0.0132784	0.00229179	33.5693	6.90E-09
rs12348423	9	4740251	0	A	C	0.749992	1	43.9434	3.40E-11	0.0170082	0.00252253	45.4615	1.60E-11
rs7861458	9	11771159	0	C	A	0.231164	0.997256	34.6948	3.90E-09	0.0151323	0.00259227	34.0759	5.30E-09
rs1928884	9	12302048	0	G	A	0.61292	1	35.9742	2.00E-09	-0.0127824	0.00224224	32.4985	1.20E-08
rs9696084	9	13901557	0	G	T	0.662939	0.989968	34.5893	4.10E-09	-0.0135253	0.00232357	33.8832	5.90E-09
rs10046853	9	14456931	0	C	G	0.545302	0.9973	56.8584	4.70E-14	-0.0166872	0.00219803	57.6365	3.20E-14
rs4740625	9	15778141	0	A	G	0.546132	0.999149	30.9968	2.60E-08	-0.0121037	0.00219748	30.3379	3.60E-08
rs12335424	9	16692104	0	C	T	0.904811	0.9954	58.4915	2.00E-14	-0.0290587	0.00373771	60.442	7.60E-15
rs10756792	9	16726119	0	C	T	0.256391	0.991951	78.3075	8.80E-19	-0.0222646	0.00251362	78.4568	8.20E-19
rs13296025	9	16900507	0	G	C	0.92291	0.993898	37.5801	8.80E-10	-0.0257111	0.00411077	39.1197	4.00E-10
rs112803367	9	17023750	0	G	A	0.899004	0.99543	30.216	3.90E-08	0.019873	0.00363025	29.9677	4.40E-08
rs35568725	9	19119674	0	A	G	0.94675	1	31.0323	2.50E-08	0.0270542	0.00486794	30.8872	2.70E-08
rs1412836	9	22167207	0	G	A	0.880229	0.973969	37.6729	8.40E-10	0.0212393	0.00341269	38.7333	4.90E-10
rs1360379	9	23340616	0	C	T	0.384825	1	31.862	1.70E-08	-0.0132886	0.00224642	34.9924	3.30E-09
rs117658173	9	33762967	0	G	T	0.973075	0.960407	42.1267	8.60E-11	-0.0451147	0.00689182	42.8517	5.90E-11
rs11575580	9	34660864	0	C	T	0.978521	1	43.7141	3.80E-11	0.0501868	0.00753713	44.3371	2.80E-11
rs2093400	9	35838843	0	G	C	0.271221	0.998851	32.2394	1.40E-08	0.0144144	0.00245896	34.3626	4.60E-09
rs7847059	9	35901731	0	T	A	0.543434	0.989916	53.0003	3.30E-13	0.0164674	0.00220471	55.7888	8.10E-14
rs56113220	9	76679950	0	A	T	0.393009	0.979684	30.3554	3.60E-08	0.0130358	0.00226011	33.2672	8.00E-09
rs35307904	9	78511889	0	G	A	0.877384	0.988265	256.244	1.10E-57	0.0536307	0.00334972	256.337	1.10E-57
rs61635866	9	78555995	0	T	C	0.74761	0.997527	30.9068	2.70E-08	-0.0141166	0.0025228	31.3109	2.20E-08
rs4745496	9	78701793	0	A	G	0.918383	0.994561	32.2658	1.30E-08	0.0239063	0.00399973	35.7242	2.30E-09
rs3739728	9	78748973	0	C	T	0.943736	0.906369	44.153	3.00E-11	-0.0335938	0.00498533	45.4078	1.60E-11
rs1610363	9	78795749	0	A	G	0.718772	0.985428	40.3147	2.20E-10	0.0147507	0.0024463	36.3584	1.60E-09
rs944593	9	84226540	0	G	C	0.47307	0.99356	61.762	3.90E-15	0.0168601	0.00218433	59.5773	1.20E-14
rs1330816	9	85093919	0	C	T	0.802217	0.997566	50.6973	1.10E-12	-0.0194863	0.00273132	50.8995	9.70E-13
rs11140055	9	85978775	0	T	G	0.918057	0.924251	37.133	1.10E-09	-0.024835	0.00412154	36.3086	1.70E-09
rs696825	9	86583076	0	C	T	0.747923	0.999511	105.722	8.50E-25	-0.0259556	0.00250426	107.424	3.60E-25
rs1593438	9	88978867	0	A	C	0.655904	0.991649	46.567	8.90E-12	-0.0157103	0.00229905	46.6949	8.30E-12
rs353795	9	89093453	0	A	G	0.49596	0.998949	135.694	2.30E-31	-0.0250781	0.00217448	133.008	9.00E-31
rs4878043	9	89687854	0	C	T	0.457053	0.990699	60.3482	7.90E-15	-0.0170864	0.00219272	60.7204	6.60E-15
rs549853	9	90609104	0	T	C	0.393118	0.977071	43.8164	3.60E-11	-0.0149555	0.00225243	44.086	3.10E-11
rs10746837	9	90873653	0	G	A	0.419241	0.987104	209.012	2.30E-47	0.0318066	0.00221683	205.859	1.10E-46
rs7873096	9	92230041	0	G	A	0.790972	0.971569	44.9312	2.00E-11	0.0184329	0.00271068	46.2414	1.00E-11
rs9409429	9	94337510	0	C	T	0.806604	0.989945	57.8754	2.80E-14	-0.0210957	0.002767	58.126	2.50E-14
rs145375166	9	94937214	0	C	A	0.952992	0.931639	41.0471	1.50E-10	-0.0339188	0.00532288	40.6057	1.90E-10
rs10992395	9	95433844	0	T	C	0.433321	0.998923	123.474	1.10E-28	0.0241979	0.00219744	121.261	3.30E-28
rs72743489	9	96168483	0	G	A	0.408475	0.994228	79.1067	5.90E-19	-0.020111	0.00221973	82.0857	1.30E-19
rs7872863	9	96392815	0	T	C	0.710647	0.995363	39.1152	4.00E-10	-0.0152904	0.00240338	40.4756	2.00E-10
rs7854962	9	96900505	0	C	G	0.786575	0.980446	96.9014	7.30E-23	0.0258907	0.00267912	93.3905	4.30E-22
rs112371891	9	96937049	0	T	G	0.96669	0.978862	145.543	1.60E-33	-0.0737005	0.00612657	144.712	2.50E-33
rs532027	9	97340038	0	G	A	0.0921904	0.990215	29.7595	4.90E-08	0.0208867	0.0037799	30.5338	3.30E-08
rs79813405	9	97351549	0	C	T	0.91462	0.996529	30.5189	3.30E-08	0.0215052	0.0038931	30.5139	3.30E-08
rs4744370	9	97477793	0	C	T	0.47411	0.990853	67.8246	1.80E-16	0.0181472	0.00218535	68.9572	1.00E-16
rs4744436	9	97831581	0	G	A	0.135928	0.983881	109.2	1.50E-25	-0.0337594	0.00319541	111.618	4.30E-26
rs28701981	9	98217581	0	T	C	0.650384	0.989716	362.954	6.40E-81	-0.0435775	0.00228954	362.264	9.00E-81
rs2066830	9	98238403	0	G	A	0.985458	1	32.2802	1.30E-08	-0.050441	0.00908562	30.8219	2.80E-08
rs1984119	9	98368761	0	T	C	0.744098	0.976927	271.471	5.40E-61	0.0417081	0.00252212	273.471	2.00E-61
rs7857949	9	98449514	0	C	T	0.68187	0.993061	37.3727	9.80E-10	-0.0144745	0.00234074	38.2385	6.30E-10
rs1369156	9	98556894	0	A	G	0.501621	0.984821	83.2515	7.20E-20	0.0201502	0.00219284	84.4396	4.00E-20
rs10761022	9	99224746	0	A	T	0.782316	0.991395	323.729	2.20E-72	-0.0471044	0.00264549	317.039	6.40E-71
rs112500293	9	100763455	0	C	T	0.783123	0.991626	39.5617	3.20E-10	0.016748	0.00264667	40.0431	2.50E-10
rs7851079	9	101804416	0	A	G	0.863622	0.99795	39.4277	3.40E-10	0.0202099	0.00316739	40.7124	1.80E-10
rs72741444	9	103925498	0	G	A	0.78406	0.997577	47.5258	5.40E-12	0.0180172	0.00264407	46.4335	9.50E-12
rs2244278	9	107661129	0	C	A	0.879419	0.995175	29.3148	6.20E-08	-0.0183597	0.00334735	30.0835	4.10E-08
rs2176337	9	108959330	0	A	T	0.685024	0.998735	101.181	8.40E-24	0.0236128	0.0023444	101.446	7.30E-24
rs4434671	9	109178575	0	A	G	0.614258	0.997023	39.7418	2.90E-10	-0.0141082	0.00223771	39.7498	2.90E-10
rs375524395	9	109507030	0	A	G	0.546463	0.978621	45.6887	1.40E-11	-0.0153452	0.00220602	48.3869	3.50E-12
rs7861738	9	109518169	0	C	T	0.95028	0.98446	46.0607	1.10E-11	0.0342916	0.00503752	46.3384	9.90E-12
rs6477546	9	109616262	0	T	C	0.632541	0.997801	135.313	2.80E-31	-0.0261072	0.00225494	134.045	5.30E-31
rs16912263	9	109928973	0	G	A	0.900216	0.987045	33.0951	8.80E-09	-0.0207512	0.00365023	32.3182	1.30E-08
rs7855791	9	112921330	0	C	G	0.533156	0.998327	30.4482	3.40E-08	-0.0122272	0.0021771	31.5427	2.00E-08
rs1049927	9	113018755	0	T	C	0.858919	0.993396	39.843	2.80E-10	0.0196589	0.00313132	39.4151	3.40E-10
rs4641138	9	113421543	0	A	G	0.726571	0.997294	37.0614	1.10E-09	0.0148072	0.00244113	36.7928	1.30E-09
rs4366150	9	113739638	0	A	G	0.576689	0.989902	47.8192	4.70E-12	0.0154214	0.00220761	48.7978	2.80E-12
rs6477807	9	113939593	0	T	A	0.438954	0.99742	90.0751	2.30E-21	0.0206167	0.00219505	88.2162	5.90E-21
rs74999040	9	114335873	0	C	T	0.879182	0.986106	49.4327	2.10E-12	-0.0233827	0.00335689	48.5195	3.30E-12
rs35358414	9	116168755	0	G	A	0.89461	0.987839	51.8579	6.00E-13	0.026092	0.00356439	53.5851	2.50E-13
rs1766058	9	117039619	0	T	C	0.639569	0.995351	36.3371	1.70E-09	-0.0139134	0.00226955	37.5828	8.80E-10
rs12376870	9	117890567	0	G	A	0.761965	0.992566	53.3659	2.80E-13	-0.0184391	0.00256043	51.8624	6.00E-13
rs12344772	9	118490315	0	G	T	0.916989	0.98351	93.1404	4.90E-22	0.0389962	0.00397609	96.1905	1.00E-22
rs10982986	9	118653666	0	A	G	0.699459	0.997465	30.9236	2.70E-08	0.0131733	0.00237193	30.8448	2.80E-08
rs452312	9	118966153	0	G	A	0.583621	0.995989	69.8653	6.30E-17	0.0183034	0.00221172	68.4861	1.30E-16
rs12347137	9	119122721	0	A	C	0.797395	0.996136	266.298	7.30E-60	0.0442621	0.0027089	266.98	5.20E-60
rs4837613	9	119309525	0	G	C	0.511112	0.988829	138.341	6.10E-32	0.02607	0.00218646	142.168	8.90E-33
rs11794984	9	122652870	0	C	T	0.366297	1	45.6194	1.40E-11	0.0151956	0.00225409	45.4456	1.60E-11
rs2416797	9	123480600	0	C	A	0.303616	0.999248	86.0468	1.80E-20	0.0217852	0.00236641	84.7511	3.40E-20
rs72760242	9	123915955	0	G	A	0.900152	0.989644	42.9666	5.60E-11	-0.0238671	0.00364386	42.9021	5.80E-11
rs12351652	9	124290770	0	T	A	0.700068	0.971377	32.9072	9.70E-09	0.0136318	0.00240978	32.0003	1.50E-08
rs2793007	9	125664882	0	G	C	0.14524	0.996303	40.5306	1.90E-10	0.0193085	0.00309099	39.0211	4.20E-10
rs199955511	9	128221686	0	C	T	0.646568	0.990311	56.2386	6.40E-14	0.017203	0.00228413	56.7237	5.00E-14
rs7856756	9	129332758	0	A	G	0.65577	0.997515	31.8471	1.70E-08	0.0131839	0.00229175	33.0941	8.80E-09

rs4837126	9	129768598	0	G	A	0.281099	0.997801	64.0948	1.20E-15	-0.019766	0.00242288	66.5538	3.40E-16
rs7855784	9	131025842	0	C	G	0.756232	0.981778	29.5304	5.50E-08	0.0144643	0.0025573	31.9912	1.50E-08
rs10901216	9	133471891	0	G	A	0.651802	0.99886	177.27	1.90E-40	0.0302631	0.00228615	175.234	5.30E-40
rs11244061	9	136153981	0	C	T	0.884426	0.995637	43.4257	4.40E-11	0.0224186	0.00340565	43.3328	4.60E-11
rs9802273	9	136385453	0	A	G	0.277359	0.995275	39.6478	3.00E-10	-0.0158281	0.00243416	42.2825	7.90E-11
rs11789898	9	136925663	0	G	T	0.8329	0.995867	41.1192	1.40E-10	-0.0187774	0.00292228	41.2882	1.30E-10
rs67827752	9	139137204	0	G	A	0.340164	0.973655	138.818	4.80E-32	0.0272464	0.00232405	137.445	9.60E-32
rs34602454	9	139374457	0	A	C	0.724675	0.997764	147.943	4.90E-34	-0.0298878	0.00243325	150.874	1.10E-34
rs76088740	10	3193412	0	C	T	0.950698	0.986216	33.4063	7.50E-09	-0.0285867	0.0050876	31.572	1.90E-08
rs11597804	10	3807129	0	G	T	0.552703	0.987481	32.7262	1.10E-08	-0.0129267	0.0022143	34.0804	5.30E-09
rs67362530	10	5043504	0	G	A	0.883173	0.986286	76.5484	2.10E-18	0.0292998	0.00342367	73.2393	1.10E-17
rs10082444	10	11907982	0	T	C	0.80697	0.993756	54.7045	1.40E-13	-0.0209043	0.00277704	56.6642	5.20E-14
rs11257570	10	12199473	0	G	T	0.503257	0.997977	38.2316	6.30E-10	0.0133529	0.00218625	37.3039	1.00E-09
rs34321514	10	12949653	0	G	T	0.716917	0.990909	151.078	1.00E-34	0.0297799	0.00243605	149.443	2.30E-34
rs1243186	10	21902760	0	A	G	0.476766	0.995198	37.2482	1.00E-09	0.013193	0.00219407	36.1563	1.80E-09
rs17499297	10	22525961	0	G	A	0.917227	0.982448	38.1349	6.60E-10	-0.0244203	0.00399716	37.3248	1.00E-09
rs4333914	10	23770658	0	G	A	0.681165	0.998868	36.3403	1.70E-09	-0.0144059	0.00234818	37.6374	8.50E-10
rs72780356	10	25177056	0	C	T	0.820367	0.970522	73.4195	1.00E-17	-0.0253156	0.00288902	76.7849	1.90E-18
rs1352982	10	25332461	0	A	G	0.633135	0.998492	47.3151	6.00E-12	-0.0159331	0.00226973	49.2781	2.20E-12
rs2808290	10	27900882	0	C	T	0.496933	0.990698	123.678	9.90E-29	-0.0245113	0.00219435	124.773	5.70E-29
rs11006752	10	28160836	0	T	C	0.301896	0.991771	59.7068	1.10E-14	-0.0185734	0.00239004	60.391	7.80E-15
rs332158	10	28884362	0	G	A	0.201344	0.99749	74.3919	6.40E-18	0.0237765	0.00272781	75.9741	2.90E-18
rs10826579	10	29491536	0	G	A	0.846725	0.958022	44.4108	2.70E-11	0.0196238	0.00309891	40.1001	2.40E-10
rs2000099	10	31118096	0	T	C	0.63435	0.993975	35.0062	3.30E-09	-0.0138305	0.00227397	36.9921	1.20E-09
rs2808096	10	32128611	0	A	G	0.78551	1	56.1362	6.80E-14	-0.0199992	0.00266354	56.3779	6.00E-14
rs2435373	10	43693727	0	G	A	0.72403	0.988553	40.6683	1.80E-10	-0.0157483	0.00245651	41.0986	1.40E-10
rs10857472	10	50534599	0	G	A	0.549311	1	52.9944	3.30E-13	0.0159842	0.00219402	53.0761	3.20E-13
rs34927949	10	52668995	0	C	T	0.969305	1	29.3675	6.00E-08	-0.0348167	0.0063393	30.1642	4.00E-08
rs72791110	10	52744545	0	A	T	0.759803	0.997368	74.6937	5.50E-18	0.0228348	0.00256384	79.3256	5.30E-19
rs61849823	10	53290991	0	T	C	0.83569	0.981475	84.5143	3.80E-20	-0.0275475	0.00297448	85.7714	2.00E-20
rs7094004	10	61399418	0	A	G	0.832871	0.995638	72.6672	1.50E-17	-0.0250271	0.00293663	72.6311	1.60E-17
rs7084953	10	61755297	0	C	T	0.777193	0.997127	39.575	3.20E-10	-0.0169975	0.0026319	41.7095	1.10E-10
rs10994200	10	61863259	0	C	G	0.380379	0.992811	32.1954	1.40E-08	-0.0126772	0.00225443	31.6206	1.90E-08
rs4582919	10	62104776	0	T	C	0.489309	0.996919	51.8044	6.10E-13	-0.0158381	0.00219192	52.21	5.00E-13
rs9415635	10	63753482	0	A	G	0.658865	0.997992	48.7823	2.90E-12	-0.0160917	0.00231009	48.5227	3.30E-12
rs35482056	10	63893615	0	C	T	0.671489	0.994417	38.3667	5.90E-10	-0.014293	0.00233419	37.4952	9.20E-10
rs382424	10	64489774	0	T	C	0.395626	0.999605	68.6451	1.20E-16	0.0190452	0.00223429	72.6594	1.50E-17
rs7924036	10	65191645	0	G	T	0.496252	0.999716	117.672	2.00E-27	-0.0232693	0.00218857	113.043	2.10E-26
rs376566696	10	69956271	0	C	T	0.507846	0.994245	170.448	5.90E-39	-0.0283808	0.00219123	167.754	2.30E-38
rs117526327	10	70036064	0	C	T	0.960283	1	42.0916	8.70E-11	0.0374333	0.00558923	44.8551	2.10E-11
rs10998288	10	70331038	0	C	T	0.602616	0.998099	158.832	2.00E-36	-0.0286164	0.00223214	164.357	1.30E-37
rs72799516	10	70406518	0	A	T	0.954008	0.998695	31.8214	1.70E-08	-0.0296422	0.00521908	32.2576	1.40E-08
rs4148926	10	73737124	0	G	C	0.410428	0.99153	45.5709	1.50E-11	0.0148051	0.00222662	44.2111	2.90E-11
rs11595862	10	76856288	0	T	C	0.930706	0.975537	36.168	1.80E-09	0.0253998	0.00434423	34.1851	5.00E-09
rs7072873	10	77210191	0	C	T	0.461311	0.990234	37.8887	7.50E-10	0.013952	0.00219946	40.2383	2.20E-10
rs9663814	10	77738382	0	G	A	0.404169	0.983144	31.4921	2.00E-08	0.0125669	0.00224268	31.3993	2.10E-08
rs2165046	10	79552092	0	C	T	0.63467	0.997524	88.7738	4.40E-21	0.0212325	0.00227192	87.3406	9.10E-21
rs7916441	10	80925577	0	G	C	0.566831	0.999149	92.0112	8.60E-22	0.0209642	0.00220295	90.5623	1.80E-21
rs941873	10	81139462	0	G	A	0.541828	0.999521	231.124	3.40E-52	0.033459	0.00219334	232.709	1.50E-52
rs12767381	10	81240229	0	G	A	0.840249	0.990958	53.0268	3.30E-13	-0.0222808	0.00299822	55.2249	1.10E-13
rs77532868	10	88081438	0	C	T	0.946051	1	64.5677	9.30E-16	-0.038831	0.00482994	64.6357	9.00E-16
rs17096421	10	88820592	0	A	T	0.943046	0.969931	33.5359	7.00E-09	-0.0282192	0.00478095	34.8387	3.60E-09
rs806685	10	89765544	0	G	A	0.619567	0.983166	76.5995	2.10E-18	-0.019991	0.0022703	77.5365	1.30E-18
rs1935582	10	90192530	0	T	A	0.644022	0.996477	33.1453	8.60E-09	-0.0132697	0.00228501	33.7246	6.30E-09
rs10881893	10	92927267	0	A	G	0.820583	0.989884	32.1232	1.40E-08	-0.0162089	0.00285659	32.1968	1.40E-08
rs13675	10	93043858	0	T	C	0.78436	1	151.868	6.80E-35	-0.0330491	0.00265777	154.628	1.70E-35
rs1557116	10	93372126	0	C	T	0.728273	0.98061	58.8076	1.70E-14	-0.019196	0.00247966	59.929	9.80E-15
rs7916961	10	94997875	0	T	C	0.857823	0.989629	40.0792	2.40E-10	-0.019968	0.00314522	40.3059	2.20E-10
rs138461387	10	95062780	0	G	C	0.982393	0.872869	30.3081	3.70E-08	0.0487038	0.00887981	30.0828	4.10E-08
rs116454156	10	95347041	0	G	A	0.983561	1	39.4451	3.40E-10	-0.0538869	0.00858709	39.3798	3.50E-10
rs71482305	10	96119130	0	C	T	0.844785	0.999789	49.4935	2.00E-12	0.0210095	0.00301265	48.6335	3.10E-12
rs61856978	10	97941022	0	T	C	0.660476	0.996222	69.4881	7.70E-17	0.0189573	0.00230617	67.572	2.00E-16
rs115858856	10	98561043	0	A	G	0.901903	0.981584	49.5966	1.90E-12	-0.0261522	0.00370408	49.8489	1.70E-12
rs10882950	10	99278269	0	T	C	0.372888	0.990373	31.6188	1.90E-08	-0.0126958	0.00226882	31.3126	2.20E-08
rs1983864	10	100017453	0	T	G	0.661052	1	51.0446	9.00E-13	-0.016335	0.00230297	50.3105	1.30E-12
rs12354860	10	101902958	0	T	C	0.533058	0.983153	38.6546	5.10E-10	0.0135775	0.00220371	37.9605	7.20E-10
rs2489053	10	102353341	0	T	C	0.781769	0.994241	38.7887	4.70E-10	0.0165796	0.00264352	39.3355	3.60E-10
rs2181834	10	102661251	0	G	T	0.449537	0.99869	121.057	3.70E-28	-0.0242298	0.00219653	121.681	2.70E-28
rs7087664	10	103474098	0	T	G	0.32785	0.987753	39.3225	3.60E-10	0.014491	0.00233982	38.3561	5.90E-10
rs2281880	10	104269217	0	G	A	0.456122	1	166.004	5.50E-38	-0.0282488	0.00219297	165.935	5.70E-38
rs72841270	10	104642237	0	T	G	0.864671	0.997595	42.4979	7.10E-11	-0.021155	0.00319179	43.9296	3.40E-11
rs11596328	10	105493177	0	G	T	0.888836	0.984575	58.9272	1.60E-14	-0.0269773	0.00349417	59.6088	1.20E-14
rs2104598	10	114715598	0	G	A	0.475523	0.998148	47.9169	4.40E-12	0.0154637	0.00218925	49.8924	1.60E-12
rs73360281	10	114887817	0	A	G	0.936385	1	28.8558	7.80E-08	-0.0248164	0.00446792	30.851	2.80E-08
rs7076938	10	115789375	0	C	T	0.266103	0.99271	32.7183	1.10E-08	-0.0145429	0.00247821	34.4371	4.40E-09
rs646668	10	116138034	0	G	A	0.537718	0.982941	40.9104	1.60E-10	0.0141378	0.00220913	40.9564	1.60E-10
rs11198344	10	120031952	0	A	G	0.512511	0.990485	32.3158	1.30E-08	0.0123149	0.00219084	31.5964	1.90E-08
rs41314489	10	120514834	0	G	A	0.646074	0.993032	66.6681	3.20E-16	0.0184259	0.00228693	64.916	7.80E-16
rs11198820	10	120961043	0	G	C	0.896558	0.992746	39.2075	3.80E-10	-0.0225702	0.00359732	39.3653	3.50E-10
rs11198898	10	121118492	0	A	C	0.23671	0.990617	97.0403	6.80E-23	0.0252482	0.00257574	96.0854	1.10E-22
rs75356180	10	121657536	0	A	T	0.880122	0.993352	70.6053	4.40E-17	0.0285042	0.00336935	71.5689	2.70E-17
rs11199781	10	122882194	0	A	T	0.837327	0.981008	33.2335	8.20E-09	-0.0175746	0.0029837	34.6946	3.90E-09
rs2936853	10	123422004	0	T	C	0.0520844	0.996026	48.0243	4.20E-12	-0.0358875	0.00491386	53.3387	2.80E-13

rs11592105	10	123585371	0	T	A	0.744189	0.989215	37.5237	9.00E-10	-0.0150866	0.00251185	36.0741	1.90E-09
rs10082476	10	124164654	0	A	G	0.753144	0.997775	113.779	1.50E-26	0.0272104	0.00253484	115.231	7.00E-27
rs78305107	10	124197214	0	C	T	0.76711	0.994293	39.0668	4.10E-10	0.0165175	0.00259235	40.5975	1.90E-10
rs10510128	10	125060948	0	G	A	0.792335	0.994604	40.8924	1.60E-10	0.0173175	0.00270105	41.1063	1.40E-10
rs752116	10	126288957	0	C	T	0.53605	0.991931	66.9999	2.70E-16	0.0181377	0.00219615	68.2088	1.50E-16
rs12569940	10	126592684	0	T	C	0.859751	1	46.1438	1.10E-11	-0.0209876	0.00314403	44.5608	2.50E-11
rs1674896	10	127733174	0	G	C	0.609118	0.997284	51.8683	5.90E-13	0.0157341	0.00224091	49.2987	2.20E-12
rs7911018	10	131348554	0	C	T	0.390724	0.998193	31.7603	1.70E-08	-0.012774	0.00223875	32.5567	1.20E-08
rs9419387	10	133758358	0	G	A	0.592579	0.998454	32.0006	1.50E-08	-0.0126105	0.00222371	32.1596	1.40E-08
rs140988250	11	1489420	0	C	T	0.974181	0.903724	31.9567	1.60E-08	-0.0415952	0.00726007	32.825	1.00E-08
rs612652	11	1887216	0	T	C	0.416961	0.991018	34.2922	4.70E-09	0.0128964	0.00222046	33.7325	6.30E-09
rs217227	11	2014227	0	C	G	0.847673	0.991148	73.7046	9.10E-18	-0.0264767	0.00304769	75.4723	3.70E-18
rs114278107	11	2077056	0	T	G	0.814048	0.997279	65.5097	5.80E-16	0.0228912	0.00280728	66.4914	3.50E-16
rs35506085	11	2165576	0	G	A	0.815564	0.983997	181.644	2.10E-41	0.0383079	0.00283632	182.418	1.40E-41
rs9888189	11	2770777	0	C	T	0.855732	0.991584	192.059	1.10E-43	-0.0431298	0.00311768	191.377	1.60E-43
rs143840904	11	2813322	0	C	T	0.980282	0.937732	336.396	3.90E-75	0.148224	0.00810269	334.64	9.40E-75
rs116910736	11	2978772	0	T	C	0.978243	0.972521	32.6741	1.10E-08	-0.0432322	0.00757356	32.5848	1.10E-08
rs11042355	11	9465011	0	G	A	0.57272	0.995458	46.2185	1.10E-11	-0.0148067	0.00220964	44.9028	2.10E-11
rs2083717	11	10178135	0	T	C	0.445623	0.996537	88.5716	4.90E-21	0.0206791	0.00219927	88.4117	5.30E-21
rs10734190	11	12001587	0	T	C	0.152533	0.97016	50.9668	9.40E-13	-0.0224736	0.00308398	53.1035	3.20E-13
rs11022460	11	12663869	0	T	A	0.582201	0.989588	98.5472	3.20E-23	-0.0223975	0.00222345	101.471	7.30E-24
rs10832013	11	13295353	0	G	T	0.30485	0.999636	81.7425	1.60E-19	0.0212401	0.00236936	80.3625	3.10E-19
rs10832251	11	14418295	0	G	A	0.677349	0.988565	81.0396	2.20E-19	0.0209598	0.00234754	79.7164	4.30E-19
rs146128209	11	14683683	0	A	G	0.927904	0.990289	33.3882	7.50E-09	0.024382	0.00423995	33.0686	8.90E-09
rs117247884	11	14729856	0	T	G	0.984796	0.959109	29.8101	4.80E-08	0.0497032	0.00910324	29.811	4.80E-08
rs11600815	11	14797227	0	G	A	0.948091	0.952098	111.951	3.70E-26	-0.0535352	0.00504468	112.619	2.60E-26
rs11024127	11	17054270	0	G	A	0.725534	0.979055	55.9361	7.50E-14	-0.0185115	0.00246938	56.1965	6.60E-14
rs16934571	11	17673137	0	A	G	0.906128	0.991833	31.5277	2.00E-08	-0.0211808	0.00375054	31.8932	1.60E-08
rs2237920	11	17949838	0	A	C	0.607413	1	59.4711	1.20E-14	-0.0173229	0.0022329	60.1875	8.60E-15
rs7925445	11	18398958	0	A	G	0.443345	0.992962	53.6861	2.40E-13	-0.0159191	0.00220345	52.1948	5.00E-13
rs10832963	11	18664241	0	T	G	0.255124	0.995412	96.9812	7.00E-23	0.0249241	0.00250839	98.73	2.90E-23
rs72887634	11	26162722	0	A	T	0.905326	0.978705	40.7187	1.80E-10	0.024122	0.00376434	41.0628	1.50E-10
rs704660	11	30447998	0	C	T	0.590726	0.996095	90.0646	2.30E-21	-0.0208838	0.00222013	88.4834	5.10E-21
rs1718067	11	33759670	0	C	T	0.32374	1	30.695	3.00E-08	-0.0133922	0.00233159	32.9912	9.30E-09
rs62621409	11	36458997	0	A	G	0.957216	1	31.9421	1.60E-08	0.0296625	0.00538047	30.393	3.50E-08
rs7108028	11	45964993	0	A	C	0.339828	0.998477	36.8728	1.30E-09	-0.0141651	0.00229912	37.9589	7.20E-10
rs79728014	11	46062245	0	A	G	0.850512	0.99398	89.3308	3.30E-21	-0.0285721	0.00306947	86.6475	1.30E-20
rs1317149	11	47486885	0	C	T	0.649746	0.998938	163.641	1.80E-37	0.0292063	0.0022837	163.56	1.90E-37
rs7949044	11	49597334	0	C	T	0.357142	0.99824	33.9277	5.70E-09	0.0130219	0.00227714	32.7018	1.10E-08
rs58020986	11	57783639	0	A	C	0.717773	0.991817	38.2933	6.10E-10	0.014878	0.00243193	37.4271	9.50E-10
rs7927966	11	58376276	0	C	T	0.760488	0.997268	52.705	3.90E-13	-0.0187005	0.00256118	53.3122	2.80E-13
rs2727265	11	61609004	0	C	A	0.92355	0.997542	42.92	5.70E-11	0.026511	0.00411147	41.5773	1.10E-10
rs34894392	11	62374821	0	A	G	0.621777	0.997396	44.7362	2.30E-11	0.0153795	0.00225266	46.6114	8.70E-12
rs596002	11	65645354	0	A	G	0.20036	0.999435	72.3003	1.80E-17	-0.0228739	0.00272551	70.4344	4.80E-17
rs117807401	11	66237833	0	A	G	0.956322	0.926823	58.7231	1.80E-14	-0.0430097	0.00554002	60.2712	8.30E-15
rs117741368	11	66257508	0	G	C	0.978032	0.995231	31.4563	2.00E-08	-0.0425668	0.00745365	32.614	1.10E-08
rs7952436	11	67024534	0	C	T	0.917763	1	658.797	2.70E-145	0.101354	0.00397359	650.603	1.70E-143
rs1115051	11	67182383	0	A	G	0.935946	0.998521	40.1167	2.40E-10	-0.0276565	0.00445357	38.5637	5.30E-10
rs553714159	11	67420601	0	T	A	0.976138	0.826398	47.912	4.50E-12	0.0534619	0.00786577	46.1962	1.10E-11
rs17848255	11	68153710	0	C	T	0.843369	0.995134	34.7007	3.80E-09	-0.0175829	0.00301356	34.0427	5.40E-09
rs2513299	11	68410157	0	C	T	0.153874	0.982128	140.385	2.20E-32	-0.0356823	0.00305215	136.676	1.40E-31
rs10896415	11	68839334	0	G	A	0.638258	0.97055	85.7421	2.00E-20	0.0213425	0.00230521	85.7181	2.10E-20
rs59374155	11	68940308	0	G	C	0.904966	0.997383	31.7506	1.80E-08	-0.0211401	0.00372559	32.1976	1.40E-08
rs35769712	11	69262591	0	T	C	0.886273	0.991873	79.6073	4.60E-19	-0.031122	0.00345189	81.2873	2.00E-19
rs28532161	11	69791513	0	A	C	0.516763	1	31.4178	2.10E-08	0.0126313	0.00218509	33.4163	7.40E-09
rs61886442	11	69912037	0	C	T	0.62105	0.994258	94.8039	2.10E-22	0.0223514	0.00225918	97.8836	4.40E-23
rs2509180	11	69983292	0	G	A	0.87826	0.982773	38.8514	4.60E-10	0.0210124	0.00336955	38.8874	4.50E-10
rs36005373	11	74288717	0	T	C	0.74601	0.992651	85.3917	2.40E-20	-0.0230473	0.00252027	83.6271	6.00E-20
rs545304	11	74488404	0	A	T	0.778689	0.999569	71.0992	3.40E-17	0.0226824	0.00263084	74.3348	6.60E-18
rs606452	11	75276178	0	A	C	0.1398	1	269.254	1.60E-60	0.0518848	0.00314789	271.669	4.90E-61
rs4625500	11	76164959	0	T	G	0.561408	0.996005	30.7	3.00E-08	0.0123066	0.00220169	31.2441	2.30E-08
rs2051484	11	77595080	0	C	T	0.894165	0.995986	46.4481	9.40E-12	0.0232916	0.00355996	42.8064	6.00E-11
rs17148514	11	85526399	0	C	T	0.758397	0.989445	72.8584	1.40E-17	0.0222434	0.00256622	75.1303	4.40E-18
rs1875564	11	89079321	0	G	C	0.911006	0.977071	37.2361	1.00E-09	0.0234464	0.00389175	36.2962	1.70E-09
rs11018921	11	89953315	0	T	C	0.773442	0.994107	40.4119	2.10E-10	-0.0164075	0.0026162	39.3321	3.60E-10
rs7729	11	94865454	0	T	G	0.358322	0.998387	34.2052	5.00E-09	-0.0132128	0.00228165	33.5345	7.00E-09
rs10765754	11	95348025	0	A	G	0.650279	0.985043	57.9197	2.70E-14	-0.0172007	0.00230761	55.5606	9.10E-14
rs586143	11	100968530	0	C	T	0.837977	0.981273	40.8887	1.60E-10	0.0188345	0.00299586	39.5244	3.20E-10
rs17728834	11	110237458	0	A	T	0.761938	0.993904	43.6517	3.90E-11	-0.0169914	0.00257013	43.707	3.80E-11
rs12269901	11	116973929	0	G	C	0.714432	1	49.1185	2.40E-12	0.0170599	0.00241504	49.9003	1.60E-12
rs1064939	11	118396331	0	A	T	0.977565	0.978917	48.705	3.00E-12	-0.0519156	0.00745986	48.4323	3.40E-12
rs568688	11	118598612	0	T	G	0.603713	0.994377	77.1437	1.60E-18	-0.0195681	0.00224219	76.165	2.60E-18
rs4614	11	118952371	0	A	G	0.593816	1	33.8245	6.00E-09	0.0127286	0.00222504	32.7251	1.10E-08
rs12800456	11	120063441	0	A	G	0.685519	0.983632	34.6168	4.00E-09	-0.0140784	0.00237222	35.2203	2.90E-09
rs76693355	11	120292477	0	T	C	0.883741	0.995085	100.787	1.00E-23	0.0341532	0.00341171	100.212	1.40E-23
rs684282	11	120366078	0	T	A	0.844431	0.979717	41.4946	1.20E-10	-0.0194851	0.00304409	40.9724	1.50E-10
rs61395312	11	121942503	0	A	C	0.775909	0.993733	30.2351	3.80E-08	0.0146478	0.00262856	31.0533	2.50E-08
rs7102462	11	122828767	0	C	G	0.432318	0.996476	70.0585	5.80E-17	-0.0184607	0.00220946	69.8111	6.50E-17
rs12222197	11	125825224	0	G	T	0.418533	0.991254	67.3685	2.30E-16	-0.0181044	0.00222396	66.2698	3.90E-16
rs11606126	11	126016485	0	T	A	0.686406	0.994366	52.8531	3.60E-13	-0.0175051	0.00235804	55.1098	1.10E-13
rs2282580	11	126081403	0	T	C	0.689251	1	52.7319	3.80E-13	0.0172876	0.00235805	53.7482	2.30E-13
rs6590199	11	126235667	0	G	A	0.84203	0.985553	33.2565	8.10E-09	-0.0170277	0.00301175	31.9649	1.60E-08
rs11221158	11	127980209	0	C	T	0.774518	0.999196	45.6113	1.40E-11	0.0174001	0.00261622	44.2338	2.90E-11

rs11221356	11	128443833	0	A	C	0.539896	1	32.4959	1.20E-08	0.0120416	0.00218982	30.2381	3.80E-08
rs7941765	11	128499000	0	T	C	0.496011	0.992971	54.8219	1.30E-13	-0.0160094	0.00219202	53.3409	2.80E-13
rs648193	11	128667802	0	C	T	0.670226	0.996274	72.9316	1.30E-17	0.0196903	0.00232538	71.6996	2.50E-17
rs6590370	11	129119886	0	C	T	0.169215	0.99932	41.3732	1.30E-10	0.0184213	0.00291435	39.9539	2.60E-10
rs11222084	11	130273230	0	A	T	0.629875	1	41.6054	1.10E-10	0.0144508	0.00226142	40.8342	1.70E-10
rs12811171	12	580772	0	C	T	0.649083	0.996341	135.085	3.20E-31	-0.0265996	0.00227511	136.693	1.40E-31
rs1052454	12	672351	0	C	A	0.643597	1	37.8976	7.50E-10	-0.0145407	0.00226738	41.1265	1.40E-10
rs2968887	12	1262501	0	A	G	0.726384	0.997628	36.7637	1.30E-09	-0.0144814	0.00243394	35.3998	2.70E-09
rs12304504	12	1439642	0	C	G	0.941665	0.997058	50.4744	1.20E-12	0.0326756	0.00463406	49.7192	1.80E-12
rs16930370	12	3387697	0	T	C	0.827155	0.99015	72.2205	1.90E-17	-0.0239486	0.00287958	69.1674	9.00E-17
rs71458092	12	4360951	0	A	G	0.944729	0.904805	47.0004	7.10E-12	0.0336234	0.00499243	45.3586	1.60E-11
rs76895963	12	4384844	0	T	G	0.979213	0.82244	533.648	4.50E-118	-0.194769	0.00838283	539.829	2.10E-119
rs3217860	12	4399050	0	A	G	0.752021	0.987125	47.9192	4.40E-12	0.017522	0.0025255	48.1363	4.00E-12
rs10849094	12	4676899	0	C	G	0.938043	1	32.0622	1.50E-08	-0.0256839	0.00449177	32.6953	1.10E-08
rs2900208	12	11878464	0	C	A	0.645766	0.995708	171.804	3.00E-39	-0.0300054	0.00227167	174.466	7.80E-40
rs35756741	12	12868701	0	C	T	0.907576	0.986493	125.019	5.00E-29	0.0422621	0.00376579	125.947	3.20E-29
rs2066827	12	12871099	0	T	G	0.767655	1	88.0061	6.50E-21	0.023887	0.002565	86.7259	1.20E-20
rs11055215	12	13202294	0	A	G	0.418117	0.994626	33.9175	5.70E-09	-0.0129878	0.00220467	34.7041	3.80E-09
rs75031954	12	14431168	0	C	A	0.977941	1	34.327	4.70E-09	-0.0436965	0.00738551	35.0052	3.30E-09
rs11055965	12	14552845	0	G	C	0.566616	0.999661	84.3527	4.10E-20	-0.0203205	0.00218676	86.351	1.50E-20
rs7955800	12	14914045	0	T	C	0.450686	0.994297	33.4706	7.20E-09	0.0124391	0.00218731	32.3416	1.30E-08
rs7978269	12	15379246	0	T	C	0.677728	0.993777	34.1839	5.00E-09	0.0137808	0.00232635	35.091	3.10E-09
rs2160515	12	16753965	0	A	G	0.56222	0.982294	38.7795	4.70E-10	-0.0133019	0.00220558	36.3735	1.60E-09
rs6416208	12	19772987	0	T	C	0.0632908	1	31.7103	1.80E-08	-0.0246067	0.00445463	30.5128	3.30E-08
rs4762752	12	20543299	0	G	A	0.219218	0.995937	55.9369	7.50E-14	-0.0201483	0.00262464	58.9301	1.60E-14
rs74334253	12	20685419	0	A	C	0.951692	0.992282	33.2545	8.10E-09	-0.0285612	0.00507777	31.6379	1.90E-08
rs12426383	12	20722854	0	A	G	0.866847	0.984988	43.5925	4.00E-11	-0.0212603	0.00321591	43.705	3.80E-11
rs10770699	12	20832321	0	A	G	0.413203	0.996727	92.409	7.00E-22	0.0218288	0.00220601	97.9143	4.40E-23
rs2417969	12	21410978	0	C	T	0.595311	0.99048	30.6281	3.10E-08	0.0121283	0.00221665	29.9371	4.50E-08
rs73079245	12	21840631	0	G	A	0.951882	0.927654	34.9767	3.30E-09	-0.0315311	0.00526092	35.9214	2.10E-09
rs7134283	12	24071748	0	G	A	0.716294	0.994093	68.7277	1.10E-16	0.0197684	0.00241304	67.1139	2.60E-16
rs7302982	12	24201324	0	T	G	0.782167	0.996629	102.972	3.40E-24	-0.027066	0.00262904	105.987	7.40E-25
rs4963646	12	26228883	0	G	A	0.704267	0.997347	33.9672	5.60E-09	0.0138524	0.00238008	33.8741	5.90E-09
rs11048454	12	26460045	0	C	A	0.76429	0.998003	98.0813	4.00E-23	0.0256212	0.00255707	100.396	1.20E-23
rs12366821	12	27478930	0	T	G	0.982065	0.918319	37.6172	8.60E-10	-0.0497898	0.00853591	34.0237	5.40E-09
rs10492367	12	28014970	0	G	T	0.812001	0.993703	36.5562	1.50E-09	0.0169178	0.00278273	36.9611	1.20E-09
rs16932574	12	28214628	0	G	C	0.934127	0.976862	31.9132	1.60E-08	-0.0248986	0.00442016	31.7301	1.80E-08
rs11049708	12	28697814	0	T	C	0.706803	0.994389	299.432	4.40E-67	0.0412509	0.00238833	298.319	7.70E-67
rs1021312	12	29031496	0	C	G	0.532973	1	42.576	6.80E-11	-0.0139789	0.00217217	41.4155	1.20E-10
rs1156242	12	29523957	0	T	C	0.714757	0.994991	96.0768	1.10E-22	-0.0227942	0.00240768	89.6296	2.90E-21
rs7304221	12	30899480	0	T	C	0.496527	0.98387	39.3127	3.60E-10	-0.0134781	0.00218758	37.9599	7.20E-10
rs7974437	12	31735697	0	G	A	0.309556	0.995548	42.2489	8.00E-11	0.015438	0.00235131	43.1085	5.20E-11
rs2625905	12	34081564	0	T	C	0.172964	0.998004	45.5815	1.50E-11	-0.0193801	0.00286598	45.7264	1.40E-11
rs138198562	12	46429309	0	T	C	0.951392	0.951111	30.0469	4.20E-08	-0.0286675	0.00517027	30.7435	2.90E-08
rs2241960	12	46580618	0	A	G	0.725788	1	30.0207	4.30E-08	-0.0136251	0.00242983	31.443	2.10E-08
rs2045556	12	46673433	0	A	G	0.32156	0.991552	96.4643	9.10E-23	-0.0231653	0.00233026	98.8253	2.80E-23
rs148277035	12	46939516	0	C	T	0.950232	0.998821	32.6281	1.10E-08	-0.0286498	0.00498168	33.0744	8.90E-09
rs2711718	12	47372706	0	T	G	0.773963	0.992192	34.8093	3.60E-09	-0.0153344	0.00260361	34.6881	3.90E-09
rs76002385	12	48385695	0	G	A	0.923942	0.997356	64.0872	1.20E-15	0.0328283	0.00409725	64.1964	1.10E-15
rs77419573	12	48720810	0	C	T	0.970569	0.988889	32.8054	1.00E-08	0.0368369	0.00644744	32.643	1.10E-08
rs60613973	12	50058261	0	G	T	0.930078	0.999348	46.3988	9.60E-12	-0.028873	0.0042553	46.0389	1.20E-11
rs865489	12	51207414	0	T	C	0.68627	0.999912	79.9434	3.90E-19	-0.0211551	0.00233541	82.0545	1.30E-19
rs6580810	12	51610478	0	C	T	0.247895	0.987364	39.5491	3.20E-10	-0.0160267	0.00252587	40.2592	2.20E-10
rs11170394	12	53463972	0	T	C	0.913426	0.989504	75.3154	4.00E-18	-0.0328409	0.00388458	71.4727	2.80E-17
rs7311238	12	54020492	0	G	A	0.818135	1	44.0832	3.10E-11	0.0189179	0.00281166	45.271	1.70E-11
rs1822438	12	54342326	0	A	C	0.219248	0.999021	57.3169	3.70E-14	-0.0201804	0.00261951	59.3498	1.30E-14
rs2695788	12	56697110	0	G	A	0.0675483	0.9997	66.7175	3.10E-16	0.0350866	0.00431791	66.029	4.40E-16
rs324021	12	57445845	0	A	C	0.539716	0.994469	45.566	1.50E-11	0.0148062	0.00218116	46.0801	1.10E-11
rs11172371	12	58286188	0	C	T	0.658101	0.986601	78.2284	9.20E-19	0.0205928	0.00230643	79.7165	4.30E-19
rs11614580	12	59966623	0	G	A	0.689043	0.982292	68.0289	1.60E-16	-0.0198125	0.00236151	70.3875	4.90E-17
rs7310196	12	63036587	0	A	T	0.8343	0.984293	30.5126	3.30E-08	0.0166122	0.00293463	32.0442	1.50E-08
rs6581627	12	65719229	0	G	C	0.478148	0.996108	143.536	4.50E-33	0.0264447	0.00217531	147.787	5.30E-34
rs144699164	12	65966791	0	G	A	0.975356	0.979372	38.763	4.80E-10	0.0444078	0.00706724	39.4839	3.30E-10
rs11175904	12	66139169	0	T	G	0.936019	0.981288	49.004	2.60E-12	-0.0312167	0.00447447	48.6734	3.00E-12
rs11175915	12	66169943	0	C	G	0.926794	1	60.207	8.50E-15	-0.0321429	0.00416373	59.5943	1.20E-14
rs150236026	12	66183420	0	A	G	0.987778	0.850405	54.0403	2.00E-13	0.0749973	0.0106969	49.1559	2.40E-12
rs191372960	12	66328598	0	A	G	0.989685	0.918816	46.7867	7.90E-12	0.0760461	0.0111866	46.2123	1.10E-11
rs7306710	12	66376091	0	T	C	0.480472	0.987001	827.121	6.80E-182	0.0628036	0.00218771	824.12	3.10E-181
rs7962295	12	66409132	0	T	C	0.575889	0.991489	81.157	2.10E-19	-0.0199712	0.00220324	82.1646	1.30E-19
rs1168737	12	66568725	0	T	C	0.277911	0.994607	89.5166	3.00E-21	-0.0231927	0.00242886	91.1796	1.30E-21
rs1882281	12	67850140	0	C	T	0.468886	0.979139	38.4894	5.50E-10	-0.0132212	0.00219701	36.214	1.80E-09
rs1362463	12	68205491	0	G	C	0.175821	0.997414	45.1452	1.80E-11	-0.0193505	0.00285172	46.0437	1.20E-11
rs77105239	12	69037698	0	T	C	0.975465	0.997661	35.3647	2.70E-09	0.040374	0.00702287	33.0502	9.00E-09
rs57954211	12	69748397	0	C	A	0.529825	0.999231	40.1931	2.30E-10	-0.0138476	0.00217738	40.4465	2.00E-10
rs10748128	12	69827658	0	G	T	0.655475	1	255.211	1.90E-57	-0.0365222	0.00228639	255.16	1.90E-57
rs10879039	12	70290921	0	C	T	0.724398	0.997613	34.207	5.00E-09	0.0142401	0.00243065	34.3229	4.70E-09
rs78043843	12	71401558	0	C	A	0.713068	0.98944	30.5883	3.20E-08	-0.0137199	0.00241549	32.2618	1.30E-08
rs2369463	12	77432523	0	T	C	0.829612	0.981983	96.4403	9.20E-23	0.0281878	0.00291162	93.7243	3.60E-22
rs141956082	12	77446459	0	G	T	0.978806	0.914587	54.4569	1.60E-13	-0.0579342	0.00787378	54.1381	1.90E-13
rs310796	12	77453226	0	G	T	0.318769	0.995681	118.088	1.70E-27	-0.025354	0.00233745	117.654	2.10E-27
rs12582761	12	84952950	0	G	A	0.825044	0.999304	37.756	8.00E-10	-0.0172017	0.00285925	36.1944	1.80E-09
rs17018712	12	91496137	0	T	C	0.862957	1	30.4083	3.50E-08	-0.0174481	0.00315304	30.6224	3.10E-08
rs10777380	12	92526713	0	C	A	0.624865	0.99448	31.0618	2.50E-08	0.0122921	0.00224846	29.8871	4.60E-08

rs141573141	12	93892825	0	G	C	0.495721	0.999483	36.9784	1.20E-09	-0.0130922	0.002171	36.3665	1.60E-09
rs9634212	12	93993266	0	C	A	0.778873	0.991347	481.938	8.10E-107	-0.0578843	0.00262779	485.224	1.60E-107
rs7953280	12	94136009	0	G	C	0.49303	0.991135	320.504	1.10E-71	0.0395598	0.00218427	328.017	2.60E-73
rs7953146	12	94229728	0	G	T	0.802459	0.98562	47.2142	6.40E-12	0.0185907	0.00274566	45.8455	1.30E-11
rs7312795	12	94312891	0	G	A	0.833133	0.991301	84.3267	4.20E-20	0.02686	0.00292219	84.4882	3.90E-20
rs76371240	12	94313754	0	C	T	0.960809	0.991109	46.9719	7.20E-12	-0.0380988	0.00561807	45.9884	1.20E-11
rs78380806	12	94438293	0	G	A	0.979721	0.895235	33.1753	8.40E-09	-0.0467315	0.00813857	32.9703	9.40E-09
rs301012	12	95871029	0	A	G	0.45439	0.997832	36.6169	1.40E-09	0.0131669	0.00218149	36.4302	1.60E-09
rs61938858	12	96676943	0	G	A	0.713207	0.994121	35.0307	3.20E-09	-0.0144108	0.0024064	35.8624	2.10E-09
rs4373984	12	97792587	0	C	T	0.471841	0.998931	37.4253	9.50E-10	0.0135609	0.00217602	38.8378	4.60E-10
rs10860328	12	98781089	0	T	G	0.80009	0.975647	33.8612	5.90E-09	-0.0160039	0.00274366	34.0243	5.40E-09
rs1501348	12	101894282	0	C	T	0.420833	0.99381	29.0896	6.90E-08	-0.0121777	0.00220728	30.4378	3.40E-08
rs55764824	12	102182042	0	C	T	0.901786	0.995175	38.3824	5.80E-10	-0.0232266	0.00365755	40.3265	2.10E-10
rs117081218	12	102339359	0	G	A	0.96308	0.938008	90.1997	2.20E-21	0.0573951	0.00594335	93.2579	4.60E-22
rs7305516	12	102382052	0	A	G	0.505721	0.983456	160.46	9.00E-37	0.0277421	0.00218695	160.917	7.10E-37
rs78508617	12	102540122	0	G	A	0.98576	0.997871	170.619	5.40E-39	0.119453	0.00915466	170.258	6.50E-39
rs368746845	12	102540754	0	G	A	0.807694	0.980116	74.4567	6.20E-18	-0.0242849	0.00278612	75.9757	2.90E-18
rs703593	12	103064247	0	A	G	0.518571	0.997862	113.55	1.60E-26	0.0238038	0.00217418	119.868	6.80E-28
rs144055372	12	103145175	0	C	T	0.972147	0.929626	54.3606	1.70E-13	-0.0514459	0.00683609	56.6352	5.20E-14
rs11614216	12	103159604	0	A	G	0.933034	1	33.8473	6.00E-09	0.025396	0.0043386	34.2634	4.80E-09
rs78812993	12	103175170	0	G	C	0.948137	0.972879	88.253	5.80E-21	0.0472368	0.00496163	90.6386	1.70E-21
rs61943173	12	103296705	0	T	A	0.93075	0.978869	30.668	3.10E-08	-0.0237149	0.00431531	30.2009	3.90E-08
rs12305866	12	104842117	0	C	T	0.945386	0.994244	42.7763	6.10E-11	0.0310469	0.00479533	41.918	9.50E-11
rs1148422	12	106640981	0	G	A	0.386467	0.995879	29.5094	5.60E-08	-0.0123868	0.00223579	30.6944	3.00E-08
rs34762209	12	106722466	0	T	C	0.72851	0.993812	29.0355	7.10E-08	0.0136435	0.0024466	31.0974	2.50E-08
rs7977765	12	107205390	0	A	G	0.762793	0.999641	128.044	1.10E-29	0.0288728	0.00255425	127.777	1.30E-29
rs11836200	12	108146472	0	A	G	0.548178	0.998987	32.7417	1.10E-08	-0.012425	0.00217994	32.4866	1.20E-08
rs3184504	12	111884608	0	T	C	0.483383	1	69.6225	7.20E-17	-0.0187547	0.002173	74.4903	6.10E-18
rs1061651	12	115108361	0	T	C	0.735848	0.99882	41.9225	9.50E-11	-0.0161256	0.00246495	42.7973	6.10E-11
rs780314	12	116293945	0	A	G	0.909542	0.995959	33.8848	5.80E-09	0.0219154	0.00379403	33.3655	7.60E-09
rs73196099	12	116419017	0	C	T	0.743335	0.997211	42.2276	8.10E-11	0.015998	0.00249172	41.2222	1.40E-10
rs7973240	12	117408148	0	T	C	0.146729	0.998961	64.1779	1.10E-15	-0.0246982	0.0030701	64.718	8.60E-16
rs4448779	12	118419333	0	A	G	0.463348	0.99269	29.4492	5.70E-08	0.0122259	0.00218598	31.2802	2.20E-08
rs76929617	12	120867798	0	A	G	0.960966	0.994293	103.564	2.50E-24	0.0576137	0.00561899	105.132	1.10E-24
rs4767938	12	121261162	0	C	T	0.371314	0.992814	60.6128	6.90E-15	0.0175163	0.00225295	60.448	7.60E-15
rs28969479	12	121622641	0	G	A	0.987829	0.973293	45.2623	1.70E-11	0.0688991	0.0100418	47.0768	6.80E-12
rs148159011	12	122130320	0	G	A	0.959062	0.994147	44.8167	2.20E-11	-0.0360766	0.0054913	43.1621	5.00E-11
rs12230227	12	122490833	0	C	T	0.555862	0.992178	100.85	9.90E-24	-0.0223956	0.00219446	104.153	1.90E-24
rs10773208	12	122970156	0	T	C	0.25511	0.999485	134.337	4.60E-31	-0.0290012	0.0024919	135.447	2.60E-31
rs551692377	12	123135572	0	G	C	0.984669	0.615363	42.1292	8.50E-11	-0.0744983	0.0113108	43.3815	4.50E-11
rs12366785	12	123622449	0	A	G	0.973086	0.927093	32.5696	1.10E-08	0.0405551	0.00696934	33.8616	5.90E-09
rs11562637	12	123897747	0	A	C	0.196711	0.988578	320.637	1.10E-71	0.0489797	0.00275029	317.156	6.00E-71
rs7976110	12	124249818	0	G	A	0.690611	0.977335	45.375	1.60E-11	-0.0155621	0.00237899	42.791	6.10E-11
rs7309216	12	124567352	0	C	A	0.786907	0.996984	62.4523	2.70E-15	-0.0206143	0.0026526	60.3939	7.80E-15
rs7295354	12	124777480	0	C	T	0.6901	0.994719	75.477	3.70E-18	-0.0203904	0.00234942	75.3233	4.00E-18
rs2229840	12	124826462	0	C	T	0.840371	1	147.517	6.10E-34	-0.0351003	0.00296488	140.155	2.50E-32
rs885389	12	131621762	0	A	G	0.332748	1	54.1116	1.90E-13	0.0170268	0.0023027	54.6756	1.40E-13
rs6598200	12	132584186	0	G	A	0.841315	0.99801	40.3275	2.10E-10	-0.0184302	0.00297244	38.4444	5.60E-10
rs75174460	12	133486532	0	T	C	0.924841	0.979075	32.728	1.10E-08	-0.0239334	0.00416405	33.0351	9.10E-09
rs9579911	13	21211576	0	C	G	0.920973	0.994188	32.9043	9.70E-09	0.0234483	0.00407998	33.0299	9.10E-09
rs61954226	13	21501422	0	T	C	0.831574	0.982672	40.9129	1.60E-10	-0.01868	0.00295855	39.8655	2.70E-10
rs2770928	13	21562832	0	C	T	0.114506	1	75.5065	3.60E-18	-0.0298663	0.00345089	74.9033	4.90E-18
rs76750172	13	28395297	0	C	T	0.975987	1	31.4279	2.10E-08	-0.0406146	0.00718856	31.9213	1.60E-08
rs11618507	13	30172751	0	G	T	0.773019	0.994093	52.7469	3.80E-13	-0.0190477	0.0026278	52.5415	4.20E-13
rs1018800	13	33198176	0	A	T	0.640521	0.992978	61.947	3.50E-15	-0.0182774	0.00229711	63.309	1.80E-15
rs9575910	13	36893461	0	C	G	0.735427	0.975104	42.4289	7.30E-11	0.0162586	0.00252057	41.6072	1.10E-10
rs3922615	13	39549315	0	G	A	0.907409	0.980799	45.7292	1.40E-11	0.025912	0.00382127	45.9819	1.20E-11
rs9548943	13	40390058	0	C	T	0.385042	0.992283	38.2824	6.10E-10	0.0141649	0.00226235	39.2019	3.80E-10
rs2755237	13	41109429	0	A	C	0.851161	1	49.859	1.70E-12	0.0217412	0.00308246	49.7479	1.70E-12
rs7996228	13	41281731	0	C	T	0.699344	0.998368	65.9983	4.50E-16	0.0194313	0.00239146	66.0206	4.50E-16
rs347389	13	42766823	0	T	A	0.606123	0.999219	37.3492	9.90E-10	0.0139072	0.00224679	38.3138	6.00E-10
rs6561319	13	47112120	0	C	A	0.366708	0.996377	51.1886	8.40E-13	-0.0162748	0.00227984	50.9591	9.40E-13
rs9568025	13	48801876	0	C	T	0.762998	0.986875	33.4897	7.20E-09	-0.0154109	0.00259801	35.1863	3.00E-09
rs9316467	13	50193273	0	G	A	0.885439	0.997629	34.6455	4.00E-09	0.0201126	0.0034454	34.0768	5.30E-09
rs7338963	13	50467338	0	A	G	0.799412	0.988451	134.681	3.90E-31	0.0316355	0.00275446	131.909	1.60E-30
rs113986155	13	50521910	0	G	A	0.939594	0.998898	117.812	1.90E-27	0.0498451	0.00460358	117.234	2.60E-27
rs141391621	13	50640969	0	G	C	0.978802	0.971286	37.4932	9.20E-10	-0.0466867	0.00773135	36.4649	1.60E-09
rs41284816	13	50655989	0	G	T	0.980978	0.957907	571.507	2.60E-126	-0.195173	0.0082076	565.466	5.40E-125
rs73494012	13	50674618	0	C	T	0.985826	0.99777	40.1372	2.40E-10	0.0591635	0.00928694	40.5847	1.90E-10
rs73196764	13	50715726	0	G	C	0.973005	0.993814	70.4802	4.60E-17	-0.0558964	0.00679038	67.761	1.80E-16
rs3116602	13	51111355	0	T	G	0.784548	1	621.829	3.00E-137	0.0665749	0.0026667	623.265	1.50E-137
rs2796881	13	51290025	0	T	C	0.843342	0.988746	85.667	2.10E-20	0.0282583	0.00303763	86.5407	1.40E-20
rs71437879	13	53222628	0	C	T	0.919637	0.994379	33.7698	6.20E-09	-0.0236157	0.00404293	34.1201	5.20E-09
rs1582140	13	68687608	0	T	A	0.781738	0.99565	32.6564	1.10E-08	-0.01468	0.00266513	30.3401	3.60E-08
rs12431227	13	73619288	0	C	T	0.819906	0.992966	50.6601	1.10E-12	0.0204309	0.00286638	50.8051	1.00E-12
rs4885084	13	73851888	0	T	C	0.318318	0.999346	50.9335	9.60E-13	-0.0169564	0.00235905	51.6645	6.60E-13
rs3818416	13	78474468	0	A	C	0.235599	0.99561	49.218	2.30E-12	-0.0179223	0.00259679	47.6333	5.10E-12
rs9574556	13	80646366	0	G	C	0.793733	0.99138	49.0924	2.40E-12	-0.019027	0.0027249	48.7576	2.90E-12
rs35848816	13	85914975	0	G	A	0.622315	0.995958	33.4348	7.40E-09	-0.0130038	0.00227302	32.7289	1.10E-08
rs9602899	13	86538071	0	C	G	0.625561	0.998053	31.5549	1.90E-08	0.0130135	0.00227327	32.7708	1.00E-08
rs188265	13	91821356	0	A	C	0.814426	0.993885	36.3554	1.60E-09	0.0166669	0.00283442	34.5766	4.10E-09
rs7319045	13	92024574	0	A	G	0.369321	1	184.421	5.20E-42	0.0308595	0.00227475	184.039	6.40E-42
rs7331504	13	99560396	0	C	G	0.26646	0.998324	40.7524	1.70E-10	0.015943	0.00248545	41.1462	1.40E-10

rs9300607	13	101223459	0	A	C	0.519679	0.993106	48.1594	3.90E-12	0.0153677	0.00220375	48.6288	3.10E-12
rs6492374	13	112238664	0	G	C	0.56113	0.99613	42.8705	5.80E-11	-0.0143077	0.00221886	41.5795	1.10E-10
rs7994573	13	115008388	0	T	C	0.765277	0.998483	90.546	1.80E-21	0.0248981	0.00259333	92.1759	7.90E-22
rs8019890	14	21538067	0	C	A	0.46876	0.970882	92.1979	7.80E-22	-0.0216822	0.00223147	94.4117	2.60E-22
rs28663442	14	21921225	0	C	T	0.823687	0.980419	106.631	5.40E-25	-0.030014	0.00290723	106.583	5.50E-25
rs45528934	14	23793305	0	C	T	0.837575	0.997249	148.646	3.40E-34	-0.0360991	0.00297612	147.127	7.40E-34
rs875908	14	23907608	0	C	G	0.357617	1	55.5883	8.90E-14	-0.0169881	0.00228769	55.1434	1.10E-13
rs1046584	14	24785784	0	C	T	0.886845	0.991413	50.7557	1.00E-12	0.0247681	0.00347507	50.7994	1.00E-12
rs61998517	14	24797976	0	C	T	0.95781	0.935806	47.4823	5.60E-12	0.0385843	0.00564437	46.7293	8.10E-12
rs36226649	14	24835500	0	T	C	0.93316	1	117.319	2.40E-27	-0.0478384	0.00439661	118.39	1.40E-27
rs8904	14	35871217	0	G	A	0.637172	1	64.8176	8.20E-16	0.0180851	0.00228035	62.8987	2.20E-15
rs1169031	14	36252516	0	G	A	0.315653	0.984453	51.9947	5.60E-13	0.017012	0.00237797	51.1796	8.40E-13
rs4899401	14	37004549	0	A	G	0.44619	0.994469	47.1483	6.60E-12	0.0150888	0.00221398	46.4473	9.40E-12
rs10131337	14	37144516	0	C	T	0.755337	0.990533	53.4143	2.70E-13	-0.0186625	0.00256419	52.9716	3.40E-13
rs10483623	14	54090077	0	T	G	0.794412	0.991903	33.8176	6.10E-09	0.0159821	0.00272078	34.505	4.30E-09
rs4901534	14	55198024	0	G	A	0.443929	1	44.5319	2.50E-11	0.0147624	0.00221296	44.5006	2.50E-11
rs12586289	14	55262780	0	G	T	0.429622	0.99959	63.0827	2.00E-15	-0.0174412	0.0022184	61.812	3.80E-15
rs74502136	14	55770381	0	A	T	0.93312	0.947625	38.047	6.90E-10	-0.0273241	0.00451685	36.5949	1.50E-09
rs12892257	14	58732748	0	G	A	0.415895	0.996641	50.0473	1.50E-12	-0.0157283	0.00222926	49.7782	1.70E-12
rs150380031	14	60280825	0	T	C	0.984331	0.91187	36.3979	1.60E-09	-0.0554937	0.00925921	35.9202	2.10E-09
rs10483727	14	61072875	0	T	C	0.388398	1	394.95	6.90E-88	0.0450268	0.0022534	399.268	7.90E-89
rs72722280	14	61327987	0	T	C	0.982411	0.938376	31.2482	2.30E-08	0.0479236	0.00860169	31.0407	2.50E-08
rs12882898	14	61529501	0	C	T	0.924036	0.975552	46.5965	8.70E-12	0.0288621	0.00418842	47.485	5.50E-12
rs112631611	14	63835494	0	G	C	0.929439	0.990348	35.6806	2.30E-09	0.0260284	0.00430556	36.5458	1.50E-09
rs2987983	14	64763653	0	A	G	0.686795	0.992741	30.9836	2.60E-08	0.0129987	0.00237214	30.0277	4.30E-08
rs7147987	14	65538131	0	A	G	0.539109	0.99177	196.096	1.50E-44	0.0305477	0.00220953	191.144	1.80E-43
rs1951631	14	68717529	0	C	T	0.856214	0.997847	57.1489	4.00E-14	0.0238414	0.00313178	57.9534	2.70E-14
rs3784122	14	68915533	0	T	C	0.875455	0.998199	39.2549	3.70E-10	-0.0204338	0.00331848	37.916	7.40E-10
rs11629144	14	69131593	0	G	T	0.759402	0.992338	31.4202	2.10E-08	0.0144629	0.00257345	31.5848	1.90E-08
rs1547088	14	70413046	0	A	G	0.634923	0.991804	82.7162	9.50E-20	-0.0210632	0.00228701	84.8227	3.30E-20
rs186973720	14	70589662	0	G	A	0.986721	0.94508	28.2183	1.10E-07	0.0542559	0.00985377	30.3172	3.70E-08
rs1980413	14	73736323	0	G	C	0.819008	0.998937	58.3461	2.20E-14	0.0217864	0.00284825	58.5079	2.00E-14
rs862045	14	74984368	0	A	G	0.342877	0.997246	116.701	3.30E-27	-0.0252074	0.0023125	118.82	1.10E-27
rs10139746	14	75040338	0	A	G	0.450651	0.998313	125.062	4.90E-29	0.0245814	0.00220305	124.499	6.60E-29
rs8007160	14	76412848	0	T	C	0.232343	0.997032	80.3906	3.10E-19	0.0233356	0.00259828	80.6615	2.70E-19
rs935728	14	80957923	0	C	T	0.671882	0.994235	30.4523	3.40E-08	-0.0129872	0.00233986	30.8074	2.80E-08
rs11845222	14	88969531	0	C	T	0.966535	0.989922	34.3972	4.50E-09	0.0363298	0.00612824	35.1441	3.10E-09
rs10467747	14	92324458	0	C	T	0.1755	0.994275	72.5636	1.60E-17	0.0249912	0.00288878	74.842	5.10E-18
rs10151561	14	92430184	0	A	G	0.578536	0.993117	160.732	7.80E-37	0.0286403	0.00222909	165.082	8.80E-38
rs7156335	14	93406232	0	T	C	0.908783	0.985572	52.7219	3.80E-13	-0.0275281	0.00383458	51.5367	7.00E-13
rs28929474	14	94844947	0	C	T	0.980105	1	448.462	1.60E-99	-0.165242	0.00785724	442.285	3.40E-98
rs3783350	14	101199022	0	G	A	0.203257	0.986504	46.6225	8.60E-12	0.0187609	0.00273892	46.9191	7.40E-12
rs41286560	14	101349454	0	G	T	0.973747	1	33.2681	8.00E-09	0.0386558	0.00685819	31.7695	1.70E-08
rs8007356	14	102975266	0	G	A	0.712586	0.997891	82.0536	1.30E-19	0.0218261	0.00242595	80.945	2.30E-19
rs10459573	14	103925457	0	A	C	0.630239	0.99869	146.92	8.20E-34	0.0274492	0.00227008	146.211	1.20E-33
rs2498786	14	105262368	0	C	G	0.383588	0.994693	48.4925	3.30E-12	0.0160122	0.00225976	50.2085	1.40E-12
rs4074937	14	106000977	0	A	G	0.75448	0.973648	49.4324	2.10E-12	-0.0183681	0.00258646	50.4331	1.20E-12
rs62005437	15	38512573	0	T	C	0.311395	0.99583	54.435	1.60E-13	0.0171199	0.00237221	52.0832	5.30E-13
rs12148176	15	38656080	0	T	G	0.321181	0.996049	39.8589	2.70E-10	0.0148113	0.00234602	39.8586	2.70E-10
rs11070293	15	41041875	0	T	C	0.504567	0.998796	36.9025	1.20E-09	-0.0136176	0.00219138	38.6158	5.20E-10
rs1866399	15	41571139	0	G	A	0.738367	0.98461	76.12	2.70E-18	0.0222345	0.00250681	78.6704	7.30E-19
rs7171123	15	42026363	0	C	T	0.355115	0.998057	54.5522	1.50E-13	0.0170834	0.00229131	55.5879	8.90E-14
rs62020748	15	43341747	0	T	C	0.855008	0.987773	63.4227	1.70E-15	0.0248221	0.00312452	63.1116	2.00E-15
rs12910916	15	47675655	0	C	T	0.788064	1	29.4459	5.70E-08	0.0150393	0.00268071	31.4743	2.00E-08
rs8042740	15	48686310	0	C	T	0.909683	0.964564	72.7953	1.40E-17	0.0333318	0.00389016	73.4146	1.10E-17
rs4775769	15	48939888	0	T	G	0.0934848	0.991596	69.7272	6.80E-17	-0.0317218	0.0037733	70.6761	4.20E-17
rs139941060	15	51255217	0	C	T	0.98592	0.994077	52.7936	3.70E-13	0.0662959	0.00933359	50.4517	1.20E-12
rs73408568	15	51379196	0	C	T	0.783523	0.997315	103.345	2.80E-24	0.0277673	0.0026608	108.904	1.70E-25
rs1004983	15	51613652	0	C	A	0.618555	0.992643	58.6548	1.90E-14	0.0175845	0.00226241	60.4107	7.70E-15
rs3743266	15	60781513	0	T	C	0.665545	1	54.7572	1.40E-13	0.0168943	0.00232449	52.8231	3.60E-13
rs782932	15	61409980	0	G	A	0.658919	0.991992	55.04	1.20E-13	0.0173633	0.00231615	56.1992	6.50E-14
rs139265993	15	61499836	0	G	A	0.982734	0.983786	51.8828	5.90E-13	-0.0606493	0.00846891	51.2858	8.00E-13
rs72749770	15	62365465	0	C	T	0.546839	0.991332	122.914	1.50E-28	0.0250611	0.00220624	129.031	6.70E-30
rs11635675	15	63793238	0	T	G	0.656219	0.99797	29.3454	6.10E-08	-0.013058	0.00230562	32.0759	1.50E-08
rs8027388	15	65955516	0	A	G	0.829437	0.990594	65.274	6.50E-16	-0.0240259	0.00290554	68.3763	1.40E-16
rs12910706	15	66597329	0	T	A	0.922464	0.971897	51.1511	8.60E-13	0.0294384	0.0041271	50.8789	9.80E-13
rs56173559	15	67008443	0	A	G	0.728938	0.982135	141.867	1.00E-32	-0.0295028	0.00247157	142.489	7.60E-33
rs266344	15	67328626	0	C	A	0.324128	0.990506	47.5364	5.40E-12	0.0161645	0.00233163	48.0625	4.10E-12
rs7178291	15	67419682	0	A	G	0.323569	0.998684	30.9169	2.70E-08	-0.0127529	0.00232324	30.1321	4.00E-08
rs35874463	15	67457698	0	A	G	0.94224	1	356.089	2.00E-79	-0.0879554	0.00466131	356.048	2.00E-79
rs16953685	15	70034088	0	A	C	0.896756	0.996932	171.223	4.00E-39	0.0473499	0.00358046	174.889	6.30E-40
rs74021482	15	70355123	0	C	G	0.819843	0.992493	126.311	2.60E-29	-0.0318223	0.00284008	125.545	3.90E-29
rs11072197	15	70790049	0	T	G	0.229617	0.988054	34.1311	5.20E-09	-0.0151985	0.00260529	34.0324	5.40E-09
rs2291277	15	72195229	0	T	C	0.974501	0.990477	100.976	9.30E-24	-0.0705809	0.00692431	103.901	2.10E-24
rs75678484	15	72438453	0	T	C	0.984798	0.91601	30.0336	4.20E-08	0.0511699	0.0093007	30.269	3.80E-08
rs11633028	15	72656241	0	A	G	0.271808	0.978987	48.3073	3.60E-12	0.0171437	0.00247572	47.9521	4.40E-12
rs3784812	15	73659194	0	A	T	0.0675191	0.996324	28.7592	8.20E-08	0.0238435	0.00434183	30.1573	4.00E-08
rs72743347	15	74072916	0	C	T	0.906477	0.988668	56.645	5.20E-14	0.0287068	0.00376229	58.219	2.30E-14
rs144241237	15	74090143	0	G	A	0.985406	0.941161	50.4318	1.20E-12	-0.0676614	0.00935324	52.3309	4.70E-13
rs74888555	15	74187655	0	T	A	0.960745	0.984427	30.3846	3.50E-08	-0.0319703	0.00564629	32.0603	1.50E-08
rs16958477	15	74218466	0	A	C	0.583405	0.984429	177.436	1.80E-40	0.0299082	0.00222435	180.789	3.30E-41
rs5742915	15	74336633	0	T	C	0.539189	1	256.908	8.10E-58	-0.035082	0.0021843	257.954	4.80E-58
rs351224	15	74487036	0	T	A	0.55204	1	34.8354	3.60E-09	-0.0128407	0.00219039	34.3663	4.60E-09

rs9783698	15	74548773	0	G	A	0.72879	1	58.9558	1.60E-14	-0.0187685	0.00244989	58.6904	1.80E-14
rs150562828	15	74656895	0	C	T	0.983427	0.917072	31.9793	1.60E-08	0.051081	0.00889388	32.9866	9.30E-09
rs7174305	15	74728998	0	C	G	0.966453	0.986474	40.5634	1.90E-10	0.038028	0.00608485	39.0577	4.10E-10
rs6495182	15	75814388	0	C	T	0.750074	0.999056	159.087	1.80E-36	-0.0320025	0.00251622	161.759	4.70E-37
rs72734546	15	76188703	0	G	T	0.598459	0.987445	31.2403	2.30E-08	-0.0126466	0.00223514	32.0137	1.50E-08
rs76156143	15	77365134	0	C	T	0.910851	1	74.8191	5.20E-18	-0.0333805	0.00382302	76.2383	2.50E-18
rs112238647	15	79051705	0	C	T	0.93632	0.964557	34.6517	3.90E-09	-0.0275248	0.00454084	36.7431	1.30E-09
rs4778636	15	81591639	0	G	A	0.908082	1	33.7898	6.10E-09	-0.0219023	0.00376534	33.8353	6.00E-09
rs11857976	15	81823538	0	T	C	0.284607	0.989023	89.5253	3.00E-21	-0.0228706	0.00242533	88.9228	4.10E-21
rs3759801	15	82551777	0	T	C	0.878546	0.997928	32.0978	1.50E-08	0.0181971	0.00333543	29.7647	4.90E-08
rs7165624	15	84383062	0	G	C	0.86204	0.995248	45.5531	1.50E-11	-0.0210123	0.00316249	44.1458	3.00E-11
rs11259936	15	84580582	0	A	C	0.478027	1	478.685	4.10E-106	-0.0475031	0.00217936	475.1	2.50E-105
rs112627987	15	84717797	0	C	T	0.923168	0.997042	30.3987	3.50E-08	0.022671	0.00409566	30.6404	3.10E-08
rs185972	15	85556884	0	C	G	0.727984	0.993444	47.9908	4.30E-12	0.0171742	0.00245295	49.0204	2.50E-12
rs12907384	15	86276000	0	T	C	0.46711	0.99943	99.7929	1.70E-23	0.021923	0.00218382	100.778	1.00E-23
rs752278	15	89037134	0	G	A	0.578502	0.973865	43.7339	3.80E-11	0.015046	0.00223376	45.3701	1.60E-11
rs72765638	15	89257734	0	G	C	0.877805	1	111.283	5.10E-26	0.0352534	0.00332559	112.374	3.00E-26
rs4932200	15	89349708	0	A	G	0.517215	0.990586	260.501	1.30E-58	-0.0353075	0.00218673	260.701	1.20E-58
rs17200030	15	89379348	0	C	T	0.970358	1	121.424	3.10E-28	0.0713024	0.00642258	123.251	1.20E-28
rs11635309	15	89396532	0	A	G	0.214472	0.999009	203.532	3.50E-46	0.0376757	0.00265179	201.858	8.20E-46
rs28584580	15	89397827	0	A	G	0.970099	0.999229	547.06	5.50E-121	0.14929	0.00638476	546.726	6.50E-121
rs17791430	15	89426935	0	T	C	0.74283	0.994903	96.9585	7.10E-23	0.0247881	0.00249939	98.3594	3.50E-23
rs6496544	15	89531904	0	T	C	0.427833	0.984168	46.0913	1.10E-11	0.0151129	0.00222179	46.2687	1.00E-11
rs12591347	15	90175251	0	G	A	0.628667	0.997143	44.1932	3.00E-11	-0.015056	0.00225508	44.5757	2.40E-11
rs2074585	15	91009484	0	G	A	0.486324	1	55.5124	9.30E-14	-0.0161977	0.00217621	55.3991	9.80E-14
rs4777825	15	93840263	0	C	T	0.244054	0.994761	33.6534	6.60E-09	-0.0149538	0.00253818	34.7105	3.80E-09
rs8030277	15	94029153	0	A	T	0.683216	0.998088	40.6265	1.80E-10	0.0150237	0.00234565	41.0229	1.50E-10
rs7181724	15	94551607	0	A	G	0.568449	0.976078	94.3521	2.60E-22	-0.0212785	0.00222426	91.5192	1.10E-21
rs11631484	15	95399982	0	A	T	0.488831	0.989188	33.6617	6.60E-09	0.0123395	0.00218705	31.8328	1.70E-08
rs1424739	15	96033790	0	G	A	0.551708	0.995261	30.2745	3.80E-08	-0.0123393	0.00219459	31.6135	1.90E-08
rs8035878	15	96145098	0	T	C	0.452302	0.98353	50.525	1.20E-12	0.0160522	0.00220513	52.9904	3.40E-13
rs62011409	15	97053969	0	A	G	0.734111	0.980457	32.243	1.40E-08	0.0140773	0.00248884	31.992	1.50E-08
rs4965422	15	99105872	0	G	C	0.794041	1	35.0974	3.10E-09	-0.0163151	0.00269027	36.778	1.30E-09
rs2871865	15	99194896	0	C	G	0.884199	1	355.584	2.60E-79	0.0641163	0.00340225	355.144	3.20E-79
rs2715438	15	99398384	0	T	C	0.797167	0.986956	86.4503	1.40E-20	-0.0252259	0.00272518	85.6846	2.10E-20
rs12907693	15	99419273	0	T	A	0.974374	0.947571	41.1196	1.40E-10	-0.0454189	0.00707078	41.2609	1.30E-10
rs9672965	15	99498433	0	C	T	0.50192	0.987467	39.821	2.80E-10	-0.013486	0.00218918	37.9489	7.30E-10
rs2663126	15	99563857	0	G	A	0.309357	1	81.152	2.10E-19	0.020973	0.00235536	79.2881	5.40E-19
rs12916269	15	100530216	0	A	T	0.418829	0.988188	60.0209	9.40E-15	-0.0170469	0.00221875	59.0302	1.60E-14
rs1994010	15	100602471	0	G	A	0.202254	0.983581	41.236	1.30E-10	0.0176536	0.0027326	41.7363	1.00E-10
rs114902530	15	100678070	0	T	C	0.951029	0.991623	53.1164	3.10E-13	0.0371405	0.00506054	53.8645	2.10E-13
rs72755233	15	100692953	0	G	A	0.88798	1	558.939	1.40E-123	0.0815836	0.00344954	559.35	1.20E-123
rs4369638	15	100794363	0	C	T	0.296113	0.988223	196.809	1.00E-44	0.0338565	0.00239809	199.32	2.90E-45
rs2585225	15	100883815	0	C	A	0.741994	0.995448	34.174	5.00E-09	-0.0147874	0.00249359	35.1668	3.00E-09
rs111609923	15	101607519	0	T	C	0.8671	0.97026	35.0099	3.30E-09	0.0190144	0.00325199	34.1875	5.00E-09
rs62621400	15	101718239	0	C	G	0.942611	1	242.077	1.40E-54	0.0726039	0.00468915	239.735	4.50E-54
rs118054132	15	101744588	0	G	A	0.943765	0.995401	39.4393	3.40E-10	-0.0291486	0.00473398	37.9125	7.40E-10
rs114061155	15	101770419	0	C	T	0.974229	0.959134	30.6881	3.00E-08	-0.0401692	0.00701355	32.8028	1.00E-08
rs10902597	15	102007724	0	T	C	0.151106	0.999111	59.8908	1.00E-14	-0.0230867	0.00303613	57.8206	2.90E-14
rs113851505	16	341988	0	C	T	0.815393	0.990651	34.1485	5.10E-09	0.0163397	0.00283875	33.1311	8.60E-09
rs7193109	16	413523	0	T	G	0.611486	0.992895	93.601	3.90E-22	0.0220665	0.00225828	95.4801	1.50E-22
rs12051245	16	783865	0	T	C	0.768385	1	215.94	6.90E-49	-0.0380916	0.00260205	214.301	1.60E-48
rs3803700	16	1027099	0	A	G	0.557319	1	48.5877	3.20E-12	-0.0154211	0.00220917	48.7274	2.90E-12
rs213656	16	1113847	0	T	G	0.409534	0.989931	43.7054	3.80E-11	0.0148705	0.00224146	44.014	3.30E-11
rs71384633	16	1254791	0	C	T	0.679268	0.97441	60.9258	5.90E-15	0.0186665	0.00238455	61.2794	5.00E-15
rs67284550	16	1530949	0	C	T	0.581668	0.997359	45.6967	1.40E-11	0.0150803	0.00222429	45.9657	1.20E-11
rs1184357	16	2141330	0	G	C	0.831709	0.982291	82.8588	8.80E-20	0.0271713	0.00295955	84.2891	4.30E-20
rs39875	16	2268737	0	A	G	0.73635	0.970986	156.355	7.10E-36	-0.0312903	0.00252797	153.206	3.50E-35
rs140421601	16	2814950	0	C	T	0.988676	1	37.3279	1.00E-09	0.0647724	0.010363	39.0667	4.10E-10
rs11639564	16	3133654	0	C	A	0.53915	0.984791	35.7911	2.20E-09	-0.0133934	0.00221613	36.525	1.50E-09
rs2907272	16	4019350	0	C	T	0.178892	0.994055	61.7831	3.80E-15	-0.0221271	0.00286596	59.6084	1.20E-14
rs3901638	16	4360284	0	A	G	0.694215	1	91.3052	1.20E-21	-0.0228866	0.00238182	92.3302	7.30E-22
rs3747577	16	4415696	0	C	G	0.257831	0.988354	81.885	1.40E-19	-0.0225397	0.00252241	79.8479	4.00E-19
rs1684621	16	4710898	0	T	G	0.367638	0.987395	62.8252	2.30E-15	0.0183813	0.00228866	64.5045	9.60E-16
rs1436386	16	5917380	0	G	C	0.809547	0.992341	30.9721	2.60E-08	0.0156665	0.00280751	31.1387	2.40E-08
rs28690777	16	7613927	0	A	C	0.601449	0.98856	43.7621	3.70E-11	-0.0152576	0.00225488	45.7855	1.30E-11
rs28482987	16	9059202	0	A	G	0.678306	0.99345	63.4117	1.70E-15	0.0187621	0.00235742	63.3418	1.70E-15
rs112431913	16	9204805	0	G	T	0.72896	0.992566	32.4406	1.20E-08	-0.0137266	0.00247721	30.7043	3.00E-08
rs246184	16	14395077	0	G	C	0.676919	0.977832	99.8541	1.60E-23	-0.0236444	0.00237334	99.2508	2.20E-23
rs72774845	16	15147954	0	A	C	0.692614	0.997994	58.2309	2.30E-14	0.0179052	0.00237631	56.7743	4.90E-14
rs79686715	16	16195257	0	G	A	0.96797	1	31.8998	1.60E-08	0.0349336	0.00622336	31.5091	2.00E-08
rs1051547	16	19279380	0	T	C	0.438771	0.982057	53.494	2.60E-13	0.0157284	0.00222915	49.7841	1.70E-12
rs76568292	16	22304253	0	G	A	0.945735	1	42.0108	9.10E-11	0.0313639	0.00484328	41.9354	9.40E-11
rs28405395	16	24584801	0	T	C	0.494478	0.989276	35.3314	2.80E-09	-0.0130595	0.00220558	35.0595	3.20E-09
rs12708665	16	24728227	0	A	G	0.284498	0.996358	36.6002	1.50E-09	-0.0148778	0.00243622	37.2945	1.00E-09
rs11642740	16	30060655	0	A	G	0.597703	0.997922	63.7709	1.40E-15	-0.0178957	0.00223872	63.8991	1.30E-15
rs933561	16	49874676	0	A	G	0.653359	0.996442	37.9552	7.20E-10	0.0143106	0.00230879	38.4191	5.70E-10
rs138937927	16	51095561	0	C	T	0.97429	0.930948	56.9676	4.40E-14	0.0533668	0.00718654	55.1447	1.10E-13
rs17800727	16	53481010	0	A	G	0.699487	0.996598	218.403	2.00E-49	-0.035309	0.00239235	217.832	2.70E-49
rs13334364	16	67332365	0	T	C	0.925575	0.995083	62.0006	3.40E-15	0.033537	0.0041867	64.166	1.10E-15
rs78818722	16	67991972	0	C	T	0.932638	1	32.7712	1.00E-08	-0.0239866	0.00437509	30.0583	4.20E-08
rs9940899	16	69169927	0	T	C	0.708329	0.998569	59.443	1.30E-14	0.0185254	0.00241444	58.8709	1.70E-14
rs3790085	16	69887720	0	A	G	0.544859	0.99829	148.655	3.40E-34	0.026886	0.00220905	148.129	4.40E-34

rs150156705	16	70818599	0	C	G	0.988465	0.965111	31.2854	2.20E-08	-0.057983	0.010454	30.7636	2.90E-08
rs117655998	16	72058846	0	C	T	0.982731	0.935078	35.9511	2.00E-09	0.0512588	0.00871978	34.5562	4.10E-09
rs77303550	16	72079657	0	C	T	0.807557	0.996436	38.2086	6.40E-10	-0.0171127	0.00279024	37.6147	8.60E-10
rs9925261	16	72927533	0	A	C	0.660112	0.977161	31.1706	2.40E-08	-0.0128325	0.00234701	29.8947	4.60E-08
rs370240672	16	73095266	0	T	C	0.963763	0.964176	35.7233	2.30E-09	-0.035722	0.00598298	35.6482	2.40E-09
rs328373	16	73790993	0	A	G	0.594585	0.992696	33.938	5.70E-09	0.0128515	0.0022427	32.8373	1.00E-08
rs35772006	16	75180124	0	A	G	0.410071	0.98794	59.1637	1.50E-14	-0.0172648	0.00224483	59.1504	1.50E-14
rs7189407	16	75337332	0	G	A	0.22671	0.973697	37.3671	9.80E-10	-0.0163448	0.00265593	37.8729	7.60E-10
rs62045081	16	78132246	0	C	T	0.586329	0.993994	38.3632	5.90E-10	0.0140733	0.00223469	39.6606	3.00E-10
rs4887952	16	78347216	0	G	A	0.796162	0.995026	50.8819	9.80E-13	0.0198229	0.0027284	52.7862	3.70E-13
rs16947701	16	78518990	0	G	A	0.87658	0.996395	31.3059	2.20E-08	0.0185867	0.00334345	30.904	2.70E-08
rs71398138	16	79238563	0	A	C	0.861443	0.984035	32.6059	1.10E-08	0.017974	0.00319772	31.5944	1.90E-08
rs77384835	16	81551168	0	T	G	0.927585	0.997258	37.102	1.10E-09	0.0259786	0.00423906	37.5572	8.90E-10
rs62046625	16	81578706	0	G	A	0.883642	0.9941	83.5499	6.20E-20	-0.0314699	0.00343322	84.0211	4.90E-20
rs28375552	16	81719748	0	C	G	0.589538	0.991959	60.2729	8.30E-15	0.0172264	0.00224076	59.1013	1.50E-14
rs2967363	16	82204132	0	C	G	0.229666	0.996906	71.0854	3.40E-17	0.0219791	0.00261227	70.792	4.00E-17
rs11863406	16	84802666	0	T	G	0.73522	0.991075	56.1391	6.80E-14	-0.0185913	0.00250006	55.2991	1.00E-13
rs5022975	16	84846982	0	A	T	0.174797	0.997701	31.7037	1.80E-08	0.0159024	0.00289318	30.2116	3.90E-08
rs11149690	16	84869017	0	G	T	0.51283	0.992659	38.0262	7.00E-10	0.0139277	0.00220153	40.0231	2.50E-10
rs2641703	16	84892853	0	A	G	0.205064	0.982893	33.6426	6.60E-09	-0.0162454	0.00274108	35.1249	3.10E-09
rs9941239	16	84987947	0	A	G	0.243338	0.992787	48.256	3.70E-12	0.0179476	0.00256748	48.865	2.70E-12
rs1728383	16	86438844	0	C	G	0.740288	1	35.5063	2.50E-09	0.015009	0.00249959	36.0548	1.90E-09
rs1169644	16	86537032	0	G	A	0.225355	0.983934	41.322	1.30E-10	0.0173072	0.00264517	42.8102	6.00E-11
rs28655023	16	87250519	0	A	G	0.613626	0.997465	44.1067	3.10E-11	-0.015178	0.00225293	45.387	1.60E-11
rs4843580	16	87275136	0	C	G	0.210148	0.995703	32.1362	1.40E-08	-0.0153892	0.00269698	32.5594	1.20E-08
rs72809455	16	88670394	0	A	C	0.88387	1	30.7015	3.00E-08	-0.0191076	0.00342878	31.055	2.50E-08
rs753602	16	88807224	0	T	C	0.297177	0.997974	111.605	4.40E-26	-0.0253202	0.00240715	110.644	7.10E-26
rs56208138	16	88913107	0	T	C	0.913993	0.991104	34.1083	5.20E-09	0.0225596	0.00393195	32.9191	9.60E-09
rs4785574	16	89568875	0	A	G	0.445059	0.995178	34.2854	4.80E-09	0.0125967	0.00221534	32.332	1.30E-08
rs1126464	16	89704365	0	G	C	0.758163	1	71.9368	2.20E-17	-0.0220271	0.0025664	73.6662	9.30E-18
rs8054492	16	89802719	0	G	A	0.81227	0.993382	36.1951	1.80E-09	0.0172533	0.00281711	37.509	9.10E-10
rs2663344	17	926359	0	A	C	0.690458	0.987726	32.246	1.40E-08	0.0132552	0.00238172	30.9736	2.60E-08
rs12952797	17	1394078	0	T	C	0.897609	0.959593	34.323	4.70E-09	-0.0211697	0.00368946	32.9232	9.60E-09
rs59643265	17	1630395	0	T	C	0.734187	0.998435	43.649	3.90E-11	0.0167262	0.00247855	45.5408	1.50E-11
rs8074840	17	1674429	0	T	C	0.696852	1	63.9746	1.30E-15	-0.0190645	0.00237893	64.2223	1.10E-15
rs1131600	17	1940232	0	A	G	0.819805	1	33.5792	6.80E-09	-0.0162875	0.0028475	32.7178	1.10E-08
rs73976192	17	1971600	0	G	A	0.979998	1	56.4306	5.80E-14	-0.0582786	0.00780522	55.7505	8.20E-14
rs7219015	17	2555592	0	C	T	0.781469	0.994624	32.112	1.50E-08	0.0152009	0.00265753	32.7178	1.10E-08
rs3809817	17	7233162	0	C	G	0.64107	0.994279	33.9596	5.60E-09	-0.0134133	0.0022871	34.3956	4.50E-09
rs55749333	17	7371932	0	C	T	0.361541	0.997312	199.64	2.50E-45	0.0321362	0.00227966	198.724	4.00E-45
rs9903150	17	7478280	0	T	C	0.925363	0.996385	52.584	4.10E-13	0.0305915	0.00417478	53.695	2.30E-13
rs12949853	17	7570878	0	G	A	0.199637	0.969007	109.307	1.40E-25	-0.0290767	0.00278182	109.253	1.40E-25
rs138420351	17	7700063	0	C	T	0.988472	0.820421	49.0553	2.50E-12	-0.0797507	0.0113218	49.6183	1.90E-12
rs55809496	17	7759477	0	C	A	0.430862	0.997116	32.0031	1.50E-08	-0.0126071	0.00221404	32.4233	1.20E-08
rs4792250	17	8024218	0	T	A	0.400941	0.992106	77.4847	1.30E-18	-0.0194585	0.00224161	75.3527	3.90E-18
rs78975791	17	8145355	0	A	T	0.712265	0.981137	36.8764	1.30E-09	-0.0148156	0.00244073	36.8469	1.30E-09
rs2660834	17	17375254	0	C	T	0.234361	0.992619	47.784	4.80E-12	-0.0181999	0.00259329	49.2534	2.20E-12
rs36215896	17	17720319	0	C	T	0.984645	1	52.7118	3.90E-13	-0.0644934	0.00890212	52.486	4.30E-13
rs712274	17	18064195	0	T	C	0.258835	0.995643	49.554	1.90E-12	0.0178114	0.00250464	50.5715	1.10E-12
rs112197608	17	21107580	0	C	G	0.985266	0.944857	39.0343	4.20E-10	0.0589697	0.0093512	39.767	2.90E-10
rs12951372	17	21154654	0	G	A	0.744192	0.991009	41.1121	1.40E-10	-0.0165681	0.00252088	43.1955	5.00E-11
rs7213608	17	21279289	0	C	T	0.325265	0.979195	273.783	1.70E-61	-0.0390001	0.00236111	272.835	2.70E-61
rs11545700	17	27044482	0	C	A	0.874424	0.987581	41.3176	1.30E-10	0.0214917	0.00332112	41.8769	9.70E-11
rs150464937	17	27332778	0	C	T	0.980182	0.854827	27.6514	1.50E-07	0.0474357	0.00849733	31.1634	2.40E-08
rs11654523	17	27957545	0	T	C	0.932783	1	60.1371	8.80E-15	0.0335814	0.00438757	58.5802	2.00E-14
rs78158897	17	27967058	0	A	G	0.963536	0.995564	28.2436	1.10E-07	0.0322058	0.00585723	30.2331	3.80E-08
rs56357032	17	28474934	0	A	T	0.87	0.973839	135.706	2.30E-31	-0.0389329	0.00329493	139.618	3.20E-32
rs7223535	17	29211667	0	G	A	0.729564	0.99916	498.5	2.00E-110	0.0557727	0.00246369	512.474	1.80E-113
rs11653842	17	29848534	0	C	T	0.948344	0.951273	30.7876	2.90E-08	0.0282814	0.00506713	31.1515	2.40E-08
rs34123134	17	29903835	0	A	G	0.881955	0.961462	49.8683	1.60E-12	-0.0248621	0.00346123	51.5956	6.80E-13
rs56389115	17	30237308	0	T	C	0.843749	0.98337	85.7818	2.00E-20	-0.0286264	0.00303864	88.7513	4.50E-21
rs7211564	17	36839519	0	G	A	0.611039	0.99647	33.9389	5.70E-09	0.0129024	0.00224846	32.9286	9.60E-09
rs1043515	17	36922196	0	A	G	0.433625	1	158.572	2.30E-36	-0.0282455	0.00220771	163.687	1.80E-37
rs117574970	17	37947427	0	A	G	0.982586	1	31.0515	2.50E-08	0.0484595	0.00835888	33.6094	6.70E-09
rs62065258	17	38434002	0	G	A	0.75041	0.97798	105.714	8.50E-25	-0.0264841	0.00255437	107.498	3.50E-25
rs8082238	17	40890477	0	T	G	0.462497	0.996508	79.2985	5.30E-19	-0.0197364	0.00220009	80.4739	2.90E-19
rs7217897	17	41652878	0	T	C	0.473531	1	42.1361	8.50E-11	0.0137084	0.0021932	39.0676	4.10E-10
rs4793028	17	41857212	0	T	C	0.711256	0.997593	46.8998	7.50E-12	0.0159548	0.0024198	43.4732	4.30E-11
rs9908517	17	42672463	0	G	A	0.864093	0.998113	61.9158	3.60E-15	-0.0260917	0.00319087	66.863	2.90E-16
rs4986172	17	43216281	0	C	T	0.658627	1	155.765	9.50E-36	0.0286069	0.00230481	154.054	2.30E-35
rs55938136	17	43798360	0	A	G	0.775319	0.999881	103.872	2.20E-24	0.0268212	0.00261602	105.117	1.20E-24
rs7207400	17	43824360	0	T	C	0.728918	0.998039	116.706	3.30E-27	0.0267275	0.00245756	118.279	1.50E-27
rs113208880	17	46215302	0	G	T	0.976723	0.956155	71.9698	2.20E-17	-0.061058	0.00740545	67.9801	1.70E-16
rs77244957	17	46325577	0	T	C	0.84711	0.975029	125.994	3.10E-29	0.0345183	0.00307015	126.409	2.50E-29
rs2280351	17	46830299	0	G	A	0.331253	0.992644	48.4216	3.40E-12	0.0160868	0.00232948	47.6896	5.00E-12
rs12948439	17	46967124	0	G	A	0.459306	0.998034	241.44	1.90E-54	0.033664	0.00219245	235.761	3.30E-53
rs6504608	17	47424681	0	C	A	0.632613	0.997587	137.544	9.20E-32	0.0271598	0.00227027	143.119	5.50E-33
rs4793674	17	48885634	0	T	C	0.631808	0.983004	29.8862	4.60E-08	0.0124662	0.00228211	29.8396	4.70E-08
rs2041297	17	49242036	0	G	C	0.642591	0.996341	51.6492	6.60E-13	-0.0165596	0.00228057	52.7248	3.80E-13
rs741128	17	54259113	0	G	A	0.493907	0.995637	28.187	1.10E-07	0.0122762	0.00218992	31.425	2.10E-08
rs11079248	17	54693049	0	T	C	0.0559421	0.993689	51.8604	6.00E-13	-0.034103	0.00477013	51.1122	8.70E-13
rs117223734	17	54694724	0	A	G	0.984361	1	71.9459	2.20E-17	-0.0742513	0.00879727	71.2382	3.20E-17
rs227721	17	54779929	0	G	A	0.759395	0.984403	66.1074	4.30E-16	-0.0208371	0.00257233	65.618	5.50E-16

rs17655774	17	54815076	0	G	A	0.963022	1	33.6203	6.70E-09	0.0331437	0.00578689	32.8028	1.00E-08
rs963292	17	54842555	0	C	T	0.506798	0.995082	168.499	1.60E-38	0.0288064	0.00219015	172.994	1.60E-39
rs11654634	17	56044110	0	A	C	0.927623	0.985913	31.5755	1.90E-08	0.0235037	0.00424325	30.6815	3.00E-08
rs740605	17	56604811	0	C	T	0.59939	0.99977	42.9886	5.50E-11	-0.0147113	0.00222771	43.6099	4.00E-11
rs7214743	17	59498052	0	A	G	0.329616	0.998747	285.105	5.80E-64	0.0393592	0.00232203	287.315	1.90E-64
rs35396866	17	59546787	0	C	G	0.883903	0.977778	57.5301	3.30E-14	-0.0264041	0.00344597	58.7109	1.80E-14
rs2079796	17	59608726	0	G	C	0.63064	0.994739	100.185	1.40E-23	-0.0228303	0.00226769	101.357	7.70E-24
rs12452590	17	60720058	0	T	G	0.637964	0.977663	84.7246	3.40E-20	-0.0213865	0.00229761	86.642	1.30E-20
rs78113664	17	60994706	0	C	T	0.954812	1	34.0529	5.40E-09	0.0314143	0.00525632	35.7184	2.30E-09
rs3020619	17	61993137	0	A	G	0.729394	0.988266	542.942	4.30E-120	-0.0578465	0.00247349	546.932	5.90E-121
rs2058194	17	62020348	0	T	C	0.471944	1	174.436	7.90E-40	-0.0287438	0.0021873	172.692	1.90E-39
rs11079522	17	62108467	0	A	G	0.656388	0.991068	42.8355	6.00E-11	-0.0149924	0.00230947	42.1421	8.50E-11
rs11650900	17	62656306	0	A	T	0.117339	0.976858	69.8532	6.40E-17	0.028619	0.00343392	69.4591	7.80E-17
rs12452505	17	63556402	0	C	G	0.857857	0.99295	183.856	7.00E-42	0.0431779	0.00313814	189.313	4.50E-43
rs12601850	17	64302652	0	G	A	0.610108	0.998006	81.9824	1.40E-19	0.0201353	0.00224243	80.627	2.70E-19
rs7217788	17	66208498	0	A	G	0.535044	0.987426	30.1577	4.00E-08	-0.0122759	0.00220447	31.0096	2.60E-08
rs2907384	17	66576439	0	G	T	0.750871	1	54.0011	2.00E-13	0.0183965	0.00252532	53.0686	3.20E-13
rs77542162	17	67081278	0	A	G	0.977268	1	62.6018	2.50E-15	-0.058254	0.00733622	63.0532	2.00E-15
rs864200	17	67432974	0	A	T	0.418261	0.983847	52.1089	5.30E-13	0.0161837	0.00223148	52.5984	4.10E-13
rs2521348	17	67499717	0	C	T	0.615098	0.990488	40.2361	2.30E-10	-0.0148106	0.00225352	43.1942	5.00E-11
rs11867479	17	68090207	0	C	T	0.64209	1	108.542	2.00E-25	-0.0238708	0.00227853	109.755	1.10E-25
rs6501381	17	68148350	0	T	C	0.886875	0.995193	96.1646	1.10E-22	0.0342954	0.00345871	98.3202	3.60E-23
rs4519367	17	68470163	0	A	G	0.486202	0.995192	49.2599	2.20E-12	-0.0151014	0.00218674	47.6912	5.00E-12
rs7223448	17	69311953	0	T	C	0.347786	0.995038	74.2411	6.90E-18	-0.019452	0.00229999	71.5277	2.70E-17
rs7224246	17	69958929	0	A	T	0.784954	0.9975	46.8861	7.50E-12	-0.0183216	0.00265887	47.4827	5.50E-12
rs12452423	17	70048504	0	A	T	0.702965	0.988292	36.9267	1.20E-09	-0.01416	0.00240084	34.7857	3.70E-09
rs1979110	17	71145694	0	G	C	0.744242	0.995285	39.7039	3.00E-10	-0.0159759	0.0025093	40.5344	1.90E-10
rs9894206	17	73360154	0	T	C	0.149482	0.999622	46.8826	7.50E-12	-0.0210375	0.00306407	47.1401	6.60E-12
rs894542	17	74133974	0	C	T	0.895496	0.991312	32.3141	1.30E-08	0.020457	0.00358273	32.603	1.10E-08
rs1976703	17	76401328	0	C	T	0.511408	0.995431	36.2431	1.70E-09	-0.0129021	0.00218987	34.712	3.80E-09
rs11077397	17	76796463	0	C	T	0.475489	1	50.6057	1.10E-12	0.0156916	0.00218518	51.5659	6.90E-13
rs4076427	17	79087537	0	G	C	0.60947	0.985681	64.5344	9.50E-16	0.0185083	0.00225405	67.423	2.20E-16
rs7226066	17	79354785	0	A	G	0.629912	0.997587	71.3429	3.00E-17	-0.018936	0.00226342	69.992	6.00E-17
rs12952981	17	79409189	0	G	A	0.643872	1	82.1803	1.20E-19	-0.0201652	0.00228582	77.8248	1.10E-18
rs35344256	17	79934194	0	C	A	0.695118	1	110.238	8.70E-26	0.0250474	0.00237482	111.241	5.20E-26
rs6502119	17	80504266	0	C	T	0.36629	0.999333	57.9002	2.80E-14	0.0168298	0.00226547	55.1874	1.10E-13
rs2263122	17	80697773	0	T	G	0.464254	0.997917	29.8073	4.80E-08	0.0120371	0.00219124	30.176	3.90E-08
rs621979	18	233443	0	G	A	0.771011	0.997374	43.5025	4.20E-11	-0.0174573	0.00262468	44.2383	2.90E-11
rs71356070	18	2809160	0	C	T	0.530145	0.994152	41.0007	1.50E-10	-0.014298	0.00221564	41.6441	1.10E-10
rs74810948	18	7596190	0	G	A	0.959743	0.992237	33.9425	5.70E-09	-0.0326017	0.00561632	33.6959	6.40E-09
rs552775406	18	11960224	0	A	G	0.973634	0.851264	35.4006	2.70E-09	-0.0439572	0.0074523	34.792	3.70E-09
rs8098565	18	13164588	0	A	G	0.375292	0.986642	97.058	6.70E-23	0.0223626	0.0022864	95.6626	1.40E-22
rs4800144	18	20648375	0	G	A	0.669714	0.978602	34.8804	3.50E-09	0.0140345	0.00236415	35.2404	2.90E-09
rs4369779	18	20735408	0	T	C	0.211489	1	551.633	5.60E-122	-0.063164	0.00269476	549.415	1.70E-121
rs7237939	18	22699502	0	T	G	0.369015	0.994045	60.716	6.60E-15	-0.01768	0.0022887	59.6743	1.10E-14
rs8091465	18	22811960	0	C	T	0.641796	1	63.7629	1.40E-15	0.0182073	0.00229698	62.8314	2.30E-15
rs12456337	18	24241627	0	C	T	0.440392	0.998066	30.3898	3.50E-08	-0.0124132	0.00222024	31.2586	2.30E-08
rs2289543	18	29772976	0	A	C	0.737906	1	49.6399	1.80E-12	-0.0177413	0.00250472	50.1708	1.40E-12
rs4470224	18	30070697	0	A	T	0.797156	0.998494	28.9784	7.30E-08	0.0150265	0.00274024	30.0705	4.20E-08
rs34849253	18	33024107	0	G	A	0.678359	0.977489	43.2899	4.70E-11	-0.0159936	0.0023867	44.9051	2.10E-11
rs12969480	18	35147621	0	C	G	0.246715	0.993425	45.1776	1.80E-11	-0.0170944	0.00256468	44.4264	2.60E-11
rs12457358	18	41459423	0	G	A	0.658671	0.995604	34.7517	3.70E-09	-0.0136433	0.00232474	34.4423	4.40E-09
rs4499316	18	41878328	0	G	A	0.830757	0.979676	44.3779	2.70E-11	0.0195267	0.0029655	43.3571	4.60E-11
rs16978240	18	42549257	0	C	T	0.885296	0.993244	32.1137	1.50E-08	0.0195432	0.0034687	31.7439	1.80E-08
rs2668776	18	44750365	0	C	T	0.469225	0.997085	30.8175	2.80E-08	-0.0124903	0.00221039	31.9306	1.60E-08
rs12373324	18	45344790	0	G	A	0.909354	0.96983	44.5233	2.50E-11	-0.0257123	0.00389984	43.4699	4.30E-11
rs4335832	18	45887180	0	A	C	0.598496	0.996999	52.2825	4.80E-13	-0.015866	0.00224874	49.78	1.70E-12
rs10775487	18	46247143	0	T	G	0.690543	0.987955	42.1299	8.50E-11	0.0153376	0.0023951	41.008	1.50E-10
rs16949934	18	46277226	0	G	A	0.919264	1	36.5763	1.50E-09	0.0243054	0.00404044	36.1865	1.80E-09
rs4939820	18	46370055	0	G	T	0.155475	1	36.8505	1.30E-09	0.0181955	0.00303539	35.9336	2.00E-09
rs4629039	18	46485154	0	T	A	0.35129	0.982657	73.958	8.00E-18	0.0200626	0.00232664	74.3561	6.50E-18
rs140278307	18	46553383	0	G	A	0.988689	0.94803	45.0601	1.90E-11	0.0734217	0.0106898	47.1744	6.50E-12
rs112638217	18	46632188	0	T	C	0.98664	0.956092	44.3574	2.70E-11	0.0657468	0.00981279	44.8915	2.10E-11
rs36131420	18	46748042	0	C	T	0.558074	0.993931	329.625	1.20E-73	-0.0404436	0.00222288	331.03	5.70E-74
rs72911868	18	47037089	0	A	G	0.931774	0.996859	38.8273	4.60E-10	0.0268751	0.00437045	37.8135	7.80E-10
rs11082953	18	50391870	0	A	T	0.684998	0.996193	32.505	1.20E-08	0.0134159	0.00237413	31.9322	1.60E-08
rs17522826	18	53070914	0	G	A	0.811086	0.980154	56.6501	5.20E-14	-0.0214628	0.00283984	57.1196	4.10E-14
rs6567160	18	57829135	0	T	C	0.767543	0.998838	117.053	2.80E-27	-0.0279337	0.00260692	114.816	8.60E-27
rs11662645	18	60680159	0	C	A	0.752987	0.998804	36.7827	1.30E-09	0.0156314	0.00255366	37.4688	9.30E-10
rs12955939	18	60755065	0	G	T	0.566285	0.999394	32.1054	1.50E-08	-0.0127078	0.00222506	32.6179	1.10E-08
rs59951000	18	74975828	0	C	T	0.958033	0.996296	31.7875	1.70E-08	0.0314789	0.00549375	32.8322	1.00E-08
rs62107084	18	75135258	0	T	G	0.671176	0.987571	31.4654	2.00E-08	0.0132812	0.00236082	31.6482	1.80E-08
rs59725651	18	77184667	0	A	G	0.660123	0.988956	70.39	4.90E-17	0.0197611	0.00233632	71.5418	2.70E-17
rs182209161	19	1015784	0	C	G	0.846309	0.99628	35.0624	3.20E-09	-0.0183519	0.00307286	35.668	2.30E-09
rs12985850	19	2155042	0	G	A	0.598774	0.98908	343.264	1.20E-76	-0.0419645	0.0022706	341.573	2.90E-76
rs187878341	19	2156621	0	G	A	0.983484	0.98777	31.2207	2.30E-08	0.0490615	0.00873411	31.5533	1.90E-08
rs740521	19	3367745	0	G	A	0.584105	1	41.5507	1.10E-10	0.0140523	0.00224374	39.2236	3.80E-10
rs12980469	19	3457058	0	G	A	0.770011	0.993961	138.574	5.50E-32	-0.0311309	0.00263637	139.435	3.50E-32
rs350832	19	4069426	0	G	A	0.228379	0.990927	72.1445	2.00E-17	0.022476	0.00265441	71.6976	2.50E-17
rs145882278	19	4159308	0	C	T	0.891131	0.973856	42.2089	8.20E-11	0.0234225	0.0035931	42.494	7.10E-11
rs12459155	19	4774475	0	C	G	0.869656	0.994085	50.9703	9.40E-13	0.02385	0.00329586	52.3646	4.60E-13
rs35992600	19	4906415	0	A	G	0.870548	1	53.5302	2.50E-13	-0.0241122	0.00329885	53.4253	2.70E-13
rs12185519	19	4967739	0	C	T	0.791969	0.994064	208.852	2.40E-47	0.0396283	0.00273432	210.045	1.30E-47

rs4807065	19	6226006	0	T	A	0.767555	0.989866	46.3376	1.00E-11	-0.0180401	0.00262963	47.064	6.90E-12
rs11882912	19	7149898	0	T	G	0.0656198	0.965801	56.066	7.00E-14	0.0345602	0.00455276	57.624	3.20E-14
rs891088	19	7184762	0	A	G	0.737758	1	158.57	2.30E-36	-0.0317849	0.00251377	159.878	1.20E-36
rs117162033	19	8627569	0	C	T	0.987388	0.886793	36.154	1.80E-09	-0.0646142	0.0105339	37.6251	8.60E-10
rs62621197	19	8670147	0	C	T	0.963285	0.930027	499.14	1.50E-110	0.136058	0.0061102	495.838	7.60E-110
rs78333947	19	10253761	0	G	A	0.951707	1	85.7184	2.10E-20	-0.0477647	0.0051576	85.7665	2.00E-20
rs12327774	19	10372965	0	C	G	0.825724	0.966602	70.1215	5.60E-17	0.0246413	0.0029712	68.7804	1.10E-16
rs67780133	19	10418661	0	T	C	0.726084	0.984899	38.1468	6.60E-10	-0.015436	0.00250079	38.0992	6.70E-10
rs10948	19	10754905	0	G	T	0.335973	1	146.668	9.30E-34	0.0283147	0.00234696	145.549	1.60E-33
rs56237989	19	11262969	0	G	T	0.498669	0.988867	39.1171	4.00E-10	-0.0139955	0.00222627	39.5205	3.20E-10
rs149870361	19	12172847	0	G	A	0.925875	0.999486	100.678	1.10E-23	-0.0421036	0.00422541	99.2889	2.20E-23
rs4804669	19	12502457	0	A	G	0.216868	0.980742	45.0838	1.90E-11	-0.0179533	0.00271341	43.778	3.70E-11
rs2974753	19	13061450	0	A	G	0.556684	0.995424	47.5457	5.40E-12	0.0156676	0.00223601	49.0975	2.40E-12
rs8104223	19	15363477	0	A	G	0.679425	1	36.6186	1.40E-09	0.0142407	0.00237088	36.0781	1.90E-09
rs2305758	19	17163661	0	C	T	0.717582	1	38.828	4.60E-10	-0.0156334	0.002456	40.5179	1.90E-10
rs2279008	19	17283303	0	T	C	0.748563	1	100.408	1.20E-23	0.0255943	0.00255167	100.609	1.10E-23
rs61494113	19	17401859	0	G	A	0.704679	0.994832	34.3941	4.50E-09	0.014755	0.00243321	36.7724	1.30E-09
rs8104679	19	18121967	0	T	C	0.778145	0.999161	72.1298	2.00E-17	0.0224095	0.00266471	70.7232	4.10E-17
rs10406080	19	18402142	0	C	G	0.383787	0.993148	34.2829	4.80E-09	-0.0134148	0.0022872	34.4005	4.50E-09
rs1806980	19	18566804	0	T	G	0.641446	0.995061	48.2823	3.70E-12	0.0160844	0.00231485	48.2797	3.70E-12
rs79054960	19	18876208	0	C	G	0.931053	1	32.1214	1.40E-08	-0.0246675	0.0043752	31.7874	1.70E-08
rs34647936	19	19548239	0	T	G	0.814469	0.999118	149.061	2.80E-34	0.0345767	0.00285284	146.897	8.30E-34
rs8113682	19	19743730	0	T	G	0.251154	0.994139	64.2974	1.10E-15	0.0206649	0.00256067	65.1269	7.00E-16
rs55663539	19	31041654	0	T	C	0.835452	0.99673	55.0384	1.20E-13	-0.0217846	0.0029887	53.1294	3.10E-13
rs12596	19	32877125	0	G	A	0.454804	1	28.666	8.60E-08	0.0122183	0.00222783	30.0788	4.10E-08
rs34508287	19	33794490	0	G	C	0.8632	0.993997	48.4001	3.50E-12	-0.0220018	0.00323323	46.3067	1.00E-11
rs2280743	19	36225999	0	T	C	0.771638	0.999112	44.7107	2.30E-11	-0.0176891	0.00264441	44.7459	2.20E-11
rs7255724	19	37649577	0	G	T	0.475614	0.998559	107.698	3.10E-25	0.0233376	0.00222375	110.139	9.10E-26
rs3136646	19	39399277	0	C	T	0.764475	0.988283	45.6694	1.40E-11	0.0177247	0.00262835	45.477	1.50E-11
rs268662	19	40923375	0	T	G	0.876667	0.990899	56.1278	6.80E-14	-0.0254108	0.00338743	56.2728	6.30E-14
rs112009052	19	41099501	0	T	A	0.986458	0.960478	45.2345	1.70E-11	0.0666344	0.00977246	46.4932	9.20E-12
rs4802086	19	41230146	0	G	A	0.478512	0.997516	40.4442	2.00E-10	-0.0141046	0.00222013	40.3612	2.10E-10
rs1043413	19	41939297	0	C	G	0.611853	1	153.23	3.40E-35	-0.0280351	0.00227271	152.165	5.80E-35
rs75694591	19	42690067	0	C	T	0.900605	0.995468	37.4673	9.30E-10	0.0230857	0.00371285	38.6608	5.00E-10
rs2599459	19	44037370	0	C	G	0.811371	1	54.8635	1.30E-13	-0.0208846	0.00283575	54.2396	1.80E-13
rs438811	19	45416741	0	C	T	0.763235	0.994844	34.5804	4.10E-09	-0.015645	0.00261501	35.7933	2.20E-09
rs2376868	19	45511140	0	C	A	0.545568	0.983333	40.3419	2.10E-10	-0.01415	0.00224205	39.8311	2.80E-10
rs2341097	19	46268902	0	C	T	0.639804	0.996399	63.6723	1.50E-15	0.0183167	0.00231318	62.7014	2.40E-15
rs10418627	19	46962930	0	T	G	0.0366438	0.997841	54.8452	1.30E-13	-0.0433674	0.00589826	54.0604	1.90E-13
rs3730869	19	48660067	0	G	A	0.609438	0.993834	33.9492	5.70E-09	-0.0129341	0.00227647	32.281	1.30E-08
rs4002471	19	49215095	0	C	T	0.450886	0.995052	57.7012	3.10E-14	0.0169556	0.00224099	57.2466	3.80E-14
rs73046792	19	49605705	0	G	A	0.836129	1	44.8267	2.20E-11	-0.0200399	0.00299401	44.8009	2.20E-11
rs76246107	19	50121274	0	G	A	0.919189	0.946646	60.2666	8.30E-15	0.0330298	0.0041788	62.4753	2.70E-15
rs12976868	19	54755923	0	A	G	0.775593	1	40.7583	1.70E-10	-0.0169926	0.00265823	40.8633	1.60E-10
rs2298885	19	55876240	0	C	T	0.672605	1	38.0877	6.80E-10	-0.0142588	0.00236313	36.4074	1.60E-09
rs4252548	19	55879672	0	C	T	0.97826	1	149.877	1.80E-34	0.0926596	0.00759148	148.98	2.90E-34
rs75653026	19	55885594	0	T	A	0.869973	0.985774	40.426	2.00E-10	-0.0212022	0.00332348	40.6983	1.80E-10
rs147110934	19	55993436	0	G	T	0.975828	1	200.105	2.00E-45	0.102483	0.00721227	201.909	8.00E-46
rs16987303	19	57037103	0	C	G	0.808858	1	43.098	5.20E-11	-0.0187751	0.00282097	44.2964	2.80E-11
rs6139109	20	391025	0	T	C	0.872813	1	36.9641	1.20E-09	-0.0200078	0.00328567	37.081	1.10E-09
rs683808	20	3749886	0	A	G	0.451337	0.9865	29.5155	5.50E-08	0.0121472	0.00221591	30.0505	4.20E-08
rs1741344	20	4101800	0	C	T	0.365775	1	140.914	1.70E-32	0.027224	0.00227509	143.188	5.30E-33
rs73074166	20	5112714	0	T	A	0.897685	0.991001	36.1889	1.80E-09	0.0216055	0.00363324	35.3625	2.70E-09
rs113934092	20	6205081	0	G	C	0.983173	0.996203	42.8832	5.80E-11	-0.055065	0.00853572	41.617	1.10E-10
rs4813800	20	6595646	0	A	G	0.370785	0.998715	334.855	8.40E-75	0.0413698	0.00227192	331.576	4.40E-74
rs4347920	20	6668823	0	A	C	0.402272	0.988313	50.3056	1.30E-12	0.0161225	0.00224788	51.4424	7.40E-13
rs6054494	20	6710434	0	T	G	0.671296	0.987354	126.043	3.00E-29	0.0259715	0.00234449	122.716	1.60E-28
rs1049007	20	6751034	0	A	G	0.383366	0.97515	58.6297	1.90E-14	0.0175274	0.00228685	58.7438	1.80E-14
rs6085765	20	6929131	0	C	T	0.478904	0.993635	32.3179	1.30E-08	0.0126192	0.00220129	32.8629	9.90E-09
rs6117726	20	7243540	0	T	C	0.505846	0.976785	50.3597	1.30E-12	-0.015592	0.00221661	49.4792	2.00E-12
rs911641	20	13259045	0	C	G	0.633558	0.98767	48.0614	4.10E-12	-0.0162565	0.00228982	50.4022	1.30E-12
rs6080829	20	17769853	0	G	A	0.564946	0.998603	44.4826	2.60E-11	0.0147394	0.00220861	44.5373	2.50E-11
rs73125628	20	20066701	0	C	T	0.721688	0.998797	41.6873	1.10E-10	0.0157445	0.0024504	41.2841	1.30E-10
rs8117259	20	20348253	0	C	T	0.819672	0.974785	29.457	5.70E-08	0.0158864	0.0028857	30.3074	3.70E-08
rs6082354	20	21217976	0	A	C	0.332601	1	79.1469	5.80E-19	0.0207748	0.00232728	79.6849	4.40E-19
rs113818546	20	30369090	0	C	T	0.787099	0.999768	33.3883	7.50E-09	-0.0157021	0.00267517	34.452	4.40E-09
rs4911268	20	31438954	0	A	G	0.816776	0.998683	49.8189	1.70E-12	0.0198481	0.00283598	48.9814	2.60E-12
rs141562525	20	31778416	0	G	A	0.977969	0.959932	39.7571	2.90E-10	-0.0421034	0.00761842	30.5425	3.30E-08
rs3213141	20	32274380	0	G	A	0.734079	0.987294	350.625	3.10E-78	0.0445261	0.00249964	317.303	5.60E-71
rs2626559	20	32411217	0	G	A	0.840751	0.997062	41.9575	9.30E-11	-0.01764	0.00300112	34.5487	4.20E-09
rs148962304	20	32683630	0	T	G	0.989223	0.839174	36.2375	1.70E-09	0.0725667	0.0115587	39.4144	3.40E-10
rs117915681	20	32828786	0	G	A	0.976662	1	65.0921	7.10E-16	-0.0613471	0.00725671	71.4674	2.80E-17
rs528172479	20	32846503	0	T	A	0.986637	0.959269	26.9782	2.10E-07	-0.0540664	0.00974213	30.7998	2.90E-08
rs6088638	20	33470514	0	T	C	0.826489	0.993067	223.102	1.90E-50	-0.0394355	0.00290734	183.984	6.50E-42
rs41307159	20	33586968	0	G	A	0.979907	1	98.9467	2.60E-23	0.072324	0.00781765	85.5878	2.20E-20
rs143384	20	34025756	0	A	G	0.59664	1	1779.22	0	-0.0915484	0.00223267	1681.32	0
rs151197637	20	34218087	0	G	A	0.985903	0.962757	63.4269	1.70E-15	-0.076354	0.00946381	65.0925	7.10E-16
rs151123887	20	34593288	0	G	A	0.977535	0.914773	63.1368	1.90E-15	0.0621428	0.00772848	64.6538	8.90E-16
rs8114927	20	35050323	0	T	C	0.0723685	0.97531	74.5637	5.90E-18	-0.0340229	0.00428631	63.0052	2.10E-15
rs79688337	20	35488246	0	C	A	0.919734	0.983836	41.6826	1.10E-10	-0.0247411	0.0040676	36.9964	1.20E-09
rs6017688	20	35892425	0	C	T	0.957824	0.986186	41.0414	1.50E-10	-0.0352849	0.00548552	41.3754	1.30E-10
rs6129227	20	37880233	0	A	G	0.936277	0.972258	32.2909	1.30E-08	0.0263414	0.00454544	33.5836	6.80E-09
rs2224538	20	38552078	0	T	C	0.636327	0.992119	51.6229	6.70E-13	0.016694	0.00228799	53.2369	3.00E-13

rs4812435	20	38872419	0	T	C	0.336714	0.983456	33.3347	7.80E-09	-0.0133211	0.00233987	32.4112	1.20E-08
rs35517142	20	39766116	0	G	T	0.960167	0.975035	48.1114	4.00E-12	0.0389546	0.00567479	47.1214	6.70E-12
rs6130354	20	41978786	0	T	G	0.865994	0.986465	33.7101	6.40E-09	-0.0188659	0.00323495	34.0109	5.50E-09
rs285204	20	42296961	0	T	C	0.11828	0.999349	56.8101	4.80E-14	0.0254528	0.00339149	56.3238	6.10E-14
rs2239535	20	43516156	0	G	A	0.779132	0.991617	52.3604	4.60E-13	-0.0190914	0.00265266	51.7976	6.20E-13
rs6104390	20	44524513	0	C	T	0.425143	0.998914	31.7207	1.80E-08	-0.0123618	0.00221895	31.0363	2.50E-08
rs6066104	20	45530530	0	C	T	0.675002	0.994012	69.2191	8.80E-17	-0.0198583	0.0023421	71.8908	2.30E-17
rs13041213	20	47800829	0	T	A	0.763871	0.986154	198.754	3.90E-45	-0.0364164	0.00259654	196.7	1.10E-44
rs6095728	20	48599960	0	C	T	0.881421	0.99918	87.8471	7.10E-21	0.0319057	0.00338694	88.7406	4.50E-21
rs3761181	20	48895112	0	A	G	0.466001	0.99002	31.1703	2.40E-08	-0.0123468	0.00220575	31.3326	2.20E-08
rs913678	20	48955424	0	T	C	0.669388	0.994222	33.6366	6.60E-09	0.0134012	0.00233887	32.8303	1.00E-08
rs13037515	20	49090262	0	T	C	0.834292	0.992277	57.7411	3.00E-14	-0.0224974	0.00295772	57.8563	2.80E-14
rs6063678	20	50231518	0	A	G	0.72742	0.995418	34.3883	4.50E-09	0.0144254	0.00246775	34.1703	5.00E-09
rs6013313	20	50516492	0	A	G	0.898716	0.992388	29.1577	6.70E-08	0.0202248	0.00364559	30.7775	2.90E-08
rs12106274	20	54837898	0	G	C	0.342851	0.981703	48.9712	2.60E-12	0.0162003	0.0023317	48.2728	3.70E-12
rs6024810	20	54925226	0	C	T	0.747223	0.996965	31.0626	2.50E-08	-0.0142585	0.00252467	31.8962	1.60E-08
rs185799410	20	57466093	0	G	T	0.973935	0.969436	95.455	1.50E-22	0.0680299	0.00697936	95.0098	1.90E-22
rs6100340	20	57684612	0	A	G	0.86616	0.987769	58.399	2.10E-14	-0.0250257	0.00324088	59.6273	1.10E-14
rs2236202	20	60985164	0	C	T	0.738076	0.989344	56.3505	6.10E-14	0.0190092	0.00250162	57.7412	3.00E-14
rs35628589	20	61440005	0	C	T	0.929442	0.916907	82.7781	9.20E-20	-0.040698	0.00447263	82.798	9.10E-20
rs1077418	20	61507741	0	C	T	0.92051	0.996921	39.7705	2.90E-10	-0.0257135	0.00405157	40.2787	2.20E-10
rs380158	20	62148124	0	A	T	0.712735	0.992883	38.8093	4.70E-10	0.0149982	0.00242814	38.1531	6.50E-10
rs3003137	20	62830802	0	G	T	0.571822	0.984582	38.7097	4.90E-10	0.0137664	0.00223235	38.0293	7.00E-10
rs2823096	21	16522082	0	A	G	0.814281	0.987796	30.1151	4.10E-08	-0.015791	0.0028599	30.4872	3.40E-08
rs13051770	21	17391965	0	C	T	0.242734	0.999357	50.8706	9.90E-13	0.0185866	0.00257767	51.9929	5.60E-13
rs229048	21	28314030	0	A	G	0.226473	0.992909	47.393	5.80E-12	-0.0182657	0.0026475	47.5994	5.20E-12
rs2832019	21	30112207	0	A	G	0.860447	0.997975	68.7385	1.10E-16	0.0266336	0.00319796	69.3605	8.20E-17
rs11088114	21	30612396	0	C	A	0.893115	0.98356	34.1899	5.00E-09	-0.0212706	0.00360648	34.7849	3.70E-09
rs9978987	21	33007192	0	G	A	0.771905	0.981224	34.4187	4.40E-09	-0.0153654	0.00266396	33.2685	8.00E-09
rs9979156	21	35677185	0	G	T	0.429325	0.995128	100.599	1.10E-23	-0.0224674	0.00223742	100.835	1.00E-23
rs2236433	21	37692589	0	A	T	0.858157	0.977575	49.8899	1.60E-12	0.0223729	0.00320195	48.8219	2.80E-12
rs62229404	21	37759957	0	C	T	0.907014	1	40.2062	2.30E-10	-0.024168	0.00381005	40.2365	2.30E-10
rs737380	21	38077468	0	A	G	0.265401	0.987788	36.4359	1.60E-09	-0.0151889	0.00251464	36.4839	1.50E-09
rs1155786	21	38448025	0	A	G	0.484638	0.999722	45.9188	1.20E-11	0.0150556	0.00221354	46.2616	1.00E-11
rs2298333	21	39673981	0	C	T	0.431552	0.995805	209.065	2.20E-47	0.0322541	0.00223649	207.987	3.80E-47
rs2836492	21	39913129	0	C	T	0.269585	0.991087	34.9849	3.30E-09	0.014729	0.00250174	34.6626	3.90E-09
rs12151985	21	40726813	0	G	T	0.964358	0.986261	35.119	3.10E-09	0.0356672	0.00599562	35.3891	2.70E-09
rs9974653	21	40741846	0	A	C	0.682266	0.990696	40.2696	2.20E-10	-0.0153903	0.00238171	41.7557	1.00E-10
rs7282525	21	41460412	0	C	T	0.346012	1	41.8874	9.70E-11	0.0149274	0.00231959	41.4139	1.20E-10
rs2839078	21	47429769	0	C	G	0.2297	0.993569	46.484	9.20E-12	-0.0180041	0.0026359	46.6537	8.50E-12
rs4819200	21	47516905	0	C	T	0.918491	0.978215	33.9572	5.60E-09	-0.0237018	0.00408041	33.7408	6.30E-09
rs35665085	22	17625915	0	G	A	0.943919	1	31.8063	1.70E-08	0.0269973	0.00482341	31.3279	2.20E-08
rs12628193	22	20791438	0	C	A	0.623841	1	90.7343	1.60E-21	-0.0215015	0.00229206	88.0008	6.50E-21
rs6005255	22	27376910	0	T	C	0.84459	0.996114	32.5006	1.20E-08	-0.017316	0.00307187	31.7752	1.70E-08
rs134077	22	28063227	0	A	G	0.437112	0.994627	56.731	5.00E-14	-0.0170621	0.0022446	57.7815	2.90E-14
rs79378907	22	29346667	0	C	T	0.967835	0.98973	136.597	1.50E-31	0.073741	0.00632516	135.917	2.10E-31
rs41174	22	30426069	0	C	T	0.679276	0.991754	76.3039	2.40E-18	-0.020966	0.00238897	77.0214	1.70E-18
rs718810	22	33077216	0	G	A	0.919983	0.98146	80.4756	2.90E-19	0.0373743	0.00413083	81.8599	1.50E-19
rs1053593	22	35660875	0	G	T	0.349885	1	62.8177	2.30E-15	-0.0183262	0.00232859	61.9383	3.50E-15
rs77149271	22	36769402	0	T	G	0.911993	0.994221	32.1604	1.40E-08	-0.0224466	0.00393935	32.4678	1.20E-08
rs6000890	22	38187301	0	C	T	0.365276	0.997454	49.9998	1.50E-12	-0.0163116	0.00230839	49.9313	1.60E-12
rs2064103	22	38608227	0	T	C	0.44781	0.997098	58.6735	1.90E-14	0.0170442	0.00223725	58.0396	2.60E-14
rs4361209	22	39281636	0	A	G	0.776794	0.999348	86.7174	1.30E-20	-0.0246136	0.00266881	85.0583	2.90E-20
rs139358	22	39513530	0	C	T	0.62112	0.987481	51.6186	6.70E-13	-0.0164679	0.00230399	51.0876	8.80E-13
rs58401738	22	39733487	0	G	A	0.849962	0.981511	31.3946	2.10E-08	0.0174822	0.00314147	30.9689	2.60E-08
rs7423	22	39781429	0	C	T	0.322737	0.993837	49.5906	1.90E-12	-0.0169476	0.00238574	50.4625	1.20E-12
rs112119625	22	41208244	0	C	T	0.960861	0.936827	36.9218	1.20E-09	0.036311	0.005905	37.8125	7.80E-10
rs2092665	22	43270877	0	A	G	0.527848	0.98078	72.09	2.10E-17	0.0190138	0.0022466	71.6283	2.60E-17
rs34074034	22	43568512	0	C	T	0.753887	1	30.2866	3.70E-08	0.0141644	0.00257885	30.1679	4.00E-08
rs6007043	22	45838646	0	T	C	0.799357	0.995098	81.2551	2.00E-19	-0.0250006	0.00277756	81.0165	2.20E-19
rs7293204	22	46231145	0	G	T	0.581039	0.990252	64.12	1.20E-15	-0.0180694	0.00226392	63.7041	1.40E-15
rs28573340	22	46417269	0	A	G	0.936088	0.995068	50.2544	1.40E-12	-0.0319119	0.00455176	49.1527	2.40E-12

Summary statistics for the genetic association with body shape PC3

rsid	CHR	BP	GENPOS	ALLELE1	ALLELE0	A1FREQ	INFO	CHISQ_LINREG	P_LINREG	BETA	SE	CHISQ_BOLT_LMM_INF	pval
rs10458575	1	65569765	0	T	C	0.695009	0.993029	41.254	1.30E-10	0.0123586	0.00195365	40.017	2.50E-10
rs10494421	1	164738727	0	C	T	0.881145	1	28.2061	1.10E-07	-0.0151435	0.00276574	29.98	4.40E-08
rs10752944	1	172363524	0	C	T	0.433821	0.998568	192.778	7.90E-44	0.0254125	0.00180797	197.566	7.10E-45
rs10797938	1	184019954	0	C	A	0.6547	0.999618	111.489	4.60E-26	-0.0196307	0.00188274	108.715	1.90E-25
rs10863669	1	222097527	0	T	C	0.49153	0.99299	31.5454	1.90E-08	0.00998591	0.00179622	30.9069	2.70E-08
rs111297064	1	176279844	0	C	A	0.522994	0.999908	50.4024	1.30E-12	0.0127593	0.00178969	50.8274	1.00E-12
rs11205303	1	149906413	0	T	C	0.593201	1	42.5046	7.10E-11	-0.0117421	0.00182507	41.3934	1.20E-10
rs112835528	1	155122335	0	C	T	0.888693	0.978764	33.5184	7.10E-09	0.0165896	0.00287644	33.2631	8.00E-09
rs114848253	1	119049675	0	A	T	0.961831	0.925582	63.108	2.00E-15	-0.0390228	0.00484831	64.7821	8.40E-16
rs115276619	1	184865132	0	T	A	0.983113	0.939309	31.685	1.80E-08	0.041018	0.00717171	32.7118	1.10E-08
rs115370145	1	165308253	0	C	T	0.957012	0.965901	34.8464	3.60E-09	-0.0264727	0.00448673	34.8126	3.60E-09
rs12030612	1	113215637	0	C	T	0.796863	0.999765	28.7224	8.40E-08	0.0121897	0.00222717	29.9555	4.40E-08
rs12096239	1	26796922	0	G	C	0.746566	0.998144	29.1953	6.50E-08	0.0114236	0.00205922	30.7751	2.90E-08
rs12135916	1	22470115	0	G	A	0.241144	0.994057	36.3472	1.70E-09	0.0125432	0.00209978	35.6837	2.30E-09
rs12136856	1	156473114	0	C	G	0.347314	0.993097	72.5252	1.60E-17	0.0159678	0.00188688	71.6142	2.60E-17
rs1249558	1	160424761	0	T	A	0.730852	0.996115	52.9047	3.50E-13	0.0148274	0.00202297	53.7219	2.30E-13
rs12568411	1	22622329	0	G	A	0.83304	0.980522	31.4592	2.00E-08	0.0134454	0.00242884	30.6444	3.10E-08
rs140953793	1	155908657	0	C	G	0.980549	0.932333	75.5234	3.60E-18	0.0586375	0.00671758	76.1948	2.60E-18
rs144206004	1	39832435	0	C	T	0.96893	0.991453	37.122	1.10E-09	-0.0316933	0.00518096	37.421	9.50E-10
rs1524002	1	86011289	0	G	A	0.82362	1	32.6817	1.10E-08	-0.0135026	0.00235184	32.9627	9.40E-09
rs1531094	1	219655876	0	A	G	0.325036	0.996459	329.64	1.20E-73	-0.0347817	0.00191348	330.412	7.80E-74
rs1540322	1	170636982	0	A	G	0.860702	0.979781	37.6093	8.60E-10	0.0162021	0.00261051	38.5203	5.40E-10
rs1596173	1	221286855	0	T	A	0.701761	0.997885	97.5627	5.20E-23	-0.0193171	0.0019574	97.3919	5.70E-23
rs173273	1	212446689	0	G	T	0.409552	0.996662	86.3438	1.50E-20	0.0169755	0.00182352	86.6608	1.30E-20
rs1934852	1	218594920	0	G	T	0.712889	0.999109	60.3634	7.90E-15	-0.0153131	0.00197866	59.8943	1.00E-14
rs2265978	1	219584931	0	C	A	0.743804	0.996576	94.609	2.30E-22	-0.0201016	0.00205198	95.9648	1.20E-22
rs2274533	1	151395782	0	T	C	0.172712	0.999293	30.6191	3.10E-08	-0.0133288	0.00236824	31.676	1.80E-08
rs2284746	1	17306675	0	C	G	0.478027	1	139.777	3.00E-32	-0.0211868	0.00179251	139.703	3.10E-32
rs239341	1	42255221	0	C	A	0.469247	0.997291	38.1355	6.60E-10	-0.0107813	0.00179791	35.9587	2.00E-09
rs2639621	1	172609760	0	T	G	0.424881	0.988304	40.9416	1.60E-10	-0.0115988	0.00182146	40.5494	1.90E-10
rs2821228	1	203517723	0	C	G	0.461986	0.986644	49.2166	2.30E-12	0.0124752	0.00180715	47.6549	5.10E-12
rs2993481	1	2973433	0	A	T	0.813298	0.995523	40.9057	1.60E-10	-0.0149955	0.00230877	42.185	8.30E-11
rs3119837	1	170352113	0	C	T	0.730813	0.997164	242.749	9.90E-55	0.0318191	0.00202103	247.873	7.60E-56
rs313713	1	86253805	0	G	A	0.616403	0.993005	71.6513	2.60E-17	-0.015876	0.00184829	73.7811	8.70E-18
rs35650284	1	218966592	0	A	G	0.907112	0.999676	33.8745	5.90E-09	-0.0180089	0.00308295	34.1224	5.20E-09
rs4951373	1	204392257	0	G	A	0.890824	1	33.0339	9.10E-09	0.0163264	0.00286736	32.4201	1.20E-08
rs59885016	1	227753496	0	T	A	0.843826	0.991704	123.221	1.20E-28	0.0275056	0.0024773	123.277	1.20E-28
rs61783468	1	9341132	0	C	T	0.8618	0.984002	61.4505	4.50E-15	0.0204438	0.00261827	60.9672	5.80E-15
rs61806178	1	119408220	0	C	T	0.969733	1	35.279	2.90E-09	-0.0312247	0.00521895	35.7957	2.20E-09
rs61819927	1	200056504	0	C	G	0.91668	1	37.7185	8.20E-10	0.020052	0.00323665	38.3817	5.80E-10
rs61836042	1	220037210	0	C	T	0.966219	0.834373	39.7463	2.90E-10	-0.0337404	0.00543192	38.5828	5.20E-10
rs6428789	1	119550480	0	A	C	0.430391	0.993587	333.214	1.90E-74	-0.0331875	0.0018151	334.309	1.10E-74
rs646370	1	32401166	0	A	G	0.853666	0.997347	39.0469	4.10E-10	-0.0155847	0.00253742	37.7233	8.20E-10
rs6593925	1	205100663	0	G	C	0.0920711	0.998427	47.8108	4.70E-12	-0.0214803	0.00309329	48.2216	3.80E-12
rs721651	1	41563329	0	A	C	0.219787	0.996824	58.1787	2.40E-14	0.0165741	0.00216728	58.4833	2.10E-14
rs72641835	1	9336748	0	C	T	0.748271	0.980429	38.7347	4.90E-10	-0.0131488	0.00208859	39.6341	3.10E-10
rs72664355	1	57007791	0	T	C	0.907534	0.985646	35.6626	2.30E-09	0.018474	0.00311719	35.1232	3.10E-09
rs74060619	1	25305261	0	G	A	0.871473	0.990054	34.1574	5.10E-09	-0.0157126	0.00268862	34.1537	5.10E-09
rs7519523	1	214608414	0	C	T	0.600957	0.996016	39.947	2.60E-10	-0.011561	0.00183051	39.8887	2.70E-10
rs7534091	1	118864616	0	A	G	0.737517	0.998956	195.609	1.90E-44	0.0283406	0.00203708	193.553	5.30E-44
rs7553934	1	25218685	0	G	A	0.87616	0.994876	31.9595	1.60E-08	0.0157719	0.00272872	33.4079	7.50E-09
rs805047	1	89242372	0	A	G	0.381815	0.995473	87.6228	7.90E-21	-0.0173729	0.00184739	88.4359	5.30E-21
rs10164853	2	158481992	0	A	G	0.923617	0.982175	31.3904	2.10E-08	-0.0196014	0.00339809	33.2739	8.00E-09
rs10177093	2	188213819	0	G	T	0.457529	0.996803	56.4017	5.90E-14	-0.0134836	0.00180132	56.0308	7.10E-14
rs10189479	2	219287276	0	C	A	0.567391	0.993629	65.3859	6.20E-16	0.0145805	0.00181048	64.8569	8.10E-16
rs10190249	2	66242525	0	G	A	0.823891	0.995222	81.8229	1.50E-19	-0.0211821	0.00234834	81.3609	1.90E-19
rs10192454	2	121622768	0	G	C	0.493645	0.993807	68.5007	1.30E-16	0.0145291	0.00179529	65.4948	5.80E-16
rs10202701	2	232328681	0	C	T	0.457814	0.994223	84.4059	4.00E-20	-0.0166354	0.00180393	85.0409	2.90E-20
rs113050728	2	111898984	0	T	C	0.936458	0.998727	45.0988	1.90E-11	-0.0247543	0.00366589	45.5976	1.50E-11
rs113386058	2	20143831	0	A	T	0.971032	0.970937	115.018	7.80E-27	0.0580548	0.00541431	114.971	8.00E-27
rs114416276	2	25889076	0	C	T	0.965626	1	49.4916	2.00E-12	-0.0347939	0.00490888	50.2392	1.40E-12
rs11673779	2	16846587	0	A	G	0.782631	0.99762	35.1077	3.10E-09	0.0130173	0.00217149	35.9354	2.00E-09
rs11674410	2	23877566	0	T	G	0.115086	0.949549	50.9661	9.40E-13	-0.0205622	0.00287713	51.0763	8.90E-13
rs11678026	2	25074086	0	G	T	0.863259	1	42.2599	8.00E-11	0.0168398	0.00260506	41.7866	1.00E-10
rs11688369	2	174738969	0	G	A	0.428152	0.984235	28.7887	8.10E-08	0.0100636	0.00182156	30.5226	3.30E-08
rs11695927	2	65823020	0	A	G	0.88765	0.998262	41.073	1.50E-10	0.0184418	0.00283525	42.3081	7.80E-11
rs12185751	2	219904908	0	G	A	0.899013	0.999651	86.7931	1.20E-20	0.0281099	0.0029704	89.5547	3.00E-21
rs12475377	2	134490796	0	G	C	0.822033	0.983881	38.5822	5.20E-10	0.0147359	0.00235779	39.0612	4.10E-10
rs1250258	2	216300185	0	C	T	0.263611	0.994543	86.5527	1.40E-20	0.0191371	0.00203703	88.2584	5.70E-21
rs12620853	2	33387188	0	A	G	0.495837	0.9959	59.172	1.40E-14	-0.0137421	0.00179122	58.8586	1.70E-14
rs12692387	2	9698190	0	T	C	0.326037	0.976537	63.85	1.30E-15	-0.015517	0.00192781	64.7863	8.30E-16
rs12694042	2	207029825	0	C	T	0.498495	0.988168	40.0403	2.50E-10	-0.0115462	0.00179882	41.2003	1.40E-10
rs12711783	2	114458734	0	A	G	0.569076	0.996932	32.0073	1.50E-08	0.0102407	0.00180628	32.1434	1.40E-08
rs12713370	2	58200748	0	A	G	0.390052	0.994977	42.1389	8.50E-11	-0.0121088	0.00183781	43.4114	4.40E-11
rs13007308	2	99728548	0	T	C	0.757162	0.984504	28.9144	7.60E-08	-0.0116776	0.00210074	30.9002	2.70E-08
rs13389219	2	165528876	0	C	T	0.607662	0.999694	282.061	2.70E-63	0.030932	0.00183259	284.897	6.40E-64
rs13401968	2	67764826	0	T	C	0.843883	0.984985	46.1256	1.10E-11	0.016905	0.00247938	46.488	9.20E-12
rs1346747	2	38008662	0	A	G	0.417488	0.978378	37.5549	8.90E-10	-0.0111568	0.00183256	37.0649	1.10E-09
rs1450570	2	200442061	0	A	C	0.172232	0.999302	33.1481	8.50E-09	-0.0135676	0.00237126	32.7377	1.10E-08
rs1563127	2	225073276	0	A	G	0.548326	0.997891	84.3934	4.10E-20	0.0165361	0.00179879	84.5087	3.80E-20
rs16825944	2	232291866	0	C	T	0.758737	0.984289	51.1048	8.80E-13	0.0149364	0.00210744	50.2323	1.40E-12
rs17511102	2	37960613	0	A	T	0.910678	1	104.535	1.50E-24	-0.0324227	0.00314136	106.528	5.60E-25

rs17685753	2	67785025	0	G	A	0.887478	0.989579	66.4597	3.60E-16	-0.0233049	0.00284656	67.0277	2.70E-16
rs1898711	2	216485141	0	T	A	0.207011	0.983118	49.0253	2.50E-12	0.0153366	0.00222569	47.4822	5.60E-12
rs200104212	2	112256611	0	G	C	0.790219	0.987107	89.264	3.50E-21	0.0207604	0.00221129	88.1412	6.10E-21
rs2030692	2	100287810	0	T	C	0.182912	0.999829	32.3709	1.30E-08	0.0132708	0.00231278	32.9251	9.60E-09
rs2062204	2	67472545	0	A	C	0.245189	0.99243	44.8817	2.10E-11	0.0140671	0.00208794	45.3913	1.60E-11
rs2853360	2	233120444	0	C	T	0.888069	0.99588	87.2574	9.50E-21	0.0266659	0.00284269	87.994	6.60E-21
rs2902065	2	68482327	0	A	G	0.331485	0.995718	50.4046	1.30E-12	0.0138892	0.00190615	53.0928	3.20E-13
rs35656614	2	38750533	0	T	C	0.811752	0.990959	42.8695	5.90E-11	-0.0149269	0.00230313	42.0054	9.10E-11
rs3890755	2	66744603	0	C	T	0.476946	0.982242	57.9948	2.60E-14	0.0138077	0.0018071	58.3821	2.20E-14
rs41393947	2	56011517	0	G	A	0.857585	0.987295	43.5557	4.10E-11	-0.0168471	0.00257548	42.789	6.10E-11
rs4670893	2	33360848	0	G	C	0.292147	0.995372	39.8589	2.70E-10	-0.0127109	0.00197459	41.438	1.20E-10
rs4953627	2	48990167	0	C	T	0.773746	0.975797	37.0055	1.20E-09	0.0131438	0.00216401	36.8914	1.20E-09
rs5024713	2	33568137	0	G	A	0.776789	0.97114	30.0591	4.20E-08	0.0121229	0.00218045	30.9117	2.70E-08
rs55920843	2	158412701	0	T	G	0.988129	1	55.3241	1.00E-13	0.061224	0.00826517	54.8706	1.30E-13
rs56042410	2	46914082	0	A	T	0.739577	0.98642	65.6986	5.30E-16	-0.0166713	0.00205017	66.1235	4.20E-16
rs59985551	2	56106928	0	C	T	0.774234	0.998856	129.921	4.30E-30	0.0242992	0.00213846	129.116	6.40E-30
rs62120155	2	11308842	0	G	A	0.449373	0.989721	61.8742	3.70E-15	0.0142824	0.00180908	62.329	2.90E-15
rs62141260	2	48182677	0	C	T	0.646572	0.998561	28.2813	1.00E-07	-0.0102585	0.0018734	29.9853	4.40E-08
rs62169889	2	114687328	0	A	G	0.370424	0.998719	57.6386	3.10E-14	-0.0140733	0.00185538	57.5346	3.30E-14
rs6432052	2	10189699	0	T	C	0.205024	0.997224	43.1377	5.10E-11	0.0146636	0.00221832	43.6954	3.80E-11
rs6433219	2	171421125	0	G	A	0.730675	0.997121	33.6801	6.50E-09	-0.0116007	0.00201906	33.0118	9.20E-09
rs6437056	2	233097174	0	G	A	0.0897434	1	51.1475	8.60E-13	0.0220559	0.00313203	49.5903	1.90E-12
rs6710091	2	239597	0	C	G	0.651388	0.999366	49.3872	2.10E-12	-0.013289	0.00187707	50.1213	1.40E-12
rs6739187	2	25513652	0	G	A	0.566064	0.981145	96.8301	7.60E-23	0.0178762	0.00182111	96.356	9.60E-23
rs67429428	2	66074282	0	C	T	0.779177	0.995484	44.0278	3.20E-11	-0.0142316	0.00215952	43.4302	4.40E-11
rs6752964	2	43754655	0	T	C	0.89165	0.995575	50.892	9.80E-13	-0.0205507	0.00288364	50.7889	1.00E-12
rs72836352	2	111894874	0	C	T	0.897991	0.983851	56.5799	5.40E-14	0.0220975	0.00297647	55.1165	1.10E-13
rs72927479	2	158516337	0	A	G	0.946999	1	47.5156	5.50E-12	0.0269412	0.00398419	45.725	1.40E-11
rs7569646	2	25152800	0	A	G	0.633948	0.99432	179.563	6.00E-41	0.0251657	0.00186074	182.914	1.10E-41
rs7593987	2	44393532	0	A	G	0.191381	0.995656	36.0655	1.90E-09	0.0130623	0.00227712	32.9056	9.70E-09
rs76950464	2	225549704	0	G	T	0.964705	0.986145	32.4329	1.20E-08	-0.0280231	0.0048891	32.853	9.90E-09
rs77060225	2	233060816	0	T	C	0.979285	0.996896	33.8198	6.00E-09	0.0353915	0.00628536	31.7058	1.80E-08
rs779390	2	13088063	0	T	C	0.441873	0.998849	73.1899	1.20E-17	0.0154612	0.00179359	74.3084	6.70E-18
rs78444492	2	56181371	0	C	T	0.953925	0.982852	36.9666	1.20E-09	-0.0263072	0.00430145	37.4041	9.60E-10
rs78923898	2	197363544	0	T	C	0.89868	0.998953	30.5539	3.20E-08	0.0169156	0.00296463	32.556	1.20E-08
rs79057767	2	233093733	0	A	G	0.96767	0.993648	106.66	5.30E-25	-0.0532083	0.00507315	110.003	9.80E-26
rs9742	2	37869494	0	G	T	0.730688	0.995565	29.7374	4.90E-08	-0.0110342	0.00201751	29.9121	4.50E-08
rs9752106	2	239735823	0	T	G	0.774574	0.995808	30.5309	3.30E-08	0.0119168	0.00214673	30.8153	2.80E-08
rs9973704	2	37999909	0	G	A	0.230114	0.98971	50.8402	1.00E-12	-0.0150729	0.00213451	49.8653	1.60E-12
rs112551697	3	150018637	0	G	A	0.965905	0.929432	39.1554	3.90E-10	-0.0319376	0.00511783	38.9435	4.40E-10
rs112611929	3	53218639	0	C	T	0.939107	0.960434	57.4355	3.50E-14	-0.0293259	0.00382117	58.8993	1.70E-14
rs113664481	3	33520696	0	A	G	0.96647	0.993126	42.5313	7.00E-11	-0.0331862	0.00499006	44.2287	2.90E-11
rs114496946	3	12481174	0	T	C	0.985061	0.964122	103.661	2.40E-24	0.0769489	0.00752361	104.605	1.50E-24
rs11705701	3	185544309	0	G	A	0.563822	0.992193	48.1775	3.90E-12	-0.0127557	0.00181676	49.2966	2.20E-12
rs11711770	3	43066768	0	A	G	0.829324	0.996992	45.4543	1.60E-11	0.0160656	0.00238794	45.2634	1.70E-11
rs11921117	3	47294000	0	T	C	0.610249	0.997978	76.3934	2.30E-18	0.0158054	0.00183847	73.9094	8.20E-18
rs12486852	3	157656017	0	C	G	0.862818	0.986969	68.3758	1.40E-16	-0.0221464	0.00262464	71.1977	3.20E-17
rs12634766	3	125133102	0	T	A	0.487926	0.982252	31.2166	2.30E-08	0.010092	0.00180924	31.1148	2.40E-08
rs13062095	3	101267385	0	T	C	0.66284	0.993792	41.4926	1.20E-10	-0.0121191	0.00190382	40.5219	1.90E-10
rs13072812	3	24388501	0	C	A	0.771464	0.977468	31.7025	1.80E-08	0.0119486	0.00215928	30.621	3.10E-08
rs1344674	3	141125186	0	A	G	0.554071	0.99972	133.849	5.90E-31	-0.0207664	0.00180414	132.489	1.20E-30
rs138653738	3	49194532	0	A	T	0.955564	0.999046	79.0005	6.20E-19	-0.0388672	0.00435504	79.6496	4.50E-19
rs144339338	3	49048054	0	C	T	0.9732	0.985402	36.0524	1.90E-09	-0.0332555	0.00559743	35.298	2.80E-09
rs146146633	3	129294723	0	C	T	0.98357	0.978517	57.9352	2.70E-14	-0.0539755	0.00713261	57.2659	3.80E-14
rs146167147	3	129170212	0	C	T	0.986708	0.900995	52.8531	3.60E-13	-0.0596007	0.00824243	52.2868	4.80E-13
rs147499383	3	64600350	0	T	G	0.982481	0.879382	39.9547	2.60E-10	0.0462658	0.00728572	40.3251	2.20E-10
rs17007999	3	70958673	0	A	G	0.893902	0.973375	31.7868	1.70E-08	0.0166732	0.00294798	31.9881	1.60E-08
rs17075898	3	43752187	0	T	G	0.975273	0.999754	38.9813	4.30E-10	0.0363034	0.00577147	39.5661	3.20E-10
rs1874942	3	12690343	0	G	A	0.429865	0.999071	87.2337	9.60E-21	-0.0170084	0.00181162	88.1438	6.10E-21
rs2073499	3	50374293	0	A	G	0.861073	0.999685	37.037	1.20E-09	-0.0155406	0.00259256	35.9319	2.00E-09
rs2302417	3	52814256	0	T	A	0.521098	0.987674	139.753	3.00E-32	0.0213264	0.00180733	139.239	3.90E-32
rs2507948	3	37832172	0	A	G	0.452306	0.986412	37.1902	1.10E-09	0.0112906	0.00181109	38.865	4.50E-10
rs262976	3	183443403	0	A	G	0.41312	0.988769	34.7988	3.70E-09	-0.0104721	0.00183287	32.6439	1.10E-08
rs4493414	3	12255923	0	A	G	0.103204	0.994528	31.891	1.60E-08	0.0164356	0.00295604	30.9136	2.70E-08
rs4681011	3	78835738	0	A	C	0.36564	0.994579	52.1342	5.20E-13	0.0133543	0.00186658	51.1859	8.40E-13
rs4974088	3	48898749	0	T	C	0.231838	0.999644	130.191	3.70E-30	-0.0242722	0.00212453	130.525	3.10E-30
rs56406311	3	156795408	0	C	T	0.612135	0.992775	101.749	6.30E-24	0.0186459	0.00185165	101.402	7.50E-24
rs61732778	3	187443314	0	G	A	0.928936	0.997529	31.1234	2.40E-08	-0.019546	0.00348666	31.4266	2.10E-08
rs62281759	3	196879666	0	T	C	0.863125	0.998611	33.578	6.80E-09	0.0148304	0.00261201	32.237	1.40E-08
rs6444307	3	188307518	0	A	G	0.585065	0.986301	33.179	8.40E-09	-0.0104596	0.00183608	32.4525	1.20E-08
rs66815886	3	64703394	0	G	T	0.722891	0.99656	313.671	3.50E-70	0.0355843	0.00200848	313.892	3.10E-70
rs6764325	3	129099871	0	A	G	0.0716041	0.980089	41.8982	9.60E-11	0.022355	0.00351914	40.3532	2.10E-10
rs6782394	3	107399129	0	A	G	0.501644	0.991012	57.6788	3.10E-14	0.0137006	0.00180364	57.6999	3.10E-14
rs6787775	3	57164408	0	A	T	0.864405	0.998768	51.7056	6.40E-13	-0.0189665	0.00262093	52.3677	4.60E-13
rs6806551	3	142766776	0	C	A	0.381846	0.996918	33.5769	6.90E-09	-0.0107288	0.00184692	33.7444	6.30E-09
rs7433991	3	134312292	0	A	T	0.325375	0.999923	42.0084	9.10E-11	-0.0124109	0.00191391	42.0499	8.90E-11
rs75178583	3	66477828	0	A	G	0.936553	1	33.5516	6.90E-09	0.0211742	0.00367244	33.2433	8.10E-09
rs7617908	3	61627044	0	A	G	0.599731	0.991419	32.1954	1.40E-08	-0.0103601	0.00183831	31.761	1.70E-08
rs7621604	3	61557718	0	A	G	0.55475	0.993333	102.963	3.40E-24	0.0181082	0.00180634	100.497	1.20E-23
rs7652177	3	171969077	0	C	G	0.495315	1	71.9661	2.20E-17	-0.0151212	0.00179488	70.9746	3.60E-17
rs79957430	3	52210982	0	G	A	0.981056	0.909598	31.2103	2.30E-08	0.0394261	0.00689128	32.7317	1.10E-08
rs80245809	3	129284127	0	G	A	0.985212	0.949765	33.9679	5.60E-09	0.0451864	0.00762456	35.1226	3.10E-09
rs9824346	3	100517311	0	G	C	0.586169	0.998429	35.9156	2.10E-09	-0.0108129	0.00182226	35.2096	3.00E-09
rs9832668	3	72399093	0	G	A	0.743861	0.995133	51.4164	7.50E-13	0.0149558	0.00205819	52.8013	3.70E-13
rs9840468	3	129328711	0	A	G	0.802569	0.995036	131.166	2.30E-30	0.0259388	0.00225701	132.078	1.40E-30
rs9848655	3	138108352	0	G	A	0.839762	0.998081	51.3664	7.70E-13	-0.0175831	0.00244801	51.59	6.80E-13

rs9860524	3	112847668	0	C	T	0.482453	0.998822	33.8698	5.90E-09	-0.0103197	0.00179673	32.9891	9.30E-09
rs9870122	3	135820265	0	T	G	0.727586	0.993917	89.7494	2.70E-21	0.0192857	0.0020217	90.999	1.40E-21
rs9872031	3	12496461	0	G	A	0.57625	0.997666	150.385	1.40E-34	-0.022289	0.00181676	150.517	1.30E-34
rs9872283	3	99290102	0	A	G	0.364018	0.995963	73.7053	9.10E-18	0.0156875	0.0018685	70.4886	4.60E-17
rs10028284	4	89752913	0	A	T	0.824639	0.996372	33.396	7.50E-09	0.0137369	0.00236824	33.6455	6.60E-09
rs11721374	4	8599520	0	G	A	0.563684	0.987388	42.862	5.90E-11	0.0118224	0.00182243	42.0831	8.70E-11
rs11722554	4	5016883	0	G	A	0.962089	1	84.7384	3.40E-20	0.0433836	0.00471203	84.7687	3.40E-20
rs11727676	4	145659064	0	T	C	0.90336	1	137.844	7.90E-32	-0.0361419	0.00304168	141.187	1.50E-32
rs12645165	4	106087217	0	T	C	0.635694	0.999367	106.351	6.20E-25	-0.0191538	0.00186794	105.145	1.10E-24
rs13107325	4	103188709	0	C	T	0.925028	1	173.728	1.10E-39	0.0449255	0.00341971	172.586	2.00E-39
rs13108763	4	157697086	0	A	G	0.681627	0.99735	29.8949	4.60E-08	0.010627	0.00193133	30.2767	3.70E-08
rs13137905	4	15375668	0	T	G	0.736522	0.998626	30.8926	2.70E-08	0.0113856	0.00204262	31.0696	2.50E-08
rs1394999	4	145325530	0	G	T	0.40946	0.998173	69.3334	8.30E-17	-0.0153872	0.00183019	70.6848	4.20E-17
rs147418703	4	123923158	0	A	G	0.961305	0.987048	60.9083	6.00E-15	-0.0360835	0.00469065	59.1765	1.40E-14
rs1589163	4	73472941	0	C	T	0.47706	0.994778	59.4829	1.20E-14	0.013916	0.00180483	59.451	1.30E-14
rs16888802	4	13537668	0	T	G	0.824507	1	37.2419	1.00E-09	-0.0143419	0.00236322	36.8301	1.30E-09
rs1712374	4	82154710	0	T	C	0.694688	0.998978	84.9405	3.10E-20	-0.0181178	0.00195278	86.0807	1.70E-20
rs2137234	4	26080549	0	T	C	0.805323	0.996605	45.8397	1.30E-11	-0.0155478	0.00227365	46.7619	8.00E-12
rs2167750	4	89730074	0	C	T	0.536244	0.998405	190.64	2.30E-43	-0.0249694	0.00180472	191.424	1.60E-43
rs2575580	4	145605025	0	A	G	0.866021	0.993851	36.8337	1.30E-09	0.0160648	0.00264808	36.8037	1.30E-09
rs3135890	4	1806519	0	C	T	0.885897	0.942565	36.8581	1.30E-09	0.0175172	0.00290908	36.2591	1.70E-09
rs34311866	4	951947	0	T	C	0.822132	0.989783	35.2359	2.90E-09	-0.01418	0.00236574	35.9266	2.00E-09
rs34811474	4	25408838	0	G	A	0.76873	1	71.0087	3.60E-17	-0.0176777	0.00213314	68.6769	1.20E-16
rs35917388	4	120244663	0	G	A	0.85658	0.974486	34.6154	4.00E-09	-0.0150895	0.00259787	33.7378	6.30E-09
rs4834929	4	13194260	0	A	C	0.65903	0.994604	78.5874	7.70E-19	-0.016818	0.0018993	78.4078	8.40E-19
rs62317082	4	109467764	0	T	A	0.629943	0.991423	37.9182	7.40E-10	-0.0115914	0.00187101	38.3815	5.80E-10
rs62320884	4	125207005	0	T	G	0.778598	0.99481	41.2378	1.30E-10	-0.0138482	0.00217159	40.6657	1.80E-10
rs6446312	4	5019932	0	C	G	0.185837	0.998292	85.1655	2.70E-20	0.0213514	0.00231118	85.3465	2.50E-20
rs6817286	4	45084967	0	C	T	0.737898	0.992213	31.7434	1.80E-08	-0.0116263	0.002052	32.102	1.50E-08
rs6824748	4	17997066	0	G	A	0.840859	0.998417	96.4192	9.30E-23	0.0239295	0.00245808	94.7715	2.10E-22
rs73165969	4	57750725	0	G	A	0.81717	0.987809	75.798	3.10E-18	-0.0202973	0.00234077	75.1901	4.30E-18
rs73793175	4	1255460	0	G	A	0.945045	1	40.9774	1.50E-10	0.0251367	0.00394166	40.6687	1.80E-10
rs75621580	4	12916514	0	G	A	0.954347	0.996173	70.2999	5.10E-17	0.0364021	0.00431679	71.11	3.40E-17
rs7695004	4	26303026	0	C	A	0.314399	0.991772	83.0159	8.10E-20	0.0176078	0.00194449	81.9975	1.40E-19
rs819203	4	56257103	0	A	G	0.714383	0.996896	84.0902	4.70E-20	-0.0181288	0.00199341	82.7073	9.50E-20
rs10050388	5	101576247	0	T	C	0.910362	0.98321	30.6914	3.00E-08	0.017404	0.00316842	30.1725	4.00E-08
rs10474066	5	71758502	0	T	C	0.637898	0.985709	35.5035	2.50E-09	0.0109384	0.0018802	33.8453	6.00E-09
rs10477191	5	142077715	0	A	G	0.950941	0.912998	86.6842	1.30E-20	-0.0406822	0.00434957	87.4816	8.50E-21
rs112907088	5	142083969	0	A	G	0.974967	0.981796	45.2877	1.70E-11	-0.0390027	0.00578852	45.3997	1.60E-11
rs114167666	5	176653054	0	G	A	0.975046	0.997127	110.031	9.60E-26	0.0613394	0.00576067	113.379	1.80E-26
rs1173708	5	32843583	0	G	T	0.42588	0.975272	34.2191	4.90E-09	-0.0108733	0.00183874	34.9687	3.40E-09
rs11738493	5	60683123	0	C	T	0.859694	0.999403	36.4799	1.50E-09	-0.0154477	0.00258493	35.7132	2.30E-09
rs11738946	5	170861437	0	C	T	0.834752	0.990917	35.3153	2.80E-09	0.0141188	0.00242364	33.9357	5.70E-09
rs11746028	5	180645425	0	C	T	0.824891	1	76.4438	2.30E-18	0.0203477	0.00236141	74.2484	6.90E-18
rs11749494	5	78251511	0	C	T	0.835214	0.985186	30.4072	3.50E-08	0.0135292	0.00243373	30.9028	2.70E-08
rs12108720	5	132445711	0	C	G	0.744219	0.992084	45.103	1.90E-11	0.0137689	0.00206467	44.4727	2.60E-11
rs12153230	5	171201499	0	G	C	0.683562	0.995538	33.7966	6.10E-09	0.0112558	0.00193292	33.9098	5.80E-09
rs12234016	5	64670190	0	C	T	0.819549	0.995311	72.4866	1.70E-17	-0.0202201	0.00233944	74.7039	5.50E-18
rs13169351	5	32996108	0	C	T	0.58898	0.996737	57.0877	4.20E-14	-0.0138349	0.00182477	57.4827	3.40E-14
rs1490818	5	67099598	0	A	C	0.837838	0.987523	42.5284	7.00E-11	-0.0158812	0.00244902	42.0515	8.90E-11
rs1509141	5	118692218	0	G	C	0.299966	0.99672	78.1033	9.80E-19	0.0172929	0.00195644	78.1277	9.70E-19
rs17154889	5	102305065	0	C	A	0.68751	0.995147	77.3754	1.40E-18	0.0170451	0.0019384	77.3231	1.50E-18
rs176063	5	67315148	0	G	A	0.908288	0.986409	35.7232	2.30E-09	-0.0187595	0.00313015	35.9179	2.10E-09
rs17703354	5	157986357	0	T	C	0.916725	0.989617	41.111	1.40E-10	-0.0210058	0.00326203	41.4673	1.20E-10
rs188563557	5	33272843	0	A	C	0.964094	0.97324	58.9896	1.60E-14	0.0374179	0.00488969	58.5592	2.00E-14
rs1966265	5	176516631	0	G	A	0.754001	1	274.871	9.80E-62	-0.0346767	0.00208243	277.29	2.90E-62
rs2166365	5	3597830	0	A	G	0.778289	0.981546	40.2914	2.20E-10	0.0137446	0.00217897	39.789	2.80E-10
rs2303007	5	179740827	0	T	C	0.79837	1	29.6331	5.20E-08	-0.0123889	0.00223682	30.6764	3.00E-08
rs251253	5	172480336	0	C	T	0.386024	1	43.9726	3.30E-11	0.0118357	0.00183867	41.4359	1.20E-10
rs2569216	5	171859681	0	C	G	0.568435	0.994414	43.3489	4.60E-11	0.0120425	0.00181467	44.0391	3.20E-11
rs28597856	5	118757436	0	T	C	0.783249	0.996064	37.3806	9.70E-10	0.0135508	0.00218102	38.6021	5.20E-10
rs3135913	5	176515113	0	G	A	0.971895	0.994507	63.9679	1.30E-15	-0.0439638	0.00543825	65.3541	6.30E-16
rs329120	5	133861756	0	C	T	0.580858	0.997017	32.6347	1.10E-08	-0.0107166	0.00182021	34.6631	3.90E-09
rs34000	5	141973501	0	T	C	0.59599	0.987725	35.2368	2.90E-09	0.0109234	0.00183622	35.3886	2.70E-09
rs3792752	5	32768634	0	A	G	0.74173	1	119.122	9.80E-28	-0.0224808	0.00204954	120.312	5.40E-28
rs3805599	5	108108500	0	A	G	0.772799	1	40.3731	2.10E-10	-0.013768	0.00213937	41.4163	1.20E-10
rs3822593	5	178551299	0	T	G	0.416207	0.992794	65.8587	4.80E-16	0.0148223	0.00182698	65.8208	4.90E-16
rs4280908	5	88852849	0	A	G	0.607947	0.992701	31.2195	2.30E-08	0.0102046	0.0018451	30.5882	3.20E-08
rs4291002	5	148558061	0	C	G	0.625431	0.995029	35.7629	2.20E-09	-0.0111138	0.00185655	35.8355	2.10E-09
rs4293945	5	38736142	0	A	T	0.605326	0.995471	32.7019	1.10E-08	0.0108462	0.00183711	34.8566	3.50E-09
rs440292	5	67609408	0	C	G	0.255322	0.997612	41.4026	1.20E-10	-0.0132414	0.00205917	41.3508	1.30E-10
rs465983	5	55812130	0	A	G	0.764394	0.997546	210.938	8.60E-48	-0.0309896	0.00211278	215.141	1.00E-48
rs4836109	5	124010951	0	T	C	0.825644	0.992056	30.0756	4.20E-08	-0.0129367	0.00236885	29.8245	4.70E-08
rs4976262	5	134379531	0	T	C	0.684469	0.986384	41.5661	1.10E-10	0.0126456	0.00194328	42.3454	7.60E-11
rs516632	5	4024881	0	T	C	0.552897	0.996702	44.9882	2.00E-11	0.0122135	0.00180934	45.5655	1.50E-11
rs561188083	5	32717104	0	C	A	0.64951	0.976187	39.8577	2.70E-10	0.0119719	0.00190434	39.5215	3.20E-10
rs62357886	5	55857876	0	C	T	0.803148	0.9861	31.0535	2.50E-08	0.0128489	0.00227053	32.0239	1.50E-08
rs6452812	5	88394278	0	T	C	0.613847	0.999008	80.9151	2.40E-19	0.0167299	0.00184307	82.3958	1.10E-19
rs66584692	5	158392277	0	G	A	0.612772	0.997088	57.1331	4.10E-14	0.0138475	0.00184481	56.3429	6.10E-14
rs6869221	5	54881212	0	G	T	0.310625	0.995387	202.014	7.60E-46	0.0276512	0.00194489	202.134	7.10E-46
rs6897617	5	173301982	0	G	A	0.711382	0.998357	155.416	1.10E-35	-0.0246582	0.00197996	155.098	1.30E-35
rs702101	5	171276393	0	G	A	0.40267	1	93.686	3.70E-22	-0.0176138	0.00182785	92.8592	5.60E-22
rs702604	5	53166636	0	T	C	0.497805	0.993031	31.963	1.60E-08	0.0102674	0.00179873	32.5828	1.10E-08
rs72785174	5	127902765	0	T	A	0.839652	0.951371	37.5524	8.90E-10	-0.0154914	0.00250387	38.2788	6.10E-10
rs73272621	5	149854482	0	A	G	0.916737	0.968211	36.4617	1.60E-09	-0.0201901	0.00329325	37.5861	8.70E-10
rs7727038	5	131590257	0	C	T	0.440628	1	82.3415	1.10E-19	-0.0163196	0.00180571	81.6815	1.60E-19

rs7728859	5	115306226	0	C	T	0.216042	0.996733	31.1165	2.40E-08	-0.0123619	0.00217999	32.1561	1.40E-08
rs841935	5	101620985	0	T	A	0.55214	0.975109	40.367	2.10E-10	-0.0115441	0.00182556	39.9879	2.60E-10
rs959662	5	141707606	0	A	G	0.605625	0.978355	39.7867	2.80E-10	-0.0118315	0.00185751	40.5712	1.90E-10
rs975385	5	141858677	0	C	T	0.589874	0.9899	33.8615	5.90E-09	0.0106998	0.00183334	34.0613	5.30E-09
rs10223666	6	43805502	0	G	C	0.305632	0.991167	124.604	6.20E-29	-0.0216746	0.00194712	123.913	8.80E-29
rs1043784	6	7881931	0	T	C	0.891032	0.9958	42.6213	6.60E-11	0.018458	0.00287769	41.1415	1.40E-10
rs10943249	6	76199219	0	C	T	0.886364	0.992253	34.9319	3.40E-09	-0.0167671	0.00282819	35.1478	3.10E-09
rs11154680	6	132779502	0	T	C	0.917341	0.997824	52.6801	3.90E-13	-0.0237647	0.00324987	53.4728	2.60E-13
rs11154720	6	133598239	0	G	A	0.898838	1	39.4828	3.30E-10	0.018657	0.002961	39.7015	3.00E-10
rs114088263	6	34187366	0	T	C	0.95267	0.996292	556.511	4.80E-123	-0.0996855	0.0042175	558.667	1.60E-123
rs114432657	6	34197457	0	C	T	0.988357	0.988977	43.798	3.60E-11	-0.0558503	0.00837701	44.4501	2.60E-11
rs117235885	6	82198915	0	C	G	0.973948	0.943092	35.7463	2.20E-09	0.0334551	0.0057796	33.5064	7.10E-09
rs11752394	6	109189664	0	C	G	0.235356	0.994454	32.5468	1.20E-08	-0.0121133	0.00210849	33.0052	9.20E-09
rs117572385	6	82017146	0	C	G	0.96802	1	39.2458	3.70E-10	0.0308265	0.00508076	36.8121	1.30E-09
rs11757455	6	112522852	0	G	A	0.93311	1	30.0073	4.30E-08	0.0195748	0.00357334	30.0086	4.30E-08
rs11967	6	30313268	0	G	A	0.737888	1	54.8353	1.30E-13	-0.0147183	0.00203627	52.2446	4.90E-13
rs12204413	6	43711366	0	A	C	0.906582	0.974549	47.8803	4.50E-12	-0.0210006	0.00311202	45.5387	1.50E-11
rs12209871	6	83746059	0	A	G	0.855076	0.995228	30.3362	3.60E-08	-0.0143879	0.00254306	32.0099	1.50E-08
rs1294415	6	6740633	0	G	A	0.382708	0.991274	209.761	1.50E-47	-0.0267522	0.00184616	209.98	1.40E-47
rs1316979	6	41708664	0	C	T	0.934155	0.990541	47.0388	7.00E-12	-0.0252836	0.00362996	48.515	3.30E-12
rs1339382	6	81436013	0	A	G	0.600118	0.997386	164.759	1.00E-37	0.0235263	0.00182551	166.088	5.30E-38
rs139242696	6	127414440	0	T	C	0.97488	0.948967	35.9085	2.10E-09	-0.0357098	0.00585751	37.1662	1.10E-09
rs1584899	6	81335888	0	G	A	0.68325	0.99706	98.8817	2.70E-23	0.018969	0.00192198	97.4073	5.60E-23
rs190569074	6	81723935	0	C	T	0.970786	0.910776	47.392	5.80E-12	-0.0369783	0.00555871	44.2534	2.90E-11
rs2073267	6	100615652	0	A	G	0.827358	1	83.6426	5.90E-20	-0.0214318	0.00236626	82.0334	1.30E-19
rs2095812	6	105383978	0	C	G	0.679625	0.998368	129.646	4.90E-30	-0.0220888	0.00191498	133.05	8.80E-31
rs210621	6	117869491	0	G	A	0.28636	0.994791	46.0657	1.10E-11	0.0134618	0.00198255	46.106	1.10E-11
rs2206030	6	35404354	0	T	C	0.250623	0.985194	59.0111	1.60E-14	-0.0158683	0.00208287	58.0414	2.60E-14
rs2235571	6	34562677	0	T	G	0.925406	0.993436	85.805	2.00E-20	0.0317448	0.00341734	86.2916	1.60E-20
rs2328723	6	22623239	0	A	G	0.267678	0.981778	35.65	2.40E-09	-0.012348	0.00203973	36.6479	1.40E-09
rs2609301	6	168809806	0	G	A	0.756284	0.982862	58.8054	1.70E-14	0.0160201	0.0020981	58.3017	2.20E-14
rs270417	6	7729614	0	C	T	0.274849	1	70.6919	4.20E-17	-0.0167706	0.00200149	70.2085	5.30E-17
rs2745596	6	1606031	0	T	G	0.452633	0.980361	45.1159	1.90E-11	-0.0124905	0.00181502	47.3587	5.90E-12
rs2768	6	31321856	0	A	G	0.749771	0.995732	69.4757	7.70E-17	-0.017383	0.0020664	70.765	4.00E-17
rs3020372	6	152384928	0	T	C	0.838601	0.997131	59.8374	1.00E-14	-0.0181614	0.00243063	55.8293	7.90E-14
rs3813498	6	108944165	0	C	T	0.187184	0.995649	46.1226	1.10E-11	-0.0156203	0.00229623	46.2752	1.00E-11
rs41271299	6	19839415	0	C	T	0.948626	1	143.983	3.60E-33	-0.048812	0.00405303	145.041	2.10E-33
rs4407684	6	85443649	0	T	C	0.460151	0.998206	97.7294	4.80E-23	0.0175721	0.0017947	95.8658	1.20E-22
rs474574	6	7074687	0	C	T	0.331614	0.992285	47.5551	5.30E-12	-0.0133102	0.0019076	48.6851	3.00E-12
rs4896582	6	142703877	0	G	A	0.697888	0.997052	56.8887	4.60E-14	0.014523	0.00194813	55.5742	9.00E-14
rs527987255	6	31422757	0	A	G	0.939912	0.86025	40.9296	1.60E-10	0.0254424	0.00405407	39.3854	3.50E-10
rs55925606	6	25878848	0	A	G	0.923704	0.991576	28.8167	8.00E-08	-0.0191666	0.00338717	32.0195	1.50E-08
rs560111	6	33706277	0	T	C	0.457353	0.9956	37.069	1.10E-09	0.0109751	0.00179933	37.205	1.10E-09
rs58321169	6	126868567	0	C	T	0.732163	0.993198	140.5	2.10E-32	-0.0245644	0.00202559	147.066	7.60E-34
rs62401178	6	43789294	0	C	T	0.986948	0.937266	36.4726	1.50E-09	-0.0490603	0.00813559	36.3649	1.60E-09
rs62438578	6	158871624	0	C	T	0.769987	0.999613	40.8276	1.70E-10	-0.0135555	0.00212398	40.7315	1.70E-10
rs673736	6	160776653	0	G	A	0.517083	0.99077	36.8092	1.30E-09	0.0108985	0.00179533	36.8509	1.30E-09
rs6931120	6	25925634	0	G	A	0.880066	0.999999	84.0048	4.90E-20	0.0254076	0.00275406	85.1097	2.80E-20
rs71562509	6	139835423	0	G	T	0.406444	0.995329	148.036	4.70E-34	0.0220534	0.00182095	146.675	9.20E-34
rs72959041	6	127454893	0	G	A	0.950665	0.970351	1260.79	3.80E-276	-0.149	0.00418476	1267.73	1.20E-277
rs73382439	6	20404420	0	T	C	0.172247	0.994881	35.9603	2.00E-09	0.0143907	0.00237478	36.7209	1.40E-09
rs7453812	6	153405199	0	T	G	0.049227	0.995797	37.3022	1.00E-09	-0.0246914	0.00413988	35.5728	2.50E-09
rs74587175	6	45404170	0	G	A	0.947527	0.954044	49.0396	2.50E-12	0.0293203	0.00410559	51.0019	9.20E-13
rs74827399	6	82529791	0	A	C	0.4644	0.979903	46.824	7.80E-12	0.0122537	0.00180945	45.8609	1.30E-11
rs80010360	6	126584910	0	G	A	0.953134	0.994536	64.2359	1.10E-15	0.0340344	0.00424375	64.3188	1.10E-15
rs9272577	6	32607325	0	G	A	0.732404	0.977669	50.071	1.50E-12	0.0145997	0.00204759	50.8398	1.00E-12
rs9296138	6	34873819	0	G	T	0.964244	0.998702	58.2588	2.30E-14	0.0371128	0.00481777	59.3411	1.30E-14
rs9350850	6	81050236	0	T	C	0.920321	0.997978	69.4084	8.00E-17	-0.0278556	0.00330105	71.2067	3.20E-17
rs9373305	6	141683547	0	T	C	0.604986	0.997038	35.4609	2.60E-09	0.0108686	0.00183216	35.1896	3.00E-09
rs9375417	6	126248374	0	T	C	0.494854	0.999094	52.8393	3.60E-13	-0.0130119	0.00178772	52.9765	3.40E-13
rs9376461	6	140091162	0	T	G	0.648669	0.992713	30.6401	3.10E-08	0.0103103	0.00187854	30.1233	4.10E-08
rs9401955	6	127719062	0	T	C	0.886124	0.979087	43.7867	3.70E-11	-0.0189592	0.00284402	44.4404	2.60E-11
rs9448852	6	80617909	0	C	A	0.676512	0.98956	62.1063	3.30E-15	0.0143509	0.00192345	55.6668	8.60E-14
rs9470226	6	36143597	0	T	C	0.828464	0.997677	43.2735	4.80E-11	-0.0156328	0.00237477	43.334	4.60E-11
rs998584	6	43757896	0	C	A	0.517209	0.994747	542.162	6.40E-120	-0.0416923	0.00179407	540.046	1.80E-119
rs10260049	7	20545830	0	T	C	0.568429	0.994773	39.3999	3.50E-10	0.0114563	0.00181809	39.7064	3.00E-10
rs10266330	7	74481593	0	G	A	0.593128	0.992003	40.9261	1.60E-10	0.0116134	0.00183787	39.9289	2.60E-10
rs10269774	7	92253972	0	G	A	0.673927	0.998874	66.6636	3.20E-16	-0.0155159	0.00191956	65.3359	6.30E-16
rs10270542	7	77523769	0	A	G	0.58315	0.998398	66.5868	3.30E-16	0.0147145	0.00182346	65.118	7.10E-16
rs11765649	7	23479013	0	T	C	0.739037	0.986149	37.7374	8.10E-10	0.012419	0.00205977	36.3525	1.60E-09
rs11772232	7	1856273	0	C	T	0.843591	0.992164	34.929	3.40E-09	-0.0148403	0.00247456	35.9656	2.00E-09
rs118064243	7	20333435	0	C	A	0.972671	1	31.4022	2.10E-08	0.0304641	0.00551242	30.5416	3.30E-08
rs11983409	7	42245761	0	G	A	0.612836	0.98746	43.1958	5.00E-11	0.0121815	0.00185659	43.0496	5.30E-11
rs11983766	7	32834368	0	A	G	0.432043	0.999568	53.3355	2.80E-13	-0.0131139	0.0018145	52.2337	4.90E-13
rs12706947	7	130307434	0	C	T	0.45241	0.999727	42.2781	7.90E-11	-0.0115169	0.00180454	40.732	1.70E-10
rs13244291	7	120893324	0	T	C	0.563453	0.998166	66.0081	4.50E-16	0.0150053	0.00181701	68.1986	1.50E-16
rs148190310	7	148564138	0	G	A	0.973748	0.975279	36.6786	1.40E-09	-0.0346888	0.00568771	37.1967	1.10E-09
rs1534696	7	26397239	0	C	A	0.459529	1	159.743	1.30E-36	0.0228662	0.00180141	161.126	6.40E-37
rs1568799	7	42667876	0	A	C	0.688577	0.995184	35.4868	2.60E-09	0.0114172	0.00194157	34.579	4.10E-09
rs17364847	7	20390109	0	C	T	0.604713	0.992443	113.574	1.60E-26	0.0197696	0.00184507	114.808	8.70E-27
rs181981038	7	72890241	0	G	A	0.934374	0.982241	61.848	3.70E-15	-0.0285624	0.00365462	61.0808	5.50E-15
rs2529411	7	50738482	0	G	C	0.355714	0.99607	46.454	9.40E-12	0.012967	0.00188051	47.547	5.40E-12
rs273964	7	137592276	0	T	A	0.435602	0.993923	43.8415	3.60E-11	-0.0120823	0.00181796	44.17	3.00E-11
rs287621	7	130435181	0	T	C	0.27909	1	95.3317	1.60E-22	0.0194673	0.00200344	94.4185	2.60E-22
rs3110697	7	45955029	0	A	G	0.422221	1	49.1729	2.30E-12	0.012871	0.00182191	49.9078	1.60E-12
rs357438	7	138023288	0	G	C	0.661053	0.995717	41.6494	1.10E-10	0.0123398	0.00190332	42.0332	9.00E-11

rs35797675	7	72878044	0	T	G	0.783795	0.981869	59.8657	1.00E-14	0.0169927	0.00220213	59.5442	1.20E-14
rs38906	7	116894865	0	T	A	0.526679	0.993269	39.1882	3.80E-10	-0.0111994	0.00180526	38.487	5.50E-10
rs41280986	7	100344028	0	C	T	0.97606	0.969391	31.9425	1.60E-08	0.0333408	0.00597247	31.1634	2.40E-08
rs4570042	7	19616074	0	G	A	0.849085	0.99729	44.7174	2.30E-11	-0.0166863	0.00251138	44.1466	3.00E-11
rs4722669	7	27226788	0	C	T	0.919637	0.968413	134.075	5.30E-31	0.0391801	0.00335664	136.246	1.80E-31
rs4730073	7	104855871	0	C	A	0.358615	0.996893	55.0596	1.20E-13	0.0140061	0.00187723	55.6671	8.60E-14
rs57246313	7	25889697	0	G	A	0.803652	0.995778	231.717	2.50E-52	-0.0344821	0.00226641	231.48	2.80E-52
rs61744408	7	27225489	0	G	A	0.97428	1	61.7698	3.90E-15	-0.0450585	0.00566395	63.287	1.80E-15
rs62487041	7	105334443	0	G	T	0.605788	0.990042	29.8093	4.80E-08	-0.0105072	0.00184986	32.2624	1.30E-08
rs62489501	7	129932009	0	T	G	0.980512	0.869382	29.886	4.60E-08	-0.0383369	0.00698577	30.1166	4.10E-08
rs6945523	7	114527369	0	C	T	0.849166	1	34.8598	3.50E-09	-0.0151516	0.00250992	36.4417	1.60E-09
rs6962887	7	135045786	0	T	G	0.692868	0.990004	40.7335	1.70E-10	0.0125844	0.00195893	41.2693	1.30E-10
rs6977081	7	150542515	0	G	T	0.666714	0.98358	33.8727	5.90E-09	-0.0111041	0.00192406	33.3062	7.90E-09
rs73085996	7	25656363	0	G	C	0.76821	0.992702	39.35	3.50E-10	0.0134359	0.00213637	39.5529	3.20E-10
rs76335902	7	107609506	0	A	G	0.90637	0.991489	64.0239	1.20E-15	0.0249365	0.00309636	64.8587	8.00E-16
rs7799400	7	30910779	0	G	T	0.960964	0.991127	35.2541	2.90E-09	-0.0272657	0.00465829	34.2595	4.80E-09
rs78743535	7	46304421	0	C	T	0.972543	1	37.6127	8.60E-10	0.0339297	0.00549727	38.0949	6.70E-10
rs79589031	7	27934475	0	A	G	0.939135	0.942591	33.042	9.00E-09	-0.0222536	0.00386367	33.1742	8.40E-09
rs798489	7	2801803	0	C	T	0.729603	1	74.0715	7.50E-18	0.0175471	0.00202292	75.2413	4.20E-18
rs822531	7	148629759	0	C	T	0.204755	0.984186	108.592	2.00E-25	-0.0231525	0.00224404	106.447	5.90E-25
rs849133	7	28192280	0	C	T	0.497938	0.999481	274.625	1.10E-61	0.0296446	0.00179635	272.337	3.50E-61
rs917191	7	80570871	0	G	C	0.418186	0.983871	48.333	3.60E-12	-0.0128076	0.00183789	48.5624	3.20E-12
rs9886260	7	140683398	0	G	A	0.276186	0.99638	30.7327	3.00E-08	0.0111562	0.00201601	30.6233	3.10E-08
rs111551563	8	76012474	0	T	A	0.763636	0.981012	54.8668	1.30E-13	0.0156523	0.00213398	53.7995	2.20E-13
rs113645256	8	10145763	0	A	G	0.960129	0.980503	34.677	3.90E-09	0.0273833	0.00463674	34.8775	3.50E-09
rs11777885	8	52759722	0	G	A	0.0948857	0.980049	31.4917	2.00E-08	0.018016	0.00309986	33.7779	6.20E-09
rs11992444	8	25464690	0	G	T	0.49065	1	104.944	1.30E-24	-0.0184864	0.00179945	105.543	9.30E-25
rs12543555	8	69562014	0	A	G	0.790959	0.984971	57.2957	3.70E-14	-0.0167783	0.00222697	56.7629	4.90E-14
rs13274301	8	128988045	0	A	C	0.86935	1	37.1106	1.10E-09	0.0160152	0.00266715	36.0553	1.90E-09
rs17818981	8	25894943	0	C	T	0.710212	1	38.0246	7.00E-10	0.0123036	0.00198292	38.4995	5.50E-10
rs2134964	8	89397637	0	A	G	0.301773	0.999132	55.0028	1.20E-13	0.0145818	0.00196049	55.3217	1.00E-13
rs2167734	8	78110704	0	G	A	0.714943	0.997115	77.5476	1.30E-18	-0.0178564	0.00199409	80.1855	3.40E-19
rs2648846	8	129179990	0	A	G	0.683279	0.996363	38.2619	6.20E-10	0.0119587	0.00193712	38.1113	6.70E-10
rs2833	8	123986649	0	A	G	0.557206	0.998335	41.2099	1.40E-10	-0.0115208	0.00181282	40.3887	2.10E-10
rs34098567	8	49361329	0	A	G	0.922252	0.999309	37.1441	1.10E-09	-0.020466	0.00335983	37.1049	1.10E-09
rs34856835	8	71970611	0	C	G	0.478945	0.994634	36.324	1.70E-09	0.0107844	0.0018062	35.6502	2.40E-09
rs366991	8	128334245	0	A	G	0.637982	0.998848	69.005	9.80E-17	0.0155718	0.00187	69.3416	8.30E-17
rs4474021	8	12632903	0	G	T	0.680287	1	36.4249	1.60E-09	-0.011501	0.00192599	35.6583	2.40E-09
rs4733727	8	130731484	0	C	T	0.510207	0.992815	68.2413	1.40E-16	0.014907	0.00180424	68.264	1.40E-16
rs62501195	8	24041988	0	A	C	0.828873	0.966724	96.5904	8.50E-23	0.0238323	0.00242581	96.5202	8.80E-23
rs62511348	8	117428055	0	T	G	0.805333	0.968738	33.0723	8.90E-09	-0.0131169	0.00230898	32.2717	1.30E-08
rs62515397	8	56972715	0	G	A	0.87329	0.958953	32.5798	1.10E-08	-0.0157795	0.0027598	32.6912	1.10E-08
rs6994124	8	72493185	0	T	C	0.739455	0.992492	120.809	4.20E-28	-0.0225531	0.00205326	120.648	4.60E-28
rs7013938	8	145050336	0	A	C	0.583167	0.986811	86.5133	1.40E-20	0.0170619	0.00183522	86.4329	1.40E-20
rs71519447	8	57157543	0	G	A	0.889883	0.998532	54.8698	1.30E-13	0.0214528	0.0028766	55.6171	8.80E-14
rs72614053	8	145503189	0	A	G	0.511324	0.991158	33.3972	7.50E-09	0.0104174	0.00180534	33.2964	7.90E-09
rs75500029	8	98939022	0	A	G	0.815826	0.999598	34.4012	4.50E-09	0.0136216	0.00231379	34.6585	3.90E-09
rs76833264	8	25428178	0	G	C	0.958988	0.994798	60.324	8.00E-15	0.0350618	0.00453751	59.708	1.10E-14
rs77541621	8	128077146	0	G	A	0.97138	0.923151	38.4707	5.60E-10	-0.0348359	0.00561088	38.5472	5.30E-10
rs7821292	8	135710348	0	C	T	0.619268	0.997842	66.6703	3.20E-16	0.0150026	0.00185369	65.5029	5.80E-16
rs7827182	8	8380471	0	G	C	0.511013	0.999347	124.124	7.90E-29	0.02009	0.00180103	124.429	6.80E-29
rs7832357	8	126516197	0	A	G	0.658267	1	60.3797	7.80E-15	-0.014734	0.00189577	60.4041	7.70E-15
rs7843326	8	120873342	0	A	G	0.660722	0.992249	35.0615	3.20E-09	-0.0112023	0.0019053	34.5691	4.10E-09
rs9314323	8	26243136	0	A	G	0.30128	0.990411	51.7833	6.20E-13	-0.0140279	0.00196986	50.7121	1.10E-12
rs9644033	8	23610639	0	A	T	0.760343	0.997524	88.8435	4.30E-21	0.0198416	0.00210792	88.6027	4.80E-21
rs10119629	9	99109372	0	C	T	0.84045	0.997241	72.3833	1.80E-17	-0.0209776	0.0024586	72.8009	1.40E-17
rs1044531	9	117098650	0	C	T	0.0889691	0.977175	32.7476	1.00E-08	0.0182499	0.00319637	32.5993	1.10E-08
rs10818577	9	124413191	0	G	C	0.761987	0.98565	37.3288	1.00E-09	-0.0130522	0.00212765	37.6329	8.50E-10
rs10820747	9	107686823	0	G	A	0.762154	0.996011	111.756	4.00E-26	-0.0226628	0.00211878	114.408	1.10E-26
rs10963067	9	17367946	0	C	A	0.912765	0.997864	49.0818	2.50E-12	0.0220377	0.00319237	47.6548	5.10E-12
rs10980797	9	113912553	0	A	G	0.511026	0.995667	65.0774	7.20E-16	-0.0145177	0.00180279	64.8494	8.10E-16
rs1121978	9	95140351	0	T	G	0.731187	0.99911	98.8043	2.80E-23	0.0201128	0.00203218	97.9535	4.30E-23
rs12005101	9	127590633	0	G	A	0.0859316	0.974938	31.4241	2.10E-08	-0.0180725	0.00324794	30.9616	2.60E-08
rs12378752	9	34083158	0	T	C	0.893702	0.976901	30.1757	3.90E-08	-0.0164418	0.00295434	30.9725	2.60E-08
rs12380852	9	139118673	0	T	C	0.888949	1	40.7285	1.70E-10	-0.0182965	0.00285804	40.9824	1.50E-10
rs1412674	9	18633901	0	T	A	0.602012	0.981906	29.2669	6.30E-08	0.0101846	0.0018559	30.115	4.10E-08
rs1800978	9	107665978	0	C	G	0.875508	0.99064	63.1232	1.90E-15	0.0217738	0.00273708	63.2841	1.80E-15
rs1984119	9	98368761	0	T	C	0.744098	0.976927	104.651	1.50E-24	0.0213704	0.00208603	104.95	1.30E-24
rs2157770	9	136921464	0	A	G	0.713186	0.996232	41.9019	9.60E-11	-0.0128367	0.00199212	41.5222	1.20E-10
rs2209815	9	112561012	0	G	T	0.593194	0.994865	40.0429	2.50E-10	0.0117243	0.00183543	40.8037	1.70E-10
rs2482080	9	117869684	0	T	G	0.57714	0.998284	41.4061	1.20E-10	0.0118763	0.00182303	42.4399	7.30E-11
rs2811709	9	21980151	0	A	G	0.114112	0.995633	32.4484	1.20E-08	0.0160313	0.00283716	31.928	1.60E-08
rs28498266	9	137031454	0	G	A	0.604021	0.98832	45.3905	1.60E-11	0.0123336	0.00184918	44.486	2.60E-11
rs28571635	9	98225658	0	C	T	0.778063	0.992602	47.3052	6.10E-12	-0.0154254	0.00217175	50.4488	1.20E-12
rs35344761	9	78510823	0	C	A	0.87763	0.9842	116.433	3.80E-27	0.0296619	0.00276913	114.739	9.00E-27
rs3927536	9	16787670	0	C	T	0.226267	0.985908	42.8069	6.00E-11	-0.0145658	0.00216741	45.1636	1.80E-11
rs405761	9	89085126	0	G	A	0.495864	0.998044	49.919	1.60E-12	-0.012632	0.00179924	49.2905	2.20E-12
rs4409452	9	103365303	0	G	A	0.497543	0.994981	29.77	4.90E-08	-0.00986719	0.00180245	29.9683	4.40E-08
rs4743123	9	98400242	0	T	C	0.366016	0.993724	85.7739	2.00E-20	-0.0173282	0.00187105	85.7698	2.00E-20
rs5020792	9	107736706	0	C	A	0.805389	0.995626	45.9032	1.20E-11	-0.0155148	0.00227688	46.4315	9.50E-12
rs556331	9	124336665	0	C	A	0.710517	0.992622	33.8113	6.10E-09	0.0115426	0.00199116	33.6041	6.80E-09
rs7021721	9	111963641	0	G	C	0.711644	0.996361	39.0932	4.00E-10	0.0124455	0.00199016	39.1065	4.00E-10
rs7021911	9	133501018	0	T	C	0.345131	0.979563	38.5757	5.30E-10	-0.0117262	0.0019123	37.6015	8.70E-10
rs7027650	9	101741969	0	A	T	0.625048	0.996641	70.9275	3.70E-17	0.015625	0.00185978	70.5861	4.40E-17
rs7041352	9	118545371	0	C	A	0.553	0.998276	43.3491	4.60E-11	0.0117325	0.00180765	42.1266	8.60E-11
rs72607124	9	107887450	0	G	A	0.960962	0.977369	111.16	5.50E-26	0.0497352	0.00469146	112.386	2.90E-26

rs73650963	9	93943033	0	T	C	0.892543	0.990485	61.3653	4.70E-15	-0.0230214	0.00291487	62.3772	2.80E-15
rs9409085	9	108909847	0	A	G	0.733383	0.991413	67.0381	2.70E-16	0.0167268	0.00204423	66.9528	2.80E-16
rs954585	9	109642696	0	A	G	0.644293	0.992896	46.2521	1.00E-11	-0.0125853	0.00188478	44.5863	2.40E-11
rs11187139	10	94466427	0	T	C	0.591774	0.99704	37.8045	7.80E-10	0.0113987	0.00183313	38.6654	5.00E-10
rs11188604	10	97862580	0	T	G	0.635631	0.997089	31.2939	2.20E-08	0.0102369	0.00186985	29.9725	4.40E-08
rs11198821	10	120965341	0	A	G	0.896552	0.990082	37.8715	7.60E-10	-0.0181651	0.00296976	37.4138	9.60E-10
rs12243124	10	95337939	0	T	C	0.776694	0.968181	55.7161	8.40E-14	-0.0165757	0.00219588	56.9807	4.40E-14
rs1411189	10	28843478	0	G	A	0.724326	1	36.4138	1.60E-09	0.0121439	0.00201932	36.1664	1.80E-09
rs1494209	10	27875006	0	G	A	0.491149	0.998646	40.2182	2.30E-10	-0.0115042	0.00180202	40.7561	1.70E-10
rs1769758	10	80898969	0	G	T	0.495375	1	58.8798	1.70E-14	-0.013715	0.00180075	58.0071	2.60E-14
rs2254074	10	122875547	0	A	C	0.876858	0.998828	53.3211	2.80E-13	-0.0200083	0.00273766	53.4149	2.70E-13
rs2532655	10	119192318	0	A	G	0.610721	0.982806	34.755	3.70E-09	0.0109085	0.00186196	34.3231	4.70E-09
rs291970	10	121123633	0	C	T	0.770874	0.996524	67.1786	2.50E-16	-0.0173515	0.00214167	65.6398	5.40E-16
rs35954730	10	12943111	0	G	A	0.710308	0.989166	92.3405	7.30E-22	0.0189993	0.00199334	90.8474	1.60E-21
rs36029788	10	61741448	0	C	T	0.749231	0.989639	42.6529	6.50E-11	0.0135308	0.00208566	42.0881	8.70E-11
rs3740237	10	32557592	0	G	C	0.856471	0.994038	71.814	2.40E-17	-0.0218424	0.00257475	71.9663	2.20E-17
rs3977756	10	104398582	0	G	A	0.397081	0.999038	124.65	6.10E-29	-0.0204999	0.00183843	124.339	7.10E-29
rs4347331	10	60452724	0	G	A	0.186165	0.994743	33.8362	6.00E-09	0.0135167	0.00232019	33.9385	5.70E-09
rs4751627	10	119312103	0	C	T	0.356741	0.992234	57.3029	3.70E-14	0.0144439	0.00188566	58.6733	1.90E-14
rs4934618	10	34167569	0	G	A	0.584492	0.995902	50.4132	1.20E-12	-0.0130259	0.00183017	50.6558	1.10E-12
rs6480914	10	80772591	0	G	A	0.420566	0.993161	34.7904	3.70E-09	-0.0106338	0.00183031	33.7539	6.30E-09
rs6585199	10	114765171	0	G	A	0.543486	0.996928	134.624	4.00E-31	-0.021036	0.00180835	135.32	2.80E-31
rs7069533	10	11904988	0	A	G	0.323833	0.996659	31.3837	2.10E-08	0.0108473	0.00192582	31.7256	1.80E-08
rs7088428	10	122945252	0	T	G	0.26886	0.99711	33.275	8.00E-09	-0.0118643	0.00203484	33.9959	5.50E-09
rs7099771	10	5654742	0	A	G	0.628172	0.993845	34.7419	3.80E-09	0.0107472	0.00186933	33.0537	9.00E-09
rs71230207	10	5017641	0	C	G	0.883899	0.992911	129.27	5.90E-30	0.0318165	0.00281791	127.483	1.50E-29
rs779933	10	80918517	0	G	A	0.567688	0.99549	134.934	3.40E-31	0.0210806	0.00182003	134.155	5.10E-31
rs7919780	10	126264950	0	C	A	0.600609	0.996869	49.0669	2.50E-12	-0.0129871	0.00183962	49.8384	1.70E-12
rs878177	10	100013815	0	C	T	0.661056	0.99952	68.6829	1.20E-16	-0.0157899	0.00189913	69.1269	9.20E-17
rs9943407	10	81169834	0	T	C	0.750367	0.984223	33.04	9.00E-09	0.0120439	0.00209655	33.0005	9.20E-09
rs10840154	11	8962289	0	A	G	0.380928	0.997222	33.4519	7.30E-09	-0.0106451	0.0018541	32.9636	9.40E-09
rs10891490	11	112885527	0	T	C	0.406845	0.997411	46.7715	8.00E-12	0.0126632	0.00183164	47.7975	4.70E-12
rs10893812	11	127932610	0	G	C	0.813681	0.974159	51.0588	9.00E-13	0.0166461	0.00234003	50.6035	1.10E-12
rs111762835	11	69018083	0	G	A	0.957898	1	32.8077	1.00E-08	0.0259038	0.0044736	33.5283	7.00E-09
rs11600312	11	68035540	0	G	A	0.897599	0.988951	36.0411	1.90E-09	-0.0181494	0.00297849	37.1307	1.10E-09
rs11605956	11	26212866	0	T	C	0.689969	0.990636	31.4648	2.00E-08	0.0108182	0.0019524	30.7025	3.00E-08
rs11606433	11	36328630	0	C	T	0.674902	0.973353	37.782	7.90E-10	0.0120432	0.00194415	38.3731	5.80E-10
rs117919244	11	47797720	0	T	C	0.979291	0.86407	32.1904	1.40E-08	-0.0385019	0.00679379	32.1174	1.50E-08
rs12417557	11	14567538	0	C	T	0.92757	1	39.3509	3.50E-10	0.0213541	0.00346914	37.8894	7.50E-10
rs12793175	11	10384303	0	G	A	0.836071	0.995874	37.2478	1.00E-09	0.0148216	0.00242974	37.211	1.10E-09
rs12793371	11	3034709	0	A	G	0.615675	0.992603	30.4691	3.40E 08	-0.0101025	0.00185095	29.7898	4.80E 08
rs140201358	11	823586	0	C	G	0.986267	1	96.2658	1.00E-22	-0.0760809	0.00771341	97.2877	6.00E-23
rs143840904	11	2813322	0	C	T	0.980282	0.937732	64.819	8.20E-16	0.053263	0.00667369	63.6969	1.50E-15
rs174559	11	61581656	0	G	A	0.720348	0.999573	39.6664	3.00E-10	0.0124437	0.00200189	38.6384	5.10E-10
rs2428548	11	62311462	0	A	G	0.615956	0.991659	63.5696	1.50E-15	-0.014961	0.00185603	64.976	7.60E-16
rs2509970	11	62188855	0	C	G	0.283321	0.97359	60.1986	8.60E-15	-0.015658	0.00201665	60.2857	8.20E-15
rs2863714	11	45952311	0	A	G	0.0875317	0.99641	33.9955	5.50E-09	-0.0188563	0.00317943	35.1736	3.00E-09
rs3017621	11	69456901	0	G	C	0.0948114	0.959492	66.7688	3.10E-16	0.0258	0.00312868	68.0015	1.60E-16
rs3824867	11	47468569	0	A	G	0.287685	0.99919	88.3645	5.40E-21	0.0184426	0.00198496	86.326	1.50E-20
rs3829258	11	111642119	0	G	A	0.61785	0.994448	116.1	4.50E-27	0.0200598	0.0018551	116.928	3.00E-27
rs4297487	11	69229628	0	A	G	0.324436	0.994311	75.7512	3.20E-18	-0.0167966	0.00192151	76.4113	2.30E-18
rs4357716	11	69163161	0	C	T	0.863407	0.990165	112.182	3.30E-26	-0.0279139	0.00262879	112.753	2.40E-26
rs4645917	11	65481640	0	G	A	0.872108	0.987923	72.7848	1.40E-17	0.0227543	0.00270632	70.6922	4.20E-17
rs4910417	11	11806753	0	A	G	0.626574	0.993878	39.6203	3.10E-10	0.0115652	0.00186377	38.5056	5.50E-10
rs4930011	11	2856658	0	C	G	0.609446	0.990043	29.6814	5.10E-08	-0.0102917	0.00184863	30.9938	2.60E-08
rs56271783	11	64004723	0	G	C	0.954595	0.977271	162.153	3.80E-37	-0.0554068	0.00436213	161.335	5.80E-37
rs606452	11	75276178	0	A	C	0.1398	1	56.8148	4.80E-14	0.0196433	0.0025912	57.4683	3.40E-14
rs61869763	11	2813345	0	C	T	0.895236	0.981033	41.3976	1.20E-10	-0.0188073	0.00296095	40.345	2.10E-10
rs6416127	11	45239959	0	G	T	0.144131	0.998189	48.5593	3.20E-12	0.0179326	0.00255864	49.121	2.40E-12
rs68162171	11	66125461	0	A	C	0.71476	0.999458	31.6542	1.80E-08	-0.0110843	0.00199248	30.9474	2.70E-08
rs7105538	11	32387919	0	G	T	0.76626	0.990625	54.1647	1.80E-13	0.0157824	0.00213146	54.8271	1.30E-13
rs7928810	11	17372443	0	C	A	0.381678	0.996441	76.912	1.80E-18	0.0162316	0.0018523	76.7892	1.90E-18
rs7932891	11	10921512	0	A	G	0.292419	0.999338	61.6345	4.10E-15	0.0153226	0.00197409	60.246	8.40E-15
rs7952436	11	67024534	0	C	T	0.917763	1	238.586	8.00E-54	0.05036	0.0032728	236.773	2.00E-53
rs10431570	12	66120654	0	T	C	0.858221	1	33.9246	5.70E-09	-0.0149842	0.00257415	33.8843	5.80E-09
rs10507146	12	102984671	0	G	A	0.914713	0.995749	37.5054	9.10E-10	-0.0193043	0.00322025	35.936	2.00E-09
rs10744012	12	13225007	0	C	T	0.140006	0.992824	33.7947	6.10E-09	-0.0149605	0.00259834	33.1513	8.50E-09
rs10850127	12	113512945	0	C	T	0.678967	0.994253	51.3981	7.50E-13	-0.0135833	0.00192747	49.6635	1.80E-12
rs10878994	12	69860696	0	G	T	0.763796	1	43.1418	5.10E-11	0.0137622	0.00211664	42.275	7.90E-11
rs11043300	12	122483853	0	G	A	0.987587	0.905298	44.2178	2.90E-11	-0.0559932	0.00852262	43.1643	5.00E-11
rs11049204	12	28013563	0	A	G	0.811879	0.993685	36.5246	1.50E-09	0.0139102	0.00230395	36.4519	1.60E-09
rs11049232	12	28092647	0	G	A	0.961645	0.988648	29.9715	4.40E-08	-0.0256731	0.00470489	29.7754	4.90E-08
rs11049727	12	28737797	0	T	A	0.693642	0.994644	88.4752	5.10E-21	0.0182584	0.00195143	87.5423	8.20E-21
rs11057452	12	124585946	0	C	T	0.638203	0.983447	173.629	1.20E-39	0.0248345	0.00188348	173.855	1.10E-39
rs11057558	12	124764128	0	C	G	0.888142	0.992643	54.0805	1.90E-13	-0.0207127	0.00286073	52.4227	4.50E-13
rs11060344	12	123329101	0	A	G	0.856446	0.997891	117.086	2.70E-27	-0.0282473	0.00256647	121.138	3.60E-28
rs11111869	12	104402485	0	G	A	0.830273	0.993899	38.5171	5.40E-10	-0.0151008	0.00240118	39.5508	3.20E-10
rs11115386	12	83160190	0	G	T	0.812339	1	32.2328	1.40E-08	-0.0128187	0.00229843	31.1046	2.40E-08
rs11147235	12	133688707	0	T	C	0.814529	1	45.2241	1.80E-11	0.0153842	0.00231054	44.3325	2.80E-11
rs117081218	12	102339359	0	G	A	0.96308	0.938008	31.2969	2.20E-08	0.0281734	0.00491723	32.8276	1.00E-08
rs12371834	12	102347801	0	C	T	0.559573	0.993314	29.9705	4.40E-08	0.00995519	0.00181488	30.0888	4.10E-08
rs1351394	12	66351826	0	T	C	0.489063	1	89.096	3.80E-21	0.0170709	0.00179914	90.0287	2.30E-21
rs1373570	12	20461604	0	A	T	0.559762	0.994266	35.6423	2.40E-09	0.0108286	0.00181395	35.6363	2.40E-09
rs139948644	12	123200016	0	C	T	0.972147	0.924606	37.1231	1.10E-09	0.0350262	0.00567831	38.0494	6.90E-10
rs141961157	12	123308271	0	C	T	0.954467	0.912773	46.2506	1.00E-11	-0.0304981	0.00451281	45.672	1.40E-11
rs143786003	12	124695007	0	C	A	0.964373	0.948163	33.1924	8.30E-09	-0.0283282	0.0049831	32.3176	1.30E-08

rs180438	12	47187260	0	G	A	0.190102	0.998975	35.0243	3.30E-09	0.0134039	0.00229119	34.2251	4.90E-09
rs2187642	12	11855624	0	A	C	0.376033	1	37.8529	7.60E-10	0.0113597	0.00185369	37.5547	8.90E-10
rs2544027	12	48216529	0	G	A	0.521706	0.991452	30.0625	4.20E-08	-0.00997454	0.00180498	30.5379	3.30E-08
rs3922628	12	123209295	0	T	A	0.789555	0.990159	109.407	1.30E-25	0.0233681	0.00221442	111.359	4.90E-26
rs4760171	12	58225904	0	T	C	0.677964	0.993174	55.7208	8.40E-14	0.0146281	0.00193094	57.3901	3.60E-14
rs4762954	12	20554110	0	C	T	0.427378	0.98888	37.5522	8.90E-10	-0.0112093	0.00182403	37.7654	8.00E-10
rs4963975	12	26443030	0	G	A	0.755944	0.993502	163.855	1.60E-37	-0.0266906	0.00209692	162.015	4.10E-37
rs56154542	12	54393783	0	G	C	0.592035	0.978926	123.993	8.50E-29	-0.0204542	0.00184805	122.5	1.80E-28
rs6581551	12	64749372	0	A	G	0.326786	0.989251	36.0528	1.90E-09	-0.0114784	0.00192519	35.5483	2.50E-09
rs6581662	12	66432657	0	T	C	0.294963	0.979095	55.2643	1.10E-13	0.0149924	0.00199195	56.6482	5.20E-14
rs67516712	12	124201524	0	G	A	0.574639	0.984536	84.7587	3.40E-20	-0.0169123	0.00183095	85.3208	2.50E-20
rs7133378	12	124409502	0	G	A	0.681211	0.995002	395.264	5.90E-88	0.0385234	0.00193209	397.553	1.90E-88
rs7135818	12	20829775	0	G	A	0.340866	0.997412	57.1766	4.00E-14	0.0141957	0.00189953	55.8497	7.80E-14
rs7294354	12	588944	0	T	G	0.436253	0.989428	46.3174	1.00E-11	0.012275	0.00182156	45.4107	1.60E-11
rs7306500	12	6661711	0	T	C	0.722942	0.986747	31.692	1.80E-08	0.01135	0.0020227	31.4865	2.00E-08
rs73080726	12	20754154	0	C	T	0.903107	1	34.0164	5.50E-09	-0.0179323	0.00303185	34.983	3.30E-09
rs73108788	12	45985272	0	G	T	0.818779	0.98942	33.7962	6.10E-09	-0.0136528	0.00233905	34.0691	5.30E-09
rs7311105	12	28216503	0	T	C	0.933753	0.978168	39.5436	3.20E-10	-0.0229202	0.00364875	39.4591	3.40E-10
rs7314177	12	38441179	0	T	C	0.617696	0.99509	35.8602	2.10E-09	0.0110136	0.00185254	35.3449	2.80E-09
rs76573653	12	49380073	0	T	G	0.961269	1	42.3068	7.80E-11	0.0301873	0.0046551	42.0525	8.90E-11
rs871130	12	56648777	0	C	T	0.933354	0.997963	46.41	9.60E-12	-0.02422	0.00360217	45.2085	1.80E-11
rs894739	12	54346869	0	T	C	0.21877	0.997181	120.686	4.50E-28	0.0238513	0.00217298	120.48	5.00E-28
rs9634212	12	93993266	0	C	A	0.778873	0.991347	57.3379	3.70E-14	-0.0164183	0.0021741	57.0297	4.30E-14
rs11616390	13	32700872	0	T	C	0.906811	1	32.7455	1.10E-08	-0.0177154	0.00309737	32.7126	1.10E-08
rs17650569	13	51576984	0	C	T	0.909693	0.997209	34.6915	3.90E-09	0.0186926	0.00315257	35.157	3.00E-09
rs2239748	13	33101817	0	C	T	0.638411	0.998541	37.9142	7.40E-10	-0.0115915	0.00187976	38.0256	7.00E-10
rs552125	13	110938813	0	T	C	0.127773	0.993084	30.0993	4.10E-08	-0.0149212	0.00270695	30.3842	3.50E-08
rs73229101	13	78195413	0	A	G	0.853928	0.980712	29.7893	4.80E-08	0.0141157	0.00257771	29.9871	4.30E-08
rs7329886	13	81386520	0	A	G	0.563212	0.996881	33.7887	6.10E-09	-0.0105786	0.00182102	33.7464	6.30E-09
rs77659092	13	51133619	0	G	T	0.961931	0.975912	57.3404	3.70E-14	0.0359659	0.00477146	56.8173	4.80E-14
rs7993238	13	22473593	0	A	C	0.629618	0.977583	49.3313	2.20E-12	-0.0131799	0.00188781	48.7428	2.90E-12
rs8002779	13	92015977	0	G	A	0.39714	1	32.1933	1.40E-08	0.0103624	0.00183687	31.8249	1.70E-08
rs952359	13	111026734	0	G	A	0.661211	0.995388	39.4536	3.40E-10	0.0119738	0.0019091	39.3373	3.60E-10
rs9526681	13	51179984	0	A	T	0.514194	0.991395	86.3399	1.50E-20	-0.0167947	0.00181026	86.0719	1.70E-20
rs9535193	13	49866322	0	C	T	0.312917	1	47.3035	6.10E-12	0.0134846	0.00194422	48.1043	4.00E-12
rs9568400	13	50958930	0	C	T	0.89532	0.995499	55.6777	8.50E-14	-0.0220781	0.00295044	55.9949	7.30E-14
rs10083447	14	92464427	0	G	A	0.534493	0.999742	84.5682	3.70E-20	0.0167214	0.00180852	85.4868	2.30E-20
rs10130842	14	98342603	0	C	T	0.397476	0.978927	43.0633	5.30E-11	-0.0120085	0.00186222	41.5828	1.10E-10
rs10131337	14	37144516	0	C	T	0.755337	0.990533	37.5038	9.10E-10	-0.0127214	0.00210672	36.4633	1.60E-09
rs112635299	14	94838142	0	G	T	0.979296	1	52.882	3.50E-13	-0.0452581	0.0063383	50.9855	9.30E-13
rs140664623	14	52321987	0	G	T	0.975901	0.976054	43.5107	4.20E-11	0.0390172	0.0059473	43.0772	5.30E-11
rs146182298	14	52531408	0	C	T	0.960471	0.990536	37.8046	7.80E-10	-0.0283271	0.00464916	37.124	1.10E-09
rs17254885	14	59349318	0	G	A	0.749994	0.990241	35.3712	2.70E-09	-0.0125387	0.00209358	35.8693	2.10E-09
rs1888344	14	54328682	0	C	T	0.142842	1	39.0427	4.10E-10	-0.0161605	0.00257575	39.3644	3.50E-10
rs1952151	14	21540863	0	G	T	0.474779	0.99741	30.5731	3.20E-08	-0.0100375	0.00180628	30.8803	2.70E-08
rs36226649	14	24835500	0	T	C	0.93316	1	79.1163	5.90E-19	-0.0318654	0.00361222	77.82	1.10E-18
rs4899143	14	65155333	0	C	G	0.422303	0.980517	38.621	5.10E-10	0.0115372	0.00184708	39.015	4.20E-10
rs4906330	14	103971202	0	T	G	0.630253	0.998838	49.5593	1.90E-12	0.0131026	0.00186644	49.2817	2.20E-12
rs58339869	14	68829763	0	C	A	0.473787	0.998807	31.3709	2.10E-08	-0.0100598	0.00180585	31.0325	2.50E-08
rs7155922	14	55238309	0	G	A	0.422529	0.995368	33.0692	8.90E-09	-0.0105812	0.00182963	33.4457	7.30E-09
rs8006644	14	91547563	0	A	C	0.684779	0.972379	116.75	3.30E-27	-0.021238	0.00196774	116.491	3.70E-27
rs862050	14	74981548	0	C	G	0.344453	0.999581	104.685	1.40E-24	-0.0195034	0.00189692	105.711	8.50E-25
rs10152595	15	67475488	0	C	G	0.750528	0.984144	42.7183	6.30E-11	0.0137101	0.0020964	42.769	6.20E-11
rs11635281	15	70515463	0	C	T	0.528535	0.987829	34.3133	4.70E-09	-0.0106308	0.0018123	34.4087	4.50E-09
rs11852383	15	100542765	0	C	T	0.423673	1	32.4518	1.20E-08	-0.0104012	0.00182099	32.6249	1.10E-08
rs11856640	15	59232040	0	T	G	0.185328	0.983737	33.068	8.90E-09	-0.013373	0.00233676	32.7515	1.00E-08
rs11857726	15	41530359	0	G	A	0.620598	0.995864	51.7483	6.30E-13	0.013629	0.00186009	53.6862	2.40E-13
rs12441765	15	31696936	0	C	T	0.76657	0.992803	94.9761	1.90E-22	0.0210383	0.00213695	96.9245	7.20E-23
rs12907359	15	72171046	0	G	T	0.979899	1	35.1718	3.00E-09	-0.0379415	0.00640004	35.1449	3.10E-09
rs12907739	15	78997980	0	G	A	0.232358	0.995115	32.8584	9.90E-09	0.0122703	0.00213598	33.0002	9.20E-09
rs12908766	15	56716130	0	G	A	0.17888	0.997722	71.8024	2.40E-17	0.0199069	0.0023522	71.6238	2.60E-17
rs1319869	15	99212485	0	G	T	0.10684	0.991312	39.81	2.80E-10	-0.0180678	0.00292816	38.0732	6.80E-10
rs140574883	15	84743080	0	C	G	0.950294	0.977125	38.8453	4.60E-10	-0.0257249	0.00419287	37.6429	8.50E-10
rs143253231	15	84531695	0	G	A	0.563531	0.998682	157.56	3.90E-36	-0.0230333	0.00181291	161.42	5.50E-37
rs17200030	15	89379348	0	C	T	0.970358	1	30.9198	2.70E-08	0.0293681	0.00530957	30.5939	3.20E-08
rs17703883	15	51530097	0	T	C	0.744859	0.995879	44.3647	2.70E-11	-0.0140009	0.0020724	45.6423	1.40E-11
rs2165241	15	74222202	0	T	C	0.491648	0.994604	130.35	3.40E-30	-0.0206352	0.00180133	131.229	2.20E-30
rs2684788	15	99504437	0	C	T	0.522841	0.992248	53.4488	2.70E-13	-0.0130869	0.00180818	52.3829	4.60E-13
rs2718926	15	56551747	0	A	G	0.556729	0.991067	32.4861	1.20E-08	0.0103242	0.00182352	32.0546	1.50E-08
rs28559926	15	89400043	0	G	C	0.960957	0.927633	127.234	1.70E-29	0.0545787	0.004817	128.379	9.30E-30
rs28583508	15	100800049	0	G	T	0.338502	0.986452	83.2789	7.10E-20	0.0175084	0.00191414	83.6659	5.90E-20
rs2925339	15	42091212	0	A	G	0.326323	1	44.8422	2.10E-11	-0.0128924	0.00192139	45.0233	1.90E-11
rs35777573	15	40644246	0	T	A	0.835525	0.997274	72.2904	1.90E-17	-0.0205283	0.00243346	71.1635	3.30E-17
rs35874463	15	67457698	0	A	G	0.94224	1	54.4462	1.60E-13	-0.0288682	0.00385352	56.1207	6.80E-14
rs3825941	15	74317362	0	G	A	0.743333	0.988225	38.1862	6.40E-10	-0.0127852	0.00207199	38.0754	6.80E-10
rs4405528	15	90620712	0	A	G	0.598794	0.980028	34.6348	4.00E-09	0.0110888	0.00185387	35.7777	2.20E-09
rs4774498	15	47873605	0	T	A	0.329755	0.997533	38.8179	4.70E-10	0.0118551	0.00191634	38.2704	6.20E-10
rs4775762	15	48744005	0	T	C	0.224058	0.997622	49.5027	2.00E-12	-0.0151017	0.0021639	48.7057	3.00E-12
rs4932200	15	89349708	0	A	G	0.517215	0.990586	30.2495	3.80E-08	-0.00988815	0.00180777	29.9187	4.50E-08
rs530742363	15	89399167	0	C	T	0.323308	0.994132	51.3002	7.90E-13	0.0137976	0.00192946	51.1372	8.60E-13
rs55932046	15	67033472	0	A	T	0.932716	0.961521	29.8826	4.60E-08	0.0200959	0.00366368	30.0871	4.10E-08
rs62011286	15	63791125	0	G	A	0.657252	0.996399	55.7611	8.20E-14	-0.0142765	0.00190082	56.4107	5.90E-14
rs7162669	15	70022164	0	G	C	0.896586	0.994349	48.1585	3.90E-12	0.020886	0.00296153	49.7366	1.80E-12
rs72755233	15	100692953	0	G	A	0.88798	1	191.671	1.40E-43	0.0397504	0.00285174	194.295	3.70E-44
rs79943855	15	48684620	0	C	T	0.910662	0.982804	44.7189	2.30E-11	0.020766	0.00318704	42.4552	7.20E-11
rs8039213	15	98346176	0	T	C	0.661624	0.980589	40.8876	1.60E-10	-0.012377	0.00192202	41.468	1.20E-10

rs813017	15	61410095	0	C	G	0.664186	0.995339	49.4119	2.10E-12	0.0134618	0.00191052	49.6482	1.80E-12
rs11149699	16	84976903	0	T	G	0.862041	0.978931	41.1769	1.40E-10	-0.0172256	0.00264218	42.5032	7.10E-11
rs11640020	16	75174721	0	G	T	0.684937	0.981421	64.5292	9.50E-16	0.0158402	0.00195868	65.4025	6.10E-16
rs12103006	16	24726237	0	A	G	0.430278	0.996753	35.5728	2.50E-09	-0.0107417	0.001825	34.6435	4.00E-09
rs12325238	16	10981518	0	C	A	0.735371	0.991427	37.6293	8.60E-10	-0.0126431	0.00205254	37.9424	7.30E-10
rs138937927	16	51095561	0	C	T	0.97429	0.930948	42.2843	7.90E-11	0.0379654	0.00591175	41.2423	1.30E-10
rs164752	16	89722390	0	G	A	0.113392	0.995154	51.2454	8.20E-13	-0.02064	0.00284936	52.4715	4.40E-13
rs2012708	16	84790559	0	A	G	0.34995	0.99769	39.0852	4.10E-10	0.0119412	0.0018945	39.7289	2.90E-10
rs2286975	16	11114006	0	G	A	0.719903	0.997052	35.1404	3.10E-09	-0.0120466	0.00201119	35.8778	2.10E-09
rs2925979	16	81534790	0	T	C	0.299874	1	163.24	2.20E-37	0.0251859	0.00197069	163.334	2.10E-37
rs30233	16	14400309	0	G	A	0.424792	0.995037	47.9465	4.40E-12	-0.0127004	0.00182898	48.2188	3.80E-12
rs34050011	16	49868513	0	C	A	0.575493	0.995019	61.952	3.50E-15	0.0143363	0.00182781	61.5195	4.40E-15
rs3893749	16	67533298	0	A	G	0.956309	0.999321	79.6241	4.50E-19	0.0402959	0.00441389	83.3447	6.90E-20
rs400223	16	73809928	0	C	T	0.524867	0.988599	31.3644	2.10E-08	-0.0100395	0.00181777	30.503	3.30E-08
rs462464	16	89613037	0	G	A	0.781858	0.99676	32.6354	1.10E-08	-0.0123511	0.00218915	31.8317	1.70E-08
rs4889634	16	30878863	0	C	T	0.618158	0.987261	42.6626	6.50E-11	-0.0122449	0.00186911	42.9183	5.70E-11
rs56094641	16	53806453	0	A	G	0.595238	0.99963	54.4638	1.60E-13	0.0136748	0.00183924	55.2792	1.00E-13
rs71385734	16	2160503	0	T	G	0.830556	0.987741	75.6559	3.40E-18	0.0210919	0.00242119	75.8879	3.00E-18
rs7184427	16	88804734	0	A	G	0.15374	0.985654	30.4308	3.50E-08	-0.0139709	0.00252517	30.6105	3.20E-08
rs7187078	16	71382420	0	T	G	0.356983	0.995344	32.7253	1.10E-08	0.0107332	0.00188695	32.3544	1.30E-08
rs7199601	16	992729	0	A	G	0.632086	0.994407	40.4626	2.00E-10	-0.0119337	0.0018755	40.487	2.00E-10
rs7200336	16	4422607	0	G	T	0.252877	0.991519	51.406	7.50E-13	0.0150174	0.0020849	51.8822	5.90E-13
rs7203193	16	11641180	0	A	G	0.512821	1	31.9292	1.60E-08	-0.0101442	0.00180277	31.6631	1.80E-08
rs9940899	16	69169927	0	T	C	0.708329	0.998569	34.4734	4.30E-09	0.0117365	0.00198479	34.9659	3.40E-09
rs10468567	17	63800288	0	C	T	0.574309	0.991885	35.389	2.70E-09	0.0107756	0.00183057	34.6502	3.90E-09
rs10512605	17	74212382	0	C	T	0.921371	0.992739	55.6337	8.70E-14	-0.0250263	0.00335847	55.5275	9.20E-14
rs11078692	17	7426065	0	C	T	0.385821	0.996732	129.196	6.10E-30	0.0212914	0.00185588	131.616	1.80E-30
rs1114297	17	59599207	0	T	C	0.32274	0.987035	38.1645	6.50E-10	0.0120299	0.00193928	38.4807	5.50E-10
rs113252144	17	62483931	0	C	T	0.92288	0.9659	31.6874	1.80E-08	-0.020048	0.00344016	33.9611	5.60E-09
rs11871722	17	61675576	0	C	T	0.737764	0.998861	50.9071	9.70E-13	-0.0145957	0.00205261	50.5634	1.20E-12
rs12452505	17	63556402	0	C	G	0.857857	0.99295	35.5933	2.40E-09	0.0155082	0.00259105	35.824	2.20E-09
rs12941356	17	17716531	0	A	G	0.409791	0.987952	123.18	1.30E-28	0.0205557	0.00184589	124.008	8.40E-29
rs1401796	17	54839759	0	C	A	0.484647	0.987785	32.3599	1.30E-08	0.0101749	0.00181608	31.3902	2.10E-08
rs1910323	17	7192696	0	G	A	0.473398	0.978693	34.7866	3.70E-09	0.0107537	0.00182612	34.6783	3.90E-09
rs1974721	17	17040820	0	G	C	0.277687	0.997169	29.3951	5.90E-08	-0.0110404	0.00201373	30.0583	4.20E-08
rs2114445	17	53703781	0	T	C	0.806435	0.996873	43.6307	4.00E-11	-0.0150292	0.00228554	43.2409	4.80E-11
rs2159437	17	68439660	0	A	G	0.483737	0.995859	127.452	1.50E-29	0.0206733	0.00180563	131.088	2.40E-30
rs2240277	17	6548168	0	T	C	0.374667	0.997273	34.6102	4.00E-09	0.0108903	0.00186562	34.0752	5.30E-09
rs227732	17	54769890	0	C	T	0.703919	0.99045	95.2533	1.70E-22	-0.0194106	0.00198206	95.9065	1.20E-22
rs2376585	17	76417883	0	T	C	0.182114	0.993914	67.0515	2.60E-16	-0.0190282	0.00234238	65.9907	4.50E-16
rs2663339	17	927516	0	A	C	0.692157	0.994338	34.768	3.70E-09	0.0114573	0.00195899	34.2058	5.00E-09
rs35848680	17	69906037	0	C	T	0.71322	0.994402	39.6924	3.00E-10	-0.0124901	0.00199907	39.037	4.20E-10
rs3760318	17	29247715	0	G	A	0.624966	1	129.064	6.60E-30	0.0209855	0.00186323	126.855	2.00E-29
rs4794033	17	47358481	0	G	A	0.897583	0.989203	43.9525	3.40E-11	0.0196971	0.00298738	43.4732	4.30E-11
rs56387760	17	27807416	0	A	G	0.970366	1	28.6408	8.70E-08	-0.0290656	0.00531962	29.8537	4.70E-08
rs58360980	17	1626478	0	G	A	0.698747	1	58.36	2.20E-14	0.014934	0.00196575	57.7163	3.00E-14
rs62062609	17	7631694	0	G	T	0.875001	0.994617	37.7708	8.00E-10	-0.0167682	0.00273788	37.5097	9.10E-10
rs62070804	17	27889643	0	C	T	0.98203	1	39.6684	3.00E-10	-0.043048	0.00680285	40.0427	2.50E-10
rs62076925	17	40395232	0	G	A	0.697763	0.989402	47.7583	4.80E-12	-0.0138784	0.00197475	49.3914	2.10E-12
rs6502953	17	1670809	0	G	A	0.65106	0.994095	48.7669	2.90E-12	-0.0130713	0.0018988	47.3892	5.80E-12
rs78581447	17	40953216	0	A	C	0.950311	0.887544	31.4416	2.10E-08	-0.0248125	0.00440711	31.698	1.80E-08
rs8066695	17	76913843	0	T	C	0.541993	0.986876	49.1257	2.40E-12	0.0127186	0.00182104	48.78	2.90E-12
rs8071080	17	68681019	0	A	G	0.699449	0.999391	38.359	5.90E-10	0.0121023	0.00196884	37.7848	7.90E-10
rs8079215	17	44064851	0	C	T	0.279435	0.980725	43.2978	4.70E-11	-0.0132123	0.00202815	42.4382	7.30E-11
rs854796	17	18070761	0	G	A	0.315866	0.99276	67.0479	2.60E-16	0.0159819	0.00194768	67.332	2.30E-16
rs8614	17	27588806	0	C	A	0.817725	1	37.8133	7.80E-10	0.0144836	0.00234011	38.307	6.00E-10
rs871841	17	8216468	0	T	C	0.502503	1	36.0261	1.90E-09	-0.0110657	0.00180639	37.5262	9.00E-10
rs8866	17	65373979	0	C	G	0.598395	0.995238	37.9463	7.30E-10	0.0115401	0.00184701	39.0373	4.20E-10
rs9282699	17	61996183	0	T	C	0.976577	0.836212	45.9138	1.20E-11	0.04379	0.00652154	45.0868	1.90E-11
rs9893997	17	76726350	0	T	G	0.11597	0.985893	38.0685	6.80E-10	0.017462	0.00283326	37.9853	7.10E-10
rs9894577	17	43223292	0	G	A	0.682235	0.997916	49.049	2.50E-12	0.0138988	0.00193985	51.3353	7.80E-13
rs9901434	17	73388770	0	A	G	0.163878	1	78.9804	6.30E-19	-0.0218948	0.00243696	80.7205	2.60E-19
rs9905385	17	59498250	0	A	G	0.329154	0.991212	299.017	5.40E-67	0.0332733	0.00192545	298.625	6.60E-67
rs9906944	17	47091420	0	C	T	0.659236	0.99131	40.3755	2.10E-10	-0.0122149	0.00191085	40.8627	1.60E-10
rs9908003	17	76165048	0	G	C	0.442152	0.990425	40.8818	1.60E-10	-0.0118008	0.00182651	41.7424	1.00E-10
rs9912305	17	59535965	0	G	C	0.619929	1	58.8328	1.70E-14	-0.0142872	0.00185613	59.2481	1.40E-14
rs112663256	18	11972074	0	A	G	0.903075	0.992677	32.0491	1.50E-08	0.0172647	0.0030613	31.8056	1.70E-08
rs12454712	18	60845884	0	T	C	0.623282	1	68.5244	1.30E-16	0.0154288	0.00186378	68.5296	1.20E-16
rs375442856	18	15373581	0	C	A	0.984522	0.822049	40.3842	2.10E-10	-0.0512394	0.00807568	40.2578	2.20E-10
rs3810068	18	2846499	0	T	C	0.596977	1	145.017	2.10E-33	0.0220991	0.00184066	144.146	3.30E-33
rs61735998	18	34289285	0	G	T	0.974771	1	37.0196	1.20E-09	0.0354696	0.00577102	37.7753	7.90E-10
rs6507603	18	42748180	0	T	C	0.754485	0.99736	32.0157	1.50E-08	0.0117669	0.00209719	31.4808	2.00E-08
rs7236494	18	20728223	0	G	A	0.215162	0.999448	251.196	1.40E-56	-0.0348249	0.00219609	251.465	1.20E-56
rs75754713	18	53254028	0	G	A	0.938233	0.956071	42.3433	7.70E-11	0.024891	0.0038323	42.1858	8.30E-11
rs8099716	18	77226947	0	A	G	0.686804	0.994066	44.3918	2.70E-11	0.0131746	0.00195208	45.5493	1.50E-11
rs117597226	19	34131328	0	C	A	0.969268	1	30.9094	2.70E-08	0.0296824	0.00528489	31.5447	1.90E-08
rs12162223	19	18635457	0	G	C	0.427512	0.992085	71.9099	2.30E-17	-0.015754	0.00184919	72.5808	1.60E-17
rs138145924	19	42801967	0	C	T	0.968703	0.952166	56.003	7.20E-14	0.0403493	0.00536991	56.4596	5.70E-14
rs140448673	19	4029056	0	G	A	0.979245	0.849478	44.2153	2.90E-11	0.0461075	0.00693116	44.2517	2.90E-11
rs142183293	19	33815690	0	G	A	0.988428	0.923098	37.4252	9.50E-10	0.054435	0.00885628	37.7792	7.90E-10
rs1469024	19	18384544	0	C	T	0.36761	0.998861	97.0817	6.70E-23	0.0186252	0.00189337	96.7676	7.80E-23
rs16996277	19	19854296	0	C	G	0.950132	0.937492	30.7802	2.90E-08	-0.0236532	0.00432408	29.9222	4.50E-08
rs17001079	19	11116159	0	G	A	0.886902	0.999211	32.7649	1.00E-08	0.0166715	0.00287998	33.5094	7.10E-09
rs1799815	19	7125519	0	G	A	0.931362	1	49.9641	1.60E-12	0.0252822	0.00360399	49.2108	2.30E-12
rs2230876	19	8468337	0	C	T	0.70552	0.987834	38.2174	6.30E-10	-0.0125664	0.00201201	39.0088	4.20E-10
rs284662	19	41932275	0	T	C	0.380318	1	31.9391	1.60E-08	0.0104565	0.00187622	31.06	2.50E-08

rs2854510	19	44074212	0	A	G	0.800339	0.996904	30.7879	2.90E-08	-0.0126819	0.00228537	30.7933	2.90E-08
rs2974755	19	13062663	0	C	T	0.397575	0.997566	45.3659	1.60E-11	0.0124803	0.0018615	44.9498	2.00E-11
rs312069	19	3207348	0	G	C	0.466997	0.99226	30.9551	2.60E-08	-0.0101084	0.00183381	30.3852	3.50E-08
rs34326794	19	17287122	0	G	A	0.836318	0.980811	39.4397	3.40E-10	0.0154197	0.00248755	38.4244	5.70E-10
rs350916	19	4094775	0	G	A	0.511219	0.99049	58.061	2.50E-14	0.0140374	0.001832	58.7113	1.80E-14
rs3786901	19	33897478	0	A	C	0.575593	0.998116	202.188	7.00E-46	-0.0261396	0.00184651	200.399	1.70E-45
rs4252548	19	55879672	0	C	T	0.97826	1	50.9557	9.40E-13	0.0441438	0.00624265	50.0037	1.50E-12
rs4804669	19	12502457	0	A	G	0.216868	0.980742	46.5358	9.00E-12	-0.0152322	0.00223387	46.4956	9.20E-12
rs4807467	19	3433202	0	T	A	0.78692	0.994751	35.3761	2.70E-09	-0.0132418	0.00223391	35.1371	3.10E-09
rs5117	19	45418790	0	T	C	0.764097	0.99272	43.6354	4.00E-11	0.0141645	0.00215536	43.1882	5.00E-11
rs62621197	19	8670147	0	C	T	0.963285	0.930027	213.251	2.70E-48	0.0733486	0.00503033	212.613	3.70E-48
rs7188	19	11275139	0	A	C	0.672178	1	72.2453	1.90E-17	0.0163549	0.00194011	71.0626	3.50E-17
rs7248169	19	13949751	0	C	T	0.774548	0.979136	38.7622	4.80E-10	0.0141265	0.00220184	41.162	1.40E-10
rs7257083	19	33943986	0	G	A	0.711461	0.99918	71.1616	3.30E-17	0.0169724	0.00201355	71.0494	3.50E-17
rs73006822	19	13109955	0	C	T	0.849662	0.997791	42.0967	8.70E-11	-0.0165311	0.00255315	41.9227	9.50E-11
rs73022871	19	30990705	0	C	G	0.840218	0.992958	50.4969	1.20E-12	-0.0179246	0.00249418	51.6468	6.60E-13
rs740404	19	2232049	0	G	A	0.879806	0.962074	31.8945	1.60E-08	-0.0158339	0.0028567	30.7218	3.00E-08
rs75282733	19	12165646	0	T	G	0.940126	0.989659	37.0001	1.20E-09	-0.0235864	0.0038612	37.3144	1.00E-09
rs80073013	19	13087831	0	T	G	0.962925	0.954813	32.507	1.20E-08	0.028447	0.0049416	33.1388	8.60E-09
rs8103017	19	55999142	0	C	G	0.708254	0.985043	39.7256	2.90E-10	-0.0128709	0.00201942	40.622	1.80E-10
rs8112895	19	10305162	0	A	G	0.935199	0.99774	29.725	5.00E-08	-0.0202617	0.0037003	29.9832	4.40E-08
rs1008228	20	6668193	0	G	A	0.610799	0.989231	40.1758	2.30E-10	-0.0117647	0.00186315	39.8715	2.70E-10
rs11086761	20	38438771	0	T	C	0.653699	0.989692	38.3821	5.80E-10	0.0119504	0.00190659	39.2873	3.70E-10
rs11907497	20	47843620	0	T	C	0.762561	0.982451	64.0855	1.20E-15	-0.0170934	0.00213679	63.9927	1.20E-15
rs11960	20	17600357	0	G	A	0.274027	1	35.2788	2.90E-09	-0.0119858	0.00202248	35.1205	3.10E-09
rs1206825	20	45758258	0	A	T	0.446901	0.998109	41.864	9.80E-11	-0.0118062	0.00181413	42.3531	7.60E-11
rs144033177	20	571467	0	A	C	0.984058	0.95325	35.9572	2.00E-09	-0.0443174	0.00737263	36.133	1.80E-09
rs1892203	20	51696096	0	C	T	0.503594	0.982354	72.1876	2.00E-17	0.0153764	0.00182097	71.3022	3.10E-17
rs2145271	20	6626140	0	T	A	0.364814	0.999705	403.753	8.40E-90	0.0376189	0.00187453	402.744	1.40E-89
rs2426433	20	50969460	0	G	A	0.373101	0.997811	49.0612	2.50E-12	-0.013215	0.0018656	50.1756	1.40E-12
rs58842569	20	4099558	0	T	G	0.654826	0.996283	49.3958	2.10E-12	-0.0134866	0.00189956	50.4082	1.20E-12
rs6013572	20	51553621	0	T	C	0.937568	1	30.706	3.00E-08	-0.0203588	0.0037225	29.9112	4.50E-08
rs6029180	20	39178923	0	A	G	0.673515	0.9785	61.7728	3.90E-15	0.0151073	0.00194387	60.4001	7.70E-15
rs6058376	20	34543834	0	A	G	0.834829	0.997477	68.8496	1.10E-16	-0.0201	0.00243288	68.2572	1.40E-16
rs6066101	20	45520152	0	A	G	0.386668	0.993173	197.007	9.40E-45	0.0259936	0.00185863	195.591	1.90E-44
rs6074197	20	10883485	0	A	G	0.673088	0.995186	47.2099	6.40E-12	-0.0132047	0.00192836	46.8897	7.50E-12
rs6077240	20	7655955	0	C	T	0.715115	0.993174	39.4729	3.30E-10	0.0124413	0.00200515	38.4984	5.50E-10
rs6090040	20	62692060	0	A	C	0.479177	0.988921	91.2494	1.30E-21	0.0174112	0.00181502	92.0231	8.60E-22
rs6102343	20	39924279	0	G	A	0.76503	0.998184	43.1464	5.10E-11	-0.013935	0.00212867	42.8549	5.90E-11
rs6120012	20	31471864	0	C	G	0.851187	0.990782	36.9178	1.20E-09	0.0151918	0.00254486	35.6362	2.40E-09
rs61734651	20	61451332	0	C	T	0.929255	0.917302	61.6243	4.20E-15	-0.0292095	0.00367552	63.1555	1.90E-15
rs67032674	20	32725947	0	A	G	0.940861	0.99686	36.241	1.70E-09	-0.0233991	0.00383161	37.2937	1.00E-09
rs74698119	20	39197335	0	A	T	0.982683	0.930318	42.4397	7.30E-11	-0.0469688	0.00716494	42.9727	5.60E-11
rs805770	20	5668714	0	C	T	0.605975	1	106.868	4.80E-25	-0.0191018	0.00184874	106.757	5.00E-25
rs1042917	21	47545768	0	G	A	0.50503	1	63.3339	1.70E-15	0.0143334	0.00180746	62.887	2.20E-15
rs11088991	21	46783285	0	T	C	0.423266	0.99121	39.443	3.40E-10	0.0115007	0.0018392	39.1014	4.00E-10
rs2830586	21	28305477	0	T	G	0.84035	0.999359	30.9641	2.60E-08	0.0136409	0.00246524	30.6173	3.10E-08
rs2838967	21	47038218	0	G	A	0.869938	0.993049	43.4948	4.30E-11	0.0177736	0.0026941	43.5237	4.20E-11
rs6517225	21	35713784	0	A	C	0.415213	0.99692	56.1463	6.70E-14	-0.0136868	0.0018388	55.4031	9.80E-14
rs73197346	21	36770189	0	T	C	0.867341	0.992786	61.8727	3.70E-15	-0.0211521	0.00267731	62.4181	2.80E-15
rs1076301	22	31044831	0	A	G	0.527182	0.994531	33.4393	7.40E-09	0.0104858	0.00182611	32.9725	9.30E-09
rs1076922	22	43560962	0	C	T	0.719841	1	37.168	1.10E-09	0.0122725	0.0020268	36.6642	1.40E-09
rs13056562	22	30677722	0	C	T	0.868026	0.980848	65.7676	5.10E-16	-0.0217814	0.00271455	64.3839	1.00E-15
rs181440924	22	29412028	0	G	A	0.98406	0.990792	44.8095	2.20E-11	0.0488177	0.00730368	44.6756	2.30E-11
rs2294239	22	29449477	0	A	G	0.571642	0.99076	91.5281	1.10E-21	0.0176611	0.00184848	91.286	1.20E-21
rs4821083	22	33056341	0	T	C	0.850232	1	55.5392	9.20E-14	0.0189408	0.00254892	55.2186	1.10E-13
rs9609263	22	31745274	0	A	C	0.577922	0.998208	41.9868	9.20E-11	0.0118475	0.00184393	41.2826	1.30E-10

Summary statistics for the genetic association with body shape PC4

rsid	CHR	BP	GENPOS	ALLELE1	ALLELE0	A1FREQ	INFO	CHISQ_LINREG	P_LINREG	BETA	SE	CHISQ_BOLT_LMM_INF	pval
rs1034528	1	11249132	0	G	C	0.741091	0.998697	39.6531	3.00E-10	-0.00507119	0.000805182	39.6672	3.00E-10
rs11205303	1	149906413	0	T	C	0.593201	1	41.0532	1.50E-10	0.00458736	0.000718346	40.7811	1.70E-10
rs12076964	1	118856134	0	C	T	0.777354	0.990463	81.9873	1.40E-19	0.00776373	0.000850758	83.2778	7.10E-20
rs12131794	1	219766226	0	C	A	0.708277	0.996198	126.75	2.10E-29	0.00879751	0.000775564	128.672	8.00E-30
rs12405515	1	172357441	0	G	T	0.431674	0.995756	44.1623	3.00E-11	0.00477112	0.000713079	44.7678	2.20E-11
rs12741800	1	26802548	0	T	C	0.462436	0.998925	34.4492	4.40E-09	0.00417431	0.000706193	34.94	3.40E-09
rs1409157	1	119504487	0	G	T	0.388121	0.999617	59.5317	1.20E-14	0.00556822	0.000723561	59.2219	1.40E-14
rs1415181	1	215031151	0	T	C	0.592782	0.998449	45.3899	1.60E-11	0.00470973	0.000717676	43.066	5.30E-11
rs157874	1	165392814	0	T	G	0.590788	0.997438	39.3925	3.50E-10	-0.00449216	0.000717717	39.1746	3.90E-10
rs17184588	1	24365512	0	T	C	0.49566	0.978987	37.3622	9.80E-10	-0.00433607	0.000712765	37.0084	1.20E-09
rs2318761	1	150257714	0	A	G	0.532416	0.978491	31.9825	1.60E-08	0.00407187	0.000712988	32.6155	1.10E-08
rs2359714	1	118770271	0	C	T	0.473078	0.980238	35.3678	2.70E-09	-0.00417743	0.000713244	34.3038	4.70E-09
rs2796243	1	208029182	0	C	T	0.478374	0.994553	29.6983	5.00E-08	0.0039018	0.000706584	30.4931	3.40E-08
rs2821226	1	203517292	0	A	G	0.472586	0.986322	61.0447	5.60E-15	0.00553959	0.000710249	60.8322	6.20E-15
rs34502377	1	170740803	0	C	T	0.846303	0.996112	66.4337	3.60E-16	0.00800195	0.000977749	66.9789	2.70E-16
rs34517439	1	78450517	0	C	A	0.877645	0.972235	43.2326	4.90E-11	-0.00707739	0.00109043	42.1262	8.60E-11
rs35208023	1	156415673	0	C	T	0.331932	0.994857	41.9226	9.50E-11	-0.00485301	0.000749624	41.9117	9.50E-11
rs36115605	1	94047210	0	C	T	0.795388	0.997971	51.1334	8.60E-13	0.00622799	0.00087489	50.6744	1.10E-12
rs368420187	1	153900067	0	T	G	0.875679	0.974431	35.2041	3.00E-09	-0.00656154	0.00108174	36.7932	1.30E-09
rs3850625	1	201016296	0	G	A	0.881729	1	40.1159	2.40E-10	0.00690861	0.00109011	40.164	2.30E-10
rs417237	1	228532195	0	G	T	0.382138	0.998967	38.3683	5.90E-10	0.0044472	0.000725668	37.5576	8.90E-10
rs4920605	1	17315425	0	G	A	0.431577	0.999727	53.9575	2.00E-13	0.00518676	0.000710857	53.2386	3.00E-13
rs713301	1	221312697	0	T	G	0.830078	0.978375	32.1281	1.40E-08	-0.00539474	0.000948818	32.3277	1.30E-08
rs72657272	1	31407314	0	C	T	0.849318	0.974248	69.787	6.60E-17	0.00833176	0.000998103	69.6824	7.00E-17
rs7534958	1	56737680	0	T	A	0.417535	0.992852	36.934	1.20E-09	0.00434183	0.000717071	36.6625	1.40E-09
rs997482	1	10273179	0	C	T	0.872229	0.999341	37.1215	1.10E-09	0.00637614	0.00105599	36.458	1.60E-09
rs10165387	2	161269546	0	A	T	0.794397	0.99281	58.2334	2.30E-14	-0.00667425	0.000874192	58.2897	2.30E-14
rs10177183	2	66095947	0	G	C	0.958377	0.973145	37.297	1.00E-09	-0.0108199	0.00178631	36.6887	1.40E-09
rs10188910	2	241941773	0	G	A	0.384457	0.975895	41.0733	1.50E-10	-0.00466798	0.000734395	40.4016	2.10E-10
rs10189912	2	144162609	0	A	G	0.630497	0.996958	35.5987	2.40E-09	0.00433118	0.000730338	35.1694	3.00E-09
rs10210385	2	58997712	0	T	C	0.630189	0.992006	32.7078	1.10E-08	-0.00411285	0.000733069	31.4773	2.00E-08
rs10497439	2	176310990	0	G	A	0.860337	0.998483	41.8152	1.00E-10	0.0065184	0.00101636	41.1331	1.40E-10
rs13390163	2	67926931	0	T	C	0.550459	0.990831	39.5428	3.20E-10	0.00457317	0.000711125	41.3565	1.30E-10
rs1548945	2	217665788	0	T	C	0.418662	0.990096	41.0415	1.50E-10	-0.00462973	0.000718374	41.5347	1.20E-10
rs17353071	2	192946327	0	A	C	0.505006	0.993758	32.6017	1.10E-08	-0.00405735	0.000706752	32.9573	9.40E-09
rs181812659	2	176816413	0	G	A	0.976839	0.927826	39.8159	2.80E-10	-0.015385	0.00243377	39.9608	2.60E-10
rs2052670	2	66218481	0	A	G	0.667685	0.99557	30.3064	3.70E-08	0.00413235	0.000749103	30.4306	3.50E-08
rs2385539	2	220366953	0	G	C	0.355535	0.996328	40.4787	2.00E-10	-0.00468652	0.000737996	40.3268	2.10E-10
rs4665972	2	27598097	0	T	C	0.395281	0.9882	42.3152	7.80E-11	-0.00472627	0.000725168	42.4776	7.10E-11
rs4671319	2	57950346	0	G	A	0.447644	0.992374	52.5659	4.20E-13	0.00516493	0.000711338	52.7203	3.80E-13
rs58533716	2	174201665	0	T	C	0.944138	1	34.2151	4.90E-09	0.00896343	0.00153274	34.1989	5.00E-09
rs62104184	2	542879	0	G	A	0.908504	0.94928	31.9155	1.60E-08	-0.0071039	0.00125471	32.0558	1.50E-08
rs6548237	2	621461	0	A	C	0.173484	0.999026	37.3173	1.00E-09	-0.00565142	0.000930428	36.8935	1.20E-09
rs6708265	2	242047750	0	A	G	0.843251	0.999664	33.1947	8.30E-09	0.00557368	0.00096887	33.0943	8.80E-09
rs6753142	2	165544071	0	T	C	0.64341	0.996939	36.4175	1.60E-09	0.00444012	0.000736907	36.3048	1.70E-09
rs6757852	2	198530293	0	G	A	0.521539	0.995248	66.5529	3.40E-16	-0.0057094	0.000707576	65.1079	7.10E-16
rs711869	2	13073967	0	G	A	0.440197	0.983771	30.0682	4.20E-08	0.00394259	0.000715125	30.3949	3.50E-08
rs807624	2	15782471	0	G	T	0.643021	0.998611	32.5576	1.20E-08	0.00418513	0.000735195	32.405	1.30E-08
rs1075469	3	129340295	0	C	T	0.804129	0.986372	75.1016	4.50E-18	0.00773788	0.000893644	74.9747	4.80E-18
rs11914389	3	38527215	0	T	C	0.438524	0.990769	30.8901	2.70E-08	-0.003948	0.000713268	30.6372	3.10E-08
rs1287283	3	99515750	0	A	G	0.333738	0.995389	72.4289	1.70E-17	-0.00631407	0.000750021	70.8715	3.80E-17
rs2230590	3	49936102	0	T	C	0.48373	1	93.7867	3.50E-22	-0.00683862	0.000706448	93.708	3.70E-22
rs28595399	3	12500065	0	T	C	0.697352	0.989053	31.2246	2.30E-08	-0.00424709	0.000772143	30.2543	3.80E-08
rs55742087	3	185830488	0	C	T	0.814718	0.994881	35.5379	2.50E-09	0.00540468	0.000909081	35.3455	2.80E-09
rs60716777	3	134373304	0	G	A	0.709181	0.998715	53.2702	2.90E-13	-0.00570068	0.0007769	53.8421	2.20E-13
rs73230069	3	136472640	0	G	A	0.825979	0.99375	33.1402	8.60E-09	0.00539026	0.000932585	33.4074	7.50E-09
rs9817452	3	156795414	0	G	T	0.612505	0.992748	78.4203	8.30E-19	-0.00643812	0.000728042	78.1997	9.30E-19
rs9827112	3	64985326	0	A	G	0.679232	0.993136	30.7583	2.90E-08	0.00418941	0.000757434	30.5926	3.20E-08
rs9838141	3	11488639	0	C	T	0.392395	0.998496	88.8891	4.20E-21	0.00684862	0.000723166	89.6872	2.80E-21
rs12648298	4	186463483	0	G	A	0.599895	1	30.748	2.90E-08	0.00404626	0.000720429	31.5447	1.90E-08
rs28701469	4	120697664	0	T	C	0.740201	0.982739	42.4134	7.40E-11	-0.00537034	0.000813042	43.6293	4.00E-11
rs72733520	4	145547185	0	A	G	0.686219	0.983691	41.3681	1.30E-10	0.00489457	0.000766215	40.8064	1.70E-10
rs7690371	4	73506076	0	C	A	0.473553	0.999004	60.6505	6.80E-15	-0.00547834	0.000707953	59.8811	1.00E-14
rs781669	4	57819794	0	C	T	0.476444	0.999247	71.7331	2.50E-17	-0.00601226	0.000707088	72.2983	1.90E-17
rs10076308	5	141804669	0	C	T	0.732411	0.990448	30.26	3.80E-08	0.00444788	0.000801125	30.8252	2.80E-08
rs10474093	5	82437431	0	T	C	0.567897	0.987699	33.6869	6.50E-09	0.00407908	0.000715802	32.4743	1.20E-08
rs115912456	5	82815158	0	A	G	0.958865	0.999736	55.7875	8.10E-14	-0.0131822	0.0017746	55.1792	1.10E-13
rs13183998	5	115022367	0	A	G	0.697986	0.998556	29.6623	5.10E-08	0.0042211	0.000770021	30.0502	4.20E-08
rs1363558	5	172904469	0	A	T	0.553398	0.998599	39.1627	3.90E-10	-0.0044747	0.000710258	39.6914	3.00E-10
rs1694068	5	53283630	0	T	A	0.382015	0.996785	34.1913	5.00E-09	0.00423856	0.000727466	33.9478	5.70E-09
rs1978463	5	52737321	0	C	T	0.705391	0.990852	49.49	2.00E-12	0.00547547	0.00077671	49.6965	1.80E-12
rs3936510	5	55860866	0	G	T	0.79893	1	43.2366	4.90E-11	0.00581819	0.000879409	43.7718	3.70E-11
rs555379172	5	317925	0	G	C	0.943797	0.969594	30.6388	3.10E-08	0.00859006	0.00155517	30.5094	3.30E-08
rs62372042	5	42674475	0	A	G	0.716601	0.995264	29.2369	6.40E-08	-0.00428391	0.000784899	29.7888	4.80E-08
rs116170242	6	53535585	0	G	A	0.923881	0.998777	61.8212	3.80E-15	0.010348	0.00133093	60.4507	7.50E-15
rs12210292	6	44925293	0	T	C	0.745247	0.991434	31.8657	1.70E-08	0.00461218	0.000813139	32.1724	1.40E-08
rs1268119	6	126375581	0	T	C	0.280273	0.990443	47.1633	6.50E-12	-0.00542257	0.000788157	47.3353	6.00E-12
rs1294404	6	6735022	0	G	A	0.396281	0.982734	49.5731	1.90E-12	-0.00514786	0.000726803	50.1671	1.40E-12
rs1931788	6	19972602	0	G	A	0.271709	1	35.4044	2.70E-09	-0.00471961	0.000793937	35.3378	2.80E-09
rs262126	6	142835364	0	A	C	0.687189	0.995058	63.97	1.30E-15	-0.00606512	0.000762259	63.3103	1.80E-15

rs377763	6	32199144	0	C	A	0.784987	1	30.3848	3.50E-08	-0.00469226	0.000858081	29.9026	4.50E-08
rs6569648	6	130349119	0	C	T	0.239587	1	61.4019	4.70E-15	0.00649672	0.00082547	61.9421	3.50E-15
rs6906737	6	98345853	0	T	A	0.530753	0.988912	39.8868	2.70E-10	0.00445011	0.000711025	39.1715	3.90E-10
rs73741365	6	53538407	0	C	T	0.911181	0.989232	48.4955	3.30E-12	-0.00865876	0.00124597	48.2945	3.70E-12
rs7756065	6	76247512	0	A	G	0.114922	0.99801	51.5517	7.00E-13	-0.00783247	0.00110493	50.2488	1.40E-12
rs9375477	6	127204623	0	A	G	0.844989	0.993171	40.7899	1.70E-10	-0.00631362	0.000978006	41.6749	1.10E-10
rs9498336	6	149695344	0	T	C	0.738018	0.997458	35.1591	3.00E-09	0.00474295	0.000802991	34.888	3.50E-09
rs113701263	7	130314333	0	G	A	0.783045	0.994646	30.4034	3.50E-08	-0.00473125	0.000860027	30.2641	3.80E-08
rs17168118	7	134576840	0	A	G	0.706902	0.976877	33.5724	6.90E-09	0.00457083	0.000785457	33.8645	5.90E-09
rs2040636	7	25693682	0	C	A	0.200247	0.981871	47.5586	5.30E-12	0.00607115	0.000890794	46.4502	9.40E-12
rs4731701	7	130430930	0	C	T	0.506341	0.994278	132.986	9.10E-31	0.00821009	0.000708564	134.257	4.80E-31
rs62471721	7	130016470	0	G	A	0.649599	0.991818	85.0736	2.90E-20	-0.00682583	0.000742395	84.5358	3.80E-20
rs6976501	7	50760220	0	G	A	0.221221	0.999076	46.0381	1.20E-11	-0.00578301	0.000850817	46.1993	1.10E-11
rs78988425	7	46046915	0	G	A	0.862346	0.986838	31.9706	1.60E-08	-0.00587099	0.00103222	32.35	1.30E-08
rs799443	7	44769013	0	T	A	0.330454	0.995906	38.3861	5.80E-10	-0.00467082	0.000752442	38.5336	5.40E-10
rs10099531	8	49551946	0	C	T	0.288679	0.98873	35.0059	3.30E-09	0.00461885	0.000782631	34.8299	3.60E-09
rs117478964	8	128167147	0	A	G	0.962499	0.977334	42.8606	5.90E-11	-0.0122246	0.00187757	42.3915	7.50E-11
rs12674908	8	121970419	0	A	G	0.452992	0.998119	31.4082	2.10E-08	-0.00396245	0.000708327	31.294	2.20E-08
rs1397104	8	78577539	0	G	A	0.43411	0.999628	39.8862	2.70E-10	0.00453137	0.000712131	40.4891	2.00E-10
rs4841457	8	10773511	0	T	G	0.460676	0.997961	84.0681	4.80E-20	0.0064833	0.000708806	83.6638	5.90E-20
rs4871827	8	121061879	0	G	A	0.673199	1	35.7984	2.20E-09	0.00451608	0.000752031	36.0622	1.90E-09
rs7839059	8	119976542	0	C	A	0.658337	0.996574	31.3544	2.10E-08	0.00416488	0.000745381	31.2211	2.30E-08
rs891637	8	13128674	0	C	T	0.405389	0.986196	33.2313	8.20E-09	-0.00416393	0.000723549	33.1185	8.70E-09
rs10512248	9	98259703	0	T	G	0.670307	1	50.8669	9.90E-13	0.00534213	0.000750963	50.6048	1.10E-12
rs4743150	9	100740124	0	C	T	0.780186	1	37.48	9.20E-10	0.00521618	0.000852329	37.4533	9.40E-10
rs7044414	9	1111049	0	T	C	0.163068	0.994789	62.0322	3.40E-15	-0.00761536	0.000957973	63.1937	1.90E-15
rs72619340	9	137177276	0	C	A	0.859585	1	31.3637	2.10E-08	0.00573911	0.00101713	31.8373	1.70E-08
rs73667911	9	126501320	0	C	T	0.863608	0.995609	31.7284	1.80E-08	0.00582411	0.0010311	31.9047	1.60E-08
rs913359	9	112551867	0	G	A	0.230252	0.978799	33.771	6.20E-09	0.00492593	0.000848325	33.7172	6.40E-09
rs10786156	10	96014622	0	C	G	0.565318	0.998774	107.053	4.30E-25	-0.0073458	0.000712902	106.174	6.80E-25
rs10886855	10	122880466	0	T	C	0.831446	0.97787	53.6839	2.40E-13	0.00696253	0.000952909	53.3865	2.70E-13
rs11199839	10	122989993	0	T	C	0.74514	0.992869	45.8939	1.20E-11	0.00551617	0.00081173	46.1799	1.10E-11
rs11638	10	96371928	0	G	A	0.556715	0.999705	45.4079	1.60E-11	-0.00477656	0.000710139	45.2423	1.70E-11
rs2435381	10	43678796	0	C	T	0.723644	0.987609	34.7668	3.70E-09	0.00464028	0.000793505	34.197	5.00E-09
rs4746822	10	70982941	0	C	T	0.307645	0.998714	33.2896	7.90E-09	-0.00437342	0.00076696	32.516	1.20E-08
rs68049170	10	72432047	0	G	A	0.723434	0.990719	33.1084	8.70E-09	0.00454346	0.000792993	32.8273	1.00E-08
rs7900751	10	88546906	0	C	G	0.577497	0.994744	32.3851	1.30E-08	-0.00406445	0.000716192	32.2065	1.40E-08
rs7914620	10	70331318	0	T	C	0.450144	0.99802	33.933	5.70E-09	-0.00410734	0.000710704	33.3998	7.50E-09
rs10047483	11	68231705	0	G	A	0.722989	0.994307	85.8064	2.00E-20	0.00732877	0.000789664	86.1347	1.70E-20
rs12285193	11	69178568	0	T	A	0.735551	0.993081	71.1685	3.30E-17	-0.00673882	0.000802983	70.4295	4.80E-17
rs2121650	11	92679138	0	G	A	0.634075	0.99856	32.8633	9.90E-09	-0.00420755	0.000732381	33.0055	9.20E-09
rs35742324	11	16386892	0	A	T	0.718056	0.998039	45.8953	1.20E-11	-0.00531927	0.000785781	45.8247	1.30E-11
rs684720	11	64548429	0	C	G	0.904266	0.997241	32.9223	9.60E-09	0.00688272	0.00120105	32.8398	1.00E-08
rs7119952	11	47235056	0	C	T	0.334731	0.99125	55.2214	1.10E-13	0.00558235	0.000750659	55.3029	1.00E-13
rs74501871	11	2665357	0	A	G	0.906295	1	39.0634	4.10E-10	0.00758303	0.0012115	39.1779	3.90E-10
rs7930706	11	68742072	0	G	A	0.735295	0.993204	52.671	3.90E-13	-0.00586346	0.000802051	53.4446	2.70E-13
rs7952436	11	67024534	0	C	T	0.917763	1	45.4726	1.50E-11	-0.00863999	0.0012857	45.1596	1.80E-11
rs948578	11	65356754	0	C	T	0.511445	0.987156	41.0589	1.50E-10	0.00454795	0.000710946	40.922	1.60E-10
rs1037747	12	114393028	0	C	G	0.409432	0.995337	40.0903	2.40E-10	0.0045595	0.000720134	40.0874	2.40E-10
rs10876864	12	56401085	0	G	A	0.425217	1	34.0881	5.30E-09	-0.00417602	0.000714186	34.1903	5.00E-09
rs10878349	12	66327632	0	A	G	0.487755	0.994253	102.473	4.40E-24	0.00716475	0.000709262	102.044	5.40E-24
rs11614913	12	54385599	0	C	T	0.582388	0.991721	109.394	1.30E-25	0.00756339	0.000719453	110.517	7.60E-26
rs1920597	12	114704092	0	G	A	0.576746	0.998054	34.8778	3.50E-09	-0.00424946	0.000716168	35.2077	3.00E-09
rs2159381	12	3351932	0	C	T	0.911147	0.982815	31.135	2.40E-08	-0.00695935	0.00125153	30.9212	2.70E-08
rs2686570	12	114874456	0	A	G	0.165396	0.990948	41.4825	1.20E-10	0.00620183	0.000955426	42.1353	8.50E-11
rs56344960	12	66410790	0	C	T	0.795158	0.994037	34.6382	4.00E-09	-0.00513719	0.000877682	34.2592	4.80E-09
rs56716492	12	3243589	0	A	G	0.837797	0.995491	32.7161	1.10E-08	-0.00546846	0.000959382	32.4898	1.20E-08
rs7132908	12	50263148	0	G	A	0.615095	1	39.039	4.20E-10	-0.00448078	0.000726554	38.034	7.00E-10
rs73045497	12	3348907	0	C	T	0.927579	0.977055	51.5039	7.10E-13	-0.0098644	0.0013772	51.3033	7.90E-13
rs75318265	12	5534214	0	C	T	0.962379	0.981199	41.7093	1.10E-10	-0.0121914	0.00187488	42.2822	7.90E-11
rs1929077	13	59090848	0	T	C	0.396027	0.993811	30.7514	2.90E-08	-0.00401723	0.000724541	30.7416	2.90E-08
rs2160251	13	51172269	0	A	G	0.454304	0.992994	72.8499	1.40E-17	-0.00604982	0.00071161	72.2771	1.90E-17
rs7994814	13	27054201	0	C	T	0.58241	0.975051	36.9857	1.20E-09	-0.00446297	0.000725906	37.7997	7.80E-10
rs11158991	14	73378501	0	A	G	0.711119	0.994535	35.5212	2.50E-09	-0.00463939	0.000781767	35.2181	2.90E-09
rs11628375	14	98432228	0	T	C	0.338626	0.991391	32.3982	1.30E-08	-0.00425725	0.00075021	32.2028	1.40E-08
rs12881869	14	50923249	0	C	T	0.929142	1	31.8083	1.70E-08	0.00778587	0.00137903	31.8761	1.60E-08
rs7153289	14	35246534	0	C	T	0.717589	0.997484	53.5784	2.50E-13	-0.00577776	0.000786235	54.0025	2.00E-13
rs754388	14	93115410	0	G	C	0.189304	0.991831	74.9942	4.70E-18	0.00781851	0.000905282	74.5899	5.80E-18
rs10083682	15	31726328	0	A	G	0.337692	0.986666	30.537	3.30E-08	-0.00413727	0.000753024	30.1863	3.90E-08
rs11852496	15	83817559	0	T	C	0.770175	0.99769	38.5327	5.40E-10	0.00522722	0.000841097	38.6233	5.10E-10
rs1498505	15	67367365	0	C	T	0.56684	0.995742	32.3799	1.30E-08	0.0040953	0.00071432	32.8691	9.90E-09
rs1919364	15	33009574	0	C	G	0.510316	0.995322	34.834	3.60E-09	-0.00422545	0.000709312	35.4872	2.60E-09
rs28781400	15	84460869	0	G	A	0.577026	0.997957	57.545	3.30E-14	0.00542969	0.000715982	57.5102	3.40E-14
rs338372	15	68217562	0	T	C	0.606668	0.989938	31.8429	1.70E-08	0.00413185	0.000726789	32.32	1.30E-08
rs62025270	15	86300198	0	G	A	0.760175	0.997931	34.9677	3.40E-09	0.00488582	0.000829423	34.6995	3.80E-09
rs7162542	15	84514290	0	C	G	0.443557	0.999001	136.599	1.50E-31	0.00830088	0.000711277	136.198	1.80E-31
rs72755233	15	100692953	0	G	A	0.88798	1	46.0233	1.20E-11	-0.00759846	0.00112029	46.0034	1.20E-11
rs73465670	15	89206798	0	C	A	0.919107	0.995413	38.5565	5.30E-10	0.0080758	0.00129844	38.6838	5.00E-10
rs75260615	15	100837822	0	C	T	0.915123	0.996364	35.7296	2.30E-09	0.00765239	0.00126901	36.3634	1.60E-09
rs12924331	16	56953261	0	A	G	0.577301	0.996514	32.2888	1.30E-08	-0.00412093	0.000718281	32.9156	9.60E-09
rs2307022	16	68381978	0	A	G	0.331206	0.999609	37.7388	8.10E-10	0.00464202	0.000752407	38.0635	6.80E-10
rs3111605	16	86426293	0	A	G	0.547665	0.994495	42.3578	7.60E-11	0.00466346	0.000714181	42.6383	6.60E-11
rs35057083	16	51841046	0	C	T	0.313691	0.992281	39.3451	3.60E-10	0.00480896	0.000766659	39.3457	3.60E-10

rs62049569	16	88277010	0	C	G	0.830685	0.996769	33.2946	7.90E-09	-0.00551038	0.00094498	34.003	5.50E-09
rs74597321	16	88792529	0	G	A	0.973013	0.974599	30.9393	2.70E-08	-0.0122402	0.00221249	30.6064	3.20E-08
rs8054079	16	19975407	0	C	T	0.858716	0.973751	42.9031	5.80E-11	0.00674107	0.00103119	42.7348	6.30E-11
rs9972653	16	53814363	0	G	T	0.600385	0.99641	80.6009	2.80E-19	-0.00655876	0.000724667	81.9156	1.40E-19
rs12941371	17	17438318	0	G	A	0.456398	0.992257	30.402	3.50E-08	0.00394223	0.000714737	30.4222	3.50E-08
rs12952730	17	57978836	0	G	A	0.643393	0.999973	48.8057	2.80E-12	-0.0052234	0.00073872	49.9973	1.50E-12
rs1396515	17	68430993	0	G	C	0.484883	0.99598	40.9117	1.60E-10	0.00453784	0.00071004	40.8443	1.60E-10
rs2239925	17	43185820	0	T	C	0.442181	0.986922	60.8417	6.20E-15	0.00553078	0.000719396	59.1067	1.50E-14
rs2273984	17	2139654	0	C	G	0.363133	0.987273	51.1854	8.40E-13	0.00527894	0.000741618	50.668	1.10E-12
rs236548	17	68231252	0	G	A	0.254399	0.99316	30.1306	4.00E-08	0.00445983	0.000816796	29.8132	4.80E-08
rs35552706	17	56185153	0	A	G	0.936485	0.948551	31.8929	1.60E-08	-0.00841516	0.00149381	31.7347	1.80E-08
rs9890200	17	48624523	0	A	C	0.628503	0.997916	35.6286	2.40E-09	-0.00438447	0.000734476	35.6353	2.40E-09
rs9907540	17	448042	0	A	G	0.534918	0.994491	153.729	2.70E-35	-0.00888633	0.000712193	155.686	9.90E-36
rs12455386	18	60111237	0	C	T	0.697916	0.987533	42.9453	5.60E-11	-0.00504018	0.000776048	42.1808	8.30E-11
rs17735872	18	42670233	0	G	C	0.740908	0.993671	31.0805	2.50E-08	0.00458474	0.000810375	32.008	1.50E-08
rs579332	18	20117594	0	C	T	0.694049	0.9903	38.0479	6.90E-10	0.00472782	0.000771013	37.6009	8.70E-10
rs663640	18	57846077	0	C	T	0.781092	0.996706	89.2779	3.40E-21	-0.00808335	0.000856683	89.0313	3.90E-21
rs62621197	19	8670147	0	C	T	0.963285	0.930027	55.432	9.70E-14	-0.0146858	0.00197694	55.1834	1.10E-13
rs3790165	20	19218127	0	C	T	0.89837	0.999831	46.6106	8.70E-12	-0.00805769	0.00117254	47.2241	6.30E-12
rs6038491	20	6410854	0	C	T	0.679712	0.993669	37.1516	1.10E-09	0.00465259	0.00075969	37.5074	9.10E-10
rs6066148	20	45602037	0	G	C	0.739517	0.996179	54.7008	1.40E-13	0.00603317	0.000808247	55.7189	8.40E-14
rs117999064	21	39977076	0	A	G	0.983765	0.974986	30.5044	3.30E-08	0.0156209	0.00284165	30.2185	3.90E-08
rs1803439	21	38885442	0	A	G	0.652342	1	30.6183	3.10E-08	-0.0041088	0.000745383	30.3857	3.50E-08
rs2824019	21	18117675	0	A	G	0.647038	0.998383	30.8068	2.90E-08	-0.00411789	0.000743449	30.6794	3.00E-08
rs9982601	21	35599128	0	C	T	0.869554	1	32.1324	1.40E-08	0.00596222	0.00105371	32.0167	1.50E-08
rs12484776	22	40652873	0	A	G	0.795475	1	45.4796	1.50E-11	0.00592464	0.000883061	45.0135	2.00E-11
rs132561	22	29351179	0	C	T	0.302934	0.991011	33.4029	7.50E-09	-0.00453006	0.000780591	33.6792	6.50E-09
rs3205187	22	31491295	0	G	C	0.339394	1	31.2801	2.20E-08	0.00424287	0.0007537	31.69	1.80E-08
rs73165104	22	42287203	0	C	G	0.958697	0.970893	29.8651	4.60E-08	0.00997112	0.00181956	30.03	4.30E-08
rs9614099	22	30288338	0	A	T	0.617853	0.984894	72.1802	2.00E-17	0.00630007	0.000740616	72.3611	1.80E-17

Supplementary Text. GECCO Funding and Acknowledgments

Funding

Genetics and Epidemiology of Colorectal Cancer Consortium (GECCO): National Cancer Institute, National Institutes of Health, U.S. Department of Health and Human Services (U01 CA137088, R01 CA059045, R01 201407). Genotyping/Sequencing services were provided by the Center for Inherited Disease Research (CIDR) contract number HHSN268201700006I and HHSN268201200008I . This research was funded in part through the NIH/NCI Cancer Center Support Grant P30 CA015704. Scientific Computing Infrastructure at Fred Hutch funded by ORIP grant S10OD028685.

ASTERISK: a Hospital Clinical Research Program (PHRC-BRD09/C) from the University Hospital Center of Nantes (CHU de Nantes) and supported by the Regional Council of Pays de la Loire, the Groupement des Entreprises Françaises dans la Lutte contre le Cancer (GEFLUC), the Association Anne de Bretagne Génétique and the Ligue Régionale Contre le Cancer (LRCC).

The ATBC Study is supported by the Intramural Research Program of the U.S. National Cancer Institute, National Institutes of Health, Department of Health and Human Services.

CLUE II funding was from the National Cancer Institute (U01 CA086308, Early Detection Research Network; P30 CA006973), National Institute on Aging (U01 AG018033), and the American Institute for Cancer Research. The content of this publication does not necessarily reflect the views or policies of the Department of Health and Human Services, nor does mention of trade names, commercial products, or organizations imply endorsement by the US government.

Maryland Cancer Registry (MCR)

Cancer data was provided by the Maryland Cancer Registry, Center for Cancer Prevention and Control, Maryland Department of Health, with funding from the State of Maryland and the Maryland Cigarette Restitution Fund. The collection and availability of cancer registry data is also supported by the Cooperative Agreement NU58DP006333, funded by the Centers for Disease Control and Prevention. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the Centers for Disease Control and Prevention or the Department of Health and Human Services.

ColoCare: This work was supported by the National Institutes of Health (grant numbers R01 CA189184 (Li/Ulrich), U01 CA206110 (Ulrich/Li/Siegel/Figueiredo/Colditz, 2P30CA015704- 40 (Gilliland), R01 CA207371 (Ulrich/Li)), the Matthias Lackas-Foundation, the German Consortium for Translational Cancer Research, and the EU TRANSCAN initiative.

The Colon Cancer Family Registry (CCFR, www.coloncfr.org) is supported in part by funding from the National Cancer Institute (NCI), National Institutes of Health (NIH) (award U01 CA167551). Support for case ascertainment was provided in part from the Surveillance, Epidemiology, and End Results (SEER) Program and the following U.S. state cancer registries: AZ, CO, MN, NC, NH; and by the Victoria Cancer Registry (Australia) and Ontario Cancer Registry (Canada). The CCFR Set-1 (Illumina 1M/1M-Duo) and Set-2 (Illumina Omni1-Quad) scans were supported by NIH awards U01 CA122839 and R01 CA143237 (to GC). The CCFR Set-3 (Affymetrix Axiom CORECT Set array) was supported by NIH award U19 CA148107 and R01 CA81488 (to SBG). The CCFR Set-4 (Illumina OncoArray 600K SNP array) was supported by NIH award U19 CA148107 (to SBG) and by the Center for Inherited Disease Research (CIDR), which is funded by the NIH to the Johns Hopkins University, contract number HHSN268201200008I. Additional funding for the OFCCR/ARCTIC was through award GL201-043 from the Ontario Research Fund (to BWZ), award 112746 from the Canadian Institutes of Health Research (to TJH), through a Cancer Risk Evaluation (CaRE) Program grant from the Canadian Cancer Society (to SG), and through generous support from the Ontario Ministry of Research and Innovation. The SFCCR Illumina HumanCytoSNP array was supported in

part through NCI/NIH awards U01/U24 CA074794 and R01 CA076366 (to PAN). The content of this manuscript does not necessarily reflect the views or policies of the NCI, NIH or any of the collaborating centers in the Colon Cancer Family Registry (CCFR), nor does mention of trade names, commercial products, or organizations imply endorsement by the US Government, any cancer registry, or the CCFR.

COLON: The COLON study is sponsored by Wereld Kanker Onderzoek Fonds, including funds from grant 2014/1179 as part of the World Cancer Research Fund International Regular Grant Programme, by Alpe d'Huzes and the Dutch Cancer Society (UM 2012–5653, UW 2013-5927, UW2015-7946), and by TRANSCAN (JTC2012-MetaboCCC, JTC2013-FOCUS). The Nqplus study is sponsored by a ZonMW investment grant (98-10030); by PREVIEW, the project PREVention of diabetes through lifestyle intervention and population studies in Europe and around the World (PREVIEW) project which received funding from the European Union Seventh Framework Programme (FP7/2007–2013) under grant no. 312057; by funds from TI Food and Nutrition (cardiovascular health theme), a public–private partnership on precompetitive research in food and nutrition; and by FOODBALL, the Food Biomarker Alliance, a project from JPI Healthy Diet for a Healthy Life.

COLO2&3: National Institutes of Health (R01 CA060987).

Colorectal Cancer Transdisciplinary (CORECT) Study: The CORECT Study was supported by the National Cancer Institute, National Institutes of Health (NCI/NIH), U.S. Department of Health and Human Services (grant numbers U19 CA148107, R01 CA081488, P30 CA014089, R01 CA197350; P01 CA196569; R01 CA201407; R01 CA242218), National Institutes of Environmental Health Sciences, National Institutes of Health (grant number T32 ES013678) and a generous gift from Daniel and Maryann Fong.

CORSA: The CORSA study was funded by Austrian Research Funding Agency (FFG) BRIDGE (grant 829675, to Andrea Gsur), the "Herzfelder'sche Familienstiftung" (grant to Andrea Gsur) and was supported by COST Action BM1206.

CPS-II: The American Cancer Society funds the creation, maintenance, and updating of the Cancer Prevention Study-II (CPS-II) cohort. The study protocol was approved by the institutional review boards of Emory University, and those of participating registries as required.

CRCGEN: Colorectal Cancer Genetics & Genomics, Spanish study was supported by Instituto de Salud Carlos III, co-funded by FEDER funds –a way to build Europe– (grants PI14-613 and PI09-1286), Agency for Management of University and Research Grants (AGAUR) of the Catalan Government (grant 2017SGR723), Junta de Castilla y León (grant LE22A10-2), the Spanish Association Against Cancer (AECC) Scientific Foundation grant GCTRA18022MORE and the Consortium for Biomedical Research in Epidemiology and Public Health (CIBERESP), action Genrisk. Sample collection of this work was supported by the Xarxa de Bancs de Tumors de Catalunya sponsored by Pla Director d'Oncología de Catalunya (XBTC), Plataforma Biobancos PT13/0010/0013 and ICOBIOBANC, sponsored by the Catalan Institute of Oncology. We thank CERCA Programme, Generalitat de Catalunya for institutional support.

Czech Republic CCS: This work was supported by the Grant Agency of the Czech Republic (21-04607X, 20-03997S), by the Grant Agency of the Ministry of Health of the Czech Republic (grants AZV NU21-07-00247 and AZV NU21-03-00506), and Charles University Research Fund (Cooperation 43-Surgical disciplines)

DACHS: This work was supported by the German Research Council (BR 1704/6-1, BR 1704/6-3, BR 1704/6-4, CH 117/1-1, HO 5117/2-1, HE 5998/2-1, KL 2354/3-1, RO 2270/8-1 and BR 1704/17-1), the Interdisciplinary Research Program of the National Center for Tumor Diseases (NCT), Germany, and the German Federal Ministry of Education and Research (01KH0404, 01ER0814, 01ER0815, 01ER1505A and 01ER1505B).

DALS: National Institutes of Health (R01 CA048998 to M. L. Slattery).

EDRN: This work is funded and supported by the NCI, EDRN Grant (U01-CA152753).

EPIC: The coordination of EPIC is financially supported by International Agency for Research on Cancer (IARC) and also by the Department of Epidemiology and Biostatistics, School of Public Health, Imperial College London which has additional infrastructure support provided by the NIHR Imperial Biomedical Research Centre (BRC). The national cohorts are supported by: Danish Cancer Society (Denmark); Ligue Contre le Cancer, Institut Gustave Roussy, Mutuelle Générale de l'Education Nationale, Institut National de la Santé et de la Recherche Médicale (INSERM) (France); German Cancer Aid, German Cancer Research Center (DKFZ), German Institute of Human Nutrition Potsdam- Rehbruecke (DIfE), Federal Ministry of Education and Research (BMBF) (Germany); Associazione Italiana per la Ricerca sul Cancro-AIRC-Italy, Compagnia di SanPaolo and National Research Council (Italy); Dutch Ministry of Public Health, Welfare and Sports (VWS), Netherlands Cancer Registry (NKR), LK Research Funds, Dutch Prevention Funds, Dutch ZON (Zorg Onderzoek Nederland), World Cancer Research Fund (WCRF), Statistics Netherlands (The Netherlands); Health Research Fund (FIS) - Instituto de Salud Carlos III (ISCIII), Regional Governments of Andalucía, Asturias, Basque Country, Murcia and Navarra, and the Catalan Institute of Oncology - ICO (Spain); Swedish Cancer Society, Swedish Research Council and and Region Skåne and Region Västerbotten (Sweden); Cancer Research UK (14136 to EPIC-Norfolk; C8221/A29017 to EPIC-Oxford), Medical Research Council (1000143 to EPIC-Norfolk; MR/M012190/1 to EPIC-Oxford). (United Kingdom).

EPICOLON: This work was supported by grants from Fondo de Investigación Sanitaria/FEDER (PI08/0024, PI08/1276, PS09/02368, P111/00219, PI11/00681, PI14/00173, PI14/00230, PI17/00509, 17/00878, PI20/00113, PI20/00226, Acción Transversal de Cáncer), Xunta de Galicia (PGIDIT07PXIB9101209PR), Ministerio de Economia y Competitividad (SAF07-64873, SAF 2010-19273, SAF2014-54453R), Fundación Científica de la Asociación Española contra el Cáncer (GCB13131592CAST), Beca Grupo de Trabajo "Oncología" AEG (Asociación Española de Gastroenterología), Fundación Privada Olga Torres, FP7 CHIBCHA Consortium, Agència de Gestió d'Ajuts Universitaris i de Recerca (AGAUR, Generalitat de Catalunya, 2014SGR135, 2014SGR255, 2017SGR21, 2017SGR653), Catalan Tumour Bank Network (Pla Director d'Oncologia, Generalitat de Catalunya), PERIS (SLT002/16/00398, Generalitat de Catalunya), CERCA Programme (Generalitat de Catalunya) and COST Action BM1206 and CA17118. CIBERehd is funded by the Instituto de Salud Carlos III.

ESTHER/VERDI. This work was supported by grants from the Baden-Württemberg Ministry of Science, Research and Arts and the German Cancer Aid.

Harvard cohorts: HPFS is supported by the National Institutes of Health (P01 CA055075, UM1 CA167552, U01 CA167552, R01 CA137178, R01 CA151993, and R35 CA197735), NHS by the National Institutes of Health (P01 CA087969, UM1 CA186107, R01 CA137178, R01 CA151993, and R35 CA197735), and PHS by the National Institutes of Health (R01 CA042182).

Hawaii Adenoma Study: NCI grants R01 CA072520.

HCES-CRC: the Hwasun Cancer Epidemiology Study–Colon and Rectum Cancer (HCES-CRC; grants from Chonnam National University Hwasun Hospital, HCRI15011-1).

Kentucky: This work was supported by the following grant support: Clinical Investigator Award from Damon Runyon Cancer Research Foundation (CI-8); NCI R01CA136726.

LCCS: The Leeds Colorectal Cancer Study was funded by the Food Standards Agency and Cancer Research UK Programme Award (C588/A19167).

MCCS cohort recruitment was funded by VicHealth and Cancer Council Victoria. The MCCS was further supported by Australian NHMRC grants 509348, 209057, 251553 and 504711 and by

infrastructure provided by Cancer Council Victoria. Cases and their vital status were ascertained through the Victorian Cancer Registry (VCR) and the Australian Institute of Health and Welfare (AIHW), including the National Death Index and the Australian Cancer Database. BMLynch was supported by MCRF18005 from the Victorian Cancer Agency.

MEC: National Institutes of Health (R37 CA054281, P01 CA033619, and R01 CA063464).

MECC: This work was supported by the National Institutes of Health, U.S. Department of Health and Human Services (R01 CA081488, R01 CA197350, U19 CA148107, R01 CA242218, and a generous gift from Daniel and Maryann Fong.

MSKCC: The work at Sloan Kettering in New York was supported by the Robert and Kate Niehaus Center for Inherited Cancer Genomics and the Romeo Milio Foundation. Moffitt: This work was supported by funding from the National Institutes of Health (grant numbers R01 CA189184, P30 CA076292), Florida Department of Health Bankhead-Coley Grant 09BN-13, and the University of South Florida Oehler Foundation. Moffitt contributions were supported in part by the Total Cancer Care Initiative, Collaborative Data Services Core, and Tissue Core at the H. Lee Moffitt Cancer Center & Research Institute, a National Cancer Institute-designated Comprehensive Cancer Center (grant number P30 CA076292).

NCCCS I & II: We acknowledge funding support for this project from the National Institutes of Health, R01 CA066635 and P30 DK034987.

NFCCR: This work was supported by an Interdisciplinary Health Research Team award from the Canadian Institutes of Health Research (CRT 43821); the National Institutes of Health, U.S. Department of Health and Human Serivces (U01 CA074783); and National Cancer Institute of Canada grants (18223 and 18226). The authors wish to acknowledge the contribution of Alexandre Belisle and the genotyping team of the McGill University and Génome Québec Innovation Centre, Montréal, Canada, for genotyping the Sequenom panel in the NFCCR samples. Funding was provided to Michael O. Woods by the Canadian Cancer Society Research Institute.

NSHDS: The research was supported by Biobank Sweden through funding from the Swedish Research Council (VR 2017-00650, VR 2017-01737), the Swedish Cancer Society (CAN 2017/581), Region Västerbotten (VLL-841671, VLL-833291), Knut and Alice Wallenberg Foundation (VLL-765961), and the Lion's Cancer Research Foundation (several grants) and Insamlingsstiftelsen, both at Umeå University.

OSUMC: OCCPI funding was provided by Pelotonia and HNPCC funding was provided by the NCI (CA016058 and CA067941).

PLCO: Intramural Research Program of the Division of Cancer Epidemiology and Genetics and supported by contracts from the Division of Cancer Prevention, National Cancer Institute, NIH, DHHS. Funding was provided by National Institutes of Health (NIH), Genes, Environment and Health Initiative (GEI) Z01 CP 010200, NIH U01 HG004446, and NIH GEI U01 HG 004438.

SEARCH: The University of Cambridge has received salary support in respect of PDPP from the NHS in the East of England through the Clinical Academic Reserve. Cancer Research UK (C490/A16561); the UK National Institute for Health Research Biomedical Research Centres at the University of Cambridge.

SELECT: Research reported in this publication was supported in part by the National Cancer Institute of the National Institutes of Health under Award Numbers U10 CA037429 (CD Blanke), and UM1 CA182883 (CM Tangen/IM Thompson). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

SMS and REACHS: This work was supported by the National Cancer Institute (grant P01 CA074184 to J.D.P. and P.A.N., grants R01 CA097325, R03 CA153323, and K05 CA152715 to P.A.N., and the National Center for Advancing Translational Sciences at the National Institutes of Health (grant KL2 TR000421 to A.N.B.-H.)

The Swedish Low-risk Colorectal Cancer Study: The study was supported by grants from the Swedish research council; K2015-55X-22674-01-4, K2008-55X-20157-03-3, K2006-72X-20157-01-2 and the Stockholm County Council (ALF project).

Swedish Mammography Cohort and Cohort of Swedish Men: This work is supported by the Swedish Research Council /Infrastructure grant, the Swedish Cancer Foundation, and the Karolinska Institute´s Distinguished Professor Award to Alicja Wolk.

UK Biobank: This research has been conducted using the UK Biobank Resource under Application Number 8614

VITAL: National Institutes of Health (K05 CA154337).

The WHI program is funded by the National Heart, Lung, and Blood Institute, National Institutes

of Health, U.S. Department of Health and Human Services through contracts 75N92021D00001,

75N92021D00002, 75N92021D00003, 75N92021D00004, 75N92021D00005

Acknowledgments

ASTERISK: We are very grateful to those, without whom this project would not have existed. We also thank all those who agreed to participate in this study, including the patients and the healthy control persons, as well as all the physicians, technicians and students.

CCFR: The Colon CFR graciously thanks the generous contributions of their study participants, dedication of study staff, and the financial support from the U.S. National Cancer Institute, without which this important registry would not exist. The authors would like to thank the study participants and staff of the Seattle Colon Cancer Family Registry and the Hormones and Colon Cancer study (CORE Studies).

CLUE II: We thank the participants of Clue II and appreciate the continued efforts of the staff at the Johns Hopkins George W. Comstock Center for Public Health Research and Prevention in the conduct of the Clue II Cohort Study. Cancer data was provided by the Maryland Cancer Registry, Center for Cancer Prevention and Control, Maryland Department of Health, with funding from the State of Maryland and the Maryland Cigarette Restitution Fund. The collection and availability of cancer registry data is also supported by the Cooperative Agreement NU58DP006333, funded by the Centers for Disease Control and Prevention. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the Centers for Disease Control and Prevention or the Department of Health and Human Services.

COLON and NQplus: the authors would like to thank the COLON and NQplus investigators at Wageningen University & Research and the involved clinicians in the participating hospitals.

CORSA: We kindly thank all individuals who agreed to participate in the CORSA study. Furthermore, we thank all cooperating physicians and students and the Biobank Graz of the Medical University of Graz.

CPS-II: The authors express sincere appreciation to all Cancer Prevention Study-II (and/or Cancer Prevention Study-3) participants, and to each member of the study and biospecimen management group. The authors would like to acknowledge the contribution to this study from central cancer

registries supported through the Centers for Disease Control and Prevention's National Program of Cancer Registries and cancer registries supported by the National Cancer Institute's Surveillance Epidemiology and End Results Program. The authors assume full responsibility for all analyses and interpretation of results. The views expressed here are those of the authors and do not necessarily represent the American Cancer Society or the American Cancer Society – Cancer Action Network.

Czech Republic CCS: We are thankful to all clinicians in major hospitals in the Czech Republic, without whom the study would not be practicable. We are also sincerely grateful to all patients participating in this study.

DACHS: We thank all participants and cooperating clinicians, and everyone who provided excellent technical assistance.

EDRN: We acknowledge all contributors to the development of the resource at University of Pittsburgh School of Medicine, Department of Gastroenterology, Department of Pathology, Hepatology and Nutrition and Biomedical Informatics.

EPIC: Where authors are identified as personnel of the International Agency for Research on Cancer/World Health Organization, the authors alone are responsible for the views expressed in this article and they do not necessarily represent the decisions, policy or views of the International Agency for Research on Cancer/World Health Organization.

EPICOLON: We are sincerely grateful to all patients participating in this study who were recruited as part of the EPICOLON project. We acknowledge the Spanish National DNA Bank, Biobank of Hospital Clínic–IDIBAPS and Biobanco Vasco for the availability of the samples. The work was carried out (in part) at the Esther Koplowitz Centre, Barcelona.

Harvard cohorts: The study protocol was approved by the institutional review boards of the Brigham and Women's Hospital and Harvard T.H. Chan School of Public Health, and those of participating registries as required. We acknowledge Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital as home of the NHS. The authors would like to acknowledge the contribution to this study from central cancer registries supported through the Centers for Disease Control and Prevention's National Program of Cancer Registries (NPCR) and/or the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program. Central registries may also be supported by state agencies, universities, and cancer centers. Participating central cancer registries include the following: Alabama, Alaska, Arizona, Arkansas, California, Colorado, Connecticut, Delaware, Florida, Georgia, Hawaii, Idaho, Indiana, Iowa, Kentucky, Louisiana, Massachusetts, Maine, Maryland, Michigan, Mississippi, Montana, Nebraska, Nevada, New Hampshire, New Jersey, New Mexico, New York, North Carolina, North Dakota, Ohio, Oklahoma, Oregon, Pennsylvania, Puerto Rico, Rhode Island, Seattle SEER Registry, South Carolina, Tennessee, Texas, Utah, Virginia, West Virginia, Wyoming. The authors assume full responsibility for analyses and interpretation of these data.

Kentucky: We would like to acknowledge the staff at the Kentucky Cancer Registry.

LCCS: We acknowledge the contributions of Jennifer Barrett, Robin Waxman, Gillian Smith and Emma Northwood in conducting this study.

NCCCS I & II: We would like to thank the study participants, and the NC Colorectal Cancer Study staff.

NSHDS investigators thank the Västerbotten Intervention Programme, the Northern Sweden MONICA study, the Biobank Research Unit at Umeå University and Biobanken Norr at Region Västerbotten for providing data and samples and acknowledge the contribution from Biobank Sweden, supported by the Swedish Research Council.

PLCO: The authors thank the PLCO Cancer Screening Trial screening center investigators and the staff from Information Management Services Inc and Westat Inc. Most importantly, we thank the study participants for their contributions that made this study possible.

Cancer incidence data have been provided by the District of Columbia Cancer Registry, Georgia Cancer Registry, Hawaii Cancer Registry, Minnesota Cancer Surveillance System, Missouri Cancer Registry, Nevada Central Cancer Registry, Pennsylvania Cancer Registry, Texas Cancer Registry, Virginia Cancer Registry, and Wisconsin Cancer Reporting System. All are supported in part by funds from the Center for Disease Control and Prevention, National Program for Central Registries, local states or by the National Cancer Institute, Surveillance, Epidemiology, and End Results program. The results reported here and the conclusions derived are the sole responsibility of the authors.

SEARCH: We thank the SEARCH team

SELECT: We thank the research and clinical staff at the sites that participated on SELECT study, without whom the trial would not have been successful. We are also grateful to the 35,533 dedicated men who participated in SELECT.

WHI: The authors thank the WHI investigators and staff for their dedication, and the study participants for making the program possible. A full listing of WHI investigators can be found at: http://www.whi.org/researchers/Documents%20%20Write%20a%20Paper/WHI%20Investigator%20Short%20List.pdf

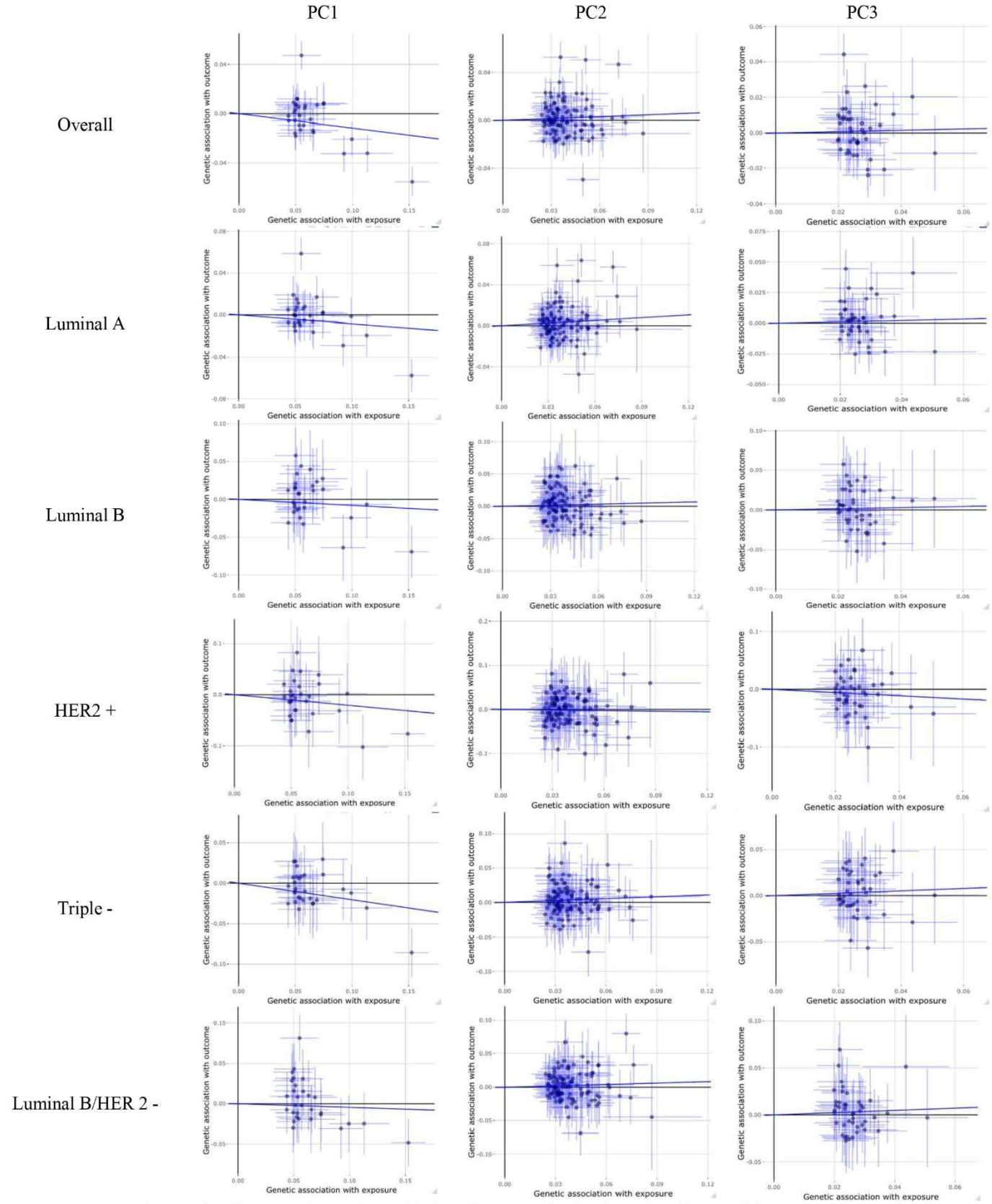
ANNEX II

SUPPLEMENTARY MATERIAL STUDY II

Body shape phenotypes and breast cancer risk: A Mendelian randomization analysis

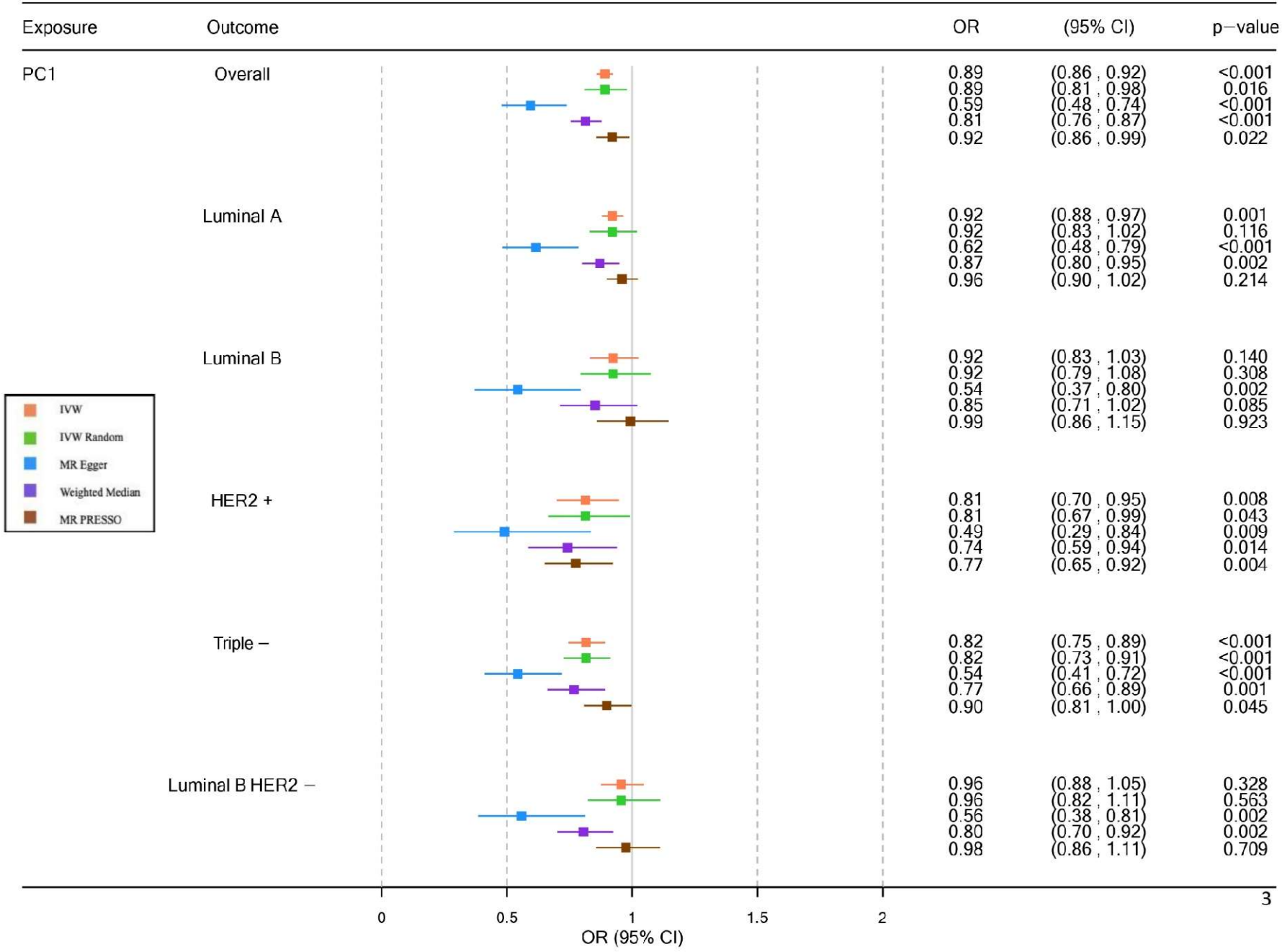
Laia Peruchet-Noray, Niki Dimou, Anja M. Sedlmeier, Béatrice Fervers, Isabelle Romieu, Vivian Viallon, Pietro Ferrari, Marc J. Gunter, Robert Carreras-Torres, Heinz Freisling

Cancers **15, 1296 (2023)**

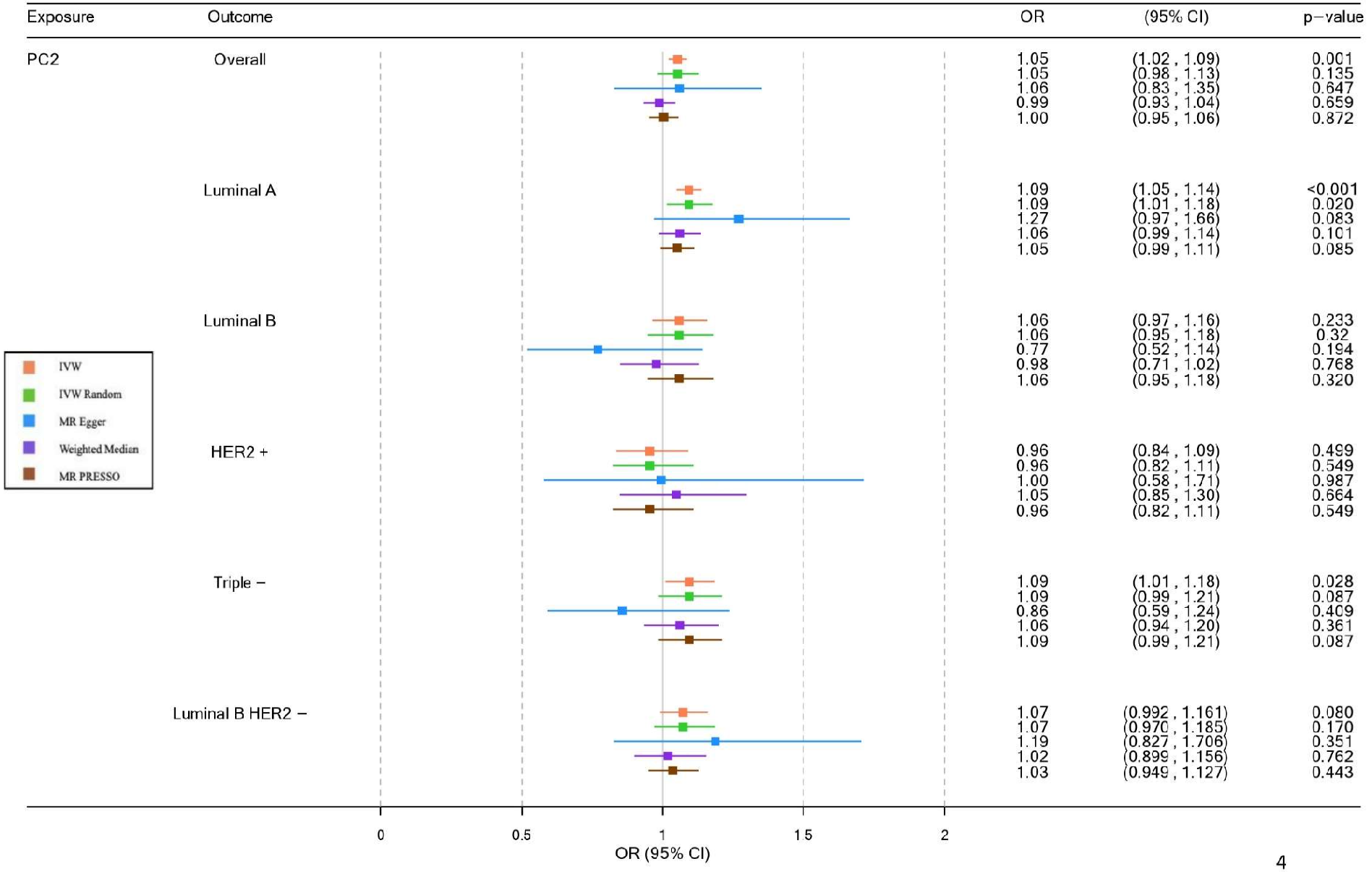


Supplementary Figure S1. Scatter plots of associations between body shapes and overall breast cancer and sub-types.

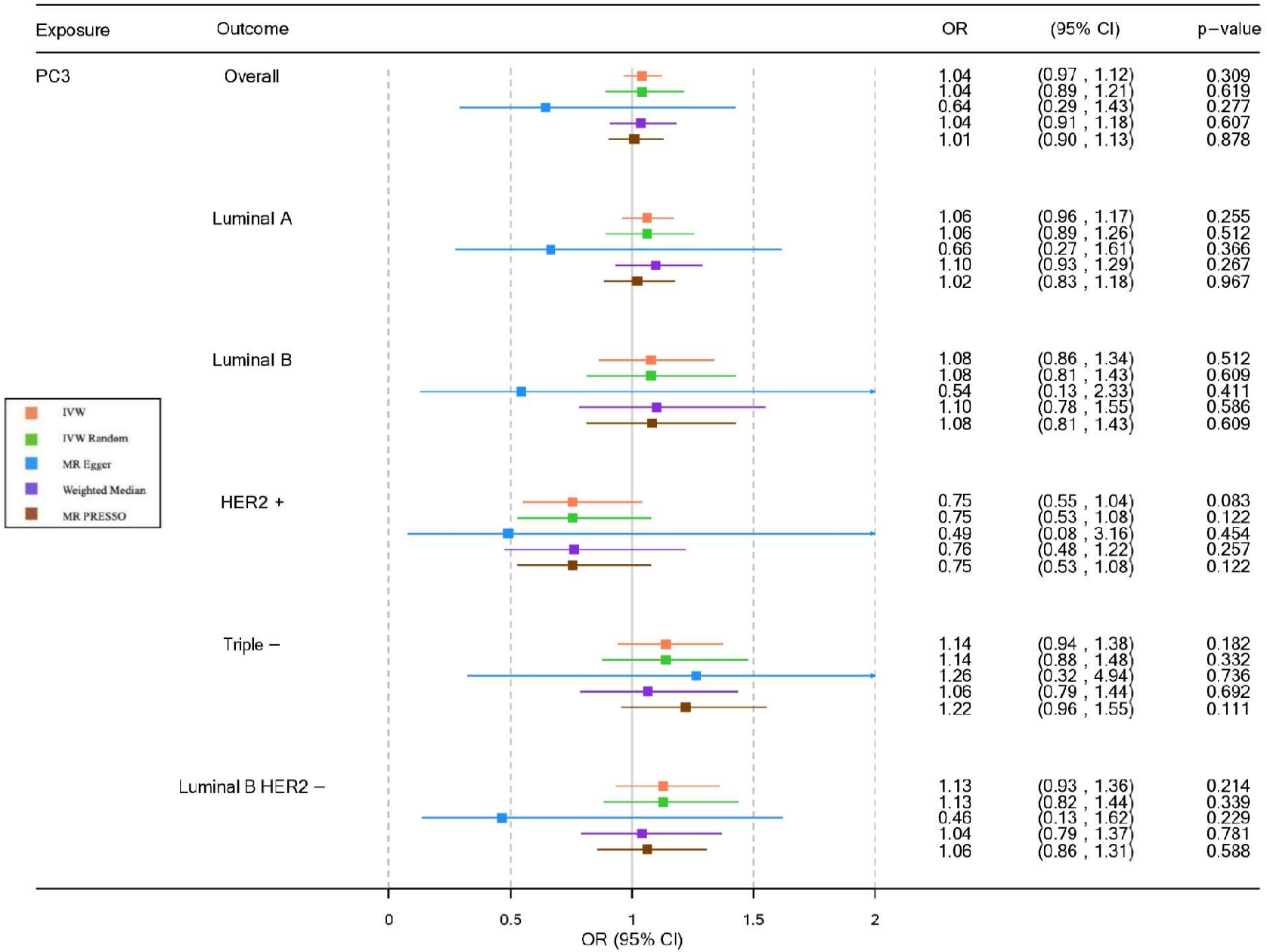
A


Exposure
Outcome
OR
(95% CI)
p−value
PC1
Overall
0.89 (0.86 , 0.92) <0.001
0.89 (0.81 , 0.98) 0.016
0.59 (0.48 , 0.74) <0.001
0.81 (0.76 , 0.87) <0.001
0.92 (0.86 , 0.99) 0.022
Luminal A
0.92 (0.88 , 0.97) 0.001
0.92 (0.83 , 1.02) 0.116
0.62 (0.48 , 0.79) <0.001
0.87 (0.80 , 0.95) 0.002
0.96 (0.90 , 1.02) 0.214
Luminal B
0.92 (0.83 , 1.03) 0.140
0.92 (0.79 , 1.08) 0.308
0.54 (0.37 , 0.80) 0.002
0.85 (0.71 , 1.02) 0.085
0.99 (0.86 , 1.15) 0.923
HER2 +
0.81 (0.70 , 0.95) 0.008
0.81 (0.67 , 0.99) 0.043
0.49 (0.29 , 0.84) 0.009
0.74 (0.59 , 0.94) 0.014
0.77 (0.65 , 0.92) 0.004
Triple −
0.82 (0.75 , 0.89) <0.001
0.82 (0.73 , 0.91) <0.001
0.54 (0.41 , 0.72) <0.001
0.77 (0.66 , 0.89) 0.001
0.90 (0.81 , 1.00) 0.045
Luminal B HER2 −
0.96 (0.88 , 1.05) 0.328
0.96 (0.82 , 1.11) 0.563
0.56 (0.38 , 0.81) 0.002
0.80 (0.70 , 0.92) 0.002
0.98 (0.86 , 1.11) 0.709
IVW
IVW Random
MR Egger
Weighted Median
MR PRESSO
0
0.5
1
1.5
2
3
OR (95% CI)

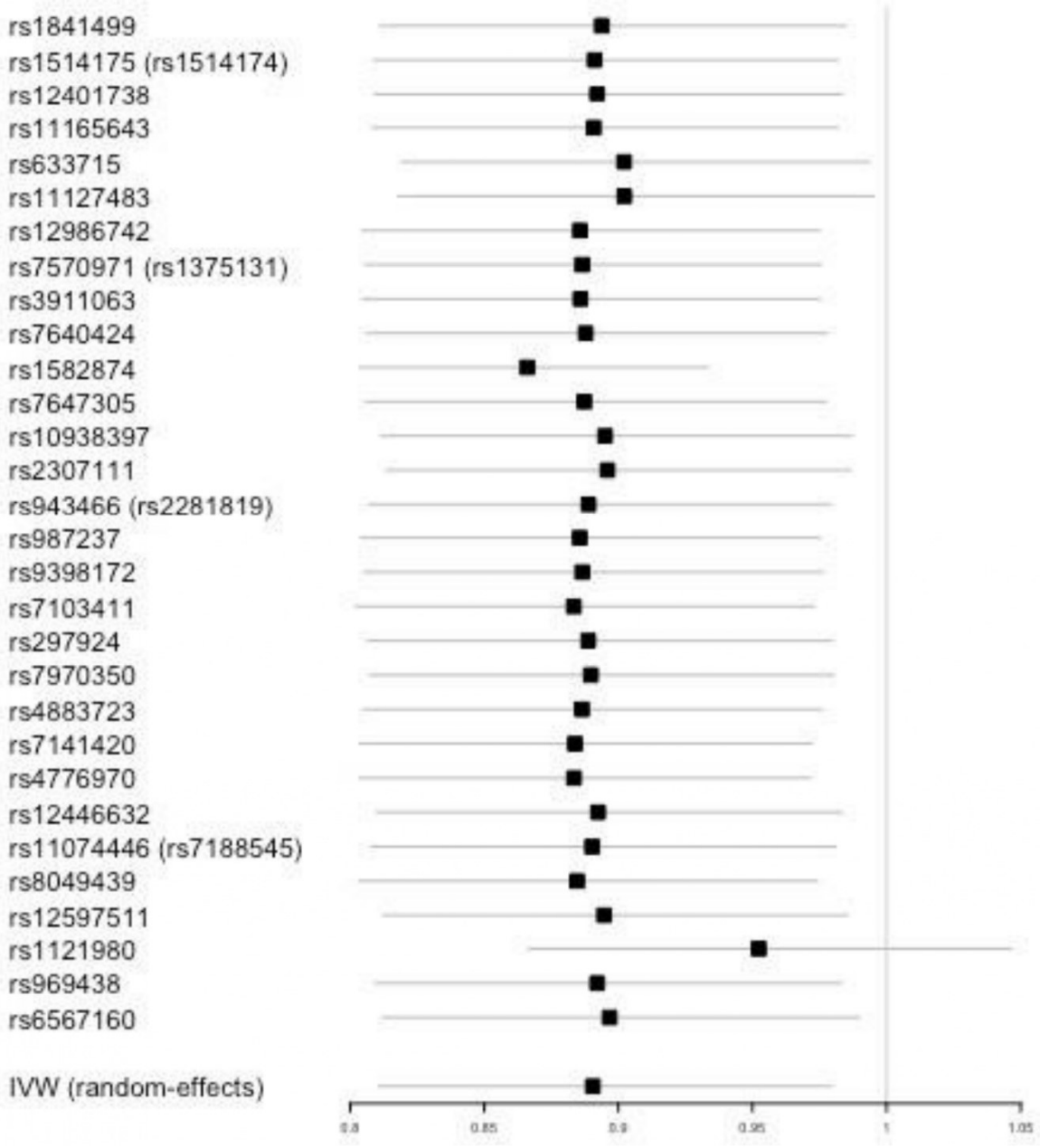
B


Exposure
Outcome
OR
(95% CI)
p−value
PC2
Overall
1.05 (1.02 , 1.09) 0.001
1.05 (0.98 , 1.13) 0.135
1.06 (0.83 , 1.35) 0.647
0.99 (0.93 , 1.04) 0.659
1.00 (0.95 , 1.06) 0.872
Luminal A
1.09 (1.05 , 1.14) <0.001
1.09 (1.01 , 1.18) 0.020
1.27 (0.97 , 1.66) 0.083
1.06 (0.99 , 1.14) 0.101
1.05 (0.99 , 1.11) 0.085
Luminal B
1.06 (0.97 , 1.16) 0.233
1.06 (0.95 , 1.18) 0.32
0.77 (0.52 , 1.14) 0.194
0.98 (0.71 , 1.02) 0.768
1.06 (0.95 , 1.18) 0.320
HER2 +
0.96 (0.84 , 1.09) 0.499
0.96 (0.82 , 1.11) 0.549
1.00 (0.58 , 1.71) 0.987
1.05 (0.85 , 1.30) 0.664
0.96 (0.82 , 1.11) 0.549
Triple −
1.09 (1.01 , 1.18) 0.028
1.09 (0.99 , 1.21) 0.087
0.86 (0.59 , 1.24) 0.409
1.06 (0.94 , 1.20) 0.361
1.09 (0.99 , 1.21) 0.087
Luminal B HER2 −
1.07 (0.992 , 1.161) 0.080
1.07 (0.970 , 1.185) 0.170
1.19 (0.827 , 1.706) 0.351
1.02 (0.899 , 1.156) 0.762
1.03 (0.949 , 1.127) 0.443
IVW
IVW Random
MR Egger
Weighted Median
MR PRESSO
0
0.5
1
1.5
2
OR (95% CI)

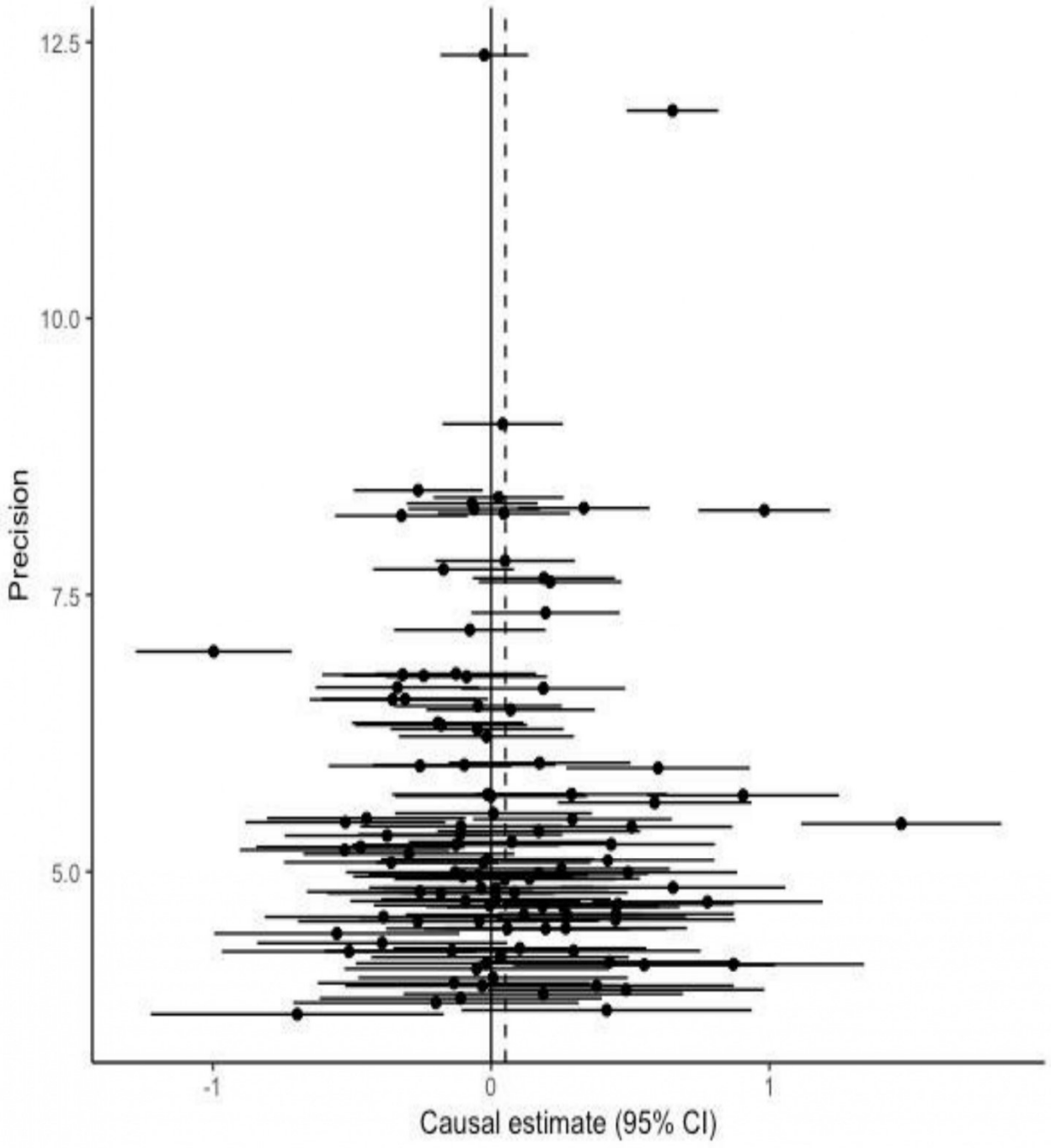
C



Supplementary Figure S2. Mendelian randomization estimates between body shape phenotype PC1 (A), PC2 (B) and PC3 (C) and overall and subtypes breast cancer risk using IVW (orange), IVW Random (green), MR Egger (blue), Weighted Median (violet) and MR PRESSO (brown) MR approaches.CI, confidence interval; OR, odds ratio.



Supplementary Figure S3. Leave-one SNP-out plot for PC1 and overall breast cancer risk.



Supplementary Figure S4. Funnel plot for PC2 and overall breast cancer risk.

	PC1	PC2	PC3
BMI	0.473	-0.128	-0.284
Height	0.131	0.803	0.513
Hip	0.444	0.197	-0.399
Waist	0.488	-0.159	0.138
Weight	0.486	0.186	-0.056
WHR	0.297	-0.490	0.689
Explained variance	64.37%	18.46%	13.79%

Supplementary Table S1. Loadings and explained variance of the three PCs.[1]

Breast cancer GWAS sample size		
Breast cancer	**Overall**	**Sub-types**
Cases	133,384	106,278 (invasive cases)
Controls	113,789	91,477
Tumor marker sub-types GWAS sample size		
Estrogen Receptor status	**Negative**	16883
	Positive	69963
	Unknown	19432
Progesterone Receptor status	**Negative**	24260
	Positive	51546
	Unknown	30472
HER2 status	**Negative**	47645
	Positive	9502
	Unknown	49131
Grade	**1**	15566
	2	37532
	3	24360
	Unknown	28820
Breast cancer sub-types description		
Luminal A	ER+ and/or PR+, HER2-, grade 1 and 2	
Luminal B	ER+ and/or PR+, HER2+	
HER2 +	ER-, PR-, HER2+	
Triple -	ER-, PR-, HER2 -	
Luminal B/HER 2 -	ER+ and/or PR+, HER2-, grade 3	

Supplementary Table S2. Sample size for overall breast cancer and sub-types GWAS as well as according to tumor marker (Estrogen Receptor (negative, positive and unknown), Progesterone Receptor (negative, positive and unknown), HER2 (negative, positive and unknown), and grade (1, 2, 3 and unknown)). Finally, sub-types studied description regarding tumor markers.[2]

Outcome	Exposure	Heterogeneity			Egger intercept		
		Cochran's Q	df	p-value	Estimate	95% CI	p-value
Overall	PC1	199.5858	29	<0.001	0.029	0.014 , 0.043	<0.001
	PC2	515.5738	113	<0.001	0	-0.010 , 0.009	0.961
	PC3	180.1254	43	<0.001	0.013	-0.008 , 0.033	0.228
Luminal A	PC1	136.8719	29	<0.001	0.029	0.012 , 0.045	0.001
	PC2	368.3768	113	<0.001	-0.006	-0.017 , 0.004	0.256
	PC3	129.4055	43	<0.001	0.012	-0.011 , 0.036	0.293
Luminal B	PC1	60.9838	29	0.0005	0.038	0.012 , 0.063	0.003
	PC2	162.6251	113	0.0016	0.013	-0.003 , 0.028	0.1
	PC3	70.7185	43	0.0049	0.018	-0.02 , 0.056	0.348
HER2 +	PC1	49.9252	29	0.0092	0.036	0.001 , 0.071	0.046
	PC2	143.6335	113	0.0273	-0.002	-0.023 , 0.02	0.876
	PC3	54.0215	43	0.1209	0.011	-0.037 , 0.06	0.644
Triple -	PC1	45.7765	29	0.0247	0.029	0.01 , 0.048	0.003
	PC2	187.1135	113	<0.001	0.01	-0.004 , 0.025	0.175
	PC3	81.4148	43	0.0004	-0.003	-0.038 , 0.033	0.878
Luminal B/ HER2 -	PC1	82.7505	29	<0.001	0.038	0.013 , 0.063	0.003
	PC2	183.9729	113	<0.001	-0.004	-0.018 , 0.01	0.565
	PC3	72.6526	43	0.0031	0.023	-0.009 , 0.056	0.156

Supplementary Table S3. Heterogeneity test and Egger intercept results for body shape phenotypes and overall breast cancer risk and sub-types.

Breast Cancer	PC1	PC2	PC3
Overall	rs1582874 rs1121980	rs11205303 rs724016 rs6569648 rs11049611 rs3764419	rs9425301 rs6726261 rs9838625 rs272885 rs1936809
	ρ = 0.130	ρ = 0.013	ρ = 0.123
Luminal A	rs1582874 rs1121980	rs11205303 rs724016 rs6569648 rs11049611 rs1182199	rs9838625 rs272885 rs1516883
	ρ = 0.053	ρ = 0.020	ρ = 0.038
Luminal B	rs3911063 rs1121980	-	-
	ρ = 0.039		
HER2 +	rs1582874	-	-
	ρ = 0.692		
Triple -	rs1121980	rs6569648 rs11049611	rs9425301
	ρ = 0.007	ρ = 0.769	ρ = 0.545
Luminal B/HER2 -	rs1582874 rs1121980	rs1415288 rs724016 rs11049611	rs9838625
	ρ = 0.334	ρ = 0.204	ρ = 0.266

Supplementary Table S4. Genetic variants considered as outliers for overall and sub-types breast cancer and each body shape phenotype. We also provide P-distortion (ρ) for each testperformed.

References

1. Ried JS, Jeff JM, Chu AY, Bragg-Gresham JL, Van Dongen J, Huffman JE, et al. A principal component meta-analysis on multiple anthropometric traits identifies novel loci for body shape. Nat Commun. 2016;7.
2. Zhang H, Ahearn TU, Lecarpentier J, Barnes D, Beesley J, Qi G, et al. Genome-wide association study identifies 32 novel breast cancer susceptibility loci from overall and subtype-specific analyses. Nat Genet. 2020;52(6).

Genetic instruments for body shape phenotypes

SNP (lead SNP)	trait	Chr	pos	beta	se(beta)	pval	N	I^2	pval(het)
rs1841499	avPC1	1	72609044	0.0544	0.009	1.35E-09	140200.52	0	0.513
rs1514175 (rs1514174)	avPC1	1	74764232	0.044	0.0078	1.65E-08	168731.8	26	0.006825
rs12401738	avPC1	1	78219349	0.057	0.008	7.25E-13	172372.36	13.4	0.1196
rs11165643	avPC1	1	96696685	0.0494	0.0078	1.80E-10	170787.55	2.9	0.3941
rs633715	avPC1	1	176119203	0.0923	0.0101	4.30E-20	157821.07	6	0.3059
rs11127483	avPC1	2	613691	0.113	0.0115	5.83E-23	140023.13	4.5	0.3573
rs12986742	avPC1	2	58828647	0.0502	0.0087	7.23E-09	140211.8	0	0.7716
rs7570971 (rs1375131)	avPC1	2	135554376	0.0482	0.0085	1.37E-08	167200.41	0	0.8471
rs3911063	avPC1	3	85989618	0.0503	0.0092	4.12E-08	139764.18	12.5	0.1652
rs7640424	avPC1	3	109302753	0.0498	0.0084	3.18E-09	171543.81	0	0.9931
rs1582874	avPC1	3	142597909	0.0552	0.0087	2.21E-10	140018.42	7.7	0.2742
rs7647305	avPC1	3	187316984	0.0581	0.0096	1.35E-09	170958.74	0.9	0.4539
rs10938397	avPC1	4	44877284	0.0659	0.0079	5.09E-17	166806.45	0	0.7582
rs2307111	avPC1	5	75039434	0.0501	0.0077	9.10E-11	168190.16	21.7	0.02314
rs943466 (rs2281819)	avPC1	6	33839765	0.0488	0.0088	3.47E-08	172173.79	0.8	0.4577
rs987237	avPC1	6	50911009	0.069	0.01	6.25E-12	172314.49	15.8	0.08052
rs9398172	avPC1	6	109101519	0.0527	0.0093	1.28E-08	140183.8	16.9	0.08998
rs7103411	avPC1	11	27656701	0.0745	0.0093	8.43E-16	172395.91	0	0.8958
rs297924	avPC1	12	48571328	0.0535	0.0091	3.74E-09	140279.65	0	0.9748
rs7970350	avPC1	12	64646431	0.0437	0.0076	1.12E-08	172336.52	16.7	0.06768
rs4883723	avPC1	13	52982033	0.0742	0.0112	3.19E-11	166981.63	2.2	0.4146
rs7141420	avPC1	14	78969207	0.0514	0.0077	2.33E-11	167294.81	16.5	0.07344
rs4776970	avPC1	15	65867940	0.0515	0.0089	7.55E-09	141181.59	0	0.5695
rs12446632	avPC1	16	19842890	0.0654	0.0112	5.91E-09	172417.32	12.4	0.1396
rs11074446 (rs7188545)	avPC1	16	20162624	0.0632	0.0112	1.74E-08	160676.8	0	0.6528
rs8049439	avPC1	16	28745016	0.0585	0.0087	2.20E-11	141257.98	16.5	0.0928
rs12597511	avPC1	16	31052720	0.0495	0.0085	4.69E-09	145592.17	0	0.698
rs1121980	avPC1	16	52366748	0.1526	0.0077	1.49E-86	151739.8	32.5	0.000541
rs969438	avPC1	18	38194401	0.0532	0.0094	1.68E-08	140192.94	0	0.7181
rs6567160	avPC1	18	55980115	0.0993	0.009	3.68E-28	172276.99	11.6	0.1568
rs2284746	avPC2	1	17179262	0.0406	0.005	4.41E-16	140074.05	10.1	0.2161
rs2903545	avPC2	1	23413695	0.0261	0.0042	6.45E-10	172749.83	5.8	0.3074
rs11209376	avPC2	1	41270935	0.0329	0.005	3.23E-11	172718.16	8.4	0.2325
rs17391694	avPC2	1	78396214	0.0422	0.0073	6.74E-09	150392.95	0	0.5906
rs7536458	avPC2	1	118666125	0.0371	0.0048	1.04E-14	172793.83	11.2	0.1659
rs11205303	avPC2	1	148173037	0.0513	0.0049	6.96E-26	153773.92	1.4	0.4392
rs1752388 (rs2298265)	avPC2	1	149549465	0.037	0.0064	8.61E-09	171962.91	27.9	0.00373
rs905938	avPC2	1	153258013	0.0375	0.0051	1.20E-13	168475.02	27.2	0.00452
rs11584955	avPC2	1	170404728	0.0365	0.0053	8.10E-12	134016.29	14.9	0.1272
rs1014719	avPC2	1	175069389	0.027	0.0042	1.56E-10	171234.78	0	0.9333
rs1046934	avPC2	1	182290152	0.0339	0.0045	4.39E-14	167040.86	9.9	0.1974
rs1415288	avPC2	1	217809168	0.0446	0.0055	6.02E-16	138945.57	1.6	0.4379
rs12093031 (rs10799424)	avPC2	1	225810498	0.0298	0.0054	3.68E-08	171116.1	25.9	0.007158
rs2278483	avPC2	2	24893586	0.0383	0.0049	3.57E-15	172790.23	4.1	0.3561
rs1545552	avPC2	2	33213842	0.0314	0.0048	5.55E-11	167297	0	0.951
rs6740539	avPC2	2	46858292	0.0256	0.0046	2.04E-08	172793.92	0	0.8005
rs3791675	avPC2	2	55964813	0.0544	0.0048	4.49E-30	172629.1	9.6	0.2017
rs1913671	avPC2	2	88680998	0.0264	0.0043	8.26E-10	172783.1	20.6	0.02958
rs1478576	avPC2	2	217992769	0.0332	0.0053	4.33E-10	139081.95	0	0.7877
rs3103267	avPC2	2	232696826	0.0346	0.0055	3.47E-10	139105.08	7.3	0.2852
rs2270894	avPC2	3	9950386	0.0488	0.0087	2.09E-08	98541.92	4.1	0.3799
rs2581830	avPC2	3	53109138	0.0302	0.0049	6.96E-10	140574.1	1.4	0.4432
rs9833926	avPC2	3	56625218	0.0293	0.0041	1.16E-12	172735.14	0	0.4971
rs6439168	avPC2	3	130533633	0.0392	0.006	4.47E-11	140524.1	4	0.3706
rs724016	avPC2	3	142588260	0.0716	0.0042	3.44E-65	167995.71	10.5	0.1821
rs13094143	avPC2	3	173456481	0.032	0.0053	1.92E-09	134453.83	25.6	0.01665
rs519384	avPC2	3	173651201	0.0383	0.0055	3.44E-12	133947.85	0	0.9284
rs720390	avPC2	3	187031377	0.0328	0.0045	1.94E-13	165823.96	10.2	0.1906
rs6853216	avPC2	4	17579753	0.0742	0.0068	9.78E-28	135973.39	13.1	0.1534
rs4694504	avPC2	4	73715555	0.028	0.0049	1.15E-08	135671.91	0	0.7609
rs1975474	avPC2	4	82397961	0.0446	0.0046	1.67E-22	163003	10.5	0.187

rs1562975	avPC2	4	109628057	0.0265	0.0046	8.53E-09	168020.95	9	0.2181
rs7689420	avPC2	4	145787802	0.0677	0.0057	1.30E-32	168135.83	7.4	0.2607
rs6450922	avPC2	5	32725475	0.0426	0.0059	3.49E-13	150100.97	3.1	0.3907
rs7733331	avPC2	5	32864603	0.0308	0.0049	4.62E-10	136769.1	0	0.5106
rs6894139	avPC2	5	88363538	0.0278	0.0043	8.54E-11	163756.44	13.2	0.1247
rs274567	avPC2	5	131742308	0.0299	0.005	2.20E-09	135891.1	0	0.9261
rs31198	avPC2	5	134400584	0.0335	0.0048	2.27E-12	168113.09	4.2	0.3542
rs4282339	avPC2	5	168188818	0.0327	0.0052	3.19E-10	166401.1	4.9	0.3348
rs153753	avPC2	5	171117576	0.0324	0.0051	2.82E-10	134493.19	0	0.8792
rs4868126	avPC2	5	171216074	0.0251	0.0045	2.60E-08	162391.1	8.5	0.235
rs4868293	avPC2	5	172935497	0.0377	0.0057	3.36E-11	131505.82	9.4	0.2354
rs2714354	avPC2	6	7257636	0.0322	0.0059	4.43E-08	123302.7	6.4	0.3126
rs3812163	avPC2	6	7670759	0.0286	0.005	1.05E-08	135750.65	4.4	0.3623
rs806794	avPC2	6	26308656	0.0556	0.0047	1.32E-32	163571.87	13.7	0.1158
rs2256183	avPC2	6	31488508	0.0487	0.0051	1.02E-21	132355.67	0	0.5568
rs9462007	avPC2	6	34823319	0.0559	0.0069	5.86E-16	135872.85	22	0.03619
rs3734254	avPC2	6	35502988	0.0451	0.0072	3.04E-10	109063	0	0.5956
rs9357470	avPC2	6	45173591	0.0302	0.0051	2.80E-09	135130.26	0	0.5861
rs12209223	avPC2	6	76221309	0.0491	0.0082	1.76E-09	135657.96	0.2	0.4738
rs920842	avPC2	6	81905390	0.0317	0.0049	9.52E-11	135632.9	0	0.8026
rs314263	avPC2	6	105499438	0.0399	0.0053	4.38E-14	134084.19	0	0.9794
rs9488923 (rs2027850)	avPC2	6	116837768	0.0256	0.0044	4.50E-09	168074.73	0	0.6765
rs9388490	avPC2	6	126746488	0.0441	0.005	1.93E-18	134271.19	7.9	0.2717
rs6569648	avPC2	6	130390812	0.0496	0.0051	1.23E-22	166644.1	1	0.4517
rs9389986	avPC2	6	142702807	0.0544	0.0047	5.52E-31	166244.92	24.8	0.01046
rs827423	avPC2	6	152197890	0.0378	0.0051	1.70E-13	132228.07	14.7	0.1296
rs1182199	avPC2	7	2829068	0.0532	0.0054	4.28E-23	135774.08	0	0.7622
rs2192476	avPC2	7	19578830	0.0294	0.0051	7.38E-09	135663.59	1.2	0.447
rs506154	avPC2	7	28168604	0.0358	0.0046	6.04E-15	168070.04	0	0.5225
rs12673331	avPC2	7	46564586	0.0277	0.0049	1.29E-08	165834.1	0	0.6295
rs2282978	avPC2	7	92102346	0.052	0.0044	9.43E-33	168134.1	0	0.8055
rs9650315	avPC2	8	57318152	0.0611	0.0075	3.55E-16	135417.94	0	0.9354
rs4130415	avPC2	8	130787894	0.0512	0.0053	3.06E-22	167801.65	6.6	0.2841
rs4909595	avPC2	8	135740900	0.0318	0.0056	1.21E-08	135861.78	27.1	0.01077
rs9407763	avPC2	9	16360680	0.0311	0.0055	1.27E-08	131198.9	0	0.51
rs11144688	avPC2	9	77732106	0.0483	0.008	1.44E-09	155164.1	17.5	0.06673
rs7855177	avPC2	9	85571402	0.0338	0.006	2.11E-08	135677.63	0	0.6002
rs3937594	avPC2	9	90071974	0.031	0.0053	4.03E-09	134349.91	3.9	0.3739
rs7043114	avPC2	9	94427804	0.0297	0.0049	1.33E-09	135983.84	29.9	0.004709
rs4448343	avPC2	9	97306191	0.0374	0.0045	6.75E-17	168117.99	0	0.928
rs2025151	avPC2	9	98201333	0.0458	0.0067	9.25E-12	135176.09	1.6	0.4374
rs4333673	avPC2	9	108650277	0.0339	0.0049	7.07E-12	168142.16	9.1	0.2153
rs7853634	avPC2	9	118161874	0.0383	0.0061	2.52E-10	135958.1	0	0.8961
rs7466269	avPC2	9	132453905	0.0293	0.0043	1.63E-11	168147.89	20.2	0.03282
rs4980067	avPC2	10	80806135	0.0313	0.0051	7.11E-10	135680.04	0	0.7245
rs1879671	avPC2	11	30311283	0.0375	0.0063	3.07E-09	102032.16	5	0.3609
rs606452	avPC2	11	74953826	0.0456	0.0062	1.66E-13	160120.93	5.8	0.3089
rs6487133	avPC2	12	20736419	0.0291	0.0053	3.33E-08	135666.1	0	0.8071
rs11049611	avPC2	12	28491511	0.0357	0.0054	3.43E-11	135976.02	8.3	0.2607
rs1351394	avPC2	12	64638093	0.0499	0.0042	7.88E-33	167776.56	12	0.1482
rs10748128	avPC2	12	68113925	0.0351	0.0048	3.53E-13	152983.98	8.1	0.2474
rs11107116 (rs3825199)	avPC2	12	92502635	0.0554	0.005	5.05E-29	168125.1	8.3	0.2366
rs11107169	avPC2	12	92650986	0.0411	0.0049	5.00E-17	135497.78	0	0.9016
rs7980687	avPC2	12	122388664	0.0394	0.0062	2.67E-10	135800.04	10.7	0.2033
rs7986486	avPC2	13	49336237	0.0326	0.0056	6.30E-09	168037.83	14.2	0.1057
rs3118905	avPC2	13	50003335	0.0552	0.0055	6.38E-24	135930.15	26	0.01425
rs1950500	avPC2	14	23900690	0.0319	0.0046	4.46E-12	168137.78	9.2	0.2129
rs2093210	avPC2	14	60027032	0.0399	0.0053	3.38E-14	135031.89	0.2	0.4746
rs5742915	avPC2	15	72123686	0.0314	0.0045	4.76E-12	157690.11	4.7	0.3422
rs4483821	avPC2	15	82279640	0.0397	0.0049	9.33E-16	136955.8	0	0.969
rs2280470	avPC2	15	87196630	0.0342	0.0045	2.69E-14	166847.87	24.2	0.01253
rs3784757	avPC2	15	87204408	0.0869	0.0149	5.26E-09	135146.07	9.7	0.2292
rs2871865	avPC2	15	97012419	0.062	0.0085	3.71E-13	128022.02	3.9	0.3763
rs8057808	avPC2	16	52078114	0.032	0.0055	4.96E-09	135622.18	0	0.8799

rs11866219	avPC2	16	68107250	0.0347	0.0051	8.88E-12	135446.87	0	0.8247
rs7213608	avPC2	17	21219882	0.0342	0.0055	4.72E-10	129903.03	8.4	0.2612
rs3764419	avPC2	17	26188149	0.0351	0.0043	3.47E-16	166767.8	8.2	0.2426
rs584828	avPC2	17	35852756	0.0295	0.0051	6.71E-09	135506.1	20.9	0.04483
rs11657325	avPC2	17	40598477	0.0297	0.0048	7.71E-10	168114.92	0	0.5004
rs12453394	avPC2	17	44349969	0.0294	0.0051	7.24E-09	132140.45	0	0.5746
rs963292	avPC2	17	52197554	0.0254	0.0042	1.17E-09	168142.79	0	0.9212
rs2079795 (rs7214743)	avPC2	17	56851431	0.0268	0.0046	4.12E-09	166772.1	7.2	0.2676
rs2727317	avPC2	17	59315034	0.0514	0.0056	2.73E-20	135634.01	7.3	0.2847
rs4239437	avPC2	18	18986222	0.0489	0.0052	1.01E-20	167141.93	0	0.9243
rs9967417	avPC2	18	45213498	0.0394	0.0051	9.69E-15	135764.75	12.6	0.163
rs12980348	avPC2	19	2132607	0.0347	0.0043	4.44E-16	167987.05	14.7	0.09822
rs891088	avPC2	19	7135762	0.0309	0.0048	1.33E-10	168027.91	0	0.8028
rs2738039 (rs1982075)	avPC2	19	10654749	0.0266	0.0045	3.99E-09	168138.91	0	0.7733
rs6038566	avPC2	20	6563197	0.0336	0.005	1.69E-11	135662.24	0	0.5138
rs7274811	avPC2	20	31796842	0.037	0.0049	4.36E-14	168149.88	16.5	0.07096
rs143384	avPC2	20	33489170	0.076	0.0045	2.67E-64	165855.86	31.1	0.001134
rs1983528 (rs17450430)	avPC2	20	47119697	0.0288	0.0049	4.67E-09	166928.2	2	0.4206
rs4821083 (rs2413143)	avPC2	22	31386341	0.0359	0.006	1.73E-09	159975.45	11.2	0.1716
rs738288	avPC2	22	38237607	0.0241	0.0043	1.52E-08	168114.9	0	0.8392
rs7536458	avPC3	1	118666125	0.0319	0.0039	2.96E-16	173016.03	6.2	0.2956
rs10923724	avPC3	1	119348365	0.0333	0.0038	4.41E-18	141812.35	0	0.7436
rs9425301	avPC3	1	170630438	0.0294	0.0041	3.70E-13	140126.89	0	0.5322
rs2274432	avPC3	1	182287568	0.0275	0.0036	1.72E-14	164801.06	8.5	0.2356
rs2791550 (rs2605108)	avPC3	1	217721992	0.0214	0.0036	2.28E-09	171471.12	17.9	0.05483
rs6726261	avPC3	2	25007490	0.0285	0.0036	1.14E-15	173002.12	4.8	0.3359
rs6715793	avPC3	2	33232767	0.0199	0.0034	4.36E-09	172882.07	26.3	0.006053
rs3791675	avPC3	2	55964813	0.0239	0.0039	8.33E-10	172851.3	0	0.8635
rs1128249	avPC3	2	165236870	0.0227	0.0034	3.05E-11	171294.17	36.6	7.42E-05
rs2342296	avPC3	2	232577269	0.0437	0.0073	2.42E-09	131221.95	5	0.3479
rs2920499	avPC3	3	12294058	0.02	0.0036	1.77E-08	167914.07	0	0.6862
rs2710323	avPC3	3	52790945	0.0217	0.0034	1.22E-10	172968.08	3.3	0.3799
rs9864077	avPC3	3	64679931	0.0288	0.0037	6.56E-15	161144.17	23.4	0.01594
rs9838625	avPC3	3	142546643	0.0218	0.0039	3.60E-08	139686.29	21.5	0.04047
rs1545854	avPC3	3	158322832	0.0264	0.0047	2.65E-08	138972.14	0	0.8973
rs4057984	avPC3	4	17566298	0.0301	0.0054	2.31E-08	140829.56	10.6	0.2053
rs1115919	avPC3	4	82392421	0.0261	0.0046	1.64E-08	128438.3	17.2	0.09417
rs7689420	avPC3	4	145787802	0.0276	0.0046	1.32E-09	172995.03	0	0.5703
rs272885	avPC3	5	131695635	0.0228	0.004	9.33E-09	168988.01	0.7	0.4616
rs6556301	avPC3	5	176460183	0.0207	0.0037	1.74E-08	163120.21	0	0.6836
rs1294421	avPC3	6	6688148	0.0215	0.0035	5.79E-10	172564.3	15.4	0.0866
rs1776897	avPC3	6	34302989	0.0508	0.0069	1.54E-13	146169.23	21.6	0.03645
rs7759938	avPC3	6	105485647	0.0282	0.0036	3.32E-15	172918.85	8.5	0.2313
rs1936809	avPC3	6	127518961	0.0293	0.0039	3.46E-14	140256.89	10.4	0.2086
rs7798002	avPC3	7	25827105	0.0346	0.0048	6.23E-13	141653.22	0	0.5051
rs7801581	avPC3	7	27190296	0.026	0.0043	1.23E-09	155923	8.7	0.2314
rs1516883	avPC3	9	107947088	0.0249	0.0041	8.34E-10	140259.06	0	0.5346
rs7021911	avPC3	9	132490839	0.0234	0.0041	1.64E-08	135141.15	0	0.9896
rs1628023	avPC3	10	80594264	0.0236	0.0039	9.32E-10	140536.02	0	0.5577
rs7917772	avPC3	10	104477433	0.0205	0.0035	3.59E-09	172836.82	11.9	0.1508
rs1317149 (rs12787112)	avPC3	11	47443461	0.0201	0.0035	9.48E-09	170038.07	0	0.7986
rs7949030	avPC3	11	62151457	0.0241	0.0041	5.58E-09	139195.14	0	0.7125
rs8756	avPC3	12	64646019	0.0249	0.0033	5.88E-14	173005.28	10.7	0.1771
rs12303671	avPC3	12	123058563	0.0262	0.0041	1.01E-10	140768.08	1.7	0.434
rs7492628	avPC3	14	90616889	0.0239	0.0042	1.90E-08	139874.3	0	0.5536
rs16976826 (rs12443429)	avPC3	15	54304816	0.0242	0.0042	5.85E-09	171990.53	0	0.5179
rs12440667	avPC3	15	72018492	0.0227	0.0039	3.86E-09	140631.88	0	0.731
rs6602997	avPC3	15	82312402	0.0232	0.0042	4.72E-08	140700.78	8.7	0.2494
rs2280470	avPC3	15	87196630	0.026	0.0036	2.60E-13	171707.07	0	0.4833
rs1879143	avPC3	17	52113556	0.0224	0.0041	3.46E-08	140201.3	0	0.6264
rs9892365	avPC3	17	56846166	0.0235	0.004	6.18E-09	140575.44	0	0.4832
rs4239436	avPC3	18	18985928	0.0302	0.0042	4.26E-13	172973.12	21.9	0.0216
rs6140050	avPC3	20	6580901	0.0376	0.0041	9.09E-20	140524.96	29.1	0.005764
rs2179129	avPC3	22	27780923	0.0206	0.0034	1.51E-09	172977.14	0	0.7555

PC1 related genetic variants and associated traits in previous GWAS ($p < 5 \times 10^{-8}$)

SNP (lead SNP)	Trait
rs1841499	Age at menarche
	Alcohol intake versus 10 years previously
	Ambidextrous
	Basal metabolic rate
	Body fat percentage
	BMI
	Fluid intelligence score
	Hayfever, allergic rhinitis or eczema
	Hip circumference
	Impedance
	Long-standing illness, disability or infirmity
	Medication for cholesterol, blood pressure or diabetes: none of the above
	No blood clot, bronchitis, emphysema, asthma, rhinitis, eczema or allergy diagnosed by doctor
	Number of self-reported non-cancer illnesses
	umber of treatments or medications taken
	Obesity class 1
	Obesity class 2
	Obesity class 3
	Overweight
	Pulse rate
	Qualifications: college or university degree
	Qualifications: none
	Qualifications: other professional qualifications
	Relative age of first facial hair
	Seen doctor for nerves, anxiety, tension or depression
	Sodium in urine
	Types of transport used, excluding work: public transport
	Waist circumference
	Weight
	Whole body fat mass
	Whole body fat-free mass
	Whole body water mass
	Years of educational attainment
rs1514175 (rs1514174)	Age at menarche
	Basal metabolic rate
	BMI
	Childhood BMI
	Childhood obesity
	Ever smoked
	Extreme obesity body mass index
	Extreme obesity with early age of onset
	Hip circumference
	Impedance
	Obesity class 1
	Obesity with early age of onset age 2
	Overweight
	Past tobacco smoking
	Relative age of first facial hair
	Relative age voice broke
	Waist circumference
	Weight
	Whole body fat mass
	Whole body fat-free mass
	Whole body water mass
rs12401738	Basal metabolic rate
	BMI
	Body fat percentage
	Height
	Hip circumference
	Impedance
	Waist circumference

	Weight
	Whole body fat mass
	Whole body fat-free mass
	Whole body water mass
	Years of educational attainment
rs11165643	Basal metabolic rate
	BMI
	Body fat percentage
	Hip circumference
	Treatment with olmesartan
	Waist circumference
	Weight
	Whole body fat mass
	Whole body fat-free mass
	Whole body water mass
rs633715	Age at menarche
	Basal metabolic rate
	BMI
	Body fat percentage
	Childhood BMI
	Childhood obesity
	Hip circumference
	Impedance
	Menarche
	Menarche age at onset
	Obesity
	Obesity class 1
	Obesity class 2
	Obesity class 3
	Obesity with early age of onset age 2
	Overweight
	Relative age of first facial hair
	Waist circumference
	Waist hip ratio
	Weight
	Whole body fat mass
	Whole body fat-free mass
	Whole body water mass
rs11127483	Age at menarche
	Basal metabolic rate
	BMI
	Body fat percentage
	Childhood BMI
	Childhood obesity
	Diastolic blood pressure
	Heel bone mineral density
	Hip circumference
	Impedance
	Obesity class 1
	Obesity class 2
	Obesity class 3
	Obesity with early age of onset age 2
	Overweight
	Past tobacco smoking
	Relative age of first facial hair
	Systolic blood pressure
	Waist circumference
	Weight
	Whole body fat mass
	Whole body fat-free mass
	Whole body water mass
	Basal metabolic rate
	BMI
	Body fat percentage

rs12986742	Getting up in morning
	Hip circumference
	Impedance
	Waist circumference
	Weight
	Whole body fat mass
	Whole body fat-free mass
	Whole body water mass
rs7570971 (rs1375131)	Blood metabolite levels
	BMI
	Body fat percentage
	Cholesterol
	Forced expiratory volume in 1 sec
	Forced vital capacity
	Hand grip strength
	Height
	Hip circumference
	LDL
	Low density lipoprotein
	Monocyte percentage of white cells
	Parkinsons disease
	Sleep duration
	Total cholesterol
	Type II diabetes
	Waist circumference
	Weight
	Whole body fat mass
rs3911063	Basal metabolic rate
	BMI
	Body fat percentage
	Ever smoked
	Hip circumference
	Impedance
	Past tobacco smoking
	Qualifications: A levels or as levels or equivalent
	Qualifications: college or university degree
	Qualifications: other professional qualifications
	Smoking status: previous
	Waist circumference
	Weight
	Whole body fat mass
	Whole body fat-free mass
	Whole body water mass
	Years of educational attainment
rs7640424	BMI
	Hip circumference
	Impedance
	Qualifications: A levels or as levels or equivalent
	Years of educational attainment
rs1582874	Allergic disease
	Basal metabolic rate
	Birth weight of first child
	Body fat percentage
	Ever had prostate specific antigen test
	Forced expiratory volume in 1 sec
	Forced vital capacity
	Hair or balding pattern
	Hand grip strength
	Hayfever, allergic rhinitis or eczema
	Heel bone mineral density
	Height
	Hip circumference
	Lymphocyte percentage of white cells
	Mean corpuscular hemoglobin

	Mean corpuscular volume
	Myopia
	Neutrophil percentage of white cells
	No blood clot, bronchitis, emphysema, asthma, rhinitis, eczema or allergy diagnosed by doctor
	Potassium in urine
	Pulse rate
	Red blood cell count
	Relative age of first facial hair
	Self-reported enlarged prostate
	Waist circumference
	Weight
	Whole body fat mass
	Whole body fat-free mass
	Whole body water mass
rs7647305	Basal metabolic rate
	BMI
	Hip circumference
	Impedance
	Obesity class 1
	Obesity class 2
	Overweight
	Waist circumference
	Weight
	Whole body fat mass
	Whole body fat-free mass
	Whole body water mass
rs10938397	Age at menarche
	Basal metabolic rate
	BMI
	Body fat percentage
	Childhood BMI
	Childhood obesity
	Extreme obesity with early age of onset
	Hip circumference
	Impedance
	log Fast insulin
	Menarche age at onset
	Obesity
	Obesity class 1
	Obesity class 2
	Obesity class 3
	Obesity with early age of onset age 2
	Overweight
	Relative age voice broke
	Waist circumference
	Waist hip ratio
	Weight
	Whole body fat mass
	Whole body fat-free mass
	Whole body water mass
rs2307111	Basal metabolic rate
	BMI
	Body fat percentage
	Diabetes diagnosed by doctor
	Diastolic blood pressure
	Hip circumference
	Impedance
	LDL cholesterol
	Low density lipoprotein
	Obesity
	Obesity class 1
	Obesity class 2
	Overweight
	Pain type experienced in last month: headache

	Platelet count
	Pulse rate
	Self-reported diabetes
	Self-reported high cholesterol
	Snoring
	Total cholesterol
	Usual walking pace
	Waist circumference
	Weight
	Whole body fat mass
	Whole body fat-free mass
	Whole body water mass
rs943466 (rs2281819)	BMI
	Body fat percentage
	Hip circumference
	Pack years adult smoking as proportion of life span exposed to smoking
	Platelet count
	Plateletcrit
	Pulse rate
	Waist circumference
	Whole body fat mass
rs987237	Adiposity
	Age at menarche
	Basal metabolic rate
	BMI
	Body fat percentage
	Chilhood BMI
	Diabetes diagnosed by doctor
	Extreme obesity with early age of onset
	Getting up in morning
	Hip circumference
	Impedance
	Medication for cholesterol, blood pressure or diabetes: blood pressure medication
	Medication for cholesterol, blood pressure or diabetes: none of the above
	Morning or evening person
	Obesity class 1
	Obesity class 2
	Obesity class 3
	Overweight
	Self-reported diabetes
	Treatment with metformin
	Waist circumference
	Waist hip ratio
	Weight
	Whole body fat mass
	Whole body fat-free mass
	Whole body water mass
rs9398172	Age at menarche
	Basal metabolic rate
	BMI
	Fluid intelligence score
	Height
	High light scatter percetage of red cells
	Hip circumference
	Impedance
	Intelligence
	Intracranial volume
	Mean time to correctly identify matches
	Number of days or week of vigorous physical activity 10+ minutes
	Peak expiratory flow
	Qualifications: college or university degree
	Qualifications: none
	Relative age of first facial hair
	Schizophrenia

	Waist circumference
	Weight
	Whole body fat mass
	Whole body fat-free mass
	Whole body water mass
rs4536164 (rs4514364)	Age at menarche
	Basal metabolic rate
	BMI
	Body fat percentage
	Hip circumference
	Impedance
	Lumbar spine bone mineral density in females
	Obesity class 1
	Overweight
	Survival in pancreatic cancer
	Waist circumference
	Weight
	Whole body fat mass
	Whole body fat-free mass
	Whole body water mass
rs7103411	Age at menarche
	Basal metabolic rate
	BMI
	Body fat percentage
	Chilhood BMI
	Coronary artery disease
	Ever smoked
	Falls in the last year
	Forced vital capacity
	Hip circumference
	Impedance
	Menarche age at onset
	Obesity class 1
	Obesity class 2
	Overweight
	Past tobacco smoking
	Relative age of first facial hair
	Relative age voice broke
	Snoring
	Waist circumference
	Waist hip ratio
	Weight
	Whole body fat mass
	Whole body fat-free mass
	Whole body water mass
rs297924	Age at menarche
	Basal metabolic rate
	BMI
	Body fat percentage
	Childhood BMI
	Chilhood obesity
	Hip circumference
	Home area population density: Scotland large urban area
	Impedance
	Obesity
	Obesity class 1
	Obesity class 2
	Obesity with early age of onset age 2
	Waist circumference
	Weight
	Whole body fat mass
	Whole body fat-free mass
	Whole body water mass
	Alcohol intake frequency

rs7970350	Basal metabolic rate Birth weight Birth weight of first child Birthlenght BMI in males less than or equal to 50 years of age Diabetes diagnosed by doctor Forced expiratory volume in 1 sec Forced vital capacity Hand grip strength Height Hip circumference Impedance Infant head circumference Infant length Maternal effects on offspring birthweight Number of self-reported non-cancer illnesses Overall health rating Peak expiratory flow Pulse rate Self-reported diabetes Self-reported high cholesterol Systolic blood pressure Treatment with metformin Waist circumference Weight Whole body fat mass Whole body fat-free mass Whole body water mass
rs4883723	Basal metabolic rate BMI Body fat percentage Childhood BMI Childhood obesity Hip circumference Leg impedance Obesity with early age of onset age 2 Waist circumference Weight Whole body fat mass Whole body fat-free mass Whole body water mass
rs7141420	Basal metabolic rate BMI Body fat percentage Hip circumference Impedance Obesity Obesity class 1 Obesity class 2 Overweight Sodium in urine Waist circumference Waist hip ratio Weight Whole body fat mass Whole body fat-free mass Whole body water mass
	Age at menarche Basal metabolic rate BMI Body fat percentage Diastolic blood pressure Hip circumference Impedance

rs4776970	Obesity class 1 Obesity class 2 Overweight Past tobacco smoking Vascular or heart problems diagnosed by doctor: high blood pressure Vascular or heart problems diagnosed by doctor: none of the above Waist circumference Waist hip ratio Weight Whole body fat mass Whole body fat-free mass Whole body water mass
rs12446632	Age at menarche Basal metabolic rate BMI Childhood BMI Hand grip strength Heel bone mineral density High density lipoprotein Hip circumference Impedance Menarche age at onset Obesity Obesity class 1 Obesity class 2 Overweight Waist circumference Weight Whole body fat mass Whole body fat-free mass Whole body water mass
rs11074446 (rs7188545)	Basal metabolic rate BMI Body fat percentage Hip circumference Impedance Overweight Waist circumference Whole body fat mass Whole body fat-free mass Whole body water mass
rs8049439	Alcohol intake frequency Basal metabolic rate BMI Body fat percentage Crohns disease Educational attainment Fluid intelligence score Gene expression Hand grip strength Hip circumference Inflammatory bowel disease Inflammatory bowel disease early onset Intelligence Intelligence multi trait analysis Leg impedance Mean corpuscular volume Nonsyndromic striar distensae stretch marks Obesity class 1 Obesity class 2 Overweight Qualifications: college or university degree Qualifications: none Red blood cell count

	Suffer from nerves
	Types of physical activity in last 4 weeks: light diy
	Usual walking pace
	Waist circumference
	Waist hip ratio
	Weight
	Whole body fat mass
	Whole body fat-free mass
	Whole body water mass
	Years of educational attainment
rs12597511	Alcohol intake frequency
	Basal metabolic rate
	BMI
	Body fat percentage
	Diastolic blood pressure
	Dose change in phenprocoumon warfarin in mgweek per allele
	Forced expiratory volume in 1 sec
	Forced vital capacity
	Hip circumference
	Illnessess of siblings: high blood pressure
	Illnessess of siblings: none of the above
	Impedance
	Lymphocyte count
	Mean corpuscular hemoglobin
	Mean corpuscular volume
	Nervous feelings
	Number of incorrect marches in round
	Overall health rating
	Self-reported hypertension
	Snoring
	Time spent watching tv
	Types of physical activity in last 4 weeks: walking for pleasure
	Usual walking pace
	Vascular or heart problems diagnosed by doctor: high blood pressure
	Vascular or heart problems diagnosed by doctor: none of the above
	Waist circumference
	Weight
	Whole body fat mass
	Whole body fat-free mass
	Whole body water mass
rs1421085	Age at menarche
	Alcohol intake frequency
	Average weekly beer plus cider intake
	Average weekly red wine intake
	Average weekly spirits intake
	Basal metabolic rate
	BMI
	Body fat percentage
	Childhood BMI
	Childhood obesity
	Creatinine in urine
	Cystatin C in serum
	Diabetes diagnosed by doctor
	Extreme obesity with early age of onset
	Getting up in morning
	HbA1c
	HDL cholesterol
	Heel bone mineral density
	High density lipoprotein
	Hip circumference
	Illnesses of father: diabetes
	Illnesses of mother: diabetes
	Illnessess of siblings: high blood pressure
	Impedance

rs1121980	log Fast insulin
	log Leptin
	Medication for cholesterol, blood pressure or diabetes: blood pressure medication
	Medication for cholesterol, blood pressure or diabetes: none of the above
	Morning or evening person
	Number of treatments or medications taken
	Obesity
	Obesity class 1
	Obesity class 2
	Obesity class 3
	Obesity early onset extreme
	Obesity with early age of onset age 2
	Overall health rating
	Overweight
	Relative age of first facial hair
	Relative age voice broke
	Self-reported breast cancer
	Self-reported diabetes
	Self-reported hypertension
	Sleep duration
	Snoring
	Sodium in urine
	Treatment with bendroflumethiazide
	Treatment with blood pressure medication
	Treatment with gliclazide
	Treatment with metformin
	Triglycerides
	Type II diabetes
	Type II diabetes combined control dataset
	Usual walking pace
	Vascular or heart problems diagnosed by doctor: high blood pressure
	Vascular or heart problems diagnosed by doctor: none of the above
	Waist circumference
	Waist hip ratio
	Weight
	Whole body fat mass
	Whole body fat-free mass
	Whole body water mass
rs969438	BMI
	Obesity class 1
	Trunk fat percentage
	Waist circumference
	Weight
rs6567160	Alcohol intake frequency
	Antipsychotic drug induced weight gain
	Basal metabolic rate
	BMI
	Body fat percentage
	Childhood BMI
	Childhood obesity
	Coronary artery disease
	Diabetes diagnosed by doctor
	Fat body mass
	Forced expiratory volume in 1 sec
	Hand grip strength
	HDL cholesterol
	Height
	High density lipoprotein
	Hip circumference
	Impedance
	Myocardial infarction
	Nervous feelings
	Obesity class 1
	Obesity class 2

Obesity with early age of onset age 2
Overweight
Self-reported diabetes
Suffer from nerves
Treatment with levothyroxine sodium
Type II diabetes
Vascular or heart problems diagnosed by doctor: high blood pressure
Vascular or heart problems diagnosed by doctor: none of the above
Waist circumference
Waist hip ratio
Weight
Whole body fat mass
Whole body fat-free mass
Whole body water mass
Worrier or anxious feelings

PC2 related genetic variants and associated traits in previous GWAS ($p < 5 \times 10-8$)

SNP (lead SNP)	Trait
rs2284746	BMI
	Forced vital capacity
	Gene expression
	Height
	Hematocrit
	Hip circumference
	Impedance
	Pulmonary function
	Waist circumference
	Whole body fat-free mass
	Whole body water mass
rs2903545	Hand grip strength
	Height
	Hip circumference
	Sum eosinophil basophil counts
	Trunk fat-free mass
	Whole body fat-free mass
	Whole body water mass
rs11209376	Creatinine in urine
	Diastolic blood pressure
	Forced expiratory volume in 1 sec
	Forced vital capacity
	Hand grip strength
	Heel bone mineral density
	Height
	Hip circumference
	Potassium in urine
	Weight
	Whole body fat-free mass
	Whole body water mass
rs17391694	Alcohol intake frequency
	Basal metabolic rate
	BMI
	Creatinine in urine
	Crohns disease
	Forced vital capacity
	Height
	Hip circumference
	Impedance
	Leg fat percentage
	Lung cancer
	Mean corpuscular hemoglobin concentration
	Time spent watching tv
	Waist circumference
	Weight
	Whole body fat-free mass
	Whole body water mass
rs7536458	Basal metabolic rate
	Forced expiratory volume in 1 sec
	Hair or balding pattern
	Height
	Hip circumference
	Infant length
	Leg impedance
	Trunk fat-free mass
	Waist circumference
	Waist hip ratio
	Whole body fat-free mass
	Whole body water mass
	Basal metabolic rate

	Body fat percentage
	Breast cancer
	Coronary artery disease
	Forced expiratory volume in 1 sec
	Forced vital capacity
	Forced vital capacity
	Granulocyte percentage of myeloid white cells
	Heel bone mineral density
	Height
rs11205303	Hip circumference
	Hip circumference
	Impedance
	Infant length
	Trunk fat mass
	Trunk fat percentage
	Waist circumference
	Weight
	Whole body fat mass
	Whole body fat-free mass
	Whole body water mass
rs1752388 (rs2298265)	Height
	Basal metabolic rate
	Birth length
	Birth weight
	BMI
	Eosinophil percentage of granulocytes
	Hayfever, allergic rhinitis or eczema
	Height
	Hip circumference
rs905938	Impedance
	Neutrophil percentage of granulocytes
	Sum eosinophil basophil counts
	Trunk fat-free mass
	Waist circumference
	Waist hip ratio
	Weight
	Whole body fat-free mass
	Whole body water mass
	Basal metabolic rate
	Forced expiratory volume in 1 sec
	Forced vital capacity
	Hair or balding pattern
	Heel bone mineral density
	Height
	Hematocrit
rs11584955	Hemoglobin concentration
	Hip circumference
	Mean platelet volum
	Platelet distribution width
	Red blood cell count
	Weight
	Whole body fat-free mass
	Whole body water mass
	Basal metabolic rate
	Forced expiratory volume in 1 sec
	Forced vital capacity
	Hand grip strength
rs1014719	Height
	Impedance
	Weight
	Whole body fat-free mass
	Whole body water mass
	Basal metabolic rate

rs1046934	Forced expiratory volume in 1 sec Forced vital capacity Gene expression Hand grip strength Height Hip circumference Impedance Myopia Waist circumference Weight Whole body fat-free mass Whole body water mass
rs1415288	Adiponectin levels Body fat percentage Coxarthrosis Falls in the last year Femoral hernia Height Hip circumference Impedance Inguinal hernia Trunk fat percentage Type II diabetes Umbilical hernia Ventral hernia Waist circumference Waist hip ratio Weight Whole body fat mass
rs12093031 (rs10799424)	Forced expiratory volume in 1 sec Forced vital capacity Hand grip strength Height Hip circumference Impedance Trunk fat-free mass Waist circumference
rs2278483	BMI Body fat percentage Childhood BMI Forced vital capacity Hand grip strength Height Hip circumference Trunk fat-free mass Waist circumference
rs2289195	Basal metabolic rate Forced expiratory volume in 1 sec Forced vital capacity Hand grip strength Height Leg impedance Waist circumference Whole body fat-free mass Whole body water mass
rs1545552	Basal metabolic rate Forced expiratory volume in 1 sec Height Hip circumference Hip circumference Weight Whole body fat-free mass Whole body water mass

rs6740539	Height
rs3791675	Basal metabolic rate Forced expiratory volume in 1 sec Forced vital capacity Height Hip circumference Impedance Inguinal hernia Mononeuropathies of upper limb Peak expiratory flow Waist circumference Weight Whole body fat mass Whole body fat-free mass Whole body water mass
rs1913671	Getting up in morning Height Hip circumference Trunk fat-free mass Waist circumference Whole body fat-free mass
rs1478576	Basal metabolic rate Height Hip circumference Impedance Weight Whole body fat mass Whole body fat-free mass Whole body water mass
rs3103267	Basal metabolic rate Forced expiratory volume in 1 sec Forced vital capacity Height Waist circumference Whole body fat-free mass Whole body water mass
rs2270894	Basal metabolic rate Birth weight Forced vital capacity Height Hip circumference Weight Whole body fat-free mass Whole body water mass
rs2581830	Arm impedance Birth weight BMI Crohns disease Forced vital capacity Hand grip strength Height Hip circumference Trunk fat-free mass Usual walking pace
rs9833926	Basal metabolic rate Hayfever, allergic rhinitis or eczema Heel bone mineral density Height Hematocrit Hemoglobin concentration Hip circumference Lymphocyte count No blood clot, bronchitis, emphysema, asthma, rhinitis, eczema or allergy diagnosed by doctor

	Red blood cell count
	Waist circumference
	Weight
	Whole body fat-free mass
	Whole body water mass
rs6439168	Basal metabolic rate
	Forced expiratory volume in 1 sec
	Forced vital capacity
	Height
	Hip circumference
	Usual walking pace
	Weight
	Whole body fat-free mass
	Whole body water mass
rs724016	Allergic disease
	Basal metabolic rate
	Birth weight of first child
	Body fat percentage
	Crohns disease
	Diastolic blood pressure
	Ever had prostate specific antigen test
	Forced expiratory volume in 1 sec
	Forced vital capacity
	Hair or balding pattern
	Hand grip strength
	Hayfever, allergic rhinitis or eczema
	Heel bone mineral density
	Height
	Hip circumference
	Infant length
	Lymphocyte count
	Lymphocyte percentage of white cells
	Mean corpuscular hemoglobin
	Mean corpuscular volume
	Myopia
	Neutrophil percentage of white cells
	No blood clot, bronchitis, emphysema, asthma, rhinitis, eczema or allergy diagnosed by doctor
	Potassium in urine
	Pulse rate
	Red blood cell count
	Relative age of first facial hair
	Self-reported enlarged prostate
	Trunk fat percentage
	Waist circumference
	Weight
	Whole body fat mass
	Whole body fat-free mass
	Whole body water mass
rs13094143	Average weekly beer plus cider intake
	Basal metabolic rate
	Height
	Hip circumference
	Monokine induced by gamma interferon levels
	Trunk fat-free mass
	Whole body fat-free mass
	Whole body water mass
rs519384	Age at menarche
	Basal metabolic rate
	Forced expiratory volume in 1 sec
	Forced vital capacity
	Height
	Impedance
	Peak expiratory flow
	Pulse rate

	Trunk fat-free mass
	Whole body fat-free mass
rs720390	Basal metabolic rate
	BMI
	Diabetes diagnosed by doctor
	Height
	Hip circumference
	Illnesses of father: daibetes
	Platelet count
	Plateletcrit
	Self-reported diabetes
	Waist circumference
	Whole body fat-free mass
	Whole body water mass
rs6853216	Age at first live birth
	Basal metabolic rate
	Birth weight
	Body fat percentage
	Diastolic blood pressure
	Fluid intellingence score
	Forced expiratory volume in 1 sec
	Forced vital capacity
	Hand grip strength
	Height
	Hip circumference
	Number of treatments or medications taken
	Peak expiratory flow
	Peritonsillar abscess
	Qualifications: A levels or as levels or equivalent
	Self-reported hypertension
	Systolic blood pressure
	Time spent watching tv
	Vascular or heart problems diagnosed by doctor: high blood pressure
	Vascular or heart problems diagnosed by doctor: none of the above
	Waist circumference
	Weight
	Whole body fat-free mass
	Whole body water mass
rs4694504	Body fat percentage
	Height
	Hip circumference
	Impedance
	Waist circumference
rs1975474	Basal metabolic rate
	Forced expiratory volume in 1 sec
	Forced vital capacity
	Height
	Hip circumference
	Overall health rating
	Unspecified haematuria
	Waist circumference
	Weight
	Whole body fat mass
	Whole body fat-free mass
	Whole body water mass
rs1562975	Height
rs12648786	Basal metabolic rate
	Birth weight
	Forced expiratory volume in 1 sec
	Forced vital capacity
	Height
	Hip circumference
	Peak expiratory flow

	Waist hip ratio
	Weight
	Whole body fat-free mass
	Whole body water mass
rs7689420	Basal metabolic rate
	Forced expiratory volume in 1 sec
	Forced vital capacity
	Hand grip strength
	Height
	Hip circumference
	Peak expiratory flow
	Waist circumference
	Weight
	Whole body fat mass
	Whole body fat-free mass
	Whole body water mass
rs6450922	Basal metabolic rate
	Height
	Hip circumference
	Whole body fat-free mass
	Whole body water mass
rs7733331	Basal metabolic rate
	Diastolic blood pressure
	Forced expiratory volume in 1 sec
	Height
	Hip circumference
	Illnesses of siblings: high blood pressure
	Illnesses of siblings: none of the above, group 1
	Medication for cholesterol, blood pressure or diabetes: blood pressure medication
	Medication for cholesterol, blood pressure or diabetes: none of the above
	Number of self-reported non-cancer illnesses
	Self-reported gestional hypertension or pre-eclampasia
	Self-reported hypertension
	Systolic blood pressure
	Treatment with bendroflumethiazide
	Treatment with blood pressure
	Treatment with lisinopril
	Vascular or heart problems diagnosed by doctor: high blood pressure
	Vascular or heart problems diagnosed by doctor: none of the above
	Waist circumference
	Weight
	Whole body fat mass
	Whole body fat-free mass
	Whole body water mass
rs6894139	Basal metabolic rate
	Bone mineral density
	Femoral neck bone mineral density
	Forced expiratory volume in 1 sec
	Forced vital capacity
	Forearm bone mineral density
	Hair or balding pattern
	Height
	Platelet count
	Platelet distribution width
	Plateletcrit
	Whole body fat-free mass
	Whole body water mass
	Asthma
	Basal metabolic rate
	Basophil count
	Blood metabolite levels
	Crohns disease
	Eosinophil percentage of granulocytes

rs274567	Eosinophil percentage of white cells Eosinophinil count Granulocyte count Hand grip strength Height High light scatter percentage of red cells Inmature fration of reticulocytes Mean platelet volum Monocyte count Myeloid white cell count Neutrophil count Neutrophil percentage of granulocytes No blood clot, bronchitis, emphysema, asthma, rhinitis, eczema or allergy diagnosed by doctor Platelet count Reticulocyte fraction of red cells Self-reported asthma Self-reported hypertension Sum basophil neutrophil counts Sum eosinophil basophil counts Sum neutrophil eosinophil counts Treatment with bendroflumethiazide Vascular or heart problems diagnosed by doctor: high blood pressure Vascular or heart problems diagnosed by doctor: none of the above Waist circumference Weight White blood cell count Whole body fat-free mass Whole body water mass
rs31198	Basal metabolic rate Forced expiratory volume in 1 sec Forced vital capacity Heel bone mineral density Height Whole body fat-free mass Whole body water mass
rs4282339	Basal metabolic rate Forced vital capacity Hand grip strength Height Weight Whole body fat-free mass Whole body water mass
rs153753	Basal metabolic rate Hand grip strength Height Hip circumference Whole body fat-free mass Whole body water mass
rs4868126	Basal metabolic rate Height Hip circumference Waist circumference Weight Whole body fat-free mass Whole body water mass
rs4868293	Height Hip circumference
rs2714354	Height
rs3812163	Basal metabolic rate Forced expiratory volume in 1 sec Hand grip strength Height Weight

	Whole body fat-free mass
	Whole body water mass
	Basal metabolic rate
	Birth weight
	BMI
	Body fat percentage
	Breastfed as a baby
	Disorders mineral metabolism
	Exposure to tobacco smoke outside home
	Forced expiratory volume in 1 sec
	Gene expression
	Hayfever, allergic rhinitis or eczema
	Hearing difficulty or problems with background noise
	Height
	Hemoglobin concentration
	High density lipoprotein
	High light scatter percentage of red cells
	Hip circumference
	Mean corpuscular hemoglobin
	Mean corpuscular hemoglobin concentration
	Mean corpuscular volume
	Medication for cholesterol, blood pressure or diabetes: blood pressure medication
	Medication for cholesterol, blood pressure or diabetes: none of the above
	Mouth or teeth dental problems: dentures
rs806794	Number of cigarettes previosly smoked daily
	Pack years adult smoking as proportion of life span exposed to smoking
	Pack years of smoking preview only
	Qualifications: A levels or as levels or equivalent
	Qualifications: college or university degree
	Red cell distribution width
	Reticulocyte count
	Reticulocyte fraction of red cells
	Self-reported hypertension
	Time spent watching tv
	Transport type for commuting to job workplace: cycle
	Types of physical activity in last 4 weeks: strenuous sports
	Usual walking pace
	Varicose veins of lower extremities
	Vascular or heart problems diagnosed by doctor: high blood pressure
	Vascular or heart problems diagnosed by doctor: none of the above
	Waist circumference
	Weight
	Whole body fat mass
	Whole body fat-free mass
	Whole body water mass
	Worry too long after embarrassment
	Years educational attainment
	Basal metabolic rate
	Basophil count
	Coronary artery disease
	Eosinophinil count
	Forced vital capacity
	Granulocyte count
	Hand grip strength
	Hearing difficulty or problems with background noise
	Height
	Hemoglobin concentration
	Hip circumference
	Intestinal malabsorption
	Lymphocyte count
	Lymphocyte percentage of white cells
	Mean corpuscular hemoglobin concentration
	Mean platelet volum
	Monocyte count

	Mouth or teeth dental problems: mouth ulcers
rs7744253	Myeloid white cell count
	Neutrophil count
	Peak expiratory flow
	Red cell distribution width
	Rheumatoid arthritis
	Rheumatoid arthritis
	Self-reported ankylosing spondylitis
	Self-reported hypothyroidism or myxoedema
	Self-reported malabsorption or coeliac disease
	Self-reported sarcoidosis
	Started insulin within one year diagnosis of diabetes
	Sum basophil neutrophil counts
	Sum neutrophil eosinophil counts
	Treatment with levothyroxine sodium
	Treatment with tyroxine product
	Weight
	White blood cell count
	Whole body fat-free mass
	Whole body water mass
	Ankylosing spondylitis
	Basal metabolic rate
	Basophil count
	Basophil percentage with white cells
	Birth weight
	Diastolic blood pressure
	Eosinophil percentage of white cells
	Eosinophinil count
	Eosiphinil percentage of granulocytes
	Forced expiratory volume in 1 sec
	Forced vital capacity
	Gene expression
	Granulocyte count
	Height
	Hip circumference
	IgA deficiency
	Intestinal malabsorption
	Lymphocyte count
	Lymphocyte percentage of white cells
	Mean platelet volum
	Medication for pain relief, constipation, heartburn: none of the above
	Monocyte count
	Mouth or teeth dental problems: mouth ulcers
	Myeloid white cell count
rs2256183	Neutrophil count
	Neutrophil percentage of granulocytes
	Neutrophil percentage of white cells
	Platelet distribution width
	Plateletcrit
	Primary sclerosing cholangitis
	Red cell distribution width
	Reticulocyte count
	Reticulocyte fraction of red cells
	Rheumatoid arthritis
	Self-reported adrenocortical insufficiency or addisons disease
	Self-reported ankylosing spondylitis
	Self-reported high cholesterol
	Self-reported hypothyroidism, thyrotocosis or myxoedema
	Self-reported malabsorption or coeliac disease
	Self-reported psoriasis
	Self-reported sarcoidosis
	Sum basophil neutrophil counts
	Sum eosinophil basophil counts
	Total cholesterol

	Treatment with levothyroxine sodium
	Unspecified haematuria
	Weight
	White blood cell count
	Whole body water mass
	Basal metabolic rate
	Basophil count
	Diastolic blood pressure
	Doctor diagnosed sarcoidosis
	DPA 22:5n3
	Drive faster than motorway speed limit
	Eosinophinil count
	Eosinophil percentage of granulocytes
	Eosinophil percentage of white cells
	Forced expiratory volume in 1 sec
	Forced vital capacity
	Frequency of tenseness or restlessness in last 2 weeks
	Granulocyte count
	Hand grip strength
	Height
	High light scatter percentage of red cells
	High light scatter reticulocyte count
	Hip circumference
	Impedance
	Intestinal malabsorption
	Lymphocyte count
	Medication for cholesterol, blood pressure or diabetes: cholesterol lowering medication
	Medication for cholesterol, blood pressure or diabetes: none of the above
	Medication for pain relief, constipation, heartburn: none of the above
	Monocyte count
	Mouth or teeth dental problems: mouth ulcers
	Multiple sclerosis
	Myeloid cell count
	Neutrophil count
	Neutrophil percentage of granulocytes
	Number of self-reported non-cancer illnesses
	Number of treatments or medications taken
	Other rheumatoid arthritis
	Overall health rating
	Primary sclerosing cholangitis
	Reticulocyte count
rs6937696	Reticulocyte fraction of red cells
	Rheumatoid arthritis
	Self-reported adrenocortical insufficiency or addisons disease
	Self-reported ankylosing spondylitis
	Self-reported high cholesterol
	Self-reported hypertension
	Self-reported hyperthyroidism or thyrotoxicosis
	Self-reported hypothyroidism or myxoedema
	Self-reported malabsorption or coeliac disease
	Self-reported multiple sclerosis
	Self-reported multiple sclerosis
	Self-reported psoriasis
	Self-reported rheumatoid arthritis
	Self-reported sarcoidosis
	Self-reported sjogrens syndrome or sicca syndrome
	Self-reported-systemic lupus erythematosis or sle
	Seropositive rheumatoid arthritis
	Sum basophil neutrophil counts
	Sum eosinophil basophil counts
	Sum neutrophil eosinophil counts
	Taking other prescription medications
	Total cholesterol
	Treatment with baclofen

	Treatment with carbimazole
	Treatment with fludrocortisone
	Treatment with methotrexate
	Treatment with simvastatin
	Treatment with sulfasalazine
	Unspecified haematuria
	Vascular or heart problems diagnosed by doctor: high blood pressure
	Vascular or heart problems diagnosed by doctor: none of the above
	Weight
	Wheeze or whistling in the chest in last year
	White blood cell count
	Whole body fat-free mass
	Whole body water mass
	Worrier or anxious feelings
rs7742369	Arm impedance
	Basal metabolic rate
	Birth weight
	Birth weight of first child
	Body height
	BMI
	Forced expiratory volume in 1 sec
	Forced vital capacity
	Height
	Hip circumference
	Home area population density: Scotland large urban area
	Mean corpuscular volume
	Peak expiratory flow
	Platelet count
	Waist circumference
	Weight
	Whole body fat mass
	Whole body fat-free mass
	Whole body water mass
rs9462007	Basal metabolic rate
	Body fat percentage
	BMI
	Coronary artery disease
	Forced expiratory volume in 1 sec
	HDL cholesterol
	Height
	High density lipoprotein
	Hip circumference
	Impedance
	Lymphocyte count
	Medication for pain relief, constipation, heartburn: none of the above
	Monocyte count
	Overall health rating
	Platelet count
	Plateletcrit
	Pulse rate
	Relative age of first facial hair
	Total cholesterol
	Treatment with omeprazole
	Usual walking pace
	Waist circumference
	Weight
	Whole body fat mass
	Whole body fat-free mass
	Whole body water mass
	Basal metabolic rate
	Diastolic blood pressure
	Forced expiratory volume in 1 sec
	Forced expiratory volume in 1 sec
	Hand grip strength

rs3734254	Height
	Monocyte percentage of white cells
	Peak expiratory flow
	Systolic blood pressure
	Weight
	Whole body fat-free mass
	Whole body water mass
rs9357470	Basal metabolic rate
	Coxarthrosis
	Heel bone mineral density
	Height
	Hip circumference
	Whole body fat-free mass
	Whole body water mass
rs12209223	Basal metabolic rate
	Forced expiratory volume in 1 sec
	Height
	Hip circumference
	Hip osteoarthritis
	Waist circumference
	Weight
	Whole body fat-free mass
	Whole body water mass
rs920842	Basal metabolic rate
	Forced vital capacity
	Height
	Weight
	Whole body fat-free mass
	Whole body water mass
rs314263	Age at menarche
	Basal metabolic rate
	Forced expiratory volume in 1 sec
	Forced vital capacity
	Hand grip strength
	Height
	Hip circumference
	Impedance
	Medication for cholesterol, blood pressure or diabetes: blood pressure medication
	Medication for pain relief, constipation, heartburn: none of the above
	Number of operations
	Number of treatments or medications taken
	Relative age of first facial hair
	Relative age voice broke
	Sleeplessness or insomnia
	Tanner stage
	Waist circumference
	Weight
	Whole body fat mass
	Whole body fat-free mass
	Whole body water mass
rs9488923 (rs2027850)	Height
	Age at menarche
	Age completed full time education
	Basal metabolic rate
	Birth weight
	Body fat percentage
	Coronary artery disease
	Diabetes diagnosed by doctor
	Forced expiratory volume in 1 sec
	Forced vital capacity
	Hair or balding pattern
	Height
	Hematocrit

rs9388490	Hemoglobin concentration
	Hip circumference
	Impedance
	Intelligence
	Intelligence multi triat analysis
	Intracranial volume
	Nervous feelings
	Pain type experienced in last month: none of the above
	Red blood cell count
	Sodium in urine
	Type II diabetes
	Weight
	Whole body fat-free mass
	Whole body water mass
rs6569648	Basal metabolic rate
	BMI
	Breast cancer
	Breast cancer estrogen receptor negative
	Creatinine in urine
	Forced expiratory volume in 1 sec
	Forced vital capacity
	Hand grip strength
	Heel bone mineral density
	Height
	Hematocrit
	Hemoglobin concentration
	High light scatter reticulocyte count
	Hip circumference
	Immature fraction of reticulocytes
	Impedance
	Lymphocyte count
	Maternal effects on offspring birthweight
	Waist hip ratio
	Weight
	White blood cell count
	Whole body fat mass
	Whole body fat-free mass
	Whole body water mass
rs9389986	Basal metabolic rate
	Birth weight
	Birthlength
	Forced expiratory volume in 1 sec
	Forced vital capacity
	Height
	Hip circumference
	Impedance
	Lung function ratio of forced expiratory volum in 1 sec
	Waist circumference
	Weight
	Whole body fat mass
	Whole body fat-free mass
	Whole body water mass
rs827423	Basal metabolic rate
	Forced expiratory volume in 1 sec
	Forced vital capacity
	Heel bone mineral density
	Height
	Hip circumference
	Weight
	Whole body fat-free mass
	Whole body water mass
	Arm impedance
	Basal metabolic rate
	Birth weight

rs1182199	Body fat percentage Forced expiratory volume in 1 sec Forced vital capacity Height Hip circumference Myeloid white cell count Not blood clot, bronchitis, emphysema, asthma, rhinitis, eczema or allergy diagnosed by doctor Platelet count Plateletcrit Ulcerative colitis Waist circumference Weight White blood cell count Whole body fat mass Whole body fat-free mass Whole body water mass
rs2192476	Height
rs506154	Basal metabolic rate Diabetes diagnosed by doctor Forced expiratory volume in 1 sec Forced vital capacity Height Hip circumference Impedance Self-reported diabetes Treatment with metformin Waist circumference Weight Whole body fat-free mass Whole body water mass
rs12673331	Basal metabolic rate Forced expiratory volume in 1 sec Forced vital capacity Height Impedance Whole body fat-free mass Whole body water mass
rs2282978	Basal metabolic rate Birth weight Body height CDK6 expression in lymphocytes Forced expiratory volume in 1 sec Forced vital capacity Granulocyte percentage of myeloid white cells Heel bone mineral density Height Hip circumference Monocyte count Monocyte percentage of white cells Pulse pressure Rheumatoid arthritis Systolic blood pressure Waist circumference Weight Whole body fat mass Whole body fat-free mass Whole body water mass
rs9650315	Basal metabolic rate Birth weight Forced expiratory volume in 1 sec Forced vital capacity Height Hip circumference

	Impedance
	Weight
	Whole body fat-free mass
	Whole body water mass
rs7463906	Basal metabolic rate
	Forced expiratory volume in 1 sec
	Forced vital capacity
	Height
	Hip circumference
	Peak expiratory flow
	Waist circumference
	Weight
	Whole body fat-free mass
	Whole body water mass
rs7463906	Basal metabolic rate
	Forced expiratory volume in 1 sec
	Forced vital capacity
	Height
	Hip circumference
	Peak expiratory flow
	Waist circumference
	Weight
	Whole body fat-free mass
	Whole body water mass
rs7463906	Basal metabolic rate
	Forced expiratory volume in 1 sec
	Forced vital capacity
	Height
	Hip circumference
	Peak expiratory flow
	Waist circumference
	Weight
	Whole body fat-free mass
	Whole body water mass
rs7463906	Basal metabolic rate
	Forced expiratory volume in 1 sec
	Forced vital capacity
	Height
	Hip circumference
	Peak expiratory flow
	Waist circumference
	Weight
	Whole body fat-free mass
	Whole body water mass
rs4130415	Basal metabolic rate
	Forced expiratory volume in 1 sec
	Forced vital capacity
	Heel bone mineral density
	Height
	Hip circumference
	Pain type experienced in last month: back pain
	Peak expiratory flow
	Self-reported prolapsed disc or slipped disc
	Waist circumference
	Weight
	Whole body fat-free mass
	Whole body water mass
rs4909595	Basal metabolic rate
	Forced expiratory volume in 1 sec
	Height
	Hip circumference
	Systolic blood pressure
	Treatment with rennie duo oral suspension

	Weight
	Whole body fat-free mass
	Whole body water mass
rs9407763	Height
rs11144688	Basal metabolic rate
	Forced expiratory volume in 1 sec
	Height
	Hip circumference
	Impedance
	Waist circumference
	Weight
	Whole body fat-free mass
	Whole body water mass
rs7855177	Alcohol usually taken with meals
	Eosinophil percentage of granulocytes
	Eosinophil percentage of white cells
	Granulocyte count
	Hair or balding pattern
	Height
	Impedance
	Mean time to correctly identify matches
	Myeloid white cell count
	Nap during day
	Neutrophil count
	Neutrophil percentage of granulocytes
	Sum basophil neutrophil counts
	Sumneutrophil eosinophil
	White blood cell count
rs3937594	Basal metabolic rate
	Forced expiratory volume in 1 sec
	Height
	Hip circumference
	Nonrheumatic aortic valve disorders
	Weight
	Whole body fat-free mass
	Whole body water mass
rs7043114	Arm impedance
	Height
rs4448343	Basal metabolic rate
	Birth weight
	Fluid intelligence score
	Forced expiratory volume in 1 sec
	Heel bone mineral density
	Height
	Hip circumference
	Time spent using computer
	Waist circumference
	Whole body fat-free mass
	Whole body water mass
rs2025151	Basal metabolic rate
	Forced vital capacity
	Height
	Hip circumference
	Job involves heavy manual or physical work
	Platelet count
	Platelet distribution width
	Pulse rate
	Time spent watching tv
	Whole body fat-free mass
	Whole body water mass
rs4333673	Basal metabolic rate
	Forced vital capacity
	Height

	Whole body fat-free mass
	Whole body water mass
rs7853634	Basal metabolic rate
	Forced expiratory volume in 1 sec
	Forced vital capacity
	Hand grip strength
	Height
	Impedance
	Weight
	Whole body fat-free mass
	Whole body water mass
rs7466269	Basal metabolic rate
	Bone mineral density paedriatric lower limb
	Bone mineral density paedriatric total body less head
	Forced expiratory volume in 1 sec
	Forced vital capacity
	Hand grip strength
	Heel bone mineral density
	Height
	Weight
	Whole body fat-free mass
	Whole body water mass
rs4980067	Basal metabolic rate
	Forced vital capacity
	Height
	High light scatter percentage of red cells
	High light scatter reticulocyte count
	Inmature fraction of reticulocytes
	Platelet count
	Reticulocyte count
	Reticulocyte fraction of red cells
	Weight
	Whole body fat-free mass
	Whole body water mass
rs234886	Basal metabolic rate
	Height
	Hip circumference
	Waist circumference
	Weight
	Whole body fat-free mass
	Whole body water mass
rs1879671	Height
	Treatment with amiodarone
rs606452	Age-related macular degeneration
	BMI
	Coronary artery disease
	Forced expiratory volume in 1 sec
	Forced vital capacity
	Height
	Hip circumference
	Impedance
	Waist circumference
rs6487133	Basal metabolic rate
	Forced expiratory volume in 1 sec
	Forced vital capacity
	Height
	Whole body fat-free mass
	Whole body water mass
	Basal metabolic rate
	Forced expiratory volume in 1 sec
	Hand grip strength

rs11049611	Height Mouth or teeth dental problems: loose teeth Waist circumference Weight Whole body fat-free mass Whole body water mass
rs1351394	Age at first tooth Alcohol intake frequency Basal metabolic rate Birth length Birth weight BMI Diabetes diagnosed by doctor Estimated total intracranial volume excluding patients with neuropsychiatric disorders Forced expiratory volume in 1 sec Forced vital capacity Hand grip strength Height Hip circumference Impedance Infant head circumference Intracranial volume Maternal effects on offspring birthweight Number of teeth Overall health rating Peak expiratory flow Pulse rate Self-reported diabetes Self-reported high cholesterol Treatment with metformin Waist circumference Weight Whole body fat mass Whole body fat-free mass Whole body water mass
rs10748128	Basal metabolic rate Height Hip circumference Waist circumference Weight Whole body fat-free mass Whole body water mass
rs11107116 (rs3825199)	Basal metabolic rate Forced expiratory volume in 1 sec Forced vital capacity Gene expression Heel bone mineral density Height Hip circumference Impedance Standarized difference in height between age 8 years and adult Weight Whole body fat-free mass Whole body water mass
rs11107169	Basal metabolic rate Heel bone mineral density Height Hip circumference Whole body fat-free mass Whole body water mass
	Age at menopause Age completed full time education

rs7980687	Alcohol intake frequency Allergic disease Average weekly red wine intake Basal metabolic rate Brain College completion Diatolic blood pressure Educational attainment Hayfever, allergic rhinitis or eczema Head circumference infant Heel bone mineral density Height Hip circumference Infant head circumference Job involves heavy manual or physical work Lymphocyte count Lymphocyte percentage of white cells Neutrophil percentage of white cells No blood clot, bronchitis, emphysema, asthma, rhinitis, eczema or allergy diagnosed by doctor Platelet count Plateletcrit Qualifications: A levels or as levels or equivalent Qualifications: college or university degree Qualifications: none Qualifications: O levels or GCSEs or equivalent Qualifications: other professional qualifications Schizophrenia Time spent watching tv Weight Whole body fat-free mass Whole body water mass Years of education Years of educational attainment
rs7986486	Basal metabolic rate Forced expiratory volume in 1 sec Forced vital capacity Height High light scatter percentage of red cells Impedance Peak expiratory flow Weight Whole body fat-free mass Whole body water mass
rs3118905	Basal metabolic rate Diastolic blood pressure Forced expiratory volume in 1 sec Forced vital capacity Hand grip strength Heel bone mineral density Height Hip circumference Hyperplasia of prostate Impedance Standarized difference in height between age 8 years and adult Systolic blood pressure Weight Whole body fat-free mass Whole body water mass
rs1950500	Basal metabolic rate Gene expression Height Weight Whole body fat-free mass Whole body water mass

rs2093210	Age at menarche Basal metabolic rate Eye problems or disorders: glaucoma Forced expiratory volume in 1 sec Forced vital capacity Glaucoma primary open angle glaucoma Heel bone mineral density Height Hip circumference Impedance Self-reported glaucoma Sodium in urine Treatment with xalatan 0.005% eye drops Weight Whole body fat mass Whole body fat-free mass Whole body water mass
rs5742915	Age at first live birth Age at menarche Basal metabolic rate Body fat percentage BMI Forced expiratory volume in 1 sec Forced vital capacity Gene expression Hand grip strength Height Hip circumference Number of fays or week of vigorous physical activity 10+ minutes Pagets disease Pulse rate Sleeplessness or insomnia Transport type for commuting to job workplace: cycle Whole body fat-free mass Whole body water mass
rs4483821	Body fat percentage Forced expiratory volume in 1 sec Forced vital capacity Height Hip circumference Impedance Myopia Waist circumference Weight Whole body fat mass
rs2280470	Arm impedance Body fat percentage Forced expiratory volume in 1 sec Forced vital capacity Height Hip circumference Infant length Waist circumference Weight Whole body fat mass Whole body fat-free mass Whole body water mass
rs3784757	Body fat percentage Forced expiratory volume in 1 sec Forced vital capacity Height Weight Whole body fat-free mass

	Whole body water mass
rs2871865	Basal metabolic rate Birth weight Birth weight of first child Forced expiratory volume in 1 sec Forced vital capacity Hand grip strength Height Weight Whole body fat-free mass Whole body water mass
rs4548838	Forced vital capacity Height Hip circumference Impedance Waist circumference
rs4548838	Forced expiratory volume in 1 sec Forced vital capacity Height Hip circumference Impedance Waist circumference
rs8057808	Basal metabolic rate Fluid intelligence score Height Hip circumference Impedance Overall health rating Pulse rate Qualifications: college or university degree Qualifications: none Self-reported hypertension Time spent watching tv Time spent watching tv Vascular or heart problems diagnosed by doctor: high blood pressure Weight Whole body fat-free mass Whole body water mass
rs11866219	Age at menarche Body fat percentage BMI Forced expiratory volume in 1 sec Forced vital capacity Hand grip strength Height Hip circumference Illness, injury, bereavement, stress in last 2 years: illness, injury or assault to yourself Leg impedance Long-standing illness, disability or infirmity Number of self-reported non-cancer illnesses Pulse rate Usual walking pace Waist circumference Whole body fat mass
rs7213608	Body fat percentage BMI Forced expiratory volume in 1 sec Height High light scatter percentage of red cells Inmature fraction of reticulocytes Mean corpuscular volume Qualifications: A levels or as levels or equivalent Treatment with simvastatin

	Waist circumference
	Whole body fat-free mass
	Whole body water mass
rs3764419	Basal metabolic rate
	BMI
	Forced expiratory volume in 1 sec
	Gene expression
	Granulocyte percentage of myeloid white cells
	Height
	Hip circumference
	Mean corpuscular hemoglobin
	Mean corpuscular volume
	Neutrophil percentage of white cells
	Waist circumference
	Weight
	Whole body fat-free mass
	Whole body water mass
rs584828	Basal metabolic rate
	Forced vital capacity
	Granulocyte count
	Height
	Hip circumference
	Neutrophil count
	Self-reported thyroid radioablation therapy
	Sum basophil neutrophil counts
	Sum neutrophil eosinophil counts
	Weight
	White blood cell count
	Whole body fat-free mass
	Whole body water mass
rs11657325	Allergic disease
	Basal metabolic rate
	Hair or balding pattern
	Hand grip strength
	Height
	Impedance
	No blood clot, bronchitis, emphysema, asthma, rhinitis, eczema or allergy diagnosed by doctor
	Overall health rating
	Sleeplessness or insomnia
	Systolic blood pressure
	Vascular or heart problems diagnosed by doctor: none of the above
	Weight
	Whole body fat-free mass
	Whole body water mass
rs12453394	Basal metabolic rate
	Coronary artery disease
	Drive faster than motorway speed limit
	Forced vital capacity
	Frequency of tiredness or lethargy in last 2 weeks
	Gene expression of UBE2Z in blood
	Height
	Illness of mother: high blood pressure
	Illness of mother: none of the above
	Type II diabetes
	Whole body fat-free mass
	Whole body water mass
rs963292	Arm fat-free mass
	Forced expiratory volume in 1 sec
	Height
	Trunk fat-free mass

rs2079795 (rs7214743)	Gene expression
	Height
	Waist circumference
	Waist hip ratio
rs2727317	Height
	Hip circumference
	Waist hip ratio
rs4239437	Acute pharyngitis
	Basal metabolic rate
	Forced expiratory volume in 1 sec
	Hand grip strength
	Heel bone mineral density
	Height
	Hip circumference
	Mean platelet volume
	Platelet count
	Platelet distribution width
	Waist circumference
	Waist hip ratio
	Weight
	Whole body fat mass
	Whole body fat-free mass
	Whole body water mass
rs9967417	Basal metabolic rate
	Forced expiratory volume in 1 sec
	Gene expression
	Hand grip strength
	Height
	Hip circumference
	Weight
	Whole body fat-free mass
	Whole body water mass
rs12980348	Basal metabolic rate
	Forced expiratory volume in 1 sec
	Hand grip strength
	Heel bone mineral density
	Height
	Hematocrit
	Hemoglobin concentration
	Hip circumference
	Red blood cell count
	Weight
	Whole body fat-free mass
	Whole body water mass
rs891088	Basal metabolic rate
	Height
	Hip circumference
	Serum urate
	Weight
	Whole body fat-free mass
	Whole body water mass
	Basal metabolic rate
	Blood clot in the lung
	Coronary artery disease
	Forced expiratory volume in 1 sec
	Forced vital capacity
	Height
	High light scatter percentage of red cells
	High light scatter reticulocyte count
	Hip circumference
	Inmature fraction of reticulocytes

rs2738039 (rs1982075)	Low density lipoprotein Morning or evening person Pain type experienced in last month: knee pain Peak expiratory flow Platelet count Plateletcrit Red cell distribution width Reticulocyte count Reticulocyte fraction of red cells Self-reported osteoarthritis Self-reported pulmonary embolism + or - dvt Time spent watching tv Total cholesterol Weight Whole body fat-free mass Whole body water mass
rs6038566	Basal metabolic rate BMI Forced expiratory volume in 1 sec Height Hip circumference Impedance Waist circumference Whole body fat-free mass Whole body water mass
rs7274811	Basal metabolic rate Forced expiratory volume in 1 sec Forced vital capacity Heel bone mineral density Height Hip circumference Impedance Weight Whole body fat mass Whole body fat-free mass Whole body water mass
rs6142159	Basal metabolic rate Forced expiratory volume in 1 sec Hair or balding pattern Hand grip strength Heel bone mineral density Height High density lipoprotein Impedance log eGFR creatinine Past tobacco smoking Peak expiratory flow Weight Whole body fat-free mass Whole body water mass
	Acquired deformities of fingers and toes Basal metabolic rate Birth weight Forced expiratory volume in 1 sec Forced vital capacity Gene expression Gonarthrosis Hand grip strength Height Hip circumference Impedance Infant length Internal derangement of knee

rs143384	Joint mobility Beighton score
	Maximum heart rate during fitness test
	Pain type experienced in last month: knee pain
	Peak expiratory flow
	Qualifications: A levels or as levels or equivalent
	Relative age voice broke
	Total cholesterol
	Usual walking pace
	Waist circumference
	Waist hip ratio
	Weight
	Whole body fat mass
	Whole body fat-free mass
	Whole body water mass
rs4821083 (rs2413143)	Advanced age related macular degeneration
	Advanced age related macular degeneration choroidal neovascularization vs no AMD
	Arm fat-free mass
	Height
	Hip circumference
	Impedance
	Neovascularization
	Trunk fat-free mass
rs738288	Guilty feelings
	Height
	IGP40
	Worry too long after embarrassment

PC3 related genetic variants and associated traits in previous GWAS ($p < 5 \times 10-8$)

SNP (lead SNP)	Trait
rs7536458	Basal metabolic rate
	Forced expiratory volume in 1 sec
	Hair or balding pattern
	Height
	Hip circumference
	Infant length
	Leg impedance
	Waist circumference
	Waist hip ratio
	Whole body fat-free mass
	Whole body water mass
rs10923724	BMI
	Hair or balding pattern
	Height
	Impedance
	Relative age of first facial hair
	Waist circumference
	Waist hip ratio
rs9425301	Height
	Hip circumference
	Inmature fraction of reticulocytes
	Mean platelet volume
	Platelet distribution width
	Waist circumference
	Waist hip ratio
	Whole body water mass
rs2274432	Basal metabolic rate
	Forced expiratory volume in 1 sec
	Forced vital capacity
	Hand grip strength
	Height
	Hip circumference
	Leg impedance
	Myopia
	Waist circumference
	Weight
	Whole body fat mass
	Whole body fat-free mass
	Whole body water mass
rs2791550 (rs2605108)	Body fat percentage
	Falls in the last year
	Hip circumference
	Impedance
	log Fasting insulin
	Type II diabetes
	Umbilical hernia
	Waist circumference
	Waist hip ratio
	Whole body fat mass
rs6726261	Age at menarche
	Body fat percentage
	BMI
	Childhood BMI
	Childhood obesity
	Forced expiratory volume in 1 sec
	Forced vital capacity
	Hand grip strength
	Height
	Hip circumference
	Impedance
	Obesity class 1
	Obesity with early age of onset age 2
	Standarized difference in height between age 8 years and adult
	Waist circumference
	Weight

	Whole body fat mass
rs2289195	Basal metabolic rate Forced expiratory volume in 1 sec Forced vital capacity Hand grip strength Height Leg impedance Waist circumference Whole body fat-free mass Whole body water mass
rs6715793	Forced expiratory volume in 1 sec Height Impedance Waist circumference
rs3791675	Basal metabolic rate Forced expiratory volume in 1 sec Forced vital capacity Height Hip circumference Impedance Inguinal hernia Mononeuropathies of upper limb Peak expiratory flow Waist circumference Weight Whole body fat mass Whole body fat-free mass Whole body water mass
rs1128249	Body fat percentage BMI Diabetes diagnosed by doctor HDL cholesterol Hemoglobin concentration High density lipoprotein High light scatter percentage of red cells High light scatter reticulocyte percentage of red cells Hip circumference Illness of mother: diabetes Illness of siblings: diabetes Impedance LDL cholesterol log Fasting insuline Low density lipoprotein Reticulocyte count Self-reported diabetes Total cholesterol Treatment with metformin Triglycerides Type II diabetes Waist circumference Waist hip ratio Weight Whole body fat mass
rs2342296	Basal metabolic rate Forced expiratory volume in 1 sec Height Waist circumference Whole body fat-free mass Whole body water mass
rs2920499	Height Lymphocyte count Mean corpuscular hemoglobin concentration Mean corpuscular volume Platelet count Plateletcrit Red cell distribution width Total cholesterol Waist hip ratio

rs2710323	Adiponectin levels Age at menarche Bipolar disorder BMI Cross disorder Glaucome primary open angle Hematocrit Hemoglobin concentration High light scatter reticulocyte percentage of red cells High light scatter reticulocyte count Hip circumference Hip osteoarthritis Impedance log Adiponectin Nervous feelings Pulse rate Red blood cell count Red cell distribution width Reticulocyte count Reticulocyte fraction of red count Schizophrenia Schizophrenia schizoaffective disorder or bipolar disorder Waist circumference Waist hip ratio Whole body water mass Worrier or anxious feeling
rs9864077	Advanced age related macular degeneration Age-related macular degeneration Arm impedance Body fat percentage BMI Hip circumference Type II diabetes Waist circumference Waist hip ratio Whole body fat mass
rs9838625	Allergic disease Basal metabolic rate Forced expiratory volume in 1 sec Forced vital capacity Hair or balding pattern Hayfever, allergic rhinitis or eczema Height Hip circumference Lymphocyte count Mean corpuscular hemoglobin Mean corpuscular volume Myopia Pulse rate Red blood cell count Waist circumference Weight Whole body fat mass Whole body fat-free mass Whole body water mass
rs1545854	Birth weight Heel bone mineral density Height Leg impedance
	Age at first live birth Basal metabolic rate Birth weight Body fat percentage Diastolic blood pressure Fluid intelligence score Forced expiratory volume in 1 sec Forced vital capacity Hand grip strength

rs4057984	Height Hip circumference Number of treatments or medications taken Peak expiratory flow Peritonsillar abscess Qualifications: A levels or as levels or equivalent Qualifications: college or university degree Self-reported hypertension Systolic blood pressure Time spent watching tv Vascular or heart problems diagnosed by doctor: high blood pressure Vascular or heart problems diagnosed by doctor: none of the above Waist circumference Weight Whole body fat-free mass Whole body water mass
rs1115919	Basal metabolic rate Forced expiratory volume in 1 sec Height Hip circumference Leg impedance Overall health rating Standarized difference in height between age 8 years and adult Waist circumference Weight Whole body fat mass Whole body fat-free mass Whole body water mass
rs7689420	Basal metabolic rate Forced expiratory volume in 1 sec Forced vital capacity Hand grip strength Height Hip circumference Peak expiratory flow Waist circumference Weight Whole body fat mass Whole body fat-free mass Whole body water mass
rs272885	Asthma Atopic dermatitis Basal metabolic rate Basophil count Eosinophil count Eosinophil percentage of granulocytes Eosinophil percentage of white cells Granulocyte count Hand grip strength Height High light scatter percentage of red cells High light scatter reticulocyte count Inmature fraction of reticulocytes Mean platelet volume Monocyte count Myeloid white cell count Neutrophil count Neutrophil percentage of granulocytes No blood, clot, bronchitis, emphysema, asthma, rhinitis, eczema or allergy diagnosed by doctor Platelet count Self-reported asthma Self-reported hypertension Sum basophil neutrophil counts Sum eosinophil basophil counts Sum neutrophil eosinophil counts Time spent using computer Vascular or heart problems diagnosed by doctor: high blood pressure Waist circumference

	White blood cell count
	Whole body fat-free mass
	Whole body water mass
rs6556301	Activated partial thromboplastin time
	Height
	Impedance
	Waist circumference
	Waist hip ratio
rs6556301	Activated partial thromboplastin time
	Height
	Impedance
	Waist circumference
	Waist hip ratio
rs1294421	Hip circumference
	Inguinal hernia
	Waist circumference
	Waist hip ratio
rs1776897	Basal metabolic rate
	Birth weight
	Birth weight of first child
	BMI
	Forced expiratory volume in 1 sec
	Forced vital capacity
	Height
	Hip circumference
	Peak expiratory flow
	Platelet count
	Plateletcrit
	Waist circumference
	Waist hip ratio
	Weight
	Whole body fat mass
	Whole body fat-free mass
	Whole body water mass
rs7759938	Age at menarche
	Basal metabolic rate
	Forced expiratory volume in 1 sec
	Forced vital capacity
	Hand grip strength
	Height
	Hip circumference
	Impedance
	log Fasting insulin
	Medication for cholesterol, blood pressure or diabetes: blood pressure medication
	Medication for pain relief, constipation, heartburn: none of the above
	Menarche
	Menarche age at onset
	Number of operations
	Number of treatments or medications taken
	Pubertal anthropometrics
	Pubertal height growth
	Relative age voice broke
	Sleeplessness or insomnia
	Standarized difference in height between age 14 years and adult
	Tanner stage
	Waist circumference
	Weight
	Whole body fat mass
	Whole body fat-free mass
	Whole body water mass
	Fracture of forearm
	Fractured bone site: wrist
	Fractured or broken bones in last 5 years
	Heel bone mineral density
	Hematocrit
	Hemoglobin concentration
	High density lipoprotein
	High light scatter reticulocyte count

rs1936809	Hip circumference
	Lymphocyte count
	Other orthopaedic follow-up care
	Red blood cell count
	Reticulocyte count
	Triglycerides
	Varicose veins of lower extremities
	Waist circumference
	Waist hip ratio
rs7798002	Basal metabolic rate
	Height
	Waist circumference
	Waist hip ratio
	Whole body fat-free mass
	Whole body water mass
rs7801581	Height
	Waist circumference
	Waist hip ratio
rs1516883	Age at menarche
	BMI
	Forced expiratory volume in 1 sec
	Forced vital capacity
	Height
	Impedance
	Relative age of first facial hair
	Relative age voice broke
	Standarized difference in height between age 14 years and adult
	Waist circumference
rs7021911	Basal metabolic rate
	Femoral neck bone mineral density
	Forced expiratory volume in 1 sec
	Heel bone mineral density
	Height
	Whole body fat-free mass
	Whole body water mass
rs1628023	Basal metabolic rate
	Diabetes diagnosed by doctor
	Height
	Monocyte percentage of white cells
	Self-reported diabetes
	Waist circumference
	Weight
	Whole body fat-free mass
	Whole body water mass
rs7917772	Allergic disease
	Basophil count
	Diastolic blood pressure
	Granulocyte count
	Hayfever, allergic rhinitis or eczema
	Height
	High light scatter percentage of red cells
	High light scatter reticulocyte count
	Leg impedance
	Mean corpuscular hemoglobin
	Mean corpuscular hemoglobin
	Myeloid white cell count
	Neutrophil count
	No blood, clot, bronchitis, emphysema, asthma, rhinitis, eczema or allergy diagnosed by doctor
	Past tobacco smoking
	Reticulocyte fraction of red cells
	Sum basophil neutrophil counts
	Sum neutrophil eosinophil counts
	Sum eosinophil basophil counts
	Waist circumference
	Waist hip ratio
	White blood cell count
	Age at menarche
	Alcohol intake frequency

rs1317149 (rs12787112)	Birth weight
	Body fat percentage
	BMI
	Current tobacco smoking
	Fluid intelligence score
	Forced expiratory volume in 1 sec
	Forced vital capacity
	Frequency of depressed mood in last 2 weeks
	Gene expression
	Granulocyte count
	Granulocyte percentage of myeloid white cells
	Hand grip strength
	HDL cholesterol
	Height
	High density lipoprotein
	Hip circumference
	Immature fraction of reticulocytes
	log Proinsulin
	Loneliness, isolation
	Miserableness
	Monocyte percentage of white cells
	Mood swings
	Neuroticism
	Neutrophil count
	Platelet count
	Plateletcrit
	Sleeplessness or insomnia
	Smoking status: current
	Suffer from nerves
	Sum basophil neutrophil counts
	Sum neutrophil eosinophil counts
	Total cholesterol
	Usual walking pace
	Waist circumference
	White blood cell count
	Whole body fat mass
rs7949030	Forced expiratory volume in 1 sec
	Forced vital capacity
	Impedance
	Pulse rate
	Waist hip ratio
rs8756	Alcohol intake frequency
	Basal metabolic rate
	Birth weight
	Birth weight of first child
	Birthlength
	BMI
	Diabetes diagnosed by doctor
	Estimated total intracranial volume excluding patients with neuropsychiatric disorders
	Forced expiratory volume in 1 sec
	Forced vital capacity
	Hand grip strength
	Height
	Hip circumference
	Impedance
	Infant head circumference
	Intracranial volume
	Maternal effects on offspring birthweight
	Overall health rating
	Peak expiratory flow
	Pulse rate
	Self-reported diabetes
	Self-reported high cholesterol
	Systolic blood pressure
	Treatment with metformin
	Waist circumference
	Weight
	Whole body fat mass

	Whole body fat-free mass
	Whole body water mass
rs12303671	Adiponectin levels
	Body fat percentage
	BMI
	Hand grip strength
	HDL cholesterol
	Heel bone mineral density
	High density lipoprotein
	High light scatter reticulocyte count
	Hip circumference
	Impedance
	log Adiponectin
	Lymphocyte count
	Reticulocyte count
	Reticulocyte fraction of red cells
	Triglycerides
	Waist circumference
	Waist hip ratio
	White blood cell count
	Whole body fat mass
rs7492628	Basal metabolic rate
	BMI
	Hip circumference
	Impedance
	Pulse rate
	Waist hip ratio
	Weight
	Whole body fat mass
	Whole body fat-free mass
	Whole body water mass
rs16976826 (rs12443429)	Waist circumference
	Waist hip ratio
rs12440667	Exfoliation glaucoma
	Forced expiratory volume in 1 sec
	Forced vital capacity
	Hand grip strength
	Height
	Impedance
	Peak expiratory flow
	Waist circumference
rs6602997	Body fat percentage
	Forced expiratory volume in 1 sec
	Forced vital capacity
	Height
	Hip circumference
	Impedance
	Waist circumference
	Weight
	Whole body fat mass
rs2280470	Arm impedance
	Basal metabolic rate
	Forced expiratory volume in 1 sec
	Forced vital capacity
	Height
	Hip circumference
	Infant length
	Waist circumference
	Weight
	Whole body fat mass
	Whole body fat-free mass
	Whole body water mass
rs1879143	Forced expiratory volume in 1 sec
	Hair or balding pattern
	Height
	Peak expiratory flow
	Trunk fat-free mass
	Waist circumference

rs9892365	Basal metabolic rate Forced expiratory volume in 1 sec Gene expression Height Systolic blood pressure Waist circumference Weight Whole body fat-free mass Whole body water mass
rs4239436	Acute pharyngitis Basal metabolic rate Forced expiratory volume in 1 sec Hand grip strength Heel bone mineral density Height Hip circumference Mean platelet volume Platelet count Platelet distribution width Waist circumference Waist hip ratio Weight Whole body fat mass Whole body fat-free mass Whole body water mass
rs6140050	BMI Forced expiratory volume in 1 sec Heel bone mineral density Height High light scatter reticulocyte count Impedance Lung function FVC Platelet count Plateletcrit Snoring Waist circumference Waist hip ratio Whole body fat-free mass Whole body water mass
rs2179129	Arm impedance Diastolic blood pressure Hair or balding pattern Systolic blood pressure Vascular or heart problems diagnosed by doctor: high blood pressure Waist circumference Waist hip ratio

STROBE-MR checklist of recommended items to address in reports of Mendelian randomization studies

Item No.	Section	Checklist item	Page No.
1	**TITLE and ABSTRACT**	Indicate Mendelian randomization (MR) as the study's design in the title and/or the abstract if that is a main purpose of the study	Page 1
	INTRODUCTION		
2	**Background**	Explain the scientific background and rationale for the reported study. What is the exposure? Is a potential causal relationship between exposure and outcome plausible? Justify why MR is a helpful method to address the study question	Page 2
3	**Objectives**	State specific objectives clearly, including pre-specified causal hypotheses (if any). State that MR is a method that, under specific assumptions, intends to estimate causal effects	
	METHODS		
4	**Study design and data sources**	Present key elements of the study design early in the article. Consider including a table listing sources of data for all phases of the study. For each data source contributing to the analysis, describe the following:	Page 3-5, Supplementary Table S2
	a)	Setting: Describe the study design and the underlying population, if possible. Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection, when available.	
	b)	Participants: Give the eligibility criteria, and the sources and methods of selection of participants. Report the sample size, and whether any power or sample size calculations were carried out prior to the main analysis	
	c)	Describe measurement, quality control and selection of genetic variants	
	d)	For each exposure, outcome, and other relevant variables, describe methods of assessment and diagnostic criteria for diseases	
	e)	Provide details of ethics committee approval and participant informed consent, if relevant	
5	**Assumptions**	Explicitly state the three core IV assumptions for the main analysis (relevance, independence and exclusion restriction) as well assumptions for any additional or sensitivity analysis	Pages 4-5

6	**Statistical methods: main analysis**	Describe statistical methods and statistics used	
	a)	Describe how quantitative variables were handled in the analyses (i.e., scale, units, model)	
	b)	Describe how genetic variants were handled in the analyses and, if applicable, how their weights were selected	
	c)	Describe the MR estimator (e.g. two-stage least squares, Wald ratio) and related statistics. Detail the included covariates and, in case of two-sample MR, whether the same covariate set was used for adjustment in the two samples	Page 3-4
	d)	Explain how missing data were addressed	
	e)	If applicable, indicate how multiple testing was addressed	
7	**Assessment of assumptions**	Describe any methods or prior knowledge used to assess the assumptions or justify their validity	Pages 4-5
8	**Sensitivity analyses and additional analyses**	Describe any sensitivity analyses or additional analyses performed (e.g., comparison of effect estimates from different approaches, independent replication, bias analytic techniques, validation of instruments, simulations)	Pages 4-5
9	**Software and pre-registration**		
	a)	Name statistical software and package(s), including version and settings used	Page 5
	b)	State whether the study protocol and details were pre-registered (as well as when and where)	No applicable
	RESULTS		
10	**Descriptive data**		
	a)	Report the numbers of individuals at each stage of included studies and reasons for exclusion. Consider use of a flow diagram	Not applicable, as we used summary statistics from previously published genome-wide association studies. We cite
	b)	Report summary statistics for phenotypic exposure(s), outcome(s), and other relevant variables (e.g. means, SDs, proportions)	
	c)	If the data sources include meta-analyses of previous studies, provide the assessments of heterogeneity across these studies	

	d)	For two-sample MR: i. Provide justification of the similarity of the genetic variant-exposure associations between the exposure and outcome samples ii. Provide information on the number of individuals who overlap between the exposure and outcome studies	these accordingly. Additionally, there is no overlap between the exposure and outcome samples.
11	**Main results**		
	a)	Report the associations between genetic variant and exposure, and between genetic variant and outcome, preferably on an interpretable scale	
	b)	Report MR estimates of the relationship between exposure and outcome, and the measures of uncertainty from the MR analysis, on an interpretable scale, such as odds ratio or relative risk per SD difference	Pages 5-7, Figure 2, Supplementary Figure S1, Supplementary File S1
	c)	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
	d)	Consider plots to visualize results (e.g. forest plot, scatterplot of associations between genetic variants and outcome versus between genetic variants and exposure)	
12	**Assessment of assumptions**		
	a)	Report the assessment of the validity of the assumptions	Pages 5-7, Supplementary Figures S1-4, Supplementary Tables S3-4
	b)	Report any additional statistics (e.g., assessments of heterogeneity across genetic variants, such as I^2, Q statistic or E-value)	
13	**Sensitivity analyses and additional analyses**		
	a)	Report any sensitivity analyses to assess the robustness of the main results to violations of the assumptions	Pages 5-7, Figure 2, Supplementary Figures S1-4, Supplementary Tables S3-4
	b)	Report results from other sensitivity analyses or additional analyses	
	c)	Report any assessment of direction of causal relationship (e.g., bidirectional MR)	

	d)	When relevant, report and compare with estimates from non-MR analyses	
	e)	Consider additional plots to visualize results (e.g., leave-one-out analyses)	
	DISCUSSION		
14	**Key results**	Summarize key results with reference to study objectives	Page 7-9
15	**Limitations**	Discuss limitations of the study, taking into account the validity of the IV assumptions, other sources of potential bias, and imprecision. Discuss both direction and magnitude of any potential bias and any efforts to address them	Page 7-9
16	**Interpretation**		
	a)	Meaning: Give a cautious overall interpretation of results in the context of their limitations and in comparison with other studies	
	b)	Mechanism: Discuss underlying biological mechanisms that could drive a potential causal relationship between the investigated exposure and the outcome, and whether the gene-environment equivalence assumption is reasonable. Use causal language carefully, clarifying that IV estimates may provide causal effects only under certain assumptions	Pages 7-9
	c)	Clinical relevance: Discuss whether the results have clinical or public policy relevance, and to what extent they inform effect sizes of possible interventions	
17	**Generalizability**	Discuss the generalizability of the study results (a) to other populations, (b) across other exposure periods/timings, and (c) across other levels of exposure	Page 9
	OTHER INFORMATION		
18	**Funding**	Describe sources of funding and the role of funders in the present study and, if applicable, sources of funding for the databases and original study or studies on which the present study is based	Page 10
19	**Data and data sharing**	Provide the data used to perform all analyses or report where and how the data can be accessed, and reference these sources in the article. Provide the statistical code needed to reproduce the results in the article, or report whether the code is publicly accessible and if so, where	Page 10
20	**Conflicts of Interest**	All authors should declare all potential conflicts of interest	Page 10

Adapted from:

1. Skrivankova VW, Richmond RC, Woolf BAR, Yarmolinsky J, Davies NM, Swanson SA, et al. Strengthening the Reporting of Observational Studies in Epidemiology using Mendelian Randomization (STROBE-MR) Statement. JAMA. 2021;under review.

2. Skrivankova VW, Richmond RC, Woolf BAR, Davies NM, Swanson SA, VanderWeele TJ, et al. Strengthening the Reporting of Observational Studies in Epidemiology using Mendelian Randomisation (STROBE-MR): Explanation and Elaboration. BMJ. 2021;375:n2233.

ANNEX III

SUPPLEMENTARY MATERIAL STUDY III

Association of body shape phenotypes and body fat distribution indexes with inflammatory biomarkers in the European Prospective Investigation into Cancer and Nutrition (EPIC) and UK Biobank

Esther M. González-Gil*, **Laia Peruchet-Noray***, Anja M. Sedlmeier, …, Sabina Rinaldi, Heinz Freisling, Laure Dossus

**These authors contributed equally*

***BMC Medicine* 22, 334 (2024)**

Fig. S1. Flowchart with the included number of subjects in EPIC and UK Biobank. IL1ra: Interleukin-1 receptor antagonist; TNF-α: Tumour necrosis factor alpha; IFN-γ: Interferon-gamma.

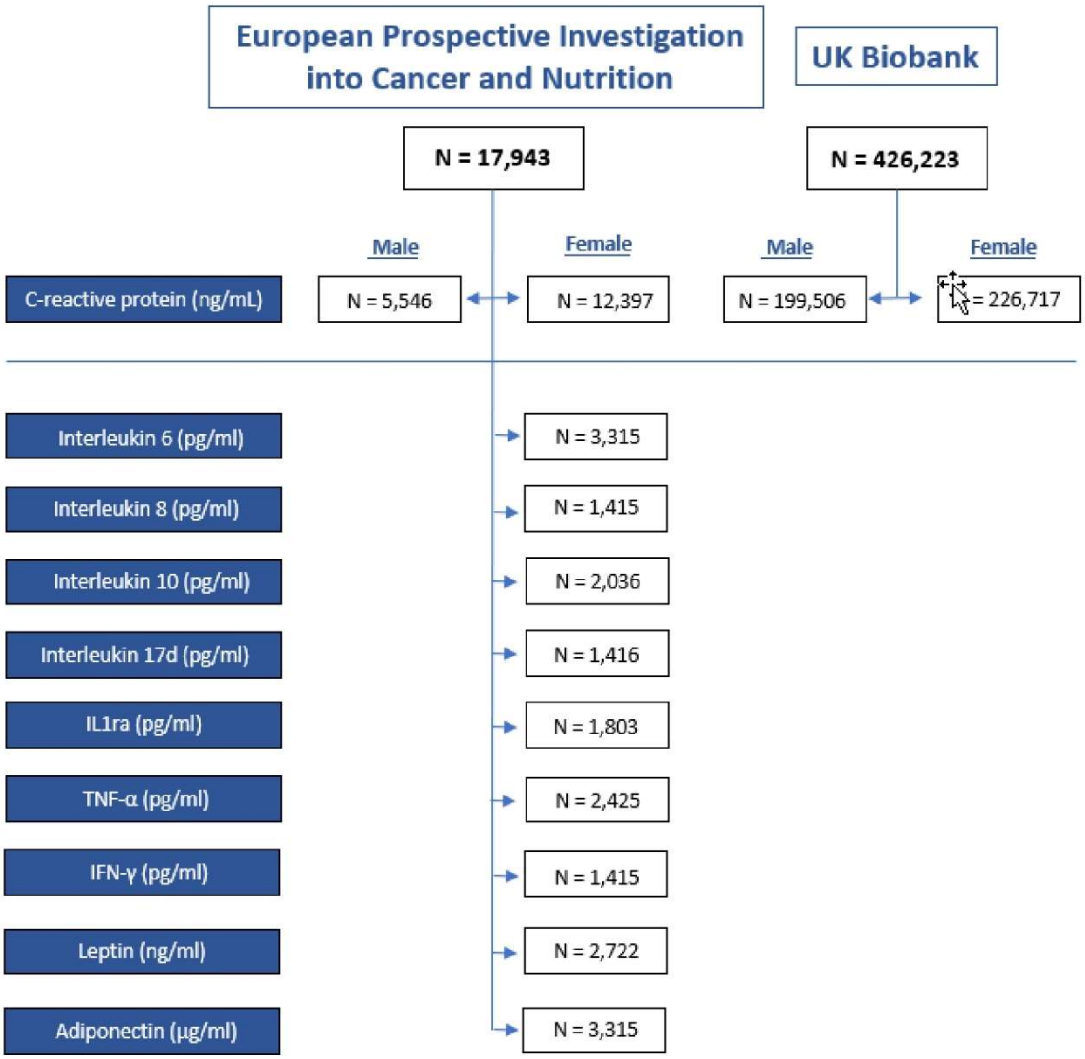
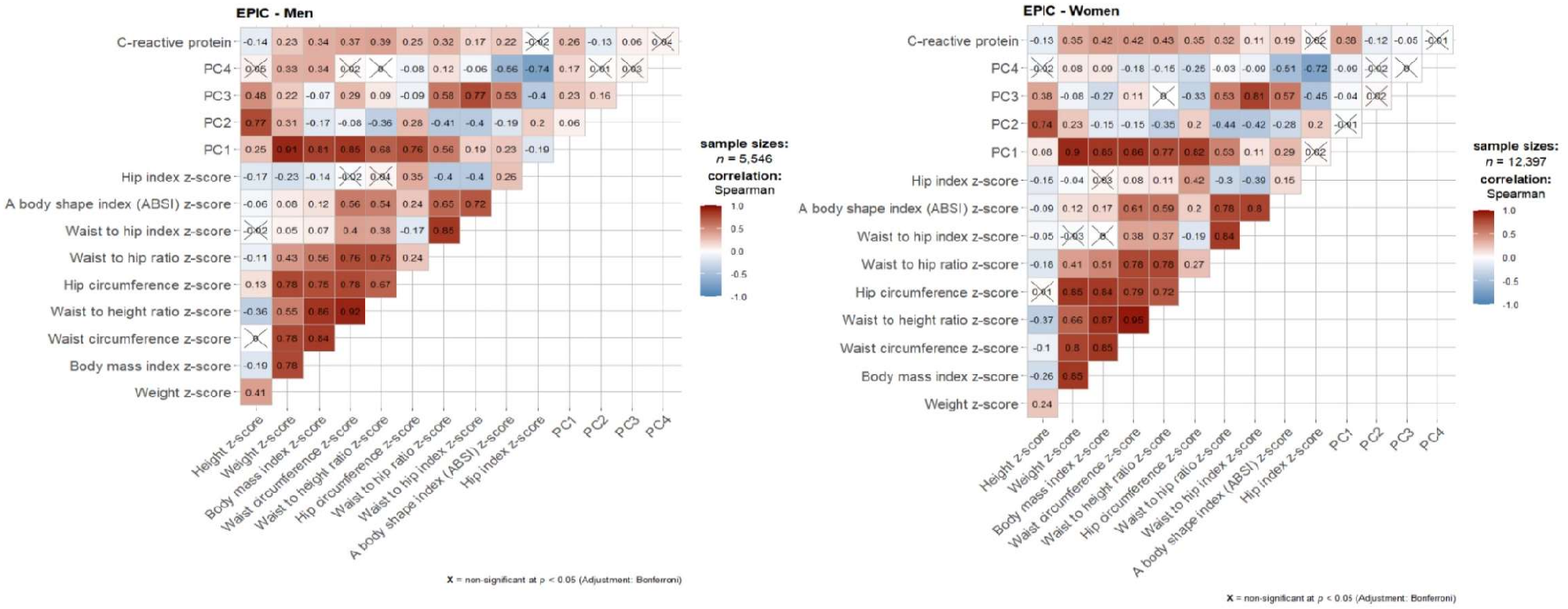
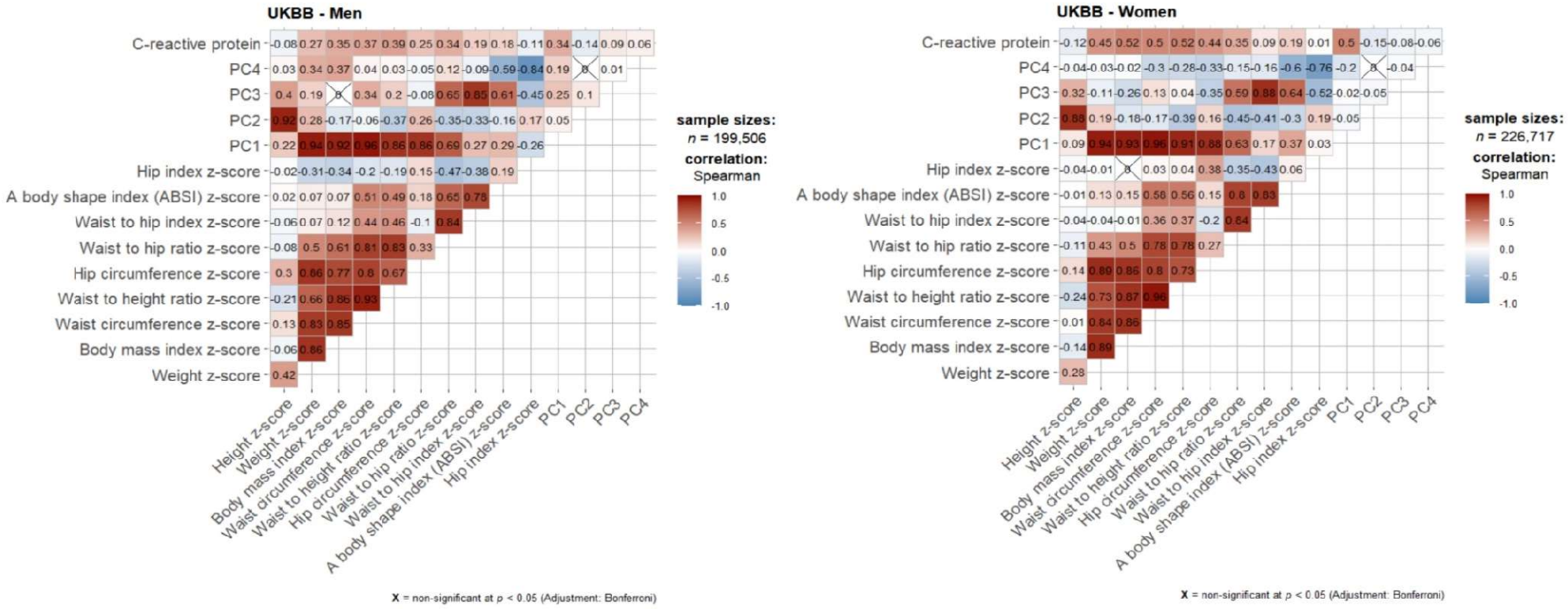


Fig. S2a. Correlations between adiposity and concentration of C-reactive protein in the EPIC study by sex.



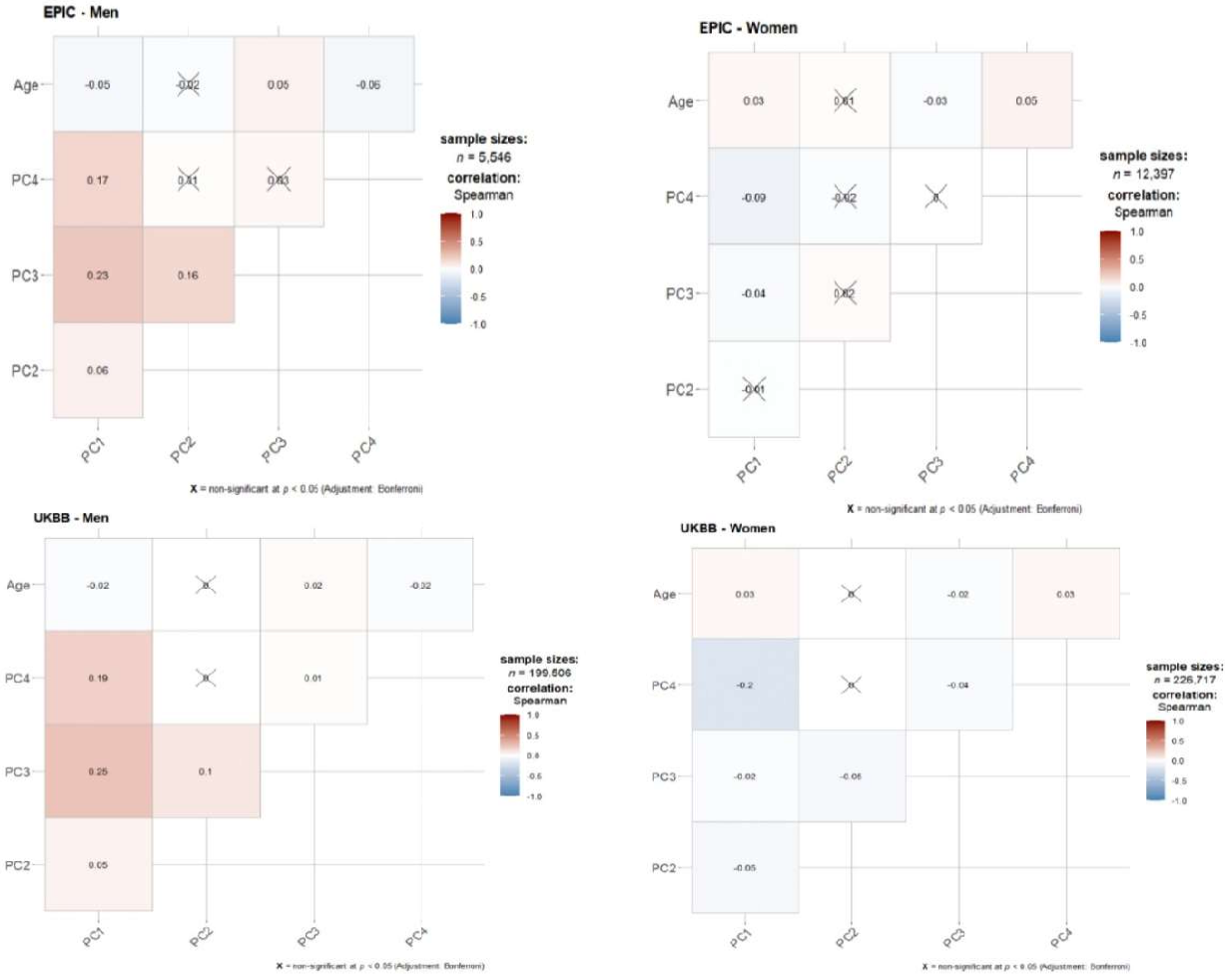
PC: principal component. PC1: overall adiposity; PC2: tall with low waist to hip ratio; PC3: tall with large waist to hip ratio, PC4: high BMI and weight with low waist circumference and hip circumference.

Fig. S2b. Correlations between adiposity and concentration of C-reactive protein in UK Biobank study by sex.



PC: principal component. PC1: overall adiposity; PC2: tall with low waist to hip ratio; PC3: tall with large waist to hip ratio, PC4: high BMI and weight with low waist circumference and hip circumference.

Fig. S3. Correlations between body shape phenotypes and age in the EPIC and UK Biobank study by sex.



PC: principal component. PC1: overall adiposity; PC2: tall with low waist to hip ratio; PC3: tall with large waist to hip ratio, PC4: high BMI and weight with low waist circumference and hip circumference.

Table S1. Loadings of the principal components derived in EPIC (n = 17,943) and UK Biobank (n = 426,223).

	EPIC				UK Biobank			
	PC1	**PC2**	**PC3**	**PC4**	**PC1**	**PC2**	**PC3**	**PC4**
Height	0.092	0.801	0.497	0.029	0.076	0.854	0.418	0.017
Weight	0.487	0.224	-0.042	0.497	0.478	0.220	-0.075	0.510
BMI	0.476	-0.149	-0.299	0.479	0.473	-0.147	-0.284	0.471
HC	0.446	0.219	-0.389	-0.595	0.449	0.177	-0.401	-0.604
WC	0.493	-0.146	0.175	-0.411	0.488	-0.109	0.166	-0.391
WHR	0.295	-0.466	0.693	-0.015	0.320	-0.396	0.742	-0.017

BMI: body mass index; WC: waist circumference; HC: hip circumference; WHR: waist to hip ratio; PC: principal component. PC1: overall adiposity; PC2: tall with low waist to hip ratio; PC3: tall with large waist to hip ratio, PC4: high BMI and weight with low waist circumference and hip circumference.

Table S2. Mean and standard deviations of age and the six anthropometric traits building the body shape phenotypes for individuals included in the top and bottom 5% of each PC in the EPIC study.

EPIC	Men								Women							
	PC1		PC2		PC3		PC4		PC1		PC2		PC3		PC4	
	5%	95%	5%	95%	5%	95%	5%	95%	5%	95%	5%	95%	5%	95%	5%	95%
Age	55.0 (9.0)	53.1 (8.4)	52.9 (7.4)	53.2 (8.3)	52.4 (9.4)	53.0 (8.4)	53.9 (9.6)	53.2 (8.4)	54.1 (9.2)	52.5 (8.9)	52.4 (9.1)	52.4 (8.9)	53.7 (8.4)	52.5 (8.8)	52.8 (9.7)	52.4 (8.9)
Height	170.0 (6.8)	173.6 (7.3)	162.2 (5.3)	173.0 (6.7)	166.2 (6.6)	173.4 (7.2)	172.8 (7.3)	173.7 (7.3)	158.5 (6.2)	161.0 (6.7)	151.6 (5.1)	160.5 (6.2)	155.6 (6.1)	160.8 (6.5)	161.1 (7.1)	161.1 (6.7)
Weight	62.0 (4.9)	79.4 (9.9)	74.4 (11.1)	80.4 (11.4)	79.0 (14.2)	80.5 (11.5)	74.8 (10.6)	80.2 (11.0)	50.5 (4.3)	65.1 (9.4)	62.4 (10.5)	66.3 (11.3)	75.2 (17.1)	66.5 (11.5)	69.0 (12.2)	66.3 (11.2)
BMI	21.5 (1.9)	26.4 (3.1)	28.2 (3.7)	26.9 (3.6)	28.6 (4.9)	26.8 (3.6)	25.1 (3.7)	26.6 (3.4)	20.1 (1.8)	25.2 (3.7)	27.2 (4.5)	25.8 (4.5)	31.0 (6.4)	25.8 (4.5)	26.7 (5.0)	25.6 (4.4)
WC	78.5 (6.2)	93.9 (8.8)	98.0 (11.9)	95.2 (10.0)	91.9 (14.3)	94.7 (9.9)	97.5 (11.6)	94.9 (9.8)	66.6 (4.6)	79.8 (9.6)	86.6 (12.9)	81.3 (11.2)	84.5 (15.1)	80.7 (11.1)	91.2 (13.3)	81.2 (11.1)
HC	91.2 (4.6)	100.3 (6.2)	97.1 (7.1)	100.9 (6.9)	104.7 (10.2)	101.1 (6.9)	104.1 (7.6)	101.1 (6.7)	89.5 (4.6)	100.5 (7.8)	98.0 (9.0)	101.4 (9.1)	113.1 (12.6)	101.8 (9.1)	109.5 (10.1)	101.7 (9.0)
WHR	0.9 (0.1)	0.9 (0.1)	1.0 (0.1)	0.9 (0.1)	0.9 (0.1)	0.9 (0.1)	0.9 (0.1)	0.9 (0.1)	0.7 (0.0)	0.8 (0.1)	0.9 (0.1)	0.8 (0.1)	0.7 (0.1)	0.8 (0.1)	0.8 (0.1)	0.8 (0.1)

BMI: body mass index; WC: waist circumference; HC: hip circumference; WHR: waist to hip ratio; PC: principal component. PC1: overall adiposity; PC2: tall with low waist to hip ratio; PC3: tall with large waist to hip ratio, PC4: high BMI and weight with low waist circumference and hip circumference.

Table S3. Mean and standard deviations of age and the six anthropometric traits building the body shape phenotypes for individuals included in the top and bottom 5% of each PC in UK Biobank study.

UK Biobank																
	Men								Women							
	PC1		PC2		PC3		PC4		PC1		PC2		PC3		PC4	
	5%	95%	5%	95%	5%	95%	5%	95%	5%	95%	5%	95%	5%	95%	5%	95%
Age	56.5 (8.3)	56.5 (8.2)	56.1 (8.3)	56.4 (8.2)	56.4 (8.5)	56.4 (8.2)	56.9 (8.5)	56.5 (8.2)	55.9 (8.0)	56.2 (8.0)	55.6 (8.1)	56.1 (8.0)	56.5 (7.9)	56.1 (8.0)	56.8 (8.0)	56.1 (8.0)
Height	171.9 (6.9)	175.5 (6.8)	162.8 (3.9)	174.9 (6.2)	169.9 (6.5)	175.4 (6.7)	175.2 (7.2)	175.6 (6.8)	159.9 (5.9)	162.4 (6.3)	151.1 (4.0)	161.8 (5.8)	158.4 (6.1)	162.3 (6.2)	162.0 (6.6)	162.5 (6.3)
Weight	63.1 (5.3)	84.1 (11.8)	77.6 (13.4)	85.5 (14.1)	87.4 (22.2)	85.6 (14.2)	80.0 (14.0)	85.1 (13.6)	51.2 (3.9)	69.5 (11.3)	66.0 (12.7)	71.1 (13.9)	88.3 (21.0)	71.4 (14.2)	78.3 (15.4)	71.1 (13.6)
BMI	21.4 (1.6)	27.3 (3.4)	29.2 (4.6)	27.9 (4.2)	30.2 (6.9)	27.8 (4.2)	26.1 (4.5)	27.6 (4.0)	20.0 (1.5)	26.4 (4.2)	28.9 (5.3)	27.1 (5.2)	35.1 (7.5)	27.1 (5.2)	29.9 (5.9)	26.9 (5.0)
WC	77.3 (4.0)	95.4 (9.5)	98.7 (11.9)	96.9 (11.3)	94.5 (17.7)	96.4 (11.1)	99.3 (11.9)	96.6 (11.0)	65.5 (3.0)	83.0 (10.6)	89.5 (12.6)	84.8 (12.5)	93.1 (17.4)	84.2 (12.4)	99.2 (12.8)	84.7 (12.4)
HC	92.0 (3.8)	102.5 (6.3)	99.4 (7.5)	103.2 (7.5)	108.9 (13.5)	103.5 (7.6)	106.5 (9.2)	103.4 (7.4)	88.7 (3.9)	102.0 (8.5)	100.0 (9.9)	103.1 (10.3)	120.9 (14.5)	103.6 (10.4)	114.8 (12.2)	103.5 (10.2)
WHR	0.8 (0.1)	0.9 (0.1)	1.0 (0.1)	0.9 (0.1)	0.9 (0.1)	0.9 (0.1)	0.9 (0.1)	0.9 (0.1)	0.7 (0.0)	0.8 (0.1)	0.9 (0.1)	0.8 (0.1)	0.8 (0.1)	0.8 (0.1)	0.9 (0.1)	0.8 (0.1)

BMI: body mass index; WC: waist circumference; HC: hip circumference; WHR: waist to hip ratio; PC: principal component. PC1: overall adiposity; PC2: tall with low waist to hip ratio; PC3: tall with large waist to hip ratio, PC4: high BMI and weight with low waist circumference and hip circumference.

Table S4. Sample size and associations between individuals with obesity and by obesity class and C-reactive protein (CRP) levels in EPIC.

CRP – EPIC								
	Men				Women			
	N (%)	Beta	95% CI[1]	*P*	N (%)	Beta	95% CI[1]	*P*
Obesity (BMI ≥30 kg/m²)	947 (17.1%)	0.502	0.436, 0.567	<0.001	1943 (15.7%)	0.779	0.732, 0.827	<0.001
Obesity class I (BMI 30 - <35 kg/m²)	829 (14.9%)	0.455	0.386, 0.524	<0.001	1468 (11.9%)	0.683	0.630, 0.736	<0.001
Obesity class II (BMI 35 - <40 kg/m²)	103 (1.9%)	0.815	0.632, 0.998	<0.001	377 (3.0%)	0.966	0.865, 1.066	<0.001
Obesity class III (BMI ≥40 kg/m²)	15 (0.3%)	0.823	0.347, 1.298	<0.001	98 (0.8%)	1.427	1.233, 1.620	<0.001
[1] CI = Confidence Interval								

All analyses were adjusted for age at recruitment, smoking status, education, and physical activity. BMI: body mass index.

Table S5. Sample size and associations between individuals with obesity and by obesity class and C-reactive protein (CRP) levels in UK Biobank.

CRP – UK Biobank								
	Men				Women			
	N (%)	Beta	95% CI[1]	*P*	N (%)	Beta	95% CI[1]	*P*
Obesity (BMI ≥30 kg/m²)	50629 (25.4%)	0.547	0.536, 0.557	<0.001	53330 (23.5%)	0.951	0.940, 0.961	<0.001
Obesity class I (BMI 30 - <35 kg/m²)	39228 (19.7%)	0.460	0.449, 0.472	<0.001	35508 (15.7%)	0.785	0.773, 0.797	<0.001
Obesity class II (BMI 35 - <40 kg/m²)	8739 (4.4%)	0.772	0.750, 0.795	<0.001	12363 (5.4%)	1.167	1.147, 1.187	<0.001
Obesity class III (BMI ≥40 kg/m²)	2662 (1.3%)	1.102	1.063, 1.143	<0.001	5459 (2.4%)	1.573	1.543, 1.603	<0.001
[1] CI = Confidence Interval								

All analyses were adjusted for age at recruitment, smoking status, education, and physical activity. BMI: body mass index.

Table S6. Associations between anthropometric indexes and C-reactive protein (CRP) in the EPIC study.

CRP – EPIC								
	Men				Women			
	N= 5,546				N= 12,397			
	Beta	**95% CI[1]**	***P***	***P*[2]**	**Beta**	**95% CI[1]**	***P***	***P*[2]**
Height z-score	−0.12	−0.15, −0.09	<0.001	<0.001	-0.10	-0.13, -0.08	<0.001	<0.001
Weight z-score	0.25	0.22, 0.28	<0.001	<0.001	0.39	0.37, 0.41	<0.001	<0.001
BMI z-score	0.36	0.33, 0.39	<0.001	<0.001	0.38	0.37, 0.40	<0.001	<0.001
Waist circumference z-score	0.39	0.36, 0.42	<0.001	<0.001	0.45	0.43, 0.47	<0.001	<0.001
Waist to Height z-score	0.40	0.37, 0.43	<0.001	<0.001	0.41	0.40, 0.43	<0.001	<0.001
Hip circumference z-score	0.29	0.26, 0.32	<0.001	<0.001	0.32	0.30, 0.33	<0.001	<0.001
Waist to hip ratio z-score	0.35	0.32, 0.39	<0.001	<0.001	0.36	0.33, 0.38	<0.001	<0.001
Waist to Hip index z score	0.16	0.12, 0.20	<0.001	<0.001	0.10	0.07, 0.12	<0.001	<0.001
ABSI index z-score	0.20	0.17, 0.24	<0.001	<0.001	0.16	0.14, 0.18	<0.001	<0.001
Hip index z-score	-0.01	-0.04, 0.03	0.724	1	0.02	0.00, 0.04	0.094	1
PC1	0.27	0.25, 0.30	<0.001	<0.001	0.36	0.34, 0.38	<0.001	<0.001
PC2	-0.09	-0.12, -0.07	<0.001	<0.001	-0.10	-0.12, -0.09	<0.001	<0.001
PC3	0.03	0.00, 0.06	0.022	0.308	-0.05	-0.06, -0.03	<0.001	<0.001
PC4	0.03	0.01, 0.06	0.006	0.084	-0.02	-0.04, 0.00	0.058	0.812
[1] CI = Confidence Interval, [2]Adjusted P (Bonferroni correction)								

All analyses were adjusted for age at recruitment, smoking status, education, and physical activity. BMI: body mass index; ABSI: a body shape index; PC: principal component. PC1: overall adiposity; PC2: tall with low waist to hip ratio; PC3: tall with large waist to hip ratio, PC4: high BMI and weight with low waist circumference and hip circumference.

Table S7. Associations between anthropometric indexes and C-reactive protein (CRP) in UK Biobank study.

CRP – UK Biobank								
	Men				Women			
	N= 199,506				N= 226,717			
	Beta	95% CI[1]	*P*	*P*[2]	Beta	95% CI[1]	*P*	*P*[2]
Height z-score	-0.07	-0.07, -0.06	<0.001	<0.001	-0.12	-0.13, -0.11	<0.001	<0.001
Weight z-score	0.30	0.29, 0.30	<0.001	<0.001	0.52	0.52, 0.53	<0.001	<0.001
BMI z-score	0.36	0.36, 0.37	<0.001	<0.001	0.48	0.47, 0.48	<0.001	<0.001
Waist circumference z-score	0.39	0.38, 0.39	<0.001	<0.001	0.53	0.53, 0.54	<0.001	<0.001
Waist to Height z-score	0.40	0.39, 0.40	<0.001	<0.001	0.48	0.48, 0.49	<0.001	<0.001
Hip circumference z-score	0.30	0.29, 0.30	<0.001	<0.001	0.40	0.39, 0.40	<0.001	<0.001
Waist to hip ratio z-score	0.39	0.39, 0.40	<0.001	<0.001	0.41	0.41, 0.42	<0.001	<0.001
Waist to Hip index z score	0.21	0.21, 0.22	<0.001	<0.001	0.07	0.07, 0.08	<0.001	<0.001
ABSI index z-score	0.18	0.17, 0.18	<0.001	<0.001	0.16	0.16, 0.17	<0.001	<0.001
Hip index z-score	-0.13	-0.14, -0.13	<0.001	<0.001	0.02	0.01, 0.02	<0.001	<0.001
PC1	0.17	0.17, 0.17	<0.001	<0.001	0.24	0.24, 0.24	<0.001	<0.001
PC2	-0.11	-0.11, -0.10	<0.001	<0.001	-0.13	-0.14, -0.13	<0.001	<0.001
PC3	0.07	0.07, 0.08	<0.001	<0.001	-0.10	-0.11, -0.10	<0.001	<0.001
PC4	0.18	0.17, 0.20	<0.001	<0.001	-0.15	-0.16, -0.14	<0.001	<0.001

[1] **CI = Confidence Interval,** [2]**Adjusted P (Bonferroni correction)**

All analyses were adjusted for age at recruitment, smoking status, education, and physical activity. BMI: body mass index; ABSI: a body shape index; PC: principal component. PC1: overall adiposity; PC2: tall with low waist to hip ratio; PC3: tall with large waist to hip ratio, PC4: high BMI and weight with low waist circumference and hip circumference.

Table S8. Meta-analysis results of the associations between anthropometric indexes and C-reactive protein (CRP) in the EPIC and UK Biobank cohorts.

CRP – Meta-analysis														
	Men							Women						
	Beta	95% CI[1]	*P*	*P*[2]	Heterogeneity			Beta	95% CI[1]	*P*	*P*[2]	Heterogeneity		
					Q	*P*	I^2					Q	*P*	I^2
Height z-score	-0.09	-0.14, -0.04	<0.001	0.003	8.99	0.003	88.9%	-0.11	-0.14, -0.09	<0.001	<0.001	3.91	0.048	74.4%
Weight z-score	0.28	0.23, 0.32	<0.001	<0.001	10.3	0.001	90.2%	0.46	0.33, 0.58	<0.001	<0.001	159.2	<0.001	99.4%
BMI z-score	0.36	0.36, 0.37	<0.001	<0.001	0.03	0.864	0.0%	0.43	0.34, 0.52	<0.001	<0.001	111.5	<0.001	99.1%
Waist circumference z-score	0.39	0.38, 0.39	<0.001	<0.001	0.00	0.962	0.0%	0.49	0.41, 0.57	<0.001	<0.001	66.0	<0.001	98.9%
Waist to Height z-score	0.40	0.39, 0.40	<0.001	<0.001	0.15	0.697	0.0%	0.45	0.38, 0.52	<0.001	<0.001	55.0	<0.001	98.2%
Hip circumference z-score	0.30	0.29, 0.30	<0.001	<0.001	0.07	0.789	0.0%	0.35	0.28, 0.43	<0.001	<0.001	93.0	<0.001	98.9%
Waist to hip ratio z-score	0.38	0.34, 0.42	<0.001	<0.001	5.05	0.025	80.2%	0.38	0.33, 0.44	<0.001	<0.001	21.3	<0.001	95.3%
Waist to Hip index z score	0.19	0.14, 0.24	<0.001	<0.001	6.16	0.013	83.8%	0.08	0.06, 0.10	<0.001	<0.001	3.09	0.079	67.6%
ABSI index z-score	0.19	0.16, 0.21	<0.001	<0.001	2.41	0.120	58.6%	0.16	0.16, 0.17	<0.001	<0.001	0.19	0.663	0.0%
Hip index z-score	-0.07	-0.19, 0.05	0.254	1	48.0	<0.001	97.9%	0.02	0.01, 0.02	<0.001	<0.001	0.00	0.963	0.0%
PC1	0.22	0.12, 0.32	<0.001	<0.001	64.6	<0.001	98.5%	0.30	0.19, 0.41	<0.001	<0.001	198.5	<0.001	99.5%
PC2	-0.10	-0.11, -0.10	<0.001	<0.001	1.15	0.285	12.7%	-0.12	-0.15, -0.09	<0.001	<0.001	10.9	0.001	90.9%
PC3	0.06	0.01, 0.10	0.008	0.112	8.95	0.003	88.9%	-0.08	-0.13, -0.02	0.005	0.070	35.6	<0.001	97.2%
PC4	0.11	-0.04, 0.26	0.147	1	117.8	<0.001	99.2%	-0.08	-0.21, 0.04	0.203	1	126.9	<0.001	99.2%

[1] CI = Confidence Interval, [2]Adjusted P (Bonferroni correction)

All analyses were adjusted for age at recruitment, smoking status, education, and physical activity. BMI: body mass index; ABSI: a body shape index; PC: principal component. PC1: overall adiposity; PC2: tall with low waist to hip ratio; PC3: tall with large waist to hip ratio, PC4: high BMI and weight with low waist circumference and hip circumference.

Table S9. Associations between anthropometric indexes and all the inflammatory biomarkers analysed in EPIC.

	Interleukin 6				Interleukin 8				Interleukin 10				Interleukin 17d			
	N= 3,315				N=1,415				N=2,036				N=1,416			
	Beta	95% CI[1]	*P*	*P*[2]	Beta	95% CI[1]	*P*	*P*[2]	Beta	95% CI[1]	*P*	*P*[2]	Beta	95% CI[1]	*P*	*P*[2]
Height z-score	-0.05	-0.09,-0.01	<0.001	<0.001	-0.04	-0.11, 0.03	0.264	1	0 05	-0.01, 0.12	0.080	1	0.02	-0.05, 0.10	0.483	1
Weight z-score	0.23	0.20, 0.27	<0.001	<0.001	0.02	-0.05, 0.08	0.558	1	-0.03	-0.08, 0.03	0.323	1	-0.09	-0.15, -0.03	0.005	0.070
BMI z-score	0.22	0.20, 0.26	<0.001	<0.001	0.04	-0.02, 0.09	0.199	1	-0.04	-0.09, 0.00	0.067	0.938	-0.09	-0.14, -0.03	0.002	0.028
WC z-score	0.26	0.22, 0.29	<0.001	<0.001	0.06	-0.01, 0.12	0.092	1	-0.03	-0.08, 0.03	0.284	1	-0.08	-0.15, -0.02	0.009	0.126
WHtR z-score	0.23	0.20,0.27	<0.001	<0.001	0.06	0.00, 0.12	0.041	0.574	-0.04	-0.09, 0.01	0.121	1	-0.08	-0.14, -0.02	0.008	0.112
HC z-score	0.18	0.15, 0.21	<0.001	<0.001	0.02	-0.04, 0.07	0.525	1	-0.03	-0.07, 0.02	0.245	1	-0.06	-0.11, 0.00	0.035	0.490
WHR z-score	0.18	0.14, 0.22	<0.001	<0.001	0.07	0.00, 0.14	0.043	0.602	-0.01	-0.07, 0.05	0.675	1	-0.06	-0.13, 0.01	0.008	0.112
WHI z-score	0.05	0.01,0.09	0.021	0.294	0.05	-0.01,0.12	0.115	1	0 01	-0.04,0.07	0.624	1	-0.01	-0.08,0.05	0.705	1
ABSI z-score	0.07	0.04, 0.10	<0.001	<0.001	0.04	-0.02, 0.10	0.205	1	0 01	-0.04, 0.06	0.755	1	0.00	-0.06, 0.06	0.920	1
HI z-score	-0.01	-0.05, 0.03	0.618	1	-0.01	-0.08, 0.06	0.687	1	0 00	-0.06, 0.06	0.968	1	0.04	-0.03, 0.11	0.234	1
PC1	0.21	0.18, 0.24	<0.001	<0.001	0.04	-0.02, 0.09	0.189	1	-0.03	-0.07, 0.02	0.249	1	-0.07	-0.12, -0.02	0.009	0.126
PC2	-0.05	-0.08,-0.02	0.001	0.014	-0.05	-0.10, 0.00	0.067	0.938	0 02	-0.02, 0.07	0.267	1	0.02	-0.03, 0.07	0.500	1
PC3	-0.02	-0.05, 0.01	0.155	1	0.02	-0.03, 0.06	0.505	1	0 02	-0.02, 0.06	0.238	1	0.00	-0.04, 0.05	0.830	1
PC4	0.01	-0.02, 0.04	0.524	1	-0.01	-0.07, 0.04	0.607	1	-0.02	-0.06, 0.03	0.489	1	-0.04	-0.09, 0.02	0.166	1

[1] **CI = Confidence Interval,** [2]**Adjusted P (Bonferroni correction)**

Adjusted for age at recruitment, smoking status, education, and physical activity. IL1ra: Interleukin-1 receptor antagonist; TNF-α: Tumour necrosis factor alpha; IFN-γ: Interferon-gamma; BMI: body mass index; WC: waist circumference; WHtR: waist to height ratio; HC: Hip circumference; WHR: Waist to hip ratio; WHI: waist to hip index; ABSI: a body shape index. PC1: Overall adiposity; PC2: tall with low Waist to hip ratio; PC3: tall with large waist to hip ratio, PC4: high BMI and weight with low waist circumference and hip circumference.

Table S9 (cont.). Associations between anthropometric indexes and all the inflammatory biomarkers analysed in EPIC.

	IL1ra N=1,803				TNF-α N=2,425				IFN-γ N=1,415				Leptin N=2,722			
	Beta	**95% CI[1]**	***P***	***P*[2]**	**Beta**	**95% CI[1]**	***P***	***P*[2]**	**Beta**	**95% CI[1]**	***P***	***P*[2]**	**Beta**	**95% CI[1]**	***P***	***P*[2]**
Height z-score	0.01	-0.06, 0.08	0.766	1	0.04	-0.02, 0.09	0.236	1	-0.01	-0.09, 0.06	0.844	1	-0.09	-0.14, -0.05	<0.001	<0.001
Weight z-score	0.31	0.25, 0.36	<0.001	<0.001	0.16	0.11, 0.21	<0.001	<0.001	0.03	-0.04, 0.10	<0.001	<0.001	0.59	0.56, 0.62	<0.001	<0.001
BMI z-score	0.28	0.23, 0.32	<0.001	<0.001	0.13	0.09, 0.17	<0.001	<0.001	0.04	-0.02, 0.09	0.248	1	0.56	0.53, 0.58	<0.001	<0.001
WC z-score	0.34	0.28, 0.39	<0.001	<0.001	0.17	0.13, 0.22	<0.001	<0.001	0.06	0.00, 0.13	0.084	1	0.58	0.55, 0.62	<0.001	<0.001
WHtR z-	0.30	0.24,0.35	<0.001	<0.001	0.15	0.10, 0.19	<0.001	<0.001	0.06	0.00, 0.12	0.074	1	0.54	0.51, 0.57	<0.001	<0.001
HC z-score	0.23	0.19, 0.28	<0.001	<0.001	0.11	0.06, 0.15	<0.001	<0.001	0.01	-0.04, 0.07	0.712	1	0.51	0.48, 0.54	<0.001	<0.001
WHR z-score	0.23	0.17, 0.29	<0.001	<0.001	0.15	0.10, 0.20	<0.001	<0.001	0.08	0.01, 0.15	0.030	0.420	0.30	0.26, 0.35	<0.001	<0.001
WHI z-score	0.09	0.03, 0.15	0.003	0.042	0.08	0.03,0.13	0.002	0.028	0.06	0.00,0.13	0.066	0.924	-0.02	-0.06,0.02	0.272	1
ABSI z-score	0.11	0.06, 0.16	<0.001	<0.001	0.07	0.02, 0.12	0.002	0.028	0.04	-0.01, 0.10	0.136	1	0.09	0.06, 0.13	<0.001	<0.001
HI z-score	-0.03	-0.10, 0.03	0.264	1	-0.05	-0.10, 0.00	0.069	0.966	-0.05	-0.12, 0.02	0.199	1	0.07	0.02, 0.11	0.002	0.028
PC1	0.27	0.23, 0.32	<0.001	<0.001	0.14	0.10, 0.18	<0.001	<0.001	0.04	-0.02, 0.09	0.209	1	0.50	0.47, 0.53	<0.001	<0.001
PC2	-0.05	-0.09, 0.00	0.040	0.560	-0.01	-0.06, 0.02	0.432	1	-0.03	-0.08, 0.02	0.267	1	-0.06	-0.10, -0.03	<0.001	<0.001
PC3	0.02	-0.02, 0.06	0.453	1	0.03	0.00, 0.07	0.076	1	0.03	-0.02, 0.08	0.191	1	-0.12	-0.15, -0.09	<0.001	<0.001
PC4	-0.01	-0.06, 0.03	0.551	1	0.00	-0.04,0.04	0.931	1	0.00	-0.05, 0.06	0.929	1	-0.03	-0.06, 0.01	0.112	1

[1] CI = Confidence Interval, [2]Adjusted P (Bonferroni correction)

Adjusted for age at recruitment, smoking status, education, and physical activity. IL1ra: Interleukin-1 receptor antagonist; TNF-α: Tumour necrosis factor alpha; IFN-γ: Interferon-gamma; BMI: body mass index; WC: waist circumference; WHtR: waist to height ratio; HC: Hip circumference; WHR: Waist to hip ratio; WHI: waist to hip index; ABSI: a body shape index. PC1: Overall adiposity; PC2: tall with low Waist to hip ratio; PC3: tall with large waist to hip ratio, PC4: high BMI and weight with low waist circumference and hip circumference

Table S9 (cont.). Associations between anthropometric indexes and all the inflammatory biomarkers analysed in EPIC.

	Adiponectin			
	N=3,315			
	Beta	**95% CI[1]**	***P***	***P*[2]**
Height z-score	0.05	0.01, 0.10	0.023	0.322
Weight z-score	-0.21	-0.25, -0.18	<0.001	<0.001
BMI z-score	-0.21	-0.24, -0.18	<0.001	<0.001
WC z-score	-0.30	-0.34, -0.27	<0.001	<0.001
WHtR z-score	-0.28	-0.31, -0.24	<0.001	<0.001
HC z-score	-0.11	-0.15, -0.08	<0.001	<0.001
WHR z-score	-0.35	-0.39, -0.30	<0.001	<0.001
WHI z-score	-0.23	-0.27, -0.19	<0.001	<0.001
ABSI z-score	-0.18	-0.21, -0.14	<0.001	<0.001
HI z-score	0.16	0.12, 0.20	<0.001	<0.001
PC1	-0.22	-0.25, -0.19	<0.001	<0.001
PC2	0.14	0.11, 0.17	<0.001	<0.001
PC3	-0.10	-0.12, -0.07	<0.001	<0.001
PC4	-0.02	-0.05, 0.02	0.330	1

[1] CI = Confidence Interval, [2]Adjusted P (Bonferroni correction)

Adjusted for age at recruitment, smoking status, education, and physical activity. IL1ra: Interleukin-1 receptor antagonist; TNF-α: Tumour necrosis factor alpha; IFN-γ: Interferon-gamma; BMI: body mass index; WC: waist circumference; WHtR: waist to height ratio; HC: Hip circumference; WHR: Waist to hip ratio; WHI: waist to hip index; ABSI: a body shape index. PC1: Overall adiposity; PC2: tall with low Waist to hip ratio; PC3: tall with large waist to hip ratio, PC4: high BMI and weight with low waist circumference and hip circumference.

Table S10. Associations between anthropometric indexes and C-reactive protein (CRP) stratifying by sex-specific median age and p-values for likelihood ratio test comparing models without and with interactions in the EPIC study.

CRP – EPIC												
	Men						Women					
	N= 5,546						N= 12,397					
	< 53 years (N = 2,689)		≥ 53 years (N = 2,857)		P interaction		< 53 years (N = 6,340)		≥ 53 years (N = 6,057)		P interaction	
	Beta	95% CI[1]	Beta	95% CI[1]	*P*	*P*[2]	Beta	95% CI[1]	Beta	95% CI[1]	*P*	*P*[2]
Height z-score	-0.14	-0.18, -0.09	-0.11	-0.15, -0.06	0.170	1	-0.08	-0.11, -0.04	-0.12	-0.16, -0.09	0.635	1
Weight z-score	0.26	0.22, 0.30	0.25	0.21, 0.29	0.113	1	0.42	0.39, 0.44	0.37	0.34, 0.39	**0.017**	0.238
BMI z-score	0.40	0.35, 0.44	0.34	0.30, 0.38	**0.003**	**0.042**	0.40	0.38, 0.43	0.37	0.35, 0.39	0.060	0.840
Waist circumference z-score	0.43	0.38, 0.47	0.37	0.33, 0.41	**0.002**	**0.028**	0.48	0.45, 0.50	0.43	0.40, 0.45	**0.048**	0.672
Waist to Height z-score	0.45	0.41, 0.49	0.37	0.33, 0.41	**0.001**	**0.014**	0.44	0.41, 0.47	0.40	0.37, 0.42	0.070	0.980
Hip circumference z-score	0.31	0.27, 0.35	0.28	0.24, 0.32	**0.011**	0.154	0.34	0.32, 0.36	0.29	0.27, 0.31	**0.001**	**0.014**
Waist to hip ratio z-score	0.37	0.32, 0.43	0.35	0.30, 0.40	0.058	0.812	0.36	0.32, 0.40	0.35	0.32, 0.39	0.539	1
Waist to Hip index z score	0.18	0.12, 0.24	0.18	0.12, 0.23	0.646	1	0.06	0.03, 0.10	0.13	0.10, 0.16	0.053	0.742
ABSI index z-score	0.23	0.18, 0.28	0.20	0.15, 0.25	0.240	1	0.15	0.12, 0.18	0.17	0.15, 0.20	0.171	1
Hip index z-score	-0.01	-0.06, 0.05	-0.02	-0.07, 0.03	0.863	1	0.03	0.00, 0.06	0.00	-0.03, 0.04	0.471	1
PC1	0.28	0.25, 0.32	0.26	0.23, 0.30	**0.042**	0.588	0.37	0.35, 0.40	0.34	0.32, 0.36	**0.046**	0.644
PC2	-0.09	-0.12, -0.05	-0.10	-0.13, -0.07	0.547	1	-0.08	-0.11, -0.06	-0.12	-0.14, -0.09	0.763	1
PC3	0.04	0.00, 0.08	0.04	0.00, 0.08	0.728	1	-0.08	-0.11, -0.05	-0.02	-0.04, 0.00	**<0.001**	**0.003**
PC4	0.04	0.01, 0.07	0.02	-0.01, 0.06	0.073	1	-0.01	-0.04, 0.01	-0.02	-0.04, 0.00	0.541	1

[1] CI = Confidence Interval, [2]Adjusted P (Bonferroni correction)

Adjusted for smoking status, education, and physical activity. Significant p-values are highlighted in bold. AT: anthropometric indexes; BMI: body mass index; WHR: waist to hip ratio; ABSI: a body shape index; PC: principal component. PC1: overall adiposity; PC2: tall with low waist to hip ratio; PC3: tall with large waist to hip ratio, PC4: high BMI and weight with low waist circumference and hip circumference. Median age EPIC among males and among women was 53 years old.

Table S11. Associations between anthropometric indexes and C-reactive protein (CRP) stratifying by smoking status and p-values for likelihood ratio test comparing models without and with interactions in the EPIC study.

CRP – EPIC												
	Men						Women					
	N= 5,546						N= 12,397					
	Never (N = 1,676)		Ever (N = 3,806)		P interaction		Never (N = 7,143)		Ever (N = 5,140)		P interaction	
	Beta	95% CI[1]	Beta	95% CI[1]	*P*	*P*[2]	Beta	95% CI[1]	Beta	95% CI[1]	*P*	*P*[2]
Height z-score	-0.09	-0.15, -0.03	-0.13	-0.17, -0.09	0.053	0.742	-0.12	-0.16, -0.09	-0.06	-0.1, -0.02	**0.006**	0.084
Weight z-score	0.34	0.28, 0.39	0.20	0.17, 0.24	**<0.001**	**<0.001**	0.40	0.38, 0.43	0.37	0.34, 0.4	0.123	1
BMI z-score	0.44	0.39, 0.49	0.31	0.28, 0.35	**<0.001**	**0.001**	0.39	0.37, 0.41	0.37	0.34, 0.39	0.275	1
Waist circumference z-score	0.47	0.41, 0.52	0.35	0.31, 0.39	**<0.001**	**0.001**	0.45	0.43, 0.48	0.44	0.41, 0.47	0.433	1
Waist to Height z-score	0.46	0.41, 0.51	0.37	0.34, 0.41	**0.005**	0.070	0.42	0.39, 0.44	0.41	0.38, 0.44	0.324	1
Hip circumference z-score	0.37	0.31, 0.42	0.25	0.22, 0.29	**<0.001**	**0.002**	0.32	0.30, 0.35	0.29	0.26, 0.32	**0.025**	0.350
Waist to hip ratio z-score	0.42	0.36, 0.49	0.33	0.28, 0.37	**0.004**	0.056	0.33	0.30, 0.37	0.38	0.34, 0.42	0.482	1
Waist to Hip index z score	0.20	0.12, 0.27	0.17	0.12, 0.21	0.461	1	0.07	0.03, 0.10	0.14	0.1, 0.18	**0.037**	0.518
ABSI index z-score	0.20	0.14, 0.27	0.22	0.18, 0.26	0.697	1	0.14	0.12, 0.17	0.19	0.16, 0.22	0.192	1
Hip index z-score	-0.07	-0.13, 0.00	0.02	-0.03, 0.06	0.125	1	0.03	0.00, 0.06	-0.01	-0.04, 0.03	0.086	1
PC1	0.34	0.30, 0.39	0.23	0.20, 0.26	**<0.001**	**<0.001**	0.37	0.35, 0.39	0.34	0.31, 0.36	0.057	0.798
PC2	-0.08	-0.12, -0.03	-0.10	-0.13, -0.07	0.105	1	-0.09	-0.12, -0.07	-0.11	-0.14, -0.08	0.899	1
PC3	0.07	0.02, 0.12	0.03	-0.01, 0.06	0.229	1	-0.06	-0.08, -0.04	-0.02	-0.05, 0.01	**0.026**	0.364
PC4	0.09	0.05, 0.14	0.01	-0.02, 0.04	**0.008**	0.112	-0.01	-0.03, 0.02	-0.04	-0.07, -0.01	0.333	1

[1] CI = Confidence Interval, [2]Adjusted P (Bonferroni correction)

Adjusted for age at recruitment, education, and physical activity. Significant p-values are highlighted in bold. AT: anthropometric indexes; BMI: body mass index; WHR: waist to hip ratio; ABSI: a body shape index; PC: principal component. PC1: overall adiposity; PC2: tall with low waist to hip ratio; PC3: tall with large waist to hip ratio, PC4: high BMI and weight with low waist circumference and hip circumference.

Table S12. Associations between anthropometric indexes and C-reactive protein (CRP) stratifying by sex-specific median age and p-values for likelihood ratio test comparing models without and with interactions in UK Biobank study.

CRP – UK Biobank												
	Men						Women					
	N= 199,506						N= 226,717					
	< 58 years (N = 98,426)		≥ 58 years (N = 101,080)		P interaction		< 57 years (N = 108,395)		≥ 57 years (N = 118,322)		P interaction	
	Beta	95% CI[1]	Beta	95% CI[1]	*P*	*P*[2]	Beta	95% CI[1]	Beta	95% CI[1]	*P*	*P*[2]
Height z-score	-0.08	-0.09, -0.07	-0.07	-0.08, -0.06	**0.028**	0.394	-0.15	-0.16, -0.14	-0.11	-0.12, -0.10	**<0.001**	**<0.001**
Weight z-score	0.33	0.32, 0.34	0.25	0.25, 0.26	**<0.001**	**<0.001**	0.55	0.54, 0.55	0.48	0.47, 0.49	**<0.001**	**<0.001**
BMI z-score	0.40	0.40, 0.41	0.31	0.31, 0.32	**<0.001**	**<0.001**	0.51	0.50, 0.51	0.44	0.43, 0.44	**<0.001**	**<0.001**
Waist circumference z-score	0.44	0.43, 0.45	0.34	0.33, 0.34	**<0.001**	**<0.001**	0.58	0.58, 0.59	0.48	0.47, 0.49	**<0.001**	**<0.001**
Waist to Height z-score	0.45	0.44, 0.46	0.34	0.34, 0.35	**<0.001**	**<0.001**	0.53	0.53, 0.54	0.43	0.43, 0.44	**<0.001**	**<0.001**
Hip circumference z-score	0.34	0.33, 0.35	0.25	0.24, 0.26	**<0.001**	**<0.001**	0.43	0.43, 0.44	0.35	0.35, 0.36	**<0.001**	**<0.001**
Waist to hip ratio z-score	0.46	0.45, 0.47	0.33	0.33, 0.34	**<0.001**	**<0.001**	0.47	0.46, 0.48	0.36	0.35, 0.37	**<0.001**	**<0.001**
Waist to Hip index z score	0.26	0.24, 0.27	0.19	0.18, 0.20	**<0.001**	**<0.001**	0.08	0.07, 0.09	0.08	0.07, 0.09	0.077	1
ABSI index z-score	0.20	0.19, 0.21	0.16	0.16, 0.17	**<0.001**	**<0.001**	0.18	0.17, 0.19	0.16	0.15, 0.17	**0.007**	0.093
Hip index z-score	-0.17	-0.18, -0.16	-0.09	-0.10, -0.08	**<0.001**	**<0.001**	0.01	0.00, 0.02	0.03	0.02, 0.04	**0.011**	0.152
PC1	0.19	0.19, 0.19	0.15	0.14, 0.15	**<0.001**	**<0.001**	0.26	0.26, 0.26	0.22	0.22, 0.22	**<0.001**	**<0.001**
PC2	-0.12	-0.12, -0.11	-0.10	-0.10, -0.09	**<0.001**	**<0.001**	-0.14	-0.15, -0.13	-0.12	-0.13, -0.11	**<0.001**	**<0.001**
PC3	0.09	0.08, 0.09	0.07	0.06, 0.08	**0.010**	0.134	-0.13	-0.14, -0.13	-0.07	-0.08, -0.06	**<0.001**	**<0.001**
PC4	0.27	0.26, 0.29	0.09	0.07, 0.11	**<0.001**	**<0.001**	-0.07	-0.09, -0.04	-0.21	-0.23, -0.19	**<0.001**	**<0.001**

[1] **CI = Confidence Interval, [2]Adjusted P (Bonferroni correction)**

Adjusted for smoking status, education, and physical activity. Significant p-values are highlighted in bold. AT: anthropometric indexes; BMI: body mass index; WHR: waist to hip ratio; ABSI: a body shape index; PC: principal component. PC1: overall adiposity; PC2: tall with low waist to hip ratio; PC3: tall with large waist to hip ratio, PC4: high BMI and weight with low waist circumference and hip circumference. In UK Biobank, median age was 58 and 57 for men and women, respectively.

Table S13. Associations between anthropometric indexes and C-reactive protein (CRP) stratifying by smoking status and p-values for likelihood ratio test comparing models without and with interactions in UK Biobank study.

CRP – UK Biobank												
	Men						Women					
	N= 199,506						N= 226,717					
	Never (N = 97,847)		Ever (N = 100,649)		P interaction		Never (N = 135,953)		Ever (N = 89,672)		P interaction	
	Beta	95% CI[1]	Beta	95% CI[1]	*P*	*P*[2]	Beta	95% CI[1]	Beta	95% CI[1]	*P*	*P*[2]
Height z-score	-0.07	-0.08, -0.06	-0.07	-0.08, -0.06	0.339	1	-0.12	-0.13, -0.11	-0.12	-0.13, -0.11	0.282	1
Weight z-score	0.33	0.32, 0.34	0.25	0.24, 0.26	**<0.001**	**<0.001**	0.53	0.52, 0.54	0.50	0.49, 0.51	**<0.001**	**<0.001**
BMI z-score	0.40	0.39, 0.41	0.31	0.30, 0.31	**<0.001**	**<0.001**	0.48	0.48, 0.49	0.46	0.45, 0.47	**<0.001**	**0.001**
Waist circumference z-score	0.42	0.41, 0.43	0.35	0.34, 0.35	**<0.001**	**<0.001**	0.54	0.53, 0.55	0.52	0.51, 0.53	**0.045**	0.637
Waist to Height z-score	0.42	0.42, 0.43	0.36	0.35, 0.37	**<0.001**	**<0.001**	0.49	0.48, 0.49	0.48	0.47, 0.48	0.894	1
Hip circumference z-score	0.33	0.33, 0.34	0.25	0.24, 0.26	**<0.001**	**<0.001**	0.40	0.40, 0.41	0.38	0.37, 0.38	**<0.001**	**<0.001**
Waist to hip ratio z-score	0.41	0.40, 0.42	0.38	0.37, 0.38	**<0.001**	**<0.001**	0.41	0.40, 0.41	0.43	0.42, 0.44	**<0.001**	**<0.001**
Waist to Hip index z score	0.21	0.20, 0.22	0.23	0.22, 0.24	0.051	0.709	0.06	0.05, 0.07	0.10	0.09, 0.11	**<0.001**	**<0.001**
ABSI index z-score	0.17	0.16, 0.18	0.19	0.18, 0.20	**0.004**	0.056	0.16	0.15, 0.16	0.18	0.17, 0.19	**<0.001**	**<0.001**
Hip index z-score	-0.15	-0.16, -0.14	-0.12	-0.13, -0.11	**<0.001**	**<0.001**	0.02	0.01, 0.03	0.01	0.00, 0.02	**0.010**	0.141
PC1	0.19	0.18, 0.19	0.15	0.15, 0.15	**<0.001**	**<0.001**	0.24	0.24, 0.25	0.23	0.23, 0.24	**<0.001**	**<0.001**
PC2	-0.11	-0.11, -0.10	-0.11	-0.11, -0.10	0.276	1	-0.13	-0.13, -0.12	-0.14	-0.15, -0.13	**0.030**	0.426
PC3	0.07	0.06, 0.08	0.09	0.08, 0.10	**<0.001**	**0.001**	-0.11	-0.12, -0.10	-0.08	-0.09, -0.07	**<0.001**	**<0.001**
PC4	0.22	0.20, 0.24	0.13	0.11, 0.15	**<0.001**	**<0.001**	-0.14	-0.16, -0.12	-0.16	-0.18, -0.13	0.138	1

[1] CI = Confidence Interval, [2]Adjusted P (Bonferroni correction)

Adjusted for age at recruitment, education, and physical activity. Significant p-values are highlighted in bold. AT: anthropometric indexes; BMI: body mass index; WHR: waist to hip ratio; ABSI: a body shape index; PC: principal component. PC1: overall adiposity; PC2: tall with low waist to hip ratio; PC3: tall with large waist to hip ratio, PC4: high BMI and weight with low waist circumference and hip circumference.

Table S14. Associations between anthropometric indexes and C-reactive protein (CRP) in the EPIC study. Data presented for all women and by menopausal status.

CRP – EPIC	All women[2]				Premenopausal				Postmenopausal[3]				Postmenopausal[4]			
	N= 12,170				N= 3,775				N = 6,058				N = 6,152			
	Beta	95% CI[1]	*P*	*P*[5]	Beta	95% CI[1]	*P*	*P*[5]	Beta	95% CI[1]	*P*	*P*[5]	Beta	95% CI[1]	*P*	*P*[5]
Height z-score	-0.10	-0.13, -0.08	<0.001	<0.001	-0.12	-0.16, -0.07	<0.001	<0.001	-0.11	-0.15, -0.08	<0.001	<0.001	-0.11	-0.15,-0.08	<0.001	<0.001
Weight z-score	0.39	0.37, 0.41	<0.001	<0.001	0.41	0.37, 0.44	<0.001	<0.001	0.38	0.35, 0.41	<0.001	<0.001	0.38	0.35, 0.40	<0.001	<0.001
BMI z-score	0.38	0.37, 0.40	<0.001	<0.001	0.40	0.37, 0.43	<0.001	<0.001	0.38	0.35, 0.40	<0.001	<0.001	0.37	0.35, 0.39	<0.001	<0.001
WC z-score	0.45	0.43, 0.47	<0.001	<0.001	0.47	0.43, 0.51	<0.001	<0.001	0.44	0.42, 0.47	<0.001	<0.001	0.44	0.41, 0.46	<0.001	<0.001
WHtR z-score	0.41	0.40, 0.43	<0.001	<0.001	0.43	0.40, 0.47	<0.001	<0.001	0.41	0.38,0.43	<0.001	<0.001	0.40	0.38, 0.42	<0.001	<0.001
HC z-score	0.32	0.30, 0.33	<0.001	<0.001	0.33	0.30, 0.37	<0.001	<0.001	0.30	0.28, 0.33	<0.001	<0.001	0.30	0.28, 0.32	<0.001	<0.001
WHR z-score	0.36	0.33, 0.38	<0.001	<0.001	0.37	0.32, 0.42	<0.001	<0.001	0.36	0.33, 0.39	<0.001	<0.001	0.36	0.32, 0.39	<0.001	<0.001
WHI z-score	0.10	0.07, 0.12	<0.001	<0.001	0.05	0.00,0.11	0.023	0.322	0.12	0.09,0.15	<0.001	<0.001	0.12	0.08,0.15	<0.001	<0.001
ABSI index z-score	0.16	0.14, 0.18	<0.001	<0.001	0.13	0.09, 0.18	<0.001	<0.001	0.18	0.15, 0.21	<0.001	<0.001	0.18	0.15, 0.21	<0.001	<0.001
HI index z-score	0.02	-0.00, 0.04	0.041	0.574	0.02	-0.02,0.06	0.379	1	0.01	-0.01,0.04	0.296	1	0.01	-0.01,0.04	0.373	1
PC1	0.36	0.34, 0.38	<0.001	<0.001	0.37	0.33, 0.40	<0.001	<0.001	0.35	0.33, 0.38	<0.001	<0.001	0.35	0.33, 0.37	<0.001	<0.001
PC2	-0.10	-0.12, -0.09	<0.001	<0.001	-0.10	-0.13, -0.06	<0.001	<0.001	-0.11	-0.13, -0.08	<0.001	<0.001	-0.11	-0.13, -0.08	<0.001	<0.001
PC3	-0.05	-0.06, -0.03	<0.001	<0.001	-0.09	-0.13, -0.06	<0.001	<0.001	-0.02	-0.04, 0.00	0.054	0.756	-0.02	-0.04, -0.00	0.043	0.602
PC4	-0.02	-0.04, 0.00	0.034	0.476	0.01	-0.02, 0.04	0.540	0.540	-0.02	-0.05, -0.00	0.036	0.504	-0.02	-0.04, 0.00	0.063	0.882

[1] CI = Confidence Interval, [5]Adjusted P (Bonferroni correction)

All analyses were adjusted for age at recruitment, smoking status, education, and physical activity. BMI: body mass index; WC: waist circumference; WHtR: waist to height ratio; HC: Hip circumference; WHR: Waist to hip ratio; WHI: waist to hip index; ABSI: a body shape index; PC: principal component. PC1: overall adiposity; PC2: tall with low waist to hip ratio; PC3: tall wi large waist to hip ratio, PC4: high BMI and weight with low waist circumference and hip circumference.[2]Additionally adjusted for menopause status and hormone replacement therapy. [3]Additionaly adjusted for hormone replacement therapy and [4]without the hormone replacement therapy adjustment.

Table S15. Associations between anthropometric indexes and C-reactive protein (CRP) in UK Biobank study. Data presented for all women and by menopausal status.

CRP – UK Biobank																
	All women[2]				Premenopausal				Postmenopausal[3]				Postmenopausal[4]			
	N = 149,980				N = 46,429				N = 103,551				N = 103,765			
	Beta	95% CI[1]	*P*	*P*[5]	Beta	95% CI[1]	*P*	*P*[5]	Beta	95% CI[1]	*P*	*P*[5]	Beta	95% CI[1]	*P*	*P*[5]
Height z-score	-0.12	-0.13, -0.11	<0.001	<0.001	-0.13	-0.14, -0.12	<0.001	<0.001	-0.11	-0.12, -0.10	<0.001	<0.001	-0.11	-0.12, -0.10	<0.001	<0.001
Weight z-score	0.52	0.52, 0.53	<0.001	<0.001	0.55	0.53, 0.55	<0.001	<0.001	0.51	0.50, 0.51	<0.001	<0.001	0.51	0.50, 0.51	<0.001	<0.001
BMI z-score	0.48	0.47, 0.48	<0.001	<0.001	0.51	0.50, 0.51	<0.001	<0.001	0.46	0.45, 0.46	<0.001	<0.001	0.46	0.45, 0.46	<0.001	<0.001
WC z-score	0.53	0.53, 0.54	<0.001	<0.001	0.58	0.57, 0.59	<0.001	<0.001	0.51	0.50, 0.51	<0.001	<0.001	0.51	0.50, 0.51	<0.001	<0.001
WHtR z-score	0.48	0.48, 0.49	<0.001	<0.001	0.53	0.52, 0.54	<0.001	<0.001	0.46	0.45, 0.46	<0.001	<0.001	0.45	0.45, 0.46	<0.001	<0.001
HC z-score	0.40	0.39, 0.40	<0.001	<0.001	0.43	0.42, 0.44	<0.001	<0.001	0.38	0.37, 0.38	<0.001	<0.001	0.38	0.37, 0.38	<0.001	<0.001
WHR z-score	0.41	0.40, 0.42	<0.001	<0.001	0.45	0.44, 0.46	<0.001	<0.001	0.39	0.38, 0.40	<0.001	<0.001	0.39	0.38, 0.39	<0.001	<0.001
WHI z-score	0.07	0.07, 0.08	<0.001	<0.001	0.05	0.03, 0.06	<0.001	<0.001	0.08	0.07, 0.08	<0.001	<0.001	0.07	0.07, 0.08	<0.001	<0.001
ABSI index z-score	0.16	0.16, 0.17	<0.001	<0.001	0.15	0.14, 0.16	<0.001	<0.001	0.16	0.15, 0.17	<0.001	<0.001	0.16	0.15, 0.17	<0.001	<0.001
HI index z-score	0.02	0.01, 0.02	<0.001	<0.001	0.01	-0.01, 0.04	0.284	1	0.05	0.03, 0.07	<0.001	<0.001	0.05	0.03, 0.07	<0.001	<0.001
PC1	0.24	0.24, 0.24	<0.001	<0.001	0.25	0.25, 0.26	<0.001	<0.001	0.23	0.23, 0.23	<0.001	<0.001	0.23	0.23, 0.23	<0.001	<0.001
PC2	-0.13	-0.14, -0.13	<0.001	<0.001	-0.13	-0.14, -0.12	<0.001	<0.001	-0.12	-0.13, -0.12	<0.001	<0.001	-0.12	-0.13, -0.12	<0.001	<0.001
PC3	-0.10	-0.11, -0.09	<0.001	<0.001	-0.14	-0.15, -0.13	<0.001	<0.001	-0.08	-0.08, -0.07	<0.001	<0.001	-0.08	-0.08, -0.07	<0.001	<0.001
PC4	-0.15	-0.17, -0.14	<0.001	<0.001	-0.03	-0.06, 0.00	0.015	0.209	-0.19	-0.21, -0.18	<0.001	<0.001	-0.19	-0.21, -0.18	<0.001	<0.001

[1] CI = Confidence Interval, [5]Adjusted P (Bonferroni correction)

All analyses were adjusted for age at recruitment, smoking status, education, and physical activity. BMI: body mass index; WC: waist circumference; WHtR: waist to height ratio; HC: Hip circumference; WHR: Waist to hip ratio; WHI: waist to hip index; ABSI: a body shape index; PC: principal component. PC1: overall adiposity; PC2: tall with low waist to hip ratio; PC3: tall wi large waist to hip ratio, PC4: high BMI and weight with low waist circumference and hip circumference.[2]Additionally adjusted for menopause status and hormone replacement therapy. [3]Additionaly adjusted for hormone replacement therapy and [4]without the hormone replacement therapy adjustment. [5]Adjusted p-value by Bonferroni correction.

Table S16. Associations between anthropometric indexes and C-reactive protein (CRP) in the EPIC study excluding 3,643 participants with CVD at baseline defined as myocardial infarction (heart attack), stroke or hypertension.

CRP – EPIC								
	Men				**Women**			
	N=3,684				N=7,995			
	Beta	**95% CI[1]**	***P***	***P*[2]**	**Beta**	**95% CI[1]**	***P***	***P*[2]**
Height z-score	-0.12	-0.16, -0.08	<0.001	<0.001	-0.08	-0.12, -0.05	<0.001	<0.001
Weight z-score	0.25	0.22, 0.28	<0.001	<0.001	0.39	0.37, 0.42	<0.001	<0.001
BMI z-score	0.38	0.34, 0.42	<0.001	<0.001	0.38	0.36, 0.40	<0.001	<0.001
Waist circumference z-score	0.40	0.36, 0.44	<0.001	<0.001	0.43	0.40, 0.46	<0.001	<0.001
Waist to Height z-score	0.41	0.38, 0.45	<0.001	<0.001	0.39	0.37, 0.41	<0.001	<0.001
Hip circumference z-score	0.31	0.27, 0.34	<0.001	<0.001	0.30	0.28, 0.33	<0.001	<0.001
Waist to hip ratio z-score	0.33	0.29, 0.38	<0.001	<0.001	0.31	0.28, 0.34	<0.001	<0.001
Waist to Hip index z score	0.13	0.08, 0.18	<0.001	<0.001	0.08	0.05, 0.11	<0.001	<0.001
ABSI index z-score	0.19	0.15, 0.23	<0.001	<0.001	0.13	0.10, 0.15	<0.001	<0.001
Hip index z-score	0.01	-0.03,0.05	0.581	1	0.00	-0.02,0.00	0.747	1
PC1	0.28	0.25, 0.31	<0.001	<0.001	0.35	0.33, 0.37	<0.001	<0.001
PC2	-0.08	-0.11, -0.05	<0.001	<0.001	-0.09	-0.11, -0.06	<0.001	<0.001
PC3	0.01	-0.01, 0.04	0.409	1	-0.04	-0.06, -0.02	0.383	1
PC4	0.02	-0.00, 0.05	0.159	1	-0.01	-0.03, 0.01	<0.001	<0.001
[1]CI = Confidence Interval, [2]Adjusted P (Bonferroni correction)								

All analyses were adjusted for age at recruitment, smoking status, education, and physical activity , including sex in the analysis for all sample. BMI: body mass index; WHR: waist to hip ratio; ABSI: a body shape index; PC: principal component. PC1: overall adiposity; PC2: tall with low waist to hip ratio; PC3: tall with large waist to hip ratio, PC4: high BMI and weight with low waist circumference and hip circumference.

Table S17. Associations between anthropometric indexes and C-reactive protein (CRP) in the EPIC Study excluding 484 participants with diabetes at baseline.

CRP – EPIC								
	Men				Women			
	N=4,785				N=11,238			
	Beta	**95% CI[1]**	***P***	***P*[2]**	**Beta**	**95% CI[1]**	***P***	***P*[2]**
Height z-score	-0.11	-0.14, -0.07	<0.001	<0.001	-0.09	-0.12, -0.06	<0.001	<0.001
Weight z-score	0.25	0.22, 0.28	<0.001	<0.001	0.39	0.37, 0.41	<0.001	<0.001
BMI z-score	0.36	0.33, 0.39	<0.001	<0.001	0.38	0.36, 0.40	<0.001	<0.001
Waist circumference z-score	0.39	0.35, 0.42	<0.001	<0.001	0.44	0.42, 0.46	<0.001	<0.001
Waist to Height z-score	0.40	0.36, 0.43	<0.001	<0.001	0.41	0.39, 0.42	<0.001	<0.001
Hip circumference z-score	0.29	0.26, 0.32	<0.001	<0.001	0.31	0.29, 0.33	<0.001	<0.001
Waist to hip ratio z-score	0.34	0.30, 0.38	<0.001	<0.001	0.34	0.31, 0.36	<0.001	<0.001
Waist to Hip index z score	0.14	0.10, 0.18	<0.001	<0.001	0.07	0.05, 0.10	<0.001	<0.001
ABSI index z-score	0.19	0.16, 0.23	<0.001	<0.001	0.15	0.12, 0.17	<0.001	<0.001
Hip index z-score	0.00	-0.03,0.04	0.847	1	0.02	-0.00,0.04	0.083	1
PC1	0.27	0.24, 0.30	<0.001	<0.001	0.36	0.34, 0.37	<0.001	<0.001
PC2	-0.08	-0.10, -0.05	<0.001	<0.001	-0.09	-0.11, -0.07	<0.001	<0.001
PC3	0.02	-0.00, 0.05	0.060	0.840	-0.05	-0.07, -0.03	<0.001	<0.001
PC4	0.03	0.00, 0.05	0.013	0.182	-0.01	-0.03, 0.00	0.121	1
[1]CI = Confidence Interval, [2]Adjusted P (Bonferroni correction)								

All analyses were adjusted for age at recruitment, smoking status, education, and physical activity , including sex in the analysis for all sample. BMI: body mass index; WHR: waist to hip ratio; ABSI: a body shape index; PC: principal component. PC1: overall adiposity; PC2: tall with low waist to hip ratio; PC3: tall with large waist to hip ratio, PC4: high BMI and weight with low waist circumference and hip circumference.

Table S18. Associations between anthropometric indexes and C-reactive protein (CRP) in UK Biobank excluding 102,020 participants with CVD at baseline defined as myocardial infarction (heart attack), stroke, or hypertension.

CRP – UK Biobank								
	Men				**Women**			
	N= 109,965				N= 133,151			
	Beta	**95% CI[1]**	***P***	***P*[2]**	**Beta**	**95% CI[1]**	***P***	***P*[2]**
Height z-score	-0.06	-0.07, -0.05	<0.001	<0.001	-0.11	-0.12, -0.10	<0.001	<0.001
Weight z-score	0.31	0.31, 0.32	<0.001	<0.001	0.53	0.52, 0.54	<0.001	<0.001
BMI z-score	0.39	0.39, 0.40	<0.001	<0.001	0.50	0.49, 0.50	<0.001	<0.001
Waist circumference z-score	0.42	0.41, 0.42	<0.001	<0.001	0.54	0.54, 0.55	<0.001	<0.001
Waist to Height z-score	0.43	0.42, 0.43	<0.001	<0.001	0.50	0.49, 0.50	<0.001	<0.001
Hip circumference z-score	0.32	0.31, 0.32	<0.001	<0.001	0.40	0.40, 0.41	<0.001	<0.001
Waist to hip ratio z-score	0.41	0.40, 0.42	<0.001	<0.001	0.40	0.40, 0.41	<0.001	<0.001
Waist to Hip index z score	0.23	0.22, 0.24	<0.001	<0.001	0.06	0.06, 0.07	<0.001	<0.001
ABSI index z-score	0.17	0.17, 0.18	<0.001	<0.001	0.15	0.14, 0.15	<0.001	<0.001
Hip index z-score	-0.15	-0.16, -0.14	<0.001	<0.001	0.01	0.00, 0.02	0.003	0.039
PC1	0.18	0.18, 0.18	<0.001	<0.001	0.25	0.24, 0.25	<0.001	<0.001
PC2	-0.10	-0.11, -0.10	<0.001	<0.001	-0.12	-0.12, -0.11	<0.001	<0.001
PC3	0.09	0.08, 0.10	<0.001	<0.001	-0.09	-0.10, -0.09	<0.001	<0.001
PC4	0.18	0.16, 0.20	<0.001	<0.001	-0.15	-0.17, -0.14	<0.001	<0.001
[1]CI = Confidence Interval, [2]Adjusted P (Bonferroni correction)								

All analyses were adjusted for age at recruitment, smoking status, education, and physical activity. BMI: body mass index; WHR: waist to hip ratio; ABSI: a body shape index; PC: principal component. PC1: overall adiposity; PC2: tall with low waist to hip ratio; PC3: tall with large waist to hip ratio, PC4: high BMI and weight with low waist circumference and hip circumference.

Table S19. Associations between anthropometric indexes and C-reactive protein (CRP) in UK Biobank excluding 26,365 participants with diabetes at baseline.

CRP – UK Biobank								
	Men				Women			
	N= 151,737				N= 167,044			
	Beta	**95% CI[1]**	***P***	***P*[2]**	**Beta**	**95% CI[1]**	***P***	***P*[2]**
Height z-score	-0.06	-0.07, -0.06	<0.001	<0.001	-0.11	-0.12, -0.10	<0.001	<0.001
Weight z-score	0.30	0.29, 0.30	<0.001	<0.001	0.52	0.51, 0.52	<0.001	<0.001
BMI z-score	0.37	0.37, 0.38	<0.001	<0.001	0.48	0.48, 0.48	<0.001	<0.001
Waist circumference z-score	0.40	0.39, 0.40	<0.001	<0.001	0.53	0.53, 0.54	<0.001	<0.001
Waist to Height z-score	0.41	0.40, 0.41	<0.001	<0.001	0.49	0.48, 0.49	<0.001	<0.001
Hip circumference z-score	0.30	0.29, 0.30	<0.001	<0.001	0.39	0.39, 0.40	<0.001	<0.001
Waist to hip ratio z-score	0.39	0.39, 0.40	<0.001	<0.001	0.40	0.39, 0.40	<0.001	<0.001
Waist to Hip index z score	0.22	0.21, 0.22	<0.001	<0.001	0.06	0.05, 0.06	<0.001	<0.001
ABSI index z-score	0.17	0.16, 0.17	<0.001	<0.001	0.15	0.14, 0.15	<0.001	<0.001
Hip index z-score	-0.14	-0.15, -0.13	<0.001	<0.001	0.02	0.01, 0.02	<0.001	<0.001
PC1	0.17	0.17, 0.17	<0.001	<0.001	0.24	0.24, 0.24	<0.001	<0.001
PC2	-0.10	-0.10, -0.10	<0.001	<0.001	-0.12	-0.12, -0.11	<0.001	<0.001
PC3	0.08	0.07, 0.09	<0.001	<0.001	-0.10	-0.10, -0.09	<0.001	<0.001
PC4	0.17	0.16, 0.18	<0.001	<0.001	-0.14	-0.16, -0.13	<0.001	<0.001
[1]CI = Confidence Interval, [2]Adjusted P (Bonferroni correction)								

All analyses were adjusted for age at recruitment, smoking status, education, and physical activity. BMI: body mass index; WHR: waist to hip ratio; ABSI: a body shape index; PC: principal component. PC1: overall adiposity; PC2: tall with low waist to hip ratio; PC3: tall with large waist to hip ratio, PC4: high BMI and weight with low waist circumference and hip circumference.

Table S20. Associations between anthropometric indexes and C-reactive protein (CRP) in UK Biobank additionally adjusted for ethnicity.

CRP – UK Biobank								
	Men				Women			
	N= 199,506				N= 226,717			
	Beta	**95% CI[1]**	***P***	***P*[2]**	**Beta**	**95% CI[1]**	***P***	***P*[2]**
Height z-score	-0.07	-0.08, -0.06	<0.001	<0.001	-0.12	-0.13, -0.11	<0.001	<0.001
Weight z-score	0.30	0.29, 0.30	<0.001	<0.001	0.52	0.52, 0.53	<0.001	<0.001
BMI z-score	0.36	0.36, 0.37	<0.001	<0.001	0.47	0.47, 0.48	<0.001	<0.001
Waist circumference z-score	0.39	0.38, 0.39	<0.001	<0.001	0.53	0.53, 0.54	<0.001	<0.001
Waist to Height z-score	0.40	0.39, 0.40	<0.001	<0.001	0.48	0.48, 0.49	<0.001	<0.001
Hip circumference z-score	0.30	0.29, 0.31	<0.001	<0.001	0.39	0.39, 0.40	<0.001	<0.001
Waist to hip ratio z-score	0.39	0.39, 0.40	<0.001	<0.001	0.41	0.41, 0.42	<0.001	<0.001
Waist to Hip index z score	0.22	0.21, 0.22	<0.001	<0.001	0.07	0.06, 0.08	<0.001	<0.001
ABSI index z-score	0.18	0.17, 0.18	<0.001	<0.001	0.16	0.16, 0.17	<0.001	<0.001
Hip index z-score	-0.13	-0.14, -0.13	<0.001	<0.001	0.02	0.01, 0.02	<0.001	<0.001
PC1	0.17	0.17, 0.17	<0.001	<0.001	0.24	0.24, 0.24	<0.001	<0.001
PC2	-0.11	-0.11, -0.10	<0.001	<0.001	-0.13	-0.14, -0.13	<0.001	<0.001
PC3	0.07	0.07, 0.08	<0.001	<0.001	-0.10	-0.11, -0.10	<0.001	<0.001
PC4	0.19	0.17, 0.20	<0.001	<0.001	-0.14	-0.16, -0.13	<0.001	<0.001
[1]CI = Confidence Interval, [2]Adjusted P (Bonferroni correction)								

All analyses were adjusted for age at recruitment, smoking status, education, physical activity, and ethnicity. BMI: body mass index; WHR: waist to hip ratio; ABSI: a body shape index; PC: principal component. PC1: overall adiposity; PC2: tall with low waist to hip ratio; PC3: tall with large waist to hip ratio, PC4: high BMI and weight with low waist circumference and hip circumference.

Table S21. Associations between body shape phenotypes and C-reactive protein (CRP) in the EPIC study excluding age as a confounder.

CRP – EPIC								
	Men				Women			
	N= 5,546				N= 12,397			
	Beta	**95% CI[1]**	***P***	**Adjusted *P***	**Beta**	**95% CI[1]**	***P***	**Adjusted *P***
PC1	0.26	0.24, 0.29	<0.001	<0.001	0.36	0.34, 0.37	<0.001	<0.001
PC2	-0.10	-0.12, -0.07	<0.001	<0.001	-0.10	-0.12, -0.08	<0.001	<0.001
PC3	0.04	0.01, 0.07	0.004	0.004	-0.05	-0.07, -0.03	<0.001	<0.001
PC4	0.03	0.00, 0.05	0.023	0.023	-0.01	-0.03, 0.00	0.132	0.527
[1] CI = Confidence Interval								

All analyses were adjusted for smoking status, education, and physical activity. PC: principal component; PC1: overall adiposity; PC2: tall with low waist to hip ratio; PC3: tall with large waist to hip ratio, PC4: high BMI and weight with low waist circumference and hip circumference.

Table S21. Associations between body shape phenotypes and C-reactive protein (CRP) in the EPIC study excluding age as a confounder.

CRP – EPIC								
	Men				Women			
	N= 5,546				N= 12,397			
	Beta	**95% CI[1]**	***P***	**Adjusted *P***	**Beta**	**95% CI[1]**	***P***	**Adjusted *P***
PC1	0.26	0.24, 0.29	<0.001	<0.001	0.36	0.34, 0.37	<0.001	<0.001
PC2	-0.10	-0.12, -0.07	<0.001	<0.001	-0.10	-0.12, -0.08	<0.001	<0.001
PC3	0.04	0.01, 0.07	0.004	0.004	-0.05	-0.07, -0.03	<0.001	<0.001
PC4	0.03	0.00, 0.05	0.023	0.023	-0.01	-0.03, 0.00	0.132	0.527

[1] **CI = Confidence Interval**

All analyses were adjusted for smoking status, education, and physical activity. PC: principal component; PC1: overall adiposity; PC2: tall with low waist to hip ratio; PC3: tall with large waist to hip ratio, PC4: high BMI and weight with low waist circumference and hip circumference.

Table S22. Associations between anthropometric indexes and C-reactive protein (CRP) in UK Biobank study excluding age as a confounder.

CRP – UK Biobank								
	Men				**Women**			
	N= 199,506				N= 226,717			
	Beta	**95% CI[1]**	***P***	**Adjusted *P***	**Beta**	**95% CI[1]**	***P***	**Adjusted *P***
PC1	0.16	0.16, 0.17	<0.001	<0.001	0.24	0.24, 0.24	<0.001	<0.001
PC2	-0.10	-0.11, -0.10	<0.001	<0.001	-0.13	-0.13, -0.12	<0.001	<0.001
PC3	0.08	0.07, 0.08	<0.001	<0.001	-0.10	-0.11, -0.10	<0.001	<0.001
PC4	0.18	0.16, 0.19	<0.001	<0.001	-0.14	-0.15, -0.12	<0.001	<0.001
[1] CI = Confidence Interval								

All analyses were adjusted for smoking status, education, and physical activity. PC: principal component. PC1: overall adiposity; PC2: tall with low waist to hip ratio; PC3: tall with large waist to hip ratio, PC4: high BMI and weight with low waist circumference and hip circumference.

ANNEX IV

SUPPLEMENTARY MATERIAL STUDY IV

Nature or nurture: genetic and environmental predictors of adiposity gain in adults

Laia Peruchet-Noray, Niki Dimou, Reynalda Cordova, …,
Catalina Bonet, Heinz Freisling, Robert Carreras-Torres

Under review in eBioMedicine

Supplemental text

The EPIC study is a prospective multicentre European cohort with most of the participants aged between 35 and 65 years and selected from the general population. However, female employees in state schools were recruited in France, women who had participated in breast cancer screening were included in Utrecht (the Netherlands) and Florence (Italy), and in some centres in Spain and Italy, registered members from blood donor registries were selected. Half of the participants from the Oxford (UK) center recruited groups of vegetarians and vegans.[1,2] Data from Greece and Norway were unavailable for this analysis. All participants provided written informed consent, and approval for the study was obtained from the International Agency for Research on Cancer (IARC) ethics review panel (No. 20-34) and from all recruiting institutions.

Body weight and height were measured in kg and m at the first and third decimal place, respectively. BMI was calculated dividing body weight (kg) by squared height (m2). Depending on the center, WC was measured either at the narrowest torso circumference or midway between the lower ribs and the iliac crest. HC was determined horizontally either at the widest point or over the buttocks.[3] WHR was calculated as WC (cm) divided by HC (cm).

A total of 245,699 and 44,190 cancer free EPIC participants with BMI and WHR data, respectively, and without genome-wide data, were used to train the environmental models. Exclusion criteria of participants included prevalent cancer at recruitment, incident cancer between recruitment and one year after follow-up assessment, being younger than 25 or older than 65 years old at recruitment, having unrealistic anthropometric measurements, having unrealistic change per year of weight or waist circumference, and having missing anthropometric and covariable data (Figure S1).

Predictors included in the proportional hazard model were selected using a stepwise forward model selection based on the Akaike Information Criterion (AIC). Potential predictors included 40 socio-demographic characteristics such as age, country, sex and level of education, as well as lifestyle factors including the anthropometric trait at baseline, smoke (status and intensity), physical activity, alcohol intake (at recruitment and pattern) and up to 30 different food groups (alcoholic beverages; cakes and biscuits; carbonated/soft/isotonic drinks, diluted syrups; cereal and cereal products; coffee, tea, herbal teas; condiments and sauces; dairy products; egg and egg products; fat; fish and shellfish; fruit and vegetable juices; fruits, nuts and seeds; legumes; meat and meat products; miscellaneous; non-alcoholic beverages; potatoes and other tubers; soups, bouillons; sugar and confectionary; USDA Alcohol, ethyl (g); USDA Carbohydrate, by difference (g); USDA Energy (kcal); USDA Protein (g); USDA Total lipid (fat)(g); vegetables; waters; and the four NOVA groups which assess the level of food processing). Food groups were measured in grams per day (g/day), unless otherwise indicated.

The 5-year absolute risks for each participant were obtained combining the Cox relative risks with the baseline survivor function.[4,5] According to the baseline probability survival function, approximately the 17% and 22% of the population are expected to experience a 5% gain in BMI and WHR gain in 5 years, respectively.

Genome-wide data on 29,953 EPIC participants from 20 case-control studies were included for this analysis after excluding individuals with cancer at baseline and 1 year subsequent. DNA samples were genotyped through different genotyping platforms. Genetic data were normalized, centralised, and imputed at the International Agency for Research on Cancer (IARC). Normalization across studies was performed to complete information on chromosome, position, and allele codes, harmonize the genome build version between studies, fix the strand orientation on the positive strand, and standardize the genetic variants annotation. Centralisation was based on the following exclusions: sample and genetic variants call rate (cut off $> 90\%$), sex discrepancies between genotype and phenotype, close relatives (>0.8), and population outliers to mitigate the variance introduced by diverse ancestries. Imputation was performed by the Michigan imputation server using the 1000 Genomes Project Phase 3 v5[6] as reference panel in the Genome Reference Consortium Human Build 37. Finally, post-imputation quality control was performed keeping the genetic variants by minor allele frequency (MAF) > 0.01 and imputation info-score > 0.3.

To develop the Bayesian-based PRS, we obtained summary statistics from the latest and largest GWAS of BMI, WHR, and PC1-3.[7,8] We performed a quality control on these GWAS results filtering them by MAF > 0.01 and imputation info-score > 0.8. Duplicated and palindromic genetic variants were excluded. PRS were computed on 5 obesity indices of interest (BMI, WHR, and PC1-3) using the LDPred2-auto computation algorithm.[9] LDpred2-auto is a Bayesian approach which has shown to improve its predictive performance compared to other methods for building PRS. LDpred2-auto estimates the regional LD structure using GWAS summary level statistics and a LD reference panel based on 1,444,196 genetic variants from HapMap3.[9] The overlapping genetic variants between the filtered GWAS summary statistics, the reference LD panel, and all EPIC sample were 1,292,486, 1,292,487, and 1,220,244 for BMI, WHR, and the body shape phenotypes, respectively.

We assessed the association between PRSs and BMI and WHR gain, separately, using Cox proportional hazard models. These were adjusted for age at baseline, country, sex, first ten genetic PCs, batch, and BMI or WHR at baseline. As sensitivity analyses, these were additionally adjusted for alcohol intake (g/d), smoking status (never, former, smoker, unknown), education level [none, primary school completed, technical/professional school, secondary school, longer education (including University degree), not specified], menopausal status [premenopausal, postmenopausal, perimenopausal, surgical postmenopausal (bilateral ovariectomy)], hormonal-replacement therapy (HRT) intake (yes, no), physical activity (inactive, moderately inactive, moderately active, active, unknown), Mediterranean diet score (low, medium, high) [10], and energy intake (kcal). Analyses were performed by sex, North and South Europe, and above and below median baseline age (55 years). North Europe category included participants from the UK, the Netherlands, Germany, Sweden, Denmark, and centers of Ile-de-France, North-West and North-East of France. South Europe category included Italy and Spain and centers of Rhone-Alpes/Auvergne, Provence/Languedoc, and South-West of France.

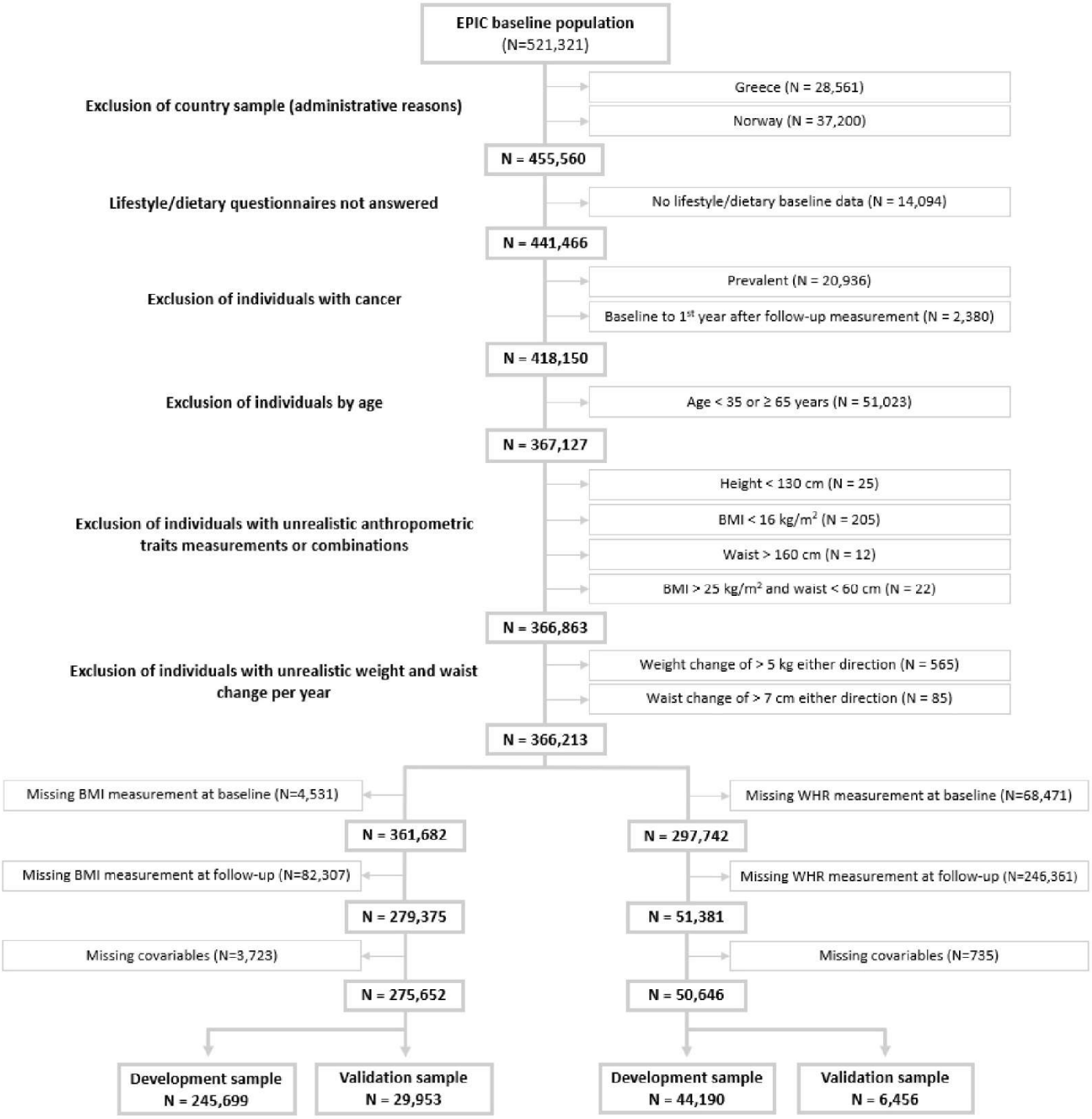


Figure S1. Flowchart of the EPIC study population. Covariables included in the BMI gain model were age, country, sex, BMI at baseline, smoking status, level of education, physical activity, alcohol intake, cakes and biscuits, condiments and sauces, egg and egg products, fish and shellfish, meat and meat products, and processed culinary ingredients (NOVA 2). For WHR gain, the model included age, country, sex, WHR at baseline, smoking status, level of education, physical activity, condiments and sauces, fat, meat and meat products, and potatoes and other tubers. BMI, body mass index; WHR, waist-hip ratio.

Table S1. Genotyping platform and sample size for each EPIC case-control study. CVD, cardiovascular disease; UADT, upper aerodigestive tract.

Study acronym	Endpoint	Genotyping platform	N participants
GW_BREA_01	Breast cancer	Illumina Human 660W-Quad	645
GW_BREA_02	Breast cancer	Illumina Infinium OncoArray-500k	4,591
GW_CLRT_01	Colorectal cancer	Illumina Human OmniExpress Exome-8v1-2	2,156
GW_ECVD_01	CVD	Illumina HumanCoreExome v24	3,606
GW_GLBD_01	Gallbladder cancer	Illumina Infinium Global Screening Array	60
GW_INTE_01	Diabetes	Illumina Human 660W-Quad	5,618
GW_INTE_02	Diabetes	Illumina HumanCoreExome v12	4,374
GW_INTE_03	Diabetes	Illumina HumanCoreExome v24	4,086
GW_KIDN_01	Renal cancer	Illumina Infinium 610-Quad	139
GW_KIDN_02	Renal cancer	Illumina Infinium Omni5	173
GW_LUNG_01	Lung cancer	Illumina Infinium OncoArray-500k	977
GW_LYMP_01	Lymphoma	Illumina OmniExpress	244
GW_OVAR_01	Ovarian cancer	Illumina Infinium OncoArray-500k	606
GW_PANC_01	Pancreatic cancer	Illumina HumanHap550	264
GW_PANC_02	Pancreatic cancer	Illumina Human OmniExpress	69
GW_PROS_01	Prostate cancer	Illumina Human 660W-Quad	394
GW_PROS_03	Prostate cancer	Illumina Infinium OncoArray-500k	847
GW_PROS_04	Prostate cancer	Illumina Infinium Global Screening Array	908
GW_STOM_01	Stomach cancer	Illumina Human 660W-Quad	73
GW_UADT_01	UADT cancer	Illumina Infinium OncoArray-500k	123

Table S2. Baseline characteristics of the study population. BMI, body mass index; WHR, waist-hip ratio.

	BMI		WHR	
	Development sample (N=245,699)	**Validation sample (N=29,953)**	**Development sample (N=44,190)**	**Validation sample (N=6,456)**
Age (years)	51 (± 7.4)	53 (± 7.3)	50 (± 7.0)	52 (± 6.9)
Age at follow-up (years)	59 (± 8.0)	60 (± 7.8)	62 (± 7.2)	64 (± 7.0)
BMI (kg/m^2) / WHR	25 (± 4.1)	27 (± 4.5)	0.81 (± 0.089)	0.84 (± 0.093)
BMI (kg/m^2) / WHR at follow-up	26 (± 4.1)	27 (± 4.4)	0.86 (± 0.090)	0.88 (± 0.094)
Sex				
Male	75,027 (30.5 %)	13,240 (44.2 %)	10,244 (23.2 %)	1,930 (29.9 %)
Female	170,672 (69.5 %)	16,713 (55.8 %)	33,946 (76.8 %)	4,526 (70.1 %)
Country				
France	49,663 (20.2 %)	1,318 (4.4 %)	14,962 (33.9 %)	1,315 (20.4 %)
Italy	28,354 (11.5 %)	4,827 (16.1 %)	21,295 (48.2 %)	4,091 (63.4 %)
Spain	31,310 (12.7 %)	6,627 (22.1 %)	0 (0.0 %)	0 (0.0 %)
United Kingdom	29,860 (12.2 %)	3,063 (10.2 %)	0 (0.0 %)	0 (0.0 %)
The Netherlands	7,933 (3.2 %)	1,050 (3.5 %)	7,933 (18.0 %)	1,050 (16.3 %)
Germany	36,509 (14.9 %)	6,528 (21.8 %)	0 (0.0 %)	0 (0.0 %)
Sweden	23,172 (9.4 %)	2,511 (8.4 %)	0 (0.0 %)	0 (0.0 %)
Denmark	38,898 (15.8 %)	4,029 (13.5 %)	0 (0.0 %)	0 (0.0 %)
Smoke Status				
Never	126,088 (51.3 %)	13,663 (45.6 %)	22,659 (51.3 %)	3,104 (48.1 %)
Former	66,206 (26.9 %)	8,484 (28.3 %)	11,907 (26.9 %)	1,776 (27.5 %)
Smoker	50,279 (20.5 %)	7,659 (25.6 %)	8,712 (19.7 %)	1,479 (22.9 %)
Unknown	3,126 (1.3 %)	147 (0.5 %)	912 (2.1 %)	97 (1.5 %)
Education level				
None	11,063 (4.5 %)	2,662 (8.9 %)	175 (0.4 %)	42 (0.7 %)
Primary school completed	60,579 (24.7 %)	9,843 (32.9 %)	12,306 (27.8 %)	2,365 (36.6 %)
Technical/professional school	52,877 (21.5 %)	6,957 (23.2 %)	6,080 (13.8 %)	971 (15.0 %)
Secondary school	50,973 (20.7 %)	3,883 (13.0 %)	14,292 (32.3 %)	1,860 (28.8 %)
Longer education	65,859 (26.8 %)	6,085 (20.3 %)	11,337 (25.7 %)	1,218 (18.9 %)
Not specified	4,348 (1.8 %)	523 (1.7 %)	0 (0.0 %)	0 (0.0 %)
Physical activity				
Inactive	48,893 (19.9 %)	6,976 (23.3 %)	7,047 (15.9 %)	1,166 (18.1 %)
Moderately inactive	87,184 (35.5 %)	10,724 (35.8 %)	16,840 (38.1 %)	2,561 (39.7 %)
Moderately active	62,522 (25.4 %)	6,678 (22.3 %)	11,111 (25.1 %)	1,461 (22.6 %)
Active	45,205 (18.4 %)	5,354 (17.9 %)	7,474 (16.9 %)	1,076 (16.7 %)
Missing	1,895 (0.8 %)	221 (0.7 %)	1,718 (3.9 %)	192 (3.0 %)
Alcohol intake (g/day)	13 (± 18)	15 (± 20)	13 (± 17)	14 (± 18)
Cakes and biscuits (g/day)	42 (± 44)	44 (± 50)	41 (± 41)	41 (± 41)
Condiments and sauces (g/day)	21 (± 19)	18 (± 18)	21 (± 16)	19 (± 16)
Egg and egg products (g/day)	20 (± 18)	19 (± 17)	19 (± 16)	18 (± 14)
Fat (g/day)	27 (± 17)	30 (± 17)	28 (± 16)	30 (± 16)
Fish and shellfish (g/day)	36 (± 31)	39 (± 35)	28 (± 23)	28 (± 23)
Meat and meat products (g/day)	110 (± 61)	120 (± 63)	110 (± 54)	110 (± 53)
Potatoes and other tubers (g/day)	90 (± 73)	94 (± 74)	55 (± 54)	51 (± 55)
Processed culinary ingredients NOVA 2 (g/day)	32 (± 24)	33 (± 24)	43 (± 23)	44 (± 23)

Table S3. Beta estimates for the association of retained predictors with BMI or WHR gain. $N_{BMI\ gain}$ = 245,699 and $N_{WHR\ gain}$ = 44,190 from the EPIC cohort. PRS were estimated in 47,014 from UK Biobank. BMI, body mass index; PC, principal component; PRS, polygenic risk score; SD, standard deviation; WHR, waist-hip ratio.

Predictor	β BMI gain	β WHR gain
Age (per year)	-0.030	Not included
BMI/WHR at baseline (per SD)	-0.175	-1.030
Italy (vs France)	-0.0002	0.567
Spain (vs France)	0.480	No WHR follow-up data available
United Kingdom (vs France)	0.651	No WHR follow-up data available
The Netherlands (vs France)	0.197	0.704
Germany (vs France)	0.420	No WHR follow-up data available
Sweden (vs France)	0.564	No WHR follow-up data available
Denmark (vs France)	0.134	No WHR follow-up data available
Smoking (Former vs Never)	0.006	0.030
Smoking (Smoker vs Never)	0.235	0.114
Smoking (Unknown vs Never)	0.034	0.085
Sex (Female vs Male)	0.201	-1.148
Primary school completed (vs None)	-0.243	-0.204
Technical/professional school (vs None)	-0.287	-0.219
Secondary school (vs None)	-0.332	-0.319
Longer education (vs None)	-0.427	-0.357
Unknown education (vs None)	-0.213	No data available
Moderately inactive (vs Inactive)	-0.063	-0.073
Moderately active (vs Inactive)	-0.116	-0.061
Active (vs Inactive)	-0.153	-0.050
Unknown (vs Inactive)	-0.150	-0.175
Alcohol intake (g/day)	-0.002	Not included
Meat and meat products (g/day)	0.001	0.001
Egg and egg products (g/day)	0.003	Not included
Processed culinary ingredients - NOVA 2 (g/day)	-0.003	Not included
Cakes and biscuits (g/day)	-0.001	Not included
Condiments and sauces (g/day)	0.002	0.001
Fish and shellfish (g/day)	0.001	Not included
Potatoes and other tubers (g/day)	Not included	0.001
Fat (g/day)	Not included	-0.002
PRS BMI	0.185	Not assessed
PRS WHR	Not assessed	0.065
PRS PC1	0.158	0.069
PRS PC2	0.079	0.015
PRS PC3	-0.061	0.012

Table S4. Beta estimates for the association of retained predictors with BMI or WHR gain for predictions models excluding country. $N_{BMI\ gain}$ = 245,699 and $N_{WHR\ gain}$ = 44,190 from the EPIC cohort. PRS were estimated in 47,014 from UK Biobank. BMI, body mass index; PC, principal component; PRS, polygenic risk score; SD, standard deviation; WHR, waist-hip ratio.

Predictor	β BMI gain	β WHR gain
Age (per year)	-0.035	Not included
BMI/WHR at baseline (per SD)	-0.039	-1.014
Smoking (Former vs Never)	0.007	0.079
Smoking (Smoker vs Never)	0.236	0.213
Smoking (Unknown vs Never)	-0.039	-0.059
Sex (Female vs Male)	0.076	-1.296
Primary school completed (vs None)	-0.430	-0.178
Technical/professional school (vs None)	-0.403	-0.131
Secondary school (vs None)	-0.585	-0.413
Longer education (vs None)	-0.623	-0.469
Unknown education (vs None)	-0.141	No data available
Moderately inactive (vs Inactive)	-0.084	-0.072
Moderately active (vs Inactive)	-0.114	-0.088
Active (vs Inactive)	-0.187	-0.012
Unknown (vs Inactive)	-0.215	0.080
Alcohol intake (g/day)	-0.003	Not included
Meat and meat products (g/day)	0.001	0.001
Egg and egg products (g/day)	0.001	Not included
Processed culinary ingredients - NOVA 2 (g/day)	-0.006	Not included
Condiments and sauces (g/day)	0.005	-0.003
Fish and shellfish (g/day)	0.001	Not included
Fat (g/day)	Not included	0.004
PRS BMI	0.185	Not assessed
PRS WHR	Not assessed	0.065
PRS PC1	0.158	0.069
PRS PC2	0.079	0.015
PRS PC3	-0.061	0.012

Table S5. Area Under de Curve (AUC) and 95% confidential intervals for BMI and WHR gain. We report environmental models for overall, by sex, and by European region. BMI, body mass index; WHR, waist-hip ratio.

	BMI gain	WHR gain
Overall	0.6873 (0.6786-0.6961)	0.7519 (0.7377-0.7661)
Men	0.6961 (0.6821-0.7101)	0.7511 (0.7232-0.7790)
Women	0.6779 (0.6666-0.6893)	0.7478 (0.7312-0.7643)
North Europe	0.6486 (0.6379-0.6593)	0.7187 (0.6900-0.7474)
South Europe	0.7744 (0.7581-0.7907)	0.7661 (0.7501-0.7821)

Table S6. Area Under de Curve (AUC) and 95% confidential intervals for BMI and WHR gain. We report environmental models for overall, and by BMI categories. BMI, body mass index; WHR, waist-hip ratio.

	N	BMI gain	N	WHR gain
Overall	29,953	0.6873 (0.6786-0.6961)	6,456	0.7519 (0.7377-0.7661)
Healthy (BMI: 18.5-24.9)	9,936	0.6747 (0.6616-0.6877)	3,063	0.7680 (0.7495-0.7864)
Overweight (BMI: 25.0-29.9)	11,546	0.7052 (0.6906-0.7198)	2,191	0.7524 (0.7277-0.7771)
Obesity (BMI: 30.0 or above)	6,099	0.6988 (0.6745-0.7231)	856	0.6927 (0.6435-0.7420)

Table S7. Associations between polygenic risk scores and BMI and WHR gain. We report associations between PRSs of BMI and PC1-3 for BMI gain and PRS of WHR and PC1-3 for WHR gain. Model 1 was adjusted by the corresponding anthropometric trait at baseline, center, sex, age at recruitment, genetic PC1-10, and genetic study (batch). Model 2 was additionally adjusted by menopausal status, use of hormone-replace therapy, alcohol intake (g/day), smoking status, education level, physical activity, Mediterranean diet score, and energy intake. BMI, body mass index; PC, principal component; PRS, polygenic risk score; WHR, waist-hip ratio.

		BMI gain		WHR gain	
	MODEL	**N**	**HR (95% CI); p-value**	**N**	**HR (95% CI); p-value**
BMI/WHR PRS	1	29,953	**1.138 (1.108, 1.169); <0.001**	6,456	**1.127 (1.086, 1.169); <0.001**
	2	26,452	**1.113 (1.081, 1.146); <0.001**	4,902	**1.116 (1.070, 1.163); <0.001**
PC1 PRS	1	29,953	**1.111 (1.082, 1.140); <0.001**	6,456	**1.079 (1.042, 1.118); <0.001**
	2	26,452	**1.084 (1.054, 1.116); <0.001**	4,902	**1.073 (1.031, 1.117); 0.001**
PC2 PRS	1	29,953	**1.067 (1.039, 1.096); <0.001**	6,456	1.035 (0.997, 1.074); 0.070
	2	26,452	**1.050 (1.020, 1.081); 0.001**	4,902	1.033 (0.991, 1.078); 0.126
PC3 PRS	1	29,953	**0.938 (0.915, 0.962); <0.001**	6,456	**1.035 (1.000, 1.072); 0.048**
	2	26,452	**0.939 (0.914, 0.964); <0.001**	4,902	1.024 (0.985, 1.065); 0.230

Table S8. Associations between polygenic risk scores and BMI gain by sex, European region, and age. Model 1 was adjusted by the corresponding BMI at baseline, center, sex (except in among men and women), age at recruitment, genetic PC1-10, and genetic study (batch). Model 2 was additionally adjusted by menopausal status (except among men), use of hormone-replace therapy (except among men), alcohol intake (g/day), smoking status, education level, physical activity, Mediterranean diet score, and energy intake. North Europe category included participants from The United Kingdom, The Netherlands, Germany, Sweden, Denmark, and centers of Ile-de-France, North-West, and North-East of France. South Europe included participants from Italy and Spain, and centers of Rhone-Alpes/Auvergne, Provence/Languedoc, and South-West of France. Age threshold was fixed at 55 years old (y). BMI, body mass index; PC, principal component; PRS, polygenic risk score; WHR, waist-hip ratio.

			BMI gain		
	MODEL	**N Men**	**HR (95% CI); p-value**	**N Women**	**HR (95% CI); p-value**
BMI PRS	1	13,240	**1.148 (1.098, 1.200); <0.001**	16,713	**1.138 (1.100, 1.178); <0.001**
	2	12,258	**1.105 (1.055, 1.157); <0.001**	14,194	**1.122 (1.080, 1.166); <0.001**
PC1 PRS	1	13,240	**1.109 (1.062, 1.157); <0.001**	16,713	**1.117 (1.080, 1.155); <0.001**
	2	12,258	**1.075 (1.028, 1.124); 0.002**	14,194	**1.094 (1.054, 1.136); <0.001**
PC2 PRS	1	13,240	**1.077 (1.031, 1.126); 0.001**	16,713	**1.059 (1.024, 1.096); 0.001**
	2	12,258	**1.061 (1.014, 1.111); 0.011**	14,194	**1.041 (1.002, 1.081); 0.041**
PC3 PRS	1	13,240	**0.946 (0.908, 0.986); 0.008**	16,713	**0.932 (0.903, 0.961); <0.001**
	2	12,258	**0.956 (0.916, 0.998); 0.039**	14,194	**0.925 (0.893, 0.958); <0.001**
	MODEL	**N North**	**HR (95% CI); p-value**	**N South**	**HR (95% CI); p-value**
BMI PRS	1	18,046	**1.141 (1.103, 1.180); <0.001**	11,907	**1.134 (1.084, 1.186); <0.001**
	2	15,624	**1.118 (1.077, 1.161); <0.001**	10,828	**1.098 (1.047, 1.151); <0.001**
PC1 PRS	1	18,046	**1.119 (1.082, 1.156); <0.001**	11,907	**1.098 (1.051, 1.147); <0.001**
	2	15,624	**1.092 (1.053, 1.132); <0.001**	10,828	**1.065 (1.017, 1.116); 0.008**
PC2 PRS	1	18,046	**1.063 (1.027, 1.099); <0.001**	11,907	**1.071 (1.024, 1.120); 0.003**
	2	15,624	**1.051 (1.012, 1.091); 0.009**	10,828	**1.051 (1.002, 1.102); 0.041**
PC3 PRS	1	18,046	**0.942 (0.914, 0.972); <0.001**	11,907	**0.930 (0.892, 0.969); 0.001**
	2	15,624	**0.940 (0.908, 0.973); <0.001**	10,828	**0.933 (0.893, 0.975); 0.002**
	MODEL	**N <55 y**	**HR (95% CI); p-value**	**N ≥55 y**	**HR (95% CI); p-value**
BMI PRS	1	16,922	**1.134 (1.097, 1.173); <0.001**	13,031	**1.157 (1.105, 1.211); <0.001**
	2	15,100	**1.113 (1.073, 1.154); <0.001**	11,352	**1.115 (1.061, 1.172); <0.001**
PC1 PRS	1	16,922	**1.110 (1.074, 1.147); <0.001**	13,031	**1.122 (1.073, 1.173); <0.001**
	2	15,100	**1.085 (1.047, 1.124); <0.001**	11,352	**1.085 (1.033, 1.139); 0.001**
PC2 PRS	1	16,922	**1.055 (1.021, 1.091); 0.001**	13,031	**1.090 (1.041, 1.142); <0.001**
	2	15,100	**1.044 (1.007, 1.082); 0.019**	11,352	**1.058 (1.005, 1.113); 0.030**
PC3 PRS	1	16,922	**0.933 (0.905, 0.962); <0.001**	13,031	**0.942 (0.903, 0.983); 0.006**
	2	15,100	**0.935 (0.904, 0.966); <0.001**	11,352	**0.942 (0.899, 0.987); 0.012**

Table S9. Associations between polygenic risk scores and WHR gain by sex, European region, and age. Model 1 was adjusted by the corresponding WHR at baseline, center, sex (except in among men and women), age at recruitment, genetic PC1-10, and genetic study (batch). Model 2 was additionally adjusted by menopausal status (except among men), use of hormone-replace therapy (except among men), alcohol intake (g/day), smoking status, education level, physical activity, Mediterranean diet score, and energy intake. North Europe category included participants from The United Kingdom, The Netherlands, Germany, Sweden, Denmark, and centers of Ile-de-France, North-West, and North-East of France. South Europe included participants from Italy and Spain, and centers of Rhone-Alpes/Auvergne, Provence/Languedoc, and South-West of France. Age threshold was fixed at 55 years old (y). BMI, body mass index; PC, principal component; PRS, polygenic risk score; WHR, waist-hip ratio.

			WHR gain		
	MODEL	**N Men**	**HR (95% CI); p-value**	**N Women**	**HR (95% CI); p-value**
WHR PRS	1	1,930	**1.155 (1.077, 1.239); <0.001**	4,526	**1.121 (1.073, 1.171); <0.001**
	2	1,830	**1.152 (1.072, 1.238); <0.001**	3,072	**1.105 (1.048, 1.164); <0.001**
PC1 PRS	1	1,930	**1.154 (1.078, 1.234); <0.001**	4,526	**1.058 (1.014, 1.103); 0.009**
	2	1,830	**1.136 (1.059, 1.219); <0.001**	3,072	1.048 (0.997, 1.101); 0.068
PC2 PRS	1	1,930	1.043 (0.972, 1.120); 0.240	4,526	1.033 (0.989, 1.079); 0.147
	2	1,830	1.001 (0.930, 1.078); 0.977	3,072	1.050 (0.996, 1.106); 0.071
PC3 PRS	1	1,930	0.993 (0.927, 1.063); 0.834	4,526	**1.053 (1.011, 1.096); 0.013**
	2	1,830	1.022 (0.951, 1.097); 0.556	3,072	1.029 (0.980, 1.080); 0.247
	MODEL	**N North**	**HR (95% CI); p-value**	**N South**	**HR (95% CI); p-value**
WHR PRS	1	1,914	**1.149 (1.070, 1.233); <0.001**	4,542	**1.122 (1.074, 1.172); <0.001**
	2	945	**1.155 (1.041, 1.282); 0.007**	3,957	**1.118 (1.067, 1.171); <0.001**
PC1 PRS	1	1,914	**1.134 (1.058, 1.214); <0.001**	4,542	**1.056 (1.013, 1.101); 0.010**
	2	945	**1.261 (1.140, 1.393); <0.001**	3,957	1.041 (0.996, 1.088); 0.077
PC2 PRS	1	1,914	1.044 (0.973, 1.122); 0.231	4,542	1.037 (0.992, 1.083); 0.106
	2	945	0.991 (0.902, 1.088); 0.843	3,957	**1.053 (1.005, 1.104); 0.029**
PC3 PRS	1	1,914	1.025 (0.959, 1.095); 0.466	4,542	**1.043 (1.002, 1.086); 0.040**
	2	945	0.986 (0.896, 1.085); 0.767	3,957	1.040 (0.996, 1.087); 0.075
	MODEL	**N <55 y**	**HR (95% CI); p-value**	**N ≥55 y**	**HR (95% CI); p-value**
WHR PRS	1	3,891	**1.142 (1.091, 1.195); <0.001**	2,565	**1.113 (1.045, 1.186); 0.001**
	2	2,921	**1.133 (1.075, 1.194); <0.001**	1,981	**1.095 (1.019, 1.177); 0.013**
PC1 PRS	1	3,891	**1.097 (1.05, 1.146); <0.001**	2,565	**1.065 (1.002, 1.132); 0.044**
	2	2,921	**1.099 (1.045, 1.155); <0.001**	1,981	1.056 (0.985, 1.132); 0.125
PC2 PRS	1	3,891	1.022 (0.975, 1.070); 0.367	2,565	1.057 (0.994, 1.124); 0.079
	2	2,921	1.019 (0.972, 1.068); 0.444	1,981	1.055 (0.982, 1.133); 0.143
PC3 PRS	1	3,891	**1.054 (1.010, 1.101); 0.015**	2,565	0.999 (0.942, 1.060); 0.985
	2	2,921	1.035 (0.985, 1.087); 0.171	1,981	0.992 (0.928, 1.060); 0.808

Table S10. Area Under de Curve (AUC) and 95% confidential intervals for BMI and WHR gain. We report genetic models for overall, by sex, and by European region. BMI, body mass index; PC, principal component; PRS, polygenic risk score; WHR, waist-hip ratio.

	BMI gain			
	BMI PRS	**PC1 PRS**	**PC2 PRS**	**PC3 PRS**
Overall	0.5167 (0.5071-0.5262)	0.5167 (0.5070-0.5263)	0.5345 (0.5248-0.5442)	0.5193 (0.5097-0.5289)
Men	0.5036 (0.4878-0.5193)	0.5016 (0.4863-0.5169)	0.5453 (0.5299-0.5607)	0.5140 (0.4988-0.5293)
Women	0.5254 (0.5130-0.5377)	0.5295 (0.5173-0.5417)	0.5247 (0.5122-0.5372)	0.5209 (0.5085-0.5333)
North Europe	0.5209 (0.5096-0.5322)	0.5215 (0.5101-0.5329)	0.5264 (0.5150-0.5378)	0.5147 (0.5034-0.5260)
South Europe	0.5106 (0.4924-0.5289)	0.5136 (0.4951-0.5320)	0.5503 (0.5319-0.5687)	0.5284 (0.5101-0.5467)
	BMI gain (early adulthood)			
Overall	0.6183 (0.6061-0.6306)	0.6010 (0.5886-0.6133)	0.5313 (0.5184-0.5441)	0.5233 (0.5105-0.5362)
	WHR gain			
	WHR PRS	**PC1 PRS**	**PC2 PRS**	**PC3 PRS**
Overall	0.4716 (0.4548-0.4883)	0.4960 (0.4789-0.5131)	0.4794 (0.4624-0. 4963)	0.4841 (0.4676-0.5006)
Men	0.4835 (0.4501-0.5169)	0.4890 (0.4551-0.5229)	0.4789 (0.4452-0.5127)	0.5061 (0.4733-0.5389)
Women	0.4694 (0.4500-0.4889)	0.5025 (0.4826-0.5224)	0.4767 (0.4570-0.4964)	0.4788 (0.4597-0.4979)
North Europe	0.4837 (0.4523-0.5151)	0.5398 (0.5090-0.5707)	0.4585 (0.4276-0.4894)	0.4920 (0.4616-0.5224)
South Europe	0.4672 (0.4474-0.4871)	0.4777 (0.4574-0.4981)	0.4846 (0.4645-0.5047)	0.4817 (0.4620-0.5013)

Table S11. Area Under de Curve (AUC) and 95% confidential intervals for BMI and WHR gain. We report combined (environmental + genetic) models for overall, by sex, and by European region. BMI, body mass index; PC, principal component; PRS, polygenic risk score; WHR, waist-hip ratio.

	BMI gain			
	BMI PRS	**PC1 PRS**	**PC2 PRS**	**PC3 PRS**
Overall	0.6873 (0.6786-0.6961)	0.6853 (0.6765-0.6940)	0.6893 (0.6805-0.6981)	0.6892 (0.6805-0.6980)
Men	0.6888 (0.6748-0.7028)	0.6919 (0.6780-0.7058)	0.6535 (0.6391-0.6679)	0.6822 (0.6680-0.6964)
Women	0.6829 (0.6716-0.6942)	0.6804 (0.6691-0.6917)	0.6797 (0.6683-0.6911)	0.6972 (0.6832-0.7112)
North Europe	0.6515 (0.6409-0.6622)	0.6500 (0.6393-0.6606)	0.6485 (0.6378-0.6592)	0.6494 (0.6387-0.6601)
South Europe	0.7708 (0.7549-0.7866)	0.7728 (0.7567-0.7889)	0.7755 (0.7593-0.7917)	0.7759 (0.7596-0.7921)
	WHR gain			
	WHR PRS	**PC1 PRS**	**PC2 PRS**	**PC3 PRS**
Overall	0.7547 (0.7405-0.7688)	0.7533 (0.7392-0.7674)	0.7518 (0.7376-0.7660)	0.7521 (0.7379-0.7663)
Men	0.7550 (0.7273-0.7826)	0.7544 (0.7270-0.7819)	0.7510 (0.7230-0.7789)	0.7513 (0.7234-0.7792)
Women	0.7502 (0.7337-0.7667)	0.7487 (0.7322-0.7652)	0.7476 (0.7310-0.7642)	0.7480 (0.7314-0.7646)
North Europe	0.7217 (0.6931-0.7503)	0.7242 (0.6959-0.7526)	0.7182 (0.6894-0.7469)	0.7187 (0.6900-0.7474)
South Europe	0.7687 (0.7528-0.7846)	0.7656 (0.7497-0.7816)	0.7662 (0.7503-0.7822)	0.7663 (0.7503-0.7823)

Table S12. Correlations between environmental score for BMI and WHR gain models and polygenic risk scores. $N_{BMI\ gain}$ = 29,953 and $N_{WHR\ gain}$ = 6,456. BMI, body mass index; PRS, polygenic risk score; WHR, waist-hip ratio.

	BMI gain environmental score	**WHR gain environmental score**
BMI PRS	-0.076	-
WHR PRS	-	-0.237
PC1 PRS	-0.072	-0.126
PC2 PRS	-0.057	0.034
PC3 PRS	-0.010	-0.123

References

[1] Riboli E. The EPIC Project: rationale and study design. European Prospective Investigation into Cancer and Nutrition. Int J Epidemiol 1997;26. https://doi.org/10.1093/ije/26.suppl_1.s6.

[2] Riboli E, Hunt K, Slimani N, Ferrari P, Norat T, Fahey M, et al. European Prospective Investigation into Cancer and Nutrition (EPIC): study populations and data collection. Public Health Nutr 2002;5. https://doi.org/10.1079/phn2002394.

[3] Haftenberger M, Lahmann P, Panico S, Gonzalez C, Seidell J, Boeing H, et al. Overweight, obesity and fat distribution in 50- to 64-year-old participants in the European Prospective Investigation into Cancer and Nutrition (EPIC). Public Health Nutr 2002;5. https://doi.org/10.1079/phn2002396.

[4] Sullivan LM, Massaro JM, D'Agostino RB. Presentation of multivariate data for clinical use: The Framingham Study risk score functions. Stat Med 2004;23. https://doi.org/10.1002/sim.1742.

[5] McLernon DJ, Giardiello D, Van Calster B, Wynants L, van Geloven N, van Smeden M, et al. Assessing Performance and Clinical Usefulness in Prediction Models with Survival Outcomes: Practical Guidance for Cox Proportional Hazards Models. Ann Intern Med 2023;176. https://doi.org/10.7326/M22-0844.

[6] Auton A, Abecasis GR, Altshuler DM, Durbin RM, Bentley DR, Chakravarti A, et al. A global reference for human genetic variation. Nature 2015;526. https://doi.org/10.1038/nature15393.

[7] Pulit SL, Stoneman C, Morris AP, Wood AR, Glastonbury CA, Tyrrell J, et al. Meta-Analysis of genome-wide association studies for body fat distribution in 694 649 individuals of European ancestry. Hum Mol Genet 2019;28. https://doi.org/10.1093/hmg/ddy327.

[8] Peruchet-Noray L, Sedlmeier AM, Dimou N, Baurecht H, Fervers B, Fontvieille E, et al. Tissue-specific genetic variation suggests distinct molecular pathways between body shape phenotypes and colorectal cancer. Sci Adv 2024;10:eadj1987. https://doi.org/10.1126/sciadv.adj1987.

[9] Privé F, Albiñana C, Arbel J, Pasaniuc B, Vilhjálmsson BJ. Inferring disease architecture and predictive ability with LDpred2-auto. The American Journal of Human Genetics 2023;110:2042–55. https://doi.org/https://doi.org/10.1016/j.ajhg.2023.10.010.

[10] Romaguera D, Norat T, Vergnaud AC, Mouw T, May AM, Agudo A, et al. Mediterranean dietary patterns and prospective weight change in participants of the EPIC-PANACEA project. American Journal of Clinical Nutrition 2010;92. https://doi.org/10.3945/ajcn.2010.29482.