


Original Investigation

Associations Between Genetic Obesity Susceptibility and Early Postnatal Fat and Lean Mass

An Individual Participant Meta-analysis

Cathy E. Elks, PhD; Barbara Heude, PhD; Francis de Zegher, MD; Sheila J. Barton, PhD; Karine Clément, PhD; Hazel M. Inskip, PhD; Yves Koudou, MSc; Cyrus Cooper, FRCP; David B. Dunger, FRCP; Lourdes Ibáñez, MD; Marie-Aline Charles, MD, PhD; Ken K. Ong, FRCPCH

 Supplemental content at jamapediatrics.com

IMPORTANCE Patterns of body size and body composition associated with genetic obesity susceptibility inform the mechanisms that increase obesity risk.

OBJECTIVE To test associations between genetic obesity susceptibility, represented by a combined obesity risk-allele score, and body size or body composition at birth to age 5 years.

DESIGN, SETTING, AND PARTICIPANTS A total of 3031 children from 4 birth cohort studies in England, France, and Spain were included in a meta-analysis.

EXPOSURES A combined obesity risk-allele score was calculated from genotypes at 16 variants identified by genome-wide association studies of adult body mass index (BMI).

MAIN OUTCOMES AND MEASURES Outcomes were age- and sex-adjusted SD scores (SDS) for weight, length/height, BMI, fat mass, lean mass, and percentage of body fat at birth as well as at ages 1, 2 to 3, and 4 to 5 years.

RESULTS The obesity risk-allele score was not associated with infant size at birth; at age 1 year it was positively associated with weight (β [SE], 0.020 [0.008] SDS per allele; $P = .009$) and length (β [SE], 0.020 [0.008] SDS per allele; $P = .01$), but not with BMI (β [SE], 0.013 [0.008] SDS per allele; $P = .11$). At age 2 to 3 years these associations were stronger (weight: β [SE], 0.033 [0.008] SDS per allele; $P < .001$; height: β [SE], 0.025 [0.008] SDS per allele; $P < .001$) and were also seen for BMI (β [SE], 0.024 [0.008] SDS per allele; $P = .003$). The obesity risk-allele score was positively associated with both postnatal fat mass (1 year: β [SE], 0.032 [0.017] SDS per allele; $P = .05$; 2-3 years: β [SE], 0.049 [0.018] SDS per allele; $P = .006$; and 4-5 years: β [SE], 0.028 [0.011] SDS per allele; $P = .009$) and postnatal lean mass (1 year: β [SE], 0.038 [0.014] SDS per allele; $P = .008$; 2-3 years: β [SE], 0.064 [0.017] SDS per allele; $P < .001$; and 4-5 years: β [SE], 0.047 [0.011] SDS per allele; $P < .001$), but not with the percentage of body fat ($P > .15$ at all ages).

CONCLUSIONS AND RELEVANCE Genetic obesity susceptibility appears to promote a normally partitioned increase in early postnatal, but not prenatal, growth. These findings suggest that symmetrical rapid growth may identify infants with high life-long susceptibility for obesity.

JAMA Pediatr. 2014;168(12):1122-1130. doi:10.1001/jamapediatrics.2014.1619
Published online October 20, 2014.

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Ken K. Ong, FRCPCH, Medical Research Council Epidemiology Unit, University of Cambridge, Addenbrooke's Hospital, Box 285, Cambridge CB2 0QQ, England (ken.ong@mrc-epid.cam.ac.uk).

Identification of the early-life indicators and mechanisms related to later obesity risk has important relevance to preventive strategies.¹ Consistent evidence from many longitudinal studies^{2,3} supports the hypothesis that rapid postnatal weight gain is a risk factor for later obesity. A recent meta-analysis³ of multiple international studies demonstrated that a 1-unit gain in weight SD score (SDS) during the first year of life conferred a 23% higher risk of adult obesity and 2-fold higher risk of childhood obesity. Studies³ relating infant growth to later obesity have largely focused on weight or weight-for-length measures, although there is some evidence⁴ that increased linear growth during the first 2 years of life is also associated with a higher risk of obesity in later childhood.

There is as yet little evidence to show whether early gains in fat mass, fat-free mass, or both are associated with susceptibility to later obesity.⁵ Body composition in infancy is infrequently measured in epidemiologic studies and is notably absent from historical cohort studies with adult outcome measurements. As such, the relevance of body composition in infancy to the programming of later obesity is poorly understood. The identification⁶ of genetic variants with robust association with complex traits by genome-wide association studies has allowed examination of the early-life phenotypes related to genetic susceptibility to disease. Using this approach, several studies⁶⁻⁸ have inferred that gains in both infancy weight and length are positively associated with lifelong obesity risk, based on associations between genetic variants that predispose to higher adult body mass index (BMI) and markers of early postnatal growth. However, studies to date have been restricted to measures of weight, length/height, and BMI and have not examined genetic associations with measures of infant body composition. To identify patterns of early life growth and body composition that are related to genetic obesity susceptibility, we combined data on these phenotypes from 4 contemporary birth cohort studies to allow a robust examination of their associations with an obesity susceptibility multiple-allelic score comprising genetic variants identified in large-scale genome-wide association studies of adult BMI.⁹

Methods

Study Descriptions

The 4 contemporary birth cohort studies used in the meta-analysis were the Cambridge Baby Growth Study (CBGS), the Southampton Women's Survey (SWS), a mother-child cohort study on prenatal and postnatal determinants of the child's development and health (EDEN), and the Barcelona study. Details on those studies are provided below.

Cambridge Baby Growth Study

Between 2001 and 2009, mothers were recruited from the Rosie Maternity Hospital, Cambridge, England, by trained research nurses for participation in the CBGS.¹⁰ Ethics approval for the study was given by the Cambridge, England, local research ethics committee, and written informed consent was obtained from the mothers. The participants did not receive financial compensation. At birth, age 1 year, and age 2 years, infant

weight was measured to the nearest 1 g using electronic scales, and supine length was measured to the nearest 0.1 cm (Kid-dimeter; Holtain Ltd). Skinfold thickness at 4 sites (triceps, subscapular, flank, and quadriceps) was measured at the same time points in triplicate by trained research nurses (Harpenden Skinfold Caliper; Holtain Ltd). The mode of infant feeding (breast milk only or formula milk) was assessed by a questionnaire completed by the parents at the 3-month clinic visit, and maternal height was measured to the nearest 0.1 cm.

Southampton Women's Survey

The SWS is a study of women aged 20 to 34 years recruited via general practitioners residing in Southampton, England.¹¹ The Southampton and South West Hampshire Research Ethics Committee approved the study. Written informed consent was obtained from all participating women and by a parent or guardian with parental responsibility on behalf of their children. At the initial recruitment visit, height was measured using a portable stadiometer (Harpenden; CMS Weighing Equipment Ltd). Infants born to the SWS participants were followed-up at ages 6, 12, and 24 months when they were visited by trained research nurses.¹² A detailed history of milk feeding (human milk, baby formulas, and other types of milk) was obtained at these visits. At age 4 years, the child's height (Leicester height measurer; Seca Ltd) and weight in underpants only (calibrated digital scales; Seca Ltd) were measured. Fat and lean mass were assessed using whole body dual-energy x-ray absorptiometry (DXA) scans (Hologic Discovery instrument; Hologic Inc) in the pediatric scan mode.¹³

The EDEN Mother-Child Cohort Study

EDEN is a population-based, prospective, mother-child cohort study on prenatal and early postnatal nutritional, environmental, and social determinants of the children's development and health.¹⁴ The study was approved by the Ethics Committee of Kremlin Bicêtre (France) and by the Data Protection Authority Commission Nationale de l'Informatique et des Libertés. All mothers provided written informed consent for themselves and their child. Recruitment of pregnant women expecting singletons took place between 2003 and 2006 at the University Hospitals in Poitiers and Nancy, France. At birth, infants were weighed using electronic scales (Seca Ltd), and length was measured using a wooden somatometer (Testut). At age 1 year, the infants' weight was obtained by subtraction of the weight of the mother alone (Terraillon SL-351) from when holding their infant wearing light clothes; infant length was measured using a somatometer (NM Medical). At ages 3 and 5 years, children were weighed with electronic scales (Seca Ltd), and standing height was measured with a wall-mounted stadiometer (Seca Ltd). At age 5 years, body composition was evaluated using a body impedance analyzer (BIA 101; Akern). Breastfeeding duration was assessed from mailed questionnaires at ages 4 and 8 months and at 1, 2, and 3 years. Maternal height was measured to the nearest 0.2 cm.

Barcelona Study

The Barcelona study was designed to assess the longitudinal associations during the first postnatal years between endo-

crine-metabolic factors and body composition.¹⁵ The study was approved by the Institutional Review Board of Barcelona University, Hospital of Sant Joan de Déu; informed written consent was obtained from at least 1 parent. The Barcelona study comprises full-term, healthy newborns born at Hospital of Sant Joan de Déu, Barcelona, Spain, from 2007 onward, categorized into 2 separate study groups of infants born (1) average birth weight for gestational age (AGA), which was considered a birth weight range between -1.0 and $+1.0$ SD, and (2) small for gestational age (SGA), which was considered a birth weight range between -2.0 and -3.0 SD. At birth, 1 year, and 2 years, length (centimeters) was measured in triplicate using a standardized plastic length board, and weight (grams) was measured to the nearest 10 g using a standard beam balance (Seca Ltd). Body composition was assessed by DXA at ages 2 weeks (range, 9-20 days), 1 year, and 2 years, using a Lunar Prodigy coupled to specific pediatric Lunar software (version 3.4/3.5; Lunar Corp) and appropriately adapted by the manufacturer for measurements in newborns and infants, as described.¹⁵

Body Composition

Fat mass and lean mass were estimated by DXA at birth and age 4 years in SWS, and at birth, age 1 year, and age 2 years in Barcelona AGA and Barcelona SGA participants. Fat mass and lean mass were estimated from bioelectric impedance measurements and triceps and subscapular skinfolds at age 5 years in EDEN, using the equation described by Goran et al,¹⁶ and from skinfold measurements at birth and ages 1 and 2 years in CBGS, using the equation described by Brook.¹⁷ In all studies, the percentage of fat was calculated as (fat mass \times 100/body weight), and the fat to lean ratio was calculated as (fat mass/lean mass).

Genotyping

In each study, DNA was extracted from cord blood samples collected at birth. Genotypes at 16 single-nucleotide polymorphisms (SNPs) were measured at the Medical Research Council Epidemiology Unit, Cambridge (iPLEX platform; Sequenom), as previously described.¹⁸ These 16 SNPs were reported as having genome-wide significant associations with BMI in adults,⁹ and also showed associations with childhood BMI either in the previous reports or in additional data (eTable in the Supplement): in or near *NRXN3* (rs10146997), *SLC39A8* (rs13107325), *TNNI3K* (rs1514175), *PTBP2* (rs1555543), *MC4R* (rs17782313), *FLJ35779* (rs2112347), *NEGR1* (rs2568958), *RPL27A* (rs4929949), *TMEM18* (rs6548238), *RBJ/POMC* (rs713586), *CADM2* (rs7640855), *TRA2B/ETV5* (rs7647305), *BDNF* (rs925946), *TFAP2B* (rs987237), *FTO* (rs9941349), and *ZNF608* (rs4836133). In each cohort study, all variants passed genotyping quality control criteria (call rate, $>95\%$; Hardy-Weinberg equilibrium, $P > .01$) (eTable in the Supplement).

Calculation of Risk-Allele Scores

Combined obesity risk-allele scores, indicating genetic susceptibility to obesity, were calculated in each participant as the sum of alleles (range, 0-2 at each locus) associated with higher adult BMI across the 16 SNP loci. To minimize dropout due to missing genotype data, infants with missing genotype data at

4 (25%) or fewer loci were imputed with the mean number of susceptibility alleles in their cohort for each locus.

Statistical Analysis

Body mass index was calculated as weight in kilograms divided by length or height in meters squared at each time point. All measures of body size and body composition were converted to sex-specific SDS by comparison with the same British 1990 growth reference.¹⁹

The obesity risk-allele score was tested for cross-sectional associations with weight, length, BMI, fat mass, lean mass, fat mass percentage, or fat to lean mass ratio SDS in separate linear regression models. Each model was adjusted for age at measurement, sex, maternal height, and exclusive breastfeeding at age 3 months (yes/no). Models were adjusted for maternal height rather than maternal BMI, because inclusion of the latter would likely represent overadjustment for transmitted obesity-susceptibility variants. Although maternal size and breastfeeding cannot confound the association between infant genes and infant growth, they contribute to the variance in infant growth and were therefore included as covariates in our analyses. Separate models were performed for each outcome at each time point and in each cohort study. The resulting summary statistics from each population-based cohort study and from Barcelona AGA infants were combined by an inverse weighted fixed-effects meta-analysis. To enable this, we grouped results for measurement ages between 2 and 3 years and between 4 and 5 years (in each age group, no individual had >1 growth assessment). β Coefficients are used to represent the per-allele effect of the risk-allele score on weight; length/height; BMI; fat mass; lean mass; percentage of body fat; and fat to lean ratio at birth, 1 year, 2 to 3 years, and 4 to 5 years. Longitudinal analyses were performed only for anthropometry variables (weight, length, and BMI) owing to the wider variability in timings of body composition measurements. For this we first performed mixed-effect models separately in each cohort study using the `xtmixed` command in Stata, version 11.1 (StataCorp), and including the interaction term (risk-allele score \times age as a continuous variable in years). The resulting interaction variables were then combined by meta-analysis as described above; these variables indicate the effects of the risk-allele score on yearly postnatal changes in weight, length/height, and BMI SDS from birth.

Various sensitivity analyses were performed. To explore whether there was any potential modifying influence of antenatal environment on the association between the genetic score and infant growth, we repeated the analyses of risk-allele score and weight SDS stratified by tertiles of standardized birth weight in each cohort, or by SGA and AGA groups in the Barcelona study, and then meta-analyzed the resulting statistics. We also tested for potential effect modification by exclusive breastfeeding at age 3 months (yes/no). All analyses were conducted in Stata, version 13 (StataCorp).

Results

Descriptive characteristics of the samples included in each cohort study are reported in **Table 1**. All 4 studies had data on

Table 1. Descriptive Characteristics of Children in 4 European Birth Cohort Studies

Characteristic	Mean (SD) ^a				
	CBGS (England)	SWS (England)	EDEN (France)	Barcelona (Spain)	
				AGA	SGA
No. of children with gene scores	618	1229	1352	235	70
Boys, No. (%)	327 (52.9)	643 (52.3)	717 (53.0)	112 (47.6)	31 (44.3)
Genetic score (16 SNPs)	13.8 (2.5)	14.1 (2.5)	13.7 (2.5)	13.8 (2.5)	13.5 (2.5)
Mother's age at birth, y	33 (4.2)	30.1 (3.7)	29 (4.9)	31 (4.9)	31 (4.8)
Mother's height, mean, cm	166 (7.0)	163 (7.0)	163 (6.1)	162 (6.3)	159 (5.9)
Mother's prepregnancy BMI	24.0 (4.1)	25.4 (4.9)	23.1 (4.4)	23.9 (4.2)	23.6 (4.9)
Birth, No.	618	1229	1351	235	70
Weight, kg	3.51 (0.5)	3.45 (0.6)	3.31 (0.48)	3.37 (0.4)	2.32 (0.2)
Length, mean, cm	51.5 (2.6)	49.8 (2.0)	49.7 (2.2)	49.8 (1.7)	45.9 (1.6)
BMI	13.2 (1.6)	13.9 (1.3)	13.4 (1.3)	13.5 (1.2)	13.5 (1.2)
Fat mass, kg	0.61 (0.2)	0.55 (0.2)	NA	0.72 (0.3)	0.42 (0.2)
Lean mass, kg	2.9 (0.4)	2.9 (0.4)	NA	3.0 (0.4)	2.4 (0.3)
Percentage of fat	17.3 (4.0)	15.1 (4.5)	NA	19.2 (6.2)	14.0 (4.9)
1 y, No.	504	1141	1142	148	55
Age, y	1.02 (0.04)	0.99 (0.28)	1.02 (0.08)	1.08 (0.11)	1.06 (0.06)
Weight, kg	10.0 (1.2)	10.1 (1.2)	9.8 (1.12)	10.1 (1.2)	10.1 (1.2)
Length, cm	76.0 (2.8)	75.8 (2.8)	74.9 (2.8)	75.6 (3.4)	75.6 (1.7)
BMI	17.3 (1.4)	17.5 (1.5)	17.5 (1.5)	17.7 (1.7)	16.9 (1.4)
Fat mass, kg	2.9 (0.4)	NA	NA	3.7 (0.8)	3.4 (0.6)
Lean mass, kg	7.6 (0.9)	NA	NA	6.5 (1.0)	5.6 (0.9)
Percentage of fat	24.5 (3.3)	NA	NA	36.0 (6.1)	37.0 (5.3)
2-3 y, No.	458	1058	929	56	46
Age, y	2.03 (0.05)	2.06 (0.14)	3.17 (0.08)	2.10 (0.12)	2.03 (0.06)
Weight, kg	12.6 (1.5)	12.7 (1.5)	14.9 (1.7)	12.5 (1.5)	11.7 (1.3)
Length, cm	87.9 (3.3)	86.6 (3.1)	97.0 (3.8)	87.5 (3.8)	85.4 (3.4)
BMI, kg/m ²	16.3 (1.4)	16.9 (1.5)	15.8 (1.1)	16.3 (1.4)	16.0 (1.2)
Fat mass, kg	3.0 (0.6)	NA	NA	4.6 (1.2)	4.0 (1.2)
Lean mass, kg	9.7 (1.1)	NA	NA	8.0 (1.2)	7.6 (1.3)
Percentage of fat	23.4 (3.5)	NA	NA	34.8 (8.4)	32.7 (8.8)
4-5 y, No.	NA	538	837	NA	NA
Age, y	NA	4.13 (0.07)	5.63 (0.16)	NA	NA
Weight, kg	NA	17.5 (2.2)	20.2 (2.7)	NA	NA
Length, cm	NA	103.9 (4.2)	114.4 (4.9)	NA	NA
BMI	NA	16.1 (1.7)	15.4 (1.3)	NA	NA
Fat mass, kg	NA	4.9 (1.2)	2.9 (1.0)	NA	NA
Lean mass, kg	NA	12.0 (1.5)	17.3 (2.1)	NA	NA
Percentage of fat	NA	27.8 (5.0)	14.3 (4.6)	NA	NA

Abbreviations: AGA, average gestational age; BMI, body mass index (calculated as weight in kilograms divided by length or height in meters squared); CBGS, Cambridge Baby Growth Study; NA, not available; SGA, small gestational age; SNPs, single-nucleotide polymorphisms; SWS, Southampton Women's Survey.

^a Empty cells indicate that variables were not measured at the times reported.

weight, length/height, and BMI at birth and at ages 1 year and 2 to 3 years; SWS and EDEN also had these data at 4 to 5 years. Body composition data were available at birth in 3 studies (CBGS, SWS, and Barcelona), at ages 1 year and 2 to 3 years in 2 studies (CBGS and Barcelona), and at age 4 to 5 years in 2 studies (SWS and EDEN).

Genetic Score Associations With Weight

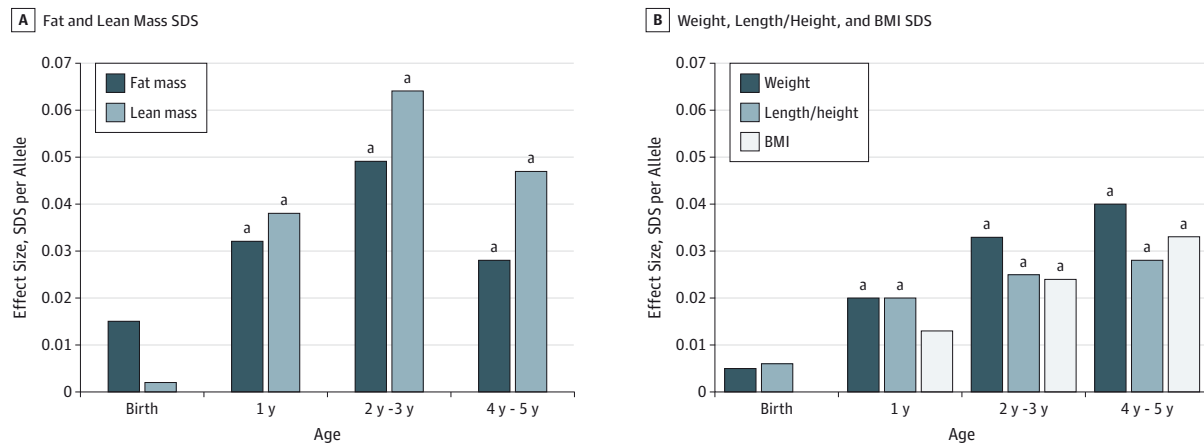
In our meta-analysis across 4 European population based-birth cohorts (Figure 1), the obesity risk-allele score showed no association with birth weight ($\beta = 0.005$ SDS per allele; $P = .53$), but indicated increasingly positive cross-sectional associations with weight at ages 1 year ($\beta = 0.020$; $P = .009$) and 2 to 3

years ($\beta = 0.033$; $P < .001$). In SWS and EDEN combined, the obesity risk-allele score was associated with weight at 4 to 5 years ($\beta = 0.040$, $P < .001$) (Table 2). There was little heterogeneity in effect estimates between the studies (I^2 at birth, 33%; at 1 year, 14%; at 2-3 years, 49%; and at 4-5 years, 0%). A meta-analysis of longitudinal age interaction terms indicated an overall positive association between the risk-allele score and change in weight SDS from birth ($\beta = 0.009$ SDS per allele per year; $P < .001$).

Genetic Score Associations With Length/Height

In the meta-analysis (Figure 1), the obesity risk-allele score was not associated with birth length ($\beta = 0.006$ SDS per allele;

Figure 1. Cross-sectional Associations Between the Obesity Risk-Allele Score and Early Childhood Body Size and Composition



A, Cross-sectional associations of the obesity risk-allele score with fat and lean mass sex-adjusted SD scores (SDS) at birth, 12 months, 2-3 years, and 4-5 years. B, Associations between the obesity-risk allele and weight, length/height, and body mass index (BMI) SDS. A meta-analysis of 4 birth cohorts was conducted.

Data at age 4-5 years are from the EDEN and Southampton Women's Survey cohorts only. ^a $P < .05$.

Table 2. Associations Between the Obesity Risk-Allele Score and Body Size From Birth to Age 4-5 Years in 4 European Birth Cohort Studies^a

Growth Variable by Cohort	Birth		Years					
	β (SE)	P Value	β (SE)	P Value	2-3		4-5	
CBGS, No. ^b	551		490		450		NA	
Weight SDS	0.029 (0.016)	.08	0.048 (0.018)	.01	0.073 (0.019)	<.001	NA	NA
Height SDS	0.009 (0.016)	.57	0.043 (0.018)	.02	0.061 (0.018)	.001	NA	NA
BMI SDS	0.034 (0.018)	.06	0.031 (0.019)	.11	0.056 (0.019)	.004	NA	NA
SWS, No.	1133		1096		1022		518	
Weight SDS	-0.014 (0.018)	.42	0.020 (0.012)	.10	0.024 (0.013)	.07	0.035 (0.018)	.048
Height SDS	-0.007 (0.013)	.60	0.015 (0.012)	.23	0.014 (0.012)	.51	0.024 (0.018)	.17
BMI SDS	-0.007 (0.014)	.62	0.019 (0.013)	.16	0.018 (0.013)	.17	0.028 (0.018)	.11
EDEN, No.	1150		1058		873		795	
Weight SDS	0.006 (0.01)	.50	0.008 (0.011)	.50	0.027 (0.011)	.02	0.042 (0.013)	.001
Height SDS	0.020 (0.012)	.09	0.009 (0.012)	.43	0.024 (0.012)	.043	0.030 (0.013)	.02
BMI SDS	-0.006 (0.012)	.60	0.003 (0.012)	.84	0.017 (0.012)	.15	0.035 (0.013)	.005
Barcelona AGA, No. ^b	197		123		88		NA	
Weight SDS	-0.022 (0.024)	.36	0.032 (0.039)	.37	-0.003 (0.046)	.95	NA	NA
Height SDS	-0.015 (0.022)	.51	0.078 (0.042)	.07	-0.016 (0.047)	.74	NA	NA
BMI SDS	-0.020 (0.029)	.49	-0.022 (0.048)	.64	0.004 (0.044)	.94	NA	NA
Meta-analysis, No.	3031		2767		2433		1313	
Weight SDS	0.005 (0.007)	.53	0.020 (0.008)	.009	0.033 (0.008)	<.001	0.040 (0.010)	<.001
Length/height SDS	0.006 (0.007)	.45	0.020 (0.008)	.01	0.025 (0.008)	<.001	0.028 (0.010)	.008
BMI SDS	0.000 (0.008)	.10	0.013 (0.008)	.11	0.024 (0.008)	.003	0.033 (0.010)	.002

Abbreviations: AGA, average gestational age; BMI, body mass index (calculated as weight in kilograms divided by length or height in meters squared); CBGS; Cambridge Baby Growth Study; NA, not available; SDS, sex-adjusted SD scores; SWS, Southampton Women's Survey.

^a Models were adjusted for age, sex, maternal height, and breastfeeding for

more than 3 months. β Indicates regression coefficient (expressed as number of SDSs in the outcome variable per additional BMI-increasing allele).

^b Variables were not measured at 4 to 5 years.

$P = .45$), but showed increasingly positive cross-sectional associations with length at age 1 year ($\beta = 0.020$ SDS per allele; $P = .01$) and with height at age 2 to 3 years ($\beta = 0.025$ SDS per allele; $P < .001$). In SWS and EDEN combined, the obesity risk-

allele score was associated with height at 4 to 5 years ($\beta = 0.028$ SDS per allele; $P = .008$) (Table 2). There was little heterogeneity between the studies in effect estimates (I^2 at birth, 8%; at 1 year, 34%; at 2-3 years, 45%; and at 4-5 years, 0%). A meta-

Table 3. Associations Between the Obesity Risk-Allele Score and Body Composition From Birth to Age 4-5 Years in 4 European Birth Cohort Studies^a

Outcome by Cohort	Birth		Age, y					
	β (SE)	P Value	1		2-3		4-5	
			β (SE)	P Value	β (SE)	P Value	β (SE)	P Value
CBGS, No. ^b	546		489		441		NA	
Fat mass	0.023 (0.015)	.13	0.038 (0.018)	.04	0.062 (0.019)	.001	NA	NA
Lean mass	0.016 (0.015)	.30	0.041 (0.019)	.01	0.064 (0.018)	<.001	NA	NA
Percentage of fat	0.016 (0.014)	.26	0.020 (0.062)	.29	0.035 (0.019)	.07	NA	NA
Fat to lean ratio	0.018 (0.014)	.21	0.021 (0.019)	.26	0.039 (0.013)	.047	NA	NA
SWS, No. ^c	402		NA		NA		427	
Fat mass	0.013 (0.020)	.48	NA	NA	NA	NA	0.019 (0.018)	.30
Lean mass	-0.016 (0.018)	.37	NA	NA	NA	NA	0.051 (0.018)	.005
Percentage of fat	0.022 (0.019)	.25	NA	NA	NA	NA	-0.011 (0.017)	.53
Fat to lean ratio	0.021 (0.019)	.27	NA	NA	NA	NA	-0.008 (0.017)	.17
EDEN, No. ^d	NA		NA		NA		795	
Fat mass	NA	NA	NA	NA	NA	NA	0.032 (0.013)	.02
Lean mass	NA	NA	NA	NA	NA	NA	0.044 (0.014)	.002
Percentage of fat	NA	NA	NA	NA	NA	NA	0.033 (0.014)	.02
Fat to lean ratio	NA	NA	NA	NA	NA	NA	0.024 (0.014)	.08
Barcelona AGA, No. ^b	197		123		48		NA	
Fat mass	-0.007 (0.027)	.79	0.005 (0.039)	.90	-0.062 (0.054)	.26	NA	NA
Lean mass	-0.003 (0.027)	.903	0.026 (0.031)	.40	0.063 (0.061)	.19	NA	NA
Percentage of fat	-0.014 (0.027)	.61	-0.017 (0.038)	.90	-0.076 (0.052)	.15	NA	NA
Fat to lean ratio	-0.010 (0.028)	.76	-0.015 (0.037)	.69	-0.066 (0.053)	.22	NA	NA
Meta-analysis, No.	1145		612		489		1222	
Fat mass	0.015 (0.011)	.17	0.032 (0.017)	.05	0.049 (0.018)	.006	0.028 (0.011)	.009
Lean mass	0.002 (0.011)	.86	0.038 (0.014)	.008	0.064 (0.017)	<.001	0.047 (0.011)	<.001
Percentage of fat	0.013 (0.011)	.20	0.013 (0.017)	.45	0.022 (0.018)	.22	0.015 (0.011)	.16
Fat to lean ratio	0.015 (0.011)	.16	0.014 (0.017)	.42	0.027 (0.018)	.15	0.011 (0.011)	.31

Abbreviations: AGA, average gestational age; CBGS; Cambridge Baby Growth Study; NA, not available; SWS, Southampton Women's Survey.

^a Models were adjusted for age, sex, maternal height, and breastfeeding for more than 3 months. The regression coefficient β is expressed as the number of SDs in the outcome variable per additional body mass index-increasing allele.

^b Variables were not measured at 4-5 years.

^c Variables were measured only at birth and 4-5 years.

^d Variables were measured only at 4-5 years.

analysis of longitudinal models indicated an overall positive association between the risk-allele score and change in length/height SDS from birth ($\beta = 0.004$ SDS per allele per year; $P = .046$).

Genetic Score Associations With BMI

In the meta-analysis (Figure 1), the obesity risk-allele score was not associated with BMI at birth, showed a nonsignificant positive trend with cross-sectional BMI at age 1 year ($\beta = 0.013$ SDS per risk allele; $P = .11$), and a positive association with BMI at age 2 to 3 years ($\beta = 0.024$ SDS per risk allele; $P = .003$). In SWS and EDEN combined, the obesity risk-allele score was associated with BMI at 4 to 5 years ($\beta = 0.033$ SDS per risk allele; $P = .002$) (Table 2). There was little heterogeneity between studies in effect estimates (I^2 at birth, 34%; at 1 year, 0%; at 2-3 years, 14%; and at 4-5 years, 0%). A meta-analysis of longitudinal models indicated an overall positive association between the risk-allele score and change in BMI SDS from birth ($\beta = 0.009$ SDS per allele per year; $P < .001$).

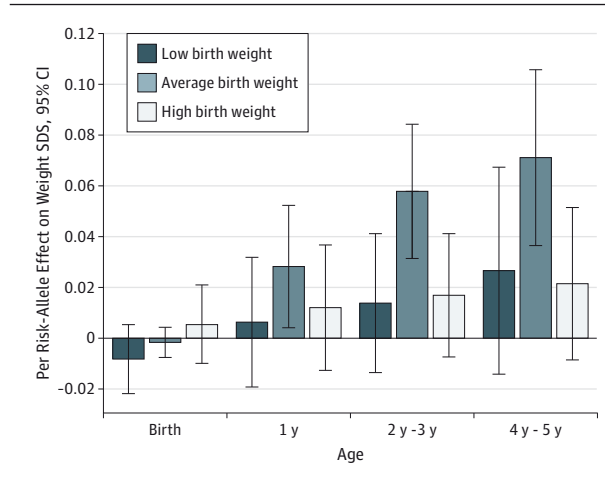
Genetic Score Associations With Body Composition

The obesity risk-allele score was not associated with any body composition variable at birth in 3 studies (Figure 1). In the meta-analysis of CBGS and Barcelona combined, the obesity risk-allele score showed increasingly positive cross-sectional associations with both fat mass and lean mass at ages 1 year and 2 to 3 years, and similarly at age 4 to 5 years it was positively associated with both fat mass ($\beta = 0.028$ SDS per allele; $P = .009$) and lean mass ($\beta = 0.047$ SDS per risk allele; $P < .001$) in SWS and EDEN combined (Table 3). No association was detected with the percentage of fat mass or fat mass to lean mass ratio at any age. With the exception of estimates for fat mass at age 2 to 3 years (I^2 , 79%), there was minimal heterogeneity between studies in effect estimates for fat mass or fat-free mass (all $I^2 = 0\%$).

Sensitivity Analysis

Associations with infant growth were similar, albeit slightly weaker, using a weighted obesity risk-allele score (in which in-

Figure 2. Cross-sectional Associations Between the Obesity Risk-Allele Score and Early Childhood Weight Sex-Adjusted SD Score (SDS) Stratified by Birth Weight



Infants were grouped within each study according to standardized birth weight tertile (Cambridge Baby Growth Study, EDEN, and Southampton Women's Survey) or whether they were small or average for gestational age (Barcelona). Limit lines indicate 95% CI.

dividual risk alleles were weighted by their reported effect size on adult BMI⁹): the association between the weighted risk-allele score and change in weight SDS from birth was $\beta = 0.006$ SDS per allele per year ($P < .001$). In sensitivity analyses of body composition, with additional adjustments for body length/height, the obesity risk-allele score associations with lean mass were attenuated but remained significant (4-5 years: $\beta = 0.021$ SDS per allele per year; $P = .03$). In analyses stratified by birth weight groups, the obesity risk-allele score showed consistently stronger associations with weight at ages 1 year, 2 to 3 years, and 4 to 5 years in infants who had average birth weights than in those in the high- or low-birth-weight groups (Figure 2). Exclusive breastfeeding at age 3 months (yes/no) did not modify the associations between the obesity risk allele score and infant weight gain (interaction coefficient for exclusive breastfeeding vs other: $\beta = 0.005$ SDS per allele per year, SE = 0.016, $P = .73$).

Discussion

Our individual data-level meta-analysis of birth cohort studies from 3 European countries confirmed the positive associations between genetic obesity susceptibility and postnatal gains in infant weight and length, previously reported in an independent study,^{6,7} and showed, for what we believe to be the first time, positive associations with both fat mass and lean mass in infancy and early childhood.

Previous studies^{8,20} have taken a similar approach, using combined scores of BMI-increasing alleles at adult BMI-related loci to indicate the genetic susceptibility to obesity. Some studies^{8,20} examined only BMI as the outcome growth variable and identified positive associations with BMI from age 3 years and onward. Similarly, a previous meta-analysis²¹ of risk alleles at only the *FTO* locus across 8 cohorts of individuals of

European ancestry reported that the BMI-increasing allele was positively associated with BMI only from age 5 years onward, but with no, or even inverse, associations at earlier ages. Our findings suggest that genetic susceptibility to obesity promotes early gains in both weight and length/height that are apparent before the positive influence on BMI. This premise is strongly supported by our novel finding of positive associations between the obesity risk-allele score and both fat mass and lean mass, but not relative body fat, in infancy and early childhood. Notably, these genetic obesity variants are unrelated to adult height,⁷ indicating that their positive association with childhood height appears to be fully countered by earlier pubertal timing and cessation of growth.²²

Our findings may be surprising considering that these obesity susceptibility loci, individually or in combinations, have been shown to have predominant positive associations with adiposity rather than lean mass in children aged 9 years⁶ and in adults.⁹ Furthermore, gains in length/height and lean mass during infancy and early childhood have been suggested to be protective against, rather than predisposing to, obesity and related metabolic disorders, possibly owing to the benefits of higher lean mass and total energy expenditure.²³⁻²⁵ However, in support of our findings, some large observational studies⁴ have reported that faster postnatal linear growth is associated with a higher subsequent risk of childhood overweight. Similarly, the long-term relevance to obesity risk of changes specifically in fat mass or fat-free mass during infancy and early childhood has not been clearly established. A recent meta-analysis²⁶ showed that formula-fed compared with breastfed infants have greater fat-free mass in early infancy, but then greater fat mass in later infancy, which could indicate that early gains in fat-free mass precede gains in fat mass. We anticipate that continued follow-up of our birth cohort studies may reveal the emergence of predominant effects of genetic obesity susceptibility on relative adiposity, possibly from near the age of the adiposity rebound, which occurs typically between ages 5 and 7 years.^{8,21}

We found that associations between the obesity risk-allele score and infancy weight were more apparent among infants born with average vs high or low birth weight, which is consistent with a previous report²⁷ comparing genetic influences on childhood BMI in AGA- vs SGA-born children. The lack of association between genetic susceptibility to obesity and birth weight has been well described,²⁸ and we suggest that other mechanisms related to catch-up and catch-down growth following intrauterine restriction and overnutrition, respectively, may have stronger influences on postnatal growth in the extreme birth-weight groups.

There are limitations of our study. Foremost, accurate measurement of body composition in infants and young children presents major practical and technical challenges, not least owing to the difficulty in achieving immobility and cooperation. Our studies used a variety of techniques (eg, DXA, skinfolds, and bioelectric impedance), each of which has limitations in the assumptions used to estimate body composition. Furthermore, the timing of measurements differed between the studies, which had not been intentionally designed to allow comparison. However, our studies bring together unique data sets on body composition in early life, and the consistency and ro-

bustness of our findings across the studies are reassuring. Future use of nonparametric growth modeling techniques may allow further harmonization of the anthropometric outcomes across the studies to allow more-detailed longitudinal analyses of growth during specific age windows. We did not have measures of body fat distribution; however, separate genetic factors likely contribute to those phenotypes.²⁹ There is debate regarding the need to adjust body composition factors in children for differences in length/height, because taller children tend to have higher fat and lean mass.³⁰ Although only associations with fat-free mass remained significant in our sensitivity analyses adjusted for infant length/height, we contend that the positive associations seen across postnatal weight, length/height, fat mass, and fat-free mass in our main unadjusted models support a broadly symmetrical effect of genetic obesity susceptibility on early postnatal growth. This interpretation is consistent with the notions that genetic susceptibility to obesity may be mediated to a large extent by central appetite and satiety regulatory mechanisms that promote eating behavior and food intake^{9,31} and that, uniquely during infancy, nutrition promotes statural growth as well as weight gain.³² Indeed, there is ample evidence for the nutritional regulation of insulinlike growth factor I in infancy, which likely explains the exquisite sensitivity of statural growth to energy intake during this early period.¹⁰

Our analyses were based on a subset of variants identified by the latest genome-wide association studies for adult BMI, in particular, those with demonstrated associations with childhood BMI; the excluded SNPs tended to have lower effects on adult BMI.⁹ However, the relevance of effect sizes on adult BMI for studies of early postnatal body size and growth is not clear. Further large replication studies in children would help to distinguish variants with predominantly childhood or adult effects on weight gain. Finally, although our observed effect sizes per allele may appear to be small (approximately 0.03-0.06 SDS per allele at age 2-5 years), they are approximately equivalent to the standardized reported effect on adult BMI (0.17 per allele) using a score of 32 SNPs,⁹ and may be scaled upward by considering the SD of the obesity risk-allele score of approximately 2.5 alleles.

Conclusions

Genetic obesity susceptibility appears to promote a normally partitioned increase in early postnatal, but not prenatal, growth. Although it is possible that relatively greater gains in total body and/or regional adiposity might confer additional risks, our findings suggest that symmetrical rapid growth may identify infants with high lifelong obesity susceptibility.

ARTICLE INFORMATION

Accepted for Publication: July 11, 2014.

Published Online: October 20, 2014.
doi:10.1001/jamapediatrics.2014.1619.

Author Affiliations: Medical Research Council Epidemiology Unit, University of Cambridge, Addenbrooke's Hospital, Cambridge, England (Elks, Ong); Institut National de la Santé et de la Recherche Médicale, Center for Research in Epidemiology and Population Health, Lifelong Epidemiology of Obesity, Diabetes and Renal Disease Team, Villejuif, France (Heude, Koudou, Charles); Medical Faculty, University Paris-Sud, Villejuif, France (Heude, Koudou, Charles); Paediatric Endocrinology, University Hospital Gasthuisberg, University of Leuven, Leuven, Belgium (de Zegher); Medical Research Council Lifecourse Epidemiology Unit, University of Southampton, Southampton General Hospital, Southampton, England (Barton, Inskip, Cooper); Institut de Cardiometabolism and Nutrition, Centre de Recherche en Nutrition Humaine Ile de France, Pitié-Salpêtrière Hospital, Paris, France (Clément); Institut National de la Santé et de la Recherche Médicale U872 team Nutriomique, Paris, France (Clément); National Institute of Health Research, Nutrition Biomedical Research Centre, University of Southampton, Southampton, England (Cooper); Department of Paediatrics, University of Cambridge, Addenbrooke's Hospital, Cambridge, England (Dunger, Ong); Department of Endocrinology, Hospital Sant Joan de Déu, University of Barcelona, Barcelona, Spain (Ibáñez); Centro de Investigación Biomédica en Red de Diabetes y Enfermedades Metabólicas Asociadas, Instituto de Salud Carlos III, Madrid, Spain (Ibáñez).

Author Contributions: Dr Elks had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Elks, Heude, Dunger, Ibáñez, Charles, Ong.

Acquisition, analysis, or interpretation of data: Elks, Heude, de Zegher, Barton, Clément, Inskip, Koudou, Cooper, Ibáñez, Charles, Ong.

Drafting of the manuscript: Elks, Dunger, Ong.
Critical revision of the manuscript for important intellectual content: Elks, Heude, de Zegher, Barton, Clément, Inskip, Koudou, Cooper, Ibáñez, Charles.

Statistical analysis: Elks, Barton, Koudou.

Obtained funding: Heude, Dunger, Ibáñez, Charles, Ong.

Administrative, technical, or material support: Inskip, Koudou.

Study supervision: Heude, de Zegher, Cooper, Charles, Ong.

Conflict of Interest Disclosures: None reported.

Funding/Support: This project was funded by a Collaborative Research Grant from the European Society for Paediatric Endocrinology and by the Medical Research Council (MC_UU_12015/2 and MC_U106179472). Dr de Zegher is a clinical investigator supported by the Clinical Research Council of the Leuven University Hospitals. Dr Ibáñez is a clinical investigator of the Centro de Investigación Biomédica en Red de Diabetes y Enfermedades Metabólicas Asociadas, Instituto de Salud Carlos III, Madrid, Spain. The Barcelona study was supported by the Ministerio de Ciencia e Innovación, Instituto de Salud Carlos III, and by the Fondo Europeo de Desarrollo Regional, Madrid, Spain (PI11/O443). The Cambridge Baby Growth Study was supported by the European Union, the World Cancer Research Foundation International, the Medical Research Council, the Newlife

Foundation, and the National Institute of Health Research Cambridge Biomedical Research Centre. The EDEN mother-child cohort was supported by grants from Fondation pour la Recherche Médicale, French Ministry of Research, Institut National de la Santé et de la Recherche Médicale, the French Ministry of Health, French Agency for Occupational and Environmental Health Safety, French National Institute for Population Health Surveillance, University of Paris-Sud, French National Institute for Health Education, Nestlé, Mutuelle Générale de l'Éducation Nationale, French Speaking Association for the Study of Diabetes and Metabolism, and French Research Agency. Funding for the components of the Southampton Women's Survey contributing to this research came from the Medical Research Council, the University of Southampton, the Dunhill Medical Trust, British Heart Foundation, Arthritis Research United Kingdom, and the UK Food Standards Agency.

Role of the Funder/Sponsor: The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Additional Contributions: *Cambridge Baby Growth Study (CBGS):* We are grateful to the children and parents who participated in this study, as well as to the staff and facilities at the Wellcome Trust Clinical Research Facility (Addenbrooke's Clinical Research Centre), Cambridge, England, for assistance in infant assessments. We thank the CBGS coinvestigators Ieuan Hughes, MD, and Carlo Acerini, MD, and pediatric research nurses Suzanne Smith, RSCN, Anne-Marie Wardell, RSCN, and Karen Forbes, RSCN (Department of Paediatrics, University of Cambridge). *Southampton Women's Survey:* We thank the general practitioners and

midwives in Southampton, England, for their support. We are grateful to the research nurses and other staff of the Southampton Women's Survey for all of their work in recruiting and interviewing the participants and processing the data and samples. We also thank the women of Southampton and their children who gave their time to take part in the study. *EDEN mother-child cohort*: We thank the families participating in this study and the midwife research assistants for their support. EDEN data were collected with contributions of the EDEN mother-child cohort study group including Isabella Annesi-Maesano, MD, PhD, Jonathan Bernard, PhD, Jérémie Botton, PhD, Marie-Aline Charles, MD, MPH, Patricia Dargent-Molina, PhD, Blandine de Lauzon-Guillain, PhD, Pierre Ducimetière, PhD, Maria de Agostini, PhD, Bernard Foliguuet, MD, PhD, Anne Forhan, MSc, Xavier Fritel, MD, PhD, Alice Germa, PhD, Valérie Goua, MD, Régis Hankard, MD, PhD, Barbara Heude, PhD, Monique Kaminski, PhD, Béatrice Larroque, MD, PhD (deceased), Nathalie Lelong, MSc, Johanna Lepeule, PhD, Guillaume Magnin, MD, PhD, Laetitia Marchand, MSc, Cathy Nabet, PhD, Fabrice Pierre, MD, PhD, Rémy Slama, PhD, Marie-Joséphine Saurel-Cubizolles, PhD, Michel Schweitzer, MD, PhD, and Olivier Thiebaugeorges, MD, PhD, MPH. We are grateful to Véronique Pelloux for EDEN DNA storage, amplification, and handling. The contributors received no financial compensation.

REFERENCES

- Lakshman R, Elks CE, Ong KK. Childhood obesity. *Circulation*. 2012;126(14):1770-1779.
- Baird J, Fisher D, Lucas P, Kleijnen J, Roberts H, Law C. Being big or growing fast: systematic review of size and growth in infancy and later obesity. *BMJ*. 2005;331(7522):929. doi:10.1136/bmj.38586.411273.E0.
- Druet C, Stettler N, Sharp S, et al. Prediction of childhood obesity by infancy weight gain: an individual-level meta-analysis. *Paediatr Perinat Epidemiol*. 2012;26(1):19-26.
- Adair LS, Fall CHD, Osmond C, et al; COHORTS group. Associations of linear growth and relative weight gain during early life with adult health and human capital in countries of low and middle income: findings from five birth cohort studies. *Lancet*. 2013;382(9891):525-534.
- Wells JCK, Chomtho S, Fewtrell MS. Programming of body composition by early growth and nutrition. *Proc Nutr Soc*. 2007;66(3):423-434.
- Elks CE, Loos RJF, Sharp SJ, et al. Genetic markers of adult obesity risk are associated with greater early infancy weight gain and growth. *PLoS Med*. 2010;7(5):e1000284. doi:10.1371/journal.pmed.1000284.
- Warrington NM, Howe LD, Wu YY, et al. Association of a body mass index genetic risk score with growth throughout childhood and adolescence. *PLoS One*. 2013;8(11):e79547. doi:10.1371/journal.pone.0079547.
- Belsky DW, Moffitt TE, Houts R, et al. Polygenic risk, rapid childhood growth, and the development of obesity: evidence from a 4-decade longitudinal study. *Arch Pediatr Adolesc Med*. 2012;166(6):515-521.
- Speliotes EK, Willer CJ, Berndt SI, et al; MAGIC Procardis Consortium. Association analyses of 249,796 individuals reveal 18 new loci associated with body mass index. *Nat Genet*. 2010;42(11):937-948.
- Ong KK, Langkamp M, Ranke MB, et al. Insulin-like growth factor I concentrations in infancy predict differential gains in body length and adiposity: the Cambridge Baby Growth Study. *Am J Clin Nutr*. 2009;90(1):156-161.
- Inskip HM, Godfrey KM, Robinson SM, Law CM, Barker DJP, Cooper C; SWS Study Group. Cohort profile: the Southampton Women's Survey. *Int J Epidemiol*. 2006;35(1):42-48.
- Robinson S, Marriott L, Poole J, et al; Southampton Women's Survey Study Group. Dietary patterns in infancy: the importance of maternal and family influences on feeding practice. *Br J Nutr*. 2007;98(5):1029-1037.
- Moon RJ, Harvey NC, Robinson SM, et al; SWS Study Group. Maternal plasma polyunsaturated fatty acid status in late pregnancy is associated with offspring body composition in childhood. *J Clin Endocrinol Metab*. 2013;98(1):299-307.
- Drouillet P, Forhan A, De Lauzon-Guillain B, et al. Maternal fatty acid intake and fetal growth: evidence for an association in overweight women: the "EDEN mother-child" cohort (study of pre- and early postnatal determinants of the child's development and health). *Br J Nutr*. 2009;101(4):583-591.
- López-Bermejo A, Petry CJ, Díaz M, et al. The association between the FTO gene and fat mass in humans develops by the postnatal age of two weeks. *J Clin Endocrinol Metab*. 2008;93(4):1501-1505.
- Goran MI, Kaskoun MC, Carpenter WH, Poehlman ET, Ravussin E, Fontvieille AM. Estimating body composition of young children by using bioelectrical resistance. *J Appl Physiol* (1985). 1993;75(4):1776-1780.
- Brook CG. Determination of body composition of children from skinfold measurements. *Arch Dis Child*. 1971;46(246):182-184.
- Li S, Zhao JH, Luan J, et al. Cumulative effects and predictive value of common obesity-susceptibility variants identified by genome-wide association studies. *Am J Clin Nutr*. 2010;91(1):184-190.
- Freeman JV, Cole TJ, Chinn S, Jones PR, White EM, Preece MA. Cross sectional stature and weight reference curves for the UK, 1990. *Arch Dis Child*. 1995;73(1):17-24.
- Mei H, Chen W, Jiang F, et al. Longitudinal replication studies of GWAS risk SNPs influencing body mass index over the course of childhood and adulthood. *PLoS One*. 2012;7(2):e31470. doi:10.1371/journal.pone.0031470.
- Sovio U, Mook-Kanamori DO, Warrington NM, et al; Early Growth Genetics Consortium. Association between common variation at the FTO locus and changes in body mass index from infancy to late childhood: the complex nature of genetic association through growth and development. *PLoS Genet*. 2011;7(2):e1001307. doi:10.1371/journal.pgen.1001307.
- Elks CE, Perry JR, Sulem P, et al; GIANT Consortium. Thirty new loci for age at menarche identified by a meta-analysis of genome-wide association studies. *Nat Genet*. 2010;42(12):1077-1085.
- Wells JCK, Hallal PC, Wright A, Singhal A, Victora CG. Fetal, infant and childhood growth: relationships with body composition in Brazilian boys aged 9 years. *Int J Obes (Lond)*. 2005;29(10):1192-1198.
- Wilson HJ, Dickinson F, Hoffman DJ, Griffiths PL, Bogin B, Varela-Silva MI. Fat free mass explains the relationship between stunting and energy expenditure in urban Mexican Maya children. *Ann Hum Biol*. 2012;39(5):432-439.
- Walker SP, Gaskin P, Powell CA, Bennett FI, Forrester TE, Grantham-McGregor S. The effects of birth weight and postnatal linear growth retardation on blood pressure at age 11-12 years. *J Epidemiol Community Health*. 2001;55(6):394-398.
- Gale C, Logan KM, Santhakumaran S, Parkinson JRC, Hyde MJ, Modi N. Effect of breastfeeding compared with formula feeding on infant body composition: a systematic review and meta-analysis. *Am J Clin Nutr*. 2012;95(3):656-669.
- Han DY, Murphy R, Morgan AR, et al. Reduced genetic influence on childhood obesity in small for gestational age children. *BMC Med Genet*. 2013;14:10. doi:10.1186/1471-2350-14-10.
- Kilpeläinen TO, den Hoed M, Ong KK, et al; Early Growth Genetics Consortium. Obesity-susceptibility loci have a limited influence on birth weight: a meta-analysis of up to 28,219 individuals. *Am J Clin Nutr*. 2011;93(4):851-860.
- Heid IM, Jackson AU, Randall JC, et al; MAGIC. Meta-analysis identifies 13 new loci associated with waist-hip ratio and reveals sexual dimorphism in the genetic basis of fat distribution. *Nat Genet*. 2010;42(11):949-960.
- Wells JCK, Cole TJ; ALSPAC study team. Adjustment of fat-free mass and fat mass for height in children aged 8 y. *Int J Obes Relat Metab Disord*. 2002;26(7):947-952.
- Llewellyn CH, Trzaskowski M, van Jaarsveld CHM, Plomin R, Wardle J. Satiety mechanisms in genetic risk of obesity. *JAMA Pediatr*. 2014;168(4):338-344.
- Karlberg J. A biologically-oriented mathematical model (ICP) for human growth. *Acta Paediatr Scand Suppl*. 1989;350:70-94.