Plant-based dietary patterns and age-specific risk of multimorbidity of cancer and cardiometabolic diseases: a prospective analysis

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Summary

Background It is currently unknown whether plant-based dietary patterns influence disease progression to multimorbidity after an initial non-communicable disease, and whether the associated risk of multimorbidity varies with age. This study aimed to investigate associations of plant-based diets with the risk of multimorbidity, defined as the co-occurrence of at least two chronic diseases in an individual (either cancer at any site, cardiovascular disease, or type 2 diabetes).

Methods This prospective cohort study used data from EPIC and UK Biobank across six European countries, with participants aged 35–70 years at recruitment. We excluded participants from these cohorts who had cancer, cardiovascular disease, or type 2 diabetes at baseline or those with missing data on diet or health outcomes. Data on dietary habits were assessed either at baseline through a validated dietary questionnaire about habits in the previous 12 months or through several 24-h recall questionnaires during approximately a year of follow-up. Multistate modelling with Cox regression was used to estimate the risk of multimorbidity according to a healthful plant-based diet index (hPDI) and, separately, an unhealthful plant-based diet index (uPDI). Risk differences in adults younger than 60 years and those age 60 years and older were estimated.

Findings 407 618 participants (226 324 from EPIC and 181 294 from UK Biobank) were included in this study. During a median follow-up time of 10·9 years in EPIC and 11·4 years in UK Biobank, 6604 cancer–cardiometabolic multimorbidity events occurred in both cohorts combined. A ten-point increment of the hPDI score was associated with a lower risk of multimorbidity, with a hazard ratio (HR) of 0·89 (95% CI 0·83–0·96) in EPIC and 0·81 (0·76–0·86) in UK Biobank. This inverse association was marginally weaker in older adults than in middle-aged adults in both cohorts. In UK Biobank, a ten-point increment of the hPDI score was associated with multivariable-adjusted HRs of 0·71 (95% CI 0·65–0·79) in adults younger than 60 years and 0·86 (0·80–0·92) in those aged 60 years and older ($p_{interaction}$=0·0016). The respective HRs in EPIC were 0·86 (95% CI 0·78–0·95) and 0·92 (0·84–1·02; $p_{interaction}$=0·32). A higher adherence to an unhealthy plant-based diet was positively associated with multimorbidity risk in UK Biobank (HR per ten-point increment of uPDI 1·22, 95% CI 1·16–1·29), but this was not replicated in EPIC (1·00, 0·94–1·08).

Interpretation A healthy plant-based diet might reduce the burden of multimorbidity of cancer and cardiometabolic diseases among middle-aged and older adults.

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Introduction

Multimorbidity, defined as the co-occurrence of at least two chronic diseases in an individual, is emerging as a global health issue, with the greatest burden among older adults.[1] In 2023, the global prevalence of multimorbidity was estimated to be 37% across all age groups, and more than 50% in adults aged 60 years and older.[2] Given that multimorbidity can include many different combinations of chronic diseases, we focused on cancer, cardiovascular disease, and type 2 diabetes, because these diseases are leading causes of mortality globally[3] and they share preventable risk factors, such as poor diet.[4]

Health benefits of plant-based diets, which are also more environmentally sustainable than diets with a higher proportion of animal products,[5] are documented for individual chronic diseases such as some cancers, cardiovascular disease, and type 2 diabetes.[6–11] Importantly, not all plant foods are equally beneficial for health, and some could even

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Research in context

Evidence before this study

We searched PubMed from database inception on Nov 1, 2023, to Oct 30, 2024, for studies exploring the relationship between plant-based dietary patterns and risk of developing multimorbidity, with no language restrictions for the papers. We used a combination of search terms such as "plant-based diet" OR "plant-based dietary pattern" OR "plant-based diet index" OR "plant-based diet quality" OR "vegetarian diet" AND "multimorbidity" OR "cardiometabolic multimorbidity" (see appendix p 4 for full list). Previous studies have found that the healthiness of plant-based diets might be important for prevention of individual chronic diseases. However, there is little evidence on the association between plant-based diets and multimorbidity risk. Only one study examined the association with multimorbidity, but this study ascertained multimorbidity from self-reported conditions and did not focus on multimorbidity of cancer and cardiometabolic diseases.

Added value of this study

This study adds evidence on how plant-based dietary patterns influence disease progression to multimorbidity after an initial major non-communicable disease. Additionally, it also assessed differences in risk of multimorbidity between middle-aged and older adults. Higher adherence to a healthy plant-based diet was associated with a lower risk of cancer and cardiometabolic multimorbidity in both adults younger than 60 years and in those age 60 years or older, although effect sizes were small. This finding suggests that a diet consisting primarily of healthy plant foods and small amounts of animal-based foods could contribute to maintaining good health into older age.

Implications of all the available evidence

Multimorbidity, which refers to the presence of two or more chronic diseases in one person, is increasingly common, but particularly affects adults aged 60 years and older. Dietary recommendations, public health policies, and interventions should consider that diets mainly composed of healthy plant foods with small amounts of animal-based foods could help prevent cancer and cardiometabolic multimorbidity. A co-benefit of plant-based diets is their contribution to environmental sustainability.

be detrimental.[12] Plant-based diet indices have been developed based on the healthiness of plant foods. These indices include the healthful plant-based diet index (hPDI), which consists of healthy plant foods, and the unhealthful plant-based diet index (uPDI), which represents a higher consumption of mainly refined plant foods.[10] A higher hPDI score has been associated with lower risk of cardiovascular disease, type 2 diabetes, some cancers, and related mortality,[7,8,10,11,13] whereas a higher uPDI score has been associated with greater risk of cardiometabolic diseases and related mortality.[7,10,11,14] However, whether plant-based diets also have a role in the sequence and co-occurrence of these diseases in an individual, defined as cancer and cardiometabolic multimorbidity, is largely unknown.[15]

We aimed to investigate associations of two plant-based diet indices with the risk of multimorbidity, defined as the co-occurrence of at least two chronic diseases in an individual (either cancer at any site, cardiovascular disease, or type 2 diabetes).

Methods

Study design and population

In this prospective cohort study, we used data from EPIC (European Prospective Investigation into Cancer and Nutrition) and UK Biobank to assess the effects of a plant-based diet on multimorbidity.

EPIC is an ongoing prospective cohort study designed to investigate the associations of diet, lifestyle, and genetic factors with the risk of cancer and other chronic diseases.[16] Participants were aged 35–70 years when recruited, and recruitment took place from 1992 to 2000 in 23 study centres located in ten European countries (appendix p 4). In most study centres, participants were invited from the general adult population residing in a selected geographical area, except participants in France who were recruited from teachers' health insurance, some centres in Spain and Italy recruited from blood donor associations, and women in Utrecht (Netherlands) and Florence (Italy) who were recruited from local breast cancer screening programmes. Participants were followed from recruitment until end of follow-up (ie, last date of centre-specific and event-specific ascertainment of cancer, cardiovascular disease, or type 2 diabetes, whichever came first), death (4·0%), or loss to follow-up (1·5%).

UK Biobank is a large, population-based, prospective cohort study consisting of participants age 40–69 years at recruitment (which was from 2006 to 2010 across 22 assessment centres in England, Scotland, and Wales).[17] Participants were followed from recruitment until end of follow-up (ie, last date of centre-specific and event-specific ascertainment of cancer, cardiovascular disease, or type 2 diabetes, whichever came first), death (3·1%), or loss to follow-up (0·3%).

In both cohorts, we excluded participants who had prevalent cancer, cardiovascular disease (myocardial infarction, angina, or stroke), or type 2 diabetes at baseline. We further excluded participants with missing information on diet, type 2 diabetes status at baseline, or in any covariate. In EPIC, the centres in France, Greece, Norway, and Sweden were excluded due to missing information on incident cardiovascular disease or type 2 diabetes events.

This study adhered to the Declaration of Helsinki. All participants from EPIC and UK Biobank provided written informed consent to participate in the respective cohorts. UK Biobank has ethical approval from the Northwest

Multi-Centre Research Ethics Committee. EPIC was approved by the Cancer Ethical Review Committee of International Agency for Research on Cancer (IARC) and by local ethical committees at the participating centres. The current study was approved by the IARC's Ethics Committee (IEC number 24–11).

Procedures

In EPIC, habitual food and beverage intake in the previous 12 months was assessed at baseline with country-specific or centre-specific validated dietary questionnaires.[16] More details are available in the appendix (p 4).

In UK Biobank, dietary intakes were assessed with the validated Oxford WebQ, a web-based, self-administered 24-h recall questionnaire. This tool was administered up to five times per participant between 2009 and 2012. The Oxford WebQ has been validated against an interviewer-administered 24-h recall, showing similar reporting of food items and estimated energy and nutrient intakes.[18] In our study, participants completed at least one of up to five dietary assessments. Our main exposure variables, the PDI scores, were averaged as a mean across multiple 24-h recalls.

We calculated scores of a hPDI and uPDI using the approach of Satija and colleagues, who classified 18 distinct food groups based on nutrient and culinary similarities (appendix pp 15–16).[10,11] In UK Biobank, only 17 groups were assessed, as information on vegetable oil consumption was unavailable.[14] We first adjusted each food group for total energy intake by regressing each food group on total energy intake and computing their standardised residuals. Participants were then ranked by quintiles of each energy-adjusted food group.[19] For the calculation of the hPDI score, healthy plant foods were positively scored (1–5, with 5 being the top quintile) and less healthy plant foods and animal products were reversely scored (5–1, with 1 being the top quintile). For the uPDI score, less healthy plant foods were positively scored and healthy plant foods and animal products were reversely scored. The theoretical range of both hPDI and uPDI was 18–90 (17–85 in UK Biobank).

In EPIC and UK Biobank, incident cancers were defined with the ICD tenth edition codes C00–C97 (excluding C44). Incident type 2 diabetes was defined as ICD code E11 in both cohorts. In EPIC, incident cardiovascular disease included ischaemic heart diseases (codes I20–I25) and cerebrovascular diseases (I60–I69). In UK Biobank, incident cardiovascular disease included codes I20–I23, I24.1, I25.2, I60, I61, I63, and I64. Ascertainment methods and censoring dates are given in appendix p 5. Any two diseases ascertained on the same day in an individual were arbitrarily separated by up to four days to establish a temporal order as follows: type 2 diabetes, cancer, and cardiovascular disease. A different ordering of this sequence did not affect risk estimates.

In EPIC and UK Biobank, information on sociodemographic, diet, and lifestyle factors and anthropometric measurements were collected at baseline.[14,20] In EPIC, biological sex was collected by self-report (with the options of female or male). In UK Biobank, biological sex assigned at birth as either female or male was acquired from population registries of the National Health Services; in some cases, the female or male category was updated by the participant. Ethnicity data in UK Biobank were collected through self-report. Further details on covariates are given in the appendix (p 17).

Outcomes

The main outcome of the study was any associations of the hPDI or uPDI with the risk of multimorbidity, defined as the co-occurrence of at least two chronic diseases in an individual (either cancer at any site, cardiovascular disease, or type 2 diabetes).

As secondary outcomes, we assessed whether these associations differ among adults younger than 60 years versus those age 60 years and older and associations of these two plant-based diet indices with a first onset of cancer, cardiovascular disease, and type 2 diabetes, and subsequent transitions to multimorbidity.

Statistical analysis

The sample sizes from both cohorts were deemed sufficient for expected effect sizes with minimally detectable hazard ratios (HRs) of 0·93 or less or at least 1·08 from previous research.[4]

We applied a multistate framework[21] for transitions from baseline to any first cancer, cardiovascular disease, or type 2 diabetes and to any combination with a second condition defined as multimorbidity. Deaths were censored as competing events and not modelled as a separate outcome. In addition, we modelled a direct transition from baseline to multimorbidity, in which follow-up was until any second condition after any first condition of cancer, cardiovascular disease, or type 2 diabetes.

Both the hPDI and uPDI scores were modelled on a continuous scale per ten-points increase (~1 standard deviation) and by quartiles, with the lowest quartile as reference category. We used multivariable-adjusted Cox proportional hazards models to estimate HRs and 95% CIs for associations between the hPDI score, and separately the uPDI score, and the outcomes of interest. Because we were addressing an aetiological question, we implemented cause-specific hazard models rather than a subdistribution hazard model, which is more appropriate for clinical prediction.[22] Entry time was age at recruitment and exit time was either age at diagnosis of the event of interest, death, or censoring date (loss to follow-up or end of follow-up), whichever occurred first.

All models were stratified by age at recruitment, sex, centre (or geographical region of recruitment in UK Biobank), and transitions in a clock forward multistate analysis with age as the primary time variable. We used a directed acyclic graph based on previous knowledge to identify confounding variables (appendix p 10). The definition of some covariates differed between the two cohorts (appendix

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See **Online** for appendix

	First quartile	Second quartile	Third quartile	Fourth quartile	Overall
Participants	66 645	57 723	52 624	49 332	226 324
hPDI score	48·0 (40·0–50·0)	54·0 (52·0–55·0)	57·0 (56·0–58·0)	62·0 (60·0–65·0)	55·0 (43·0–59·0)
Age at recruitment, years	53·8 (32·0–59·3)	52·6 (35·2–58·5)	52·0 (35·3–58·0)	51·3 (34·2–57·4)	52·6 (34·4–58·4)
Sex					
Male	27 592 (41·4%)	21 240 (36·8%)	19 171 (36·4%)	17 758 (36·0%)	85 761 (37·9%)
Female	39 053 (58·6%)	36 483 (63·2%)	33 453 (63·6%)	31 574 (64·0%)	140 563 (62·1%)
Alcohol consumption, g/d	8 (0–19)	7 (0–19)	7 (0–21)	8 (0–24)	8 (0–21)
BMI, kg/m^2	26·2 (4·2)	26·1 (4·1)	26·0 (4·1)	25·8 (4·1)	26·0 (4·1)
Smoking status					
Never	27 454 (41·2%)	26 530 (46·0%)	24 612 (46·8%)	23 250 (47·1%)	10 1846 (45·0%)
Previous	17 620 (26·4%)	16 632 (28·8%)	15 817 (30·1%)	15 512 (31·4%)	65 581 (29·0%)
Current	21 571 (32·4%)	14 561 (25·2%)	12 195 (23·2%)	10 570 (21·4%)	58 897 (26·0%)
Education					
None	2690 (4·0%)	3869 (6·7%)	4193 (8·0%)	4678 (9·5%)	15 430 (6·8%)
Primary school completed	22 077 (33·1%)	17 788 (30·8%)	15 888 (30·2%)	14 225 (28·8%)	69 978 (30·9%)
Technical or professional school	23 106 (34·7%)	16 459 (28·5%)	12 871 (24·5%)	9651 (19·6%)	62 087 (27·4%)
Secondary school	7679 (11·5%)	8006 (13·9%)	8044 (15·3%)	8164 (16·5%)	31 893 (14·1%)
Longer education	11 093 (16·6%)	11 601 (20·1%)	11 628 (22·1%)	12 614 (25·6%)	46 936 (20·7%)
Physical activity					
Inactive	12 368 (18·6%)	12 074 (20·9%)	11 470 (21·8%)	11 667 (23·7%)	47 579 (21·0%)
Moderately inactive	21 740 (32·6%)	19 852 (34·4%)	17 795 (33·8%)	15 774 (32·0%)	75 161 (33·2%)
Moderately active	15 116 (22·7%)	13 149 (22·8%)	11 996 (22·8%)	11 014 (22·3%)	51 275 (22·7%)
Active	17 421 (26·1%)	12 648 (21·9%)	11 363 (21·6%)	10 877 (22·0%)	52 309 (23·1%)
Energy intake, kcal/d	2190 (616)	2050 (611)	2100 (630)	2250 (651)	2150 (630)
Menopausal status					
Premenopausal	11 533/39 053 (29·5%)	12 873/36 483 (35·3%)	12 419/33 453 (37·1%)	11 937/31 574 (37·8%)	48 762/140 563 (34·7%)
Postmenopausal	20 509/39 053 (52·5%)	17 152/36 483 (47·0%)	15 165/33 453 (45·3%)	13 669/31 574 (43·3%)	66 495/140 563 (47·3%)
Perimenopausal	5519/39 053 (14·1%)	5084/36 483 (13·9%)	4677/33 453 (14·0%)	4742/31 574 (15·0%)	20 022/140 563 (14·2%)
Surgical postmenopausal (bilateral oophorectomy)	1492/39 053 (3·8%)	1374/36 483 (3·8%)	1192/33 453 (3·6%)	1226 (3·9%)	5284/140 563 (3·8%)
Postmenopausal hormones					
No	31 562/39 053 (80·8%)	30 474/36 483 (83·5%)	28 608/33 453 (85·5%)	27 719/31 574 (87·8%)	118 363/140 563 (84·2%)
Yes	7491/39 053 (19·2%)	6009/36 483 (16·5%)	4845/33 453 (14·5%)	3855/31 574 (12·2%)	22 200/140 563 (15·8%)

Data are n, n (%), n/N (%), median (IQR), or mean (SD). The proportion of missing values ranged from 0·9% to 1·8%, whereby a total of 3·2% of participants had at least one missing value in any of these baseline characteristics. hPDI=healthful plant-based diet index.

Table 1: **Baseline characteristics of the study population across quartiles of the hPDI score in the EPIC study**

p 17). For example, in EPIC, overall quality of the diet was modelled with the Mediterranean diet score, whereas in UK Biobank we used a healthy diet score.[23] For continuous variables, in case of non-linearity, we used restricted cubic splines with knots at Harrell's predefined percentiles (5th, 35th, 65th, and 95th). We further adjusted our main model for BMI (as a continuous variable, kg/m^2) to explore a potential mediating role of BMI.

We tested a priori for effect modification by age at recruitment (<60 years *vs* ≥60 years). Given that the prevalence of multimorbidity among adults aged 60 years or above exceeds 50%, we used this arbitrary cutoff to model potential age-specific differences in risk. We fitted a multiplicative interaction between the hPDI, and in turn uPDI, and these age group categories. Differences in estimates were quantified by calculating the ratio of the HRs in the two age groups (ie, the multiplicative interaction term and its 95% CI). For additive interaction, we grouped participants into four categories: younger than 60 years and hPDI greater than the median (reference); younger than 60 years and hPDI less than or equal to the median; age 60 years or older and hPDI greater than the median; and age 60 years and older and hPDI less than or equal to the median. Relative excess risk due to interaction (RERI) was estimated as $RERI_{RR} = RR_{11} - RR_{10} - RR_{01} + 1$, with RR_{11} the relative risk of being exposed to both factors (category 4), RR_{10} and RR_{01} to one or other (category 2 and 3). Estimations of 95% CI were based on the delta method.

We did several sensitivity analyses to evaluate the robustness of our results (appendix p 4).

In all models, we tested the proportional hazards assumption based on Schoenfeld residuals and found no violations. All analyses were done with R (version 4.1.2) and the Lexis class in the Epi R package. Statistical tests were two-sided, and p values under 0·05 were considered statistically significant.

	First quartile	Second quartile	Third quartile	Fourth quartile	Overall
Participants	51 336	47 485	41 528	40 945	181 294
hPDI score	44·0 (37·0–46·0)	49·0 (47·0–50·0)	54·0 (52·0–55·0)	59·0 (56·0–62·0)	51·0 (39·0–55·0)
Age at recruitment, years	54·0 (41·0–61·0)	57·0 (41·0–62·0)	57·0 (41·0–63·0)	58·0 (41·0–63·0)	57·0 (41·0–62·0)
Sex					
Male	21 297 (41·5%)	22 574 (47·5%)	19 673 (47·4%)	17 023 (41·6%)	80 567 (44·4%)
Female	30 039 (58·5%)	24 911 (52·5%)	21 855 (52·6%)	23 922 (58·4%)	100 727 (55·6%)
Alcohol consumption, g/d	8 (0–23)	10 (0–28)	12 (0–29)	12 (0–30)	10 (0–27)
BMI, kg/m^2	27·4 (4·8)	26·8 (4·4)	26·5 (4·3)	26·0 (4·2)	26·7 (4·5)
Smoking status					
Never	30 059 (58·6%)	27 161 (57·2%)	23 527 (56·7%)	23 380 (57·1%)	104 127 (57·4)
Previous	16 399 (31·9%)	16 557 (34·9%)	15 022 (36·2%)	14 995 (36·6%)	62 973 (34·7)
Current	4878 (9·5%)	3767 (7·9%)	2979 (7·2%)	2570 (6·3%)	14 194 (7·8)
Townsend deprivation index					
Q1	9990 (19·5%)	9935 (20·9%)	8592 (20·7%)	8381 (20·5%)	36 898 (20·4%)
Q2	10 050 (19·6%)	9577 (20·2%)	8553 (20·6%)	8318 (20·3%)	36 498 (20·1%)
Q3	10 273 (20·0%)	9505 (20·0%)	8454 (20·4%)	8199 (20·0%)	36 431 (20·1%)
Q4	10 213 (19·9%)	9610 (20·2%)	8224 (19·8%)	8181 (20·0%)	36 228 (20·0%)
Q5	10 810 (21·1%)	8858 (18·7%)	7705 (18·6%)	7866 (19·2%)	35 239 (19·4%)
Physical activity					
Q1	12 364 (24·1%)	9422 (19·8%)	7403 (17·8%)	5916 (14·4%)	35 105 (19·4%)
Q2	10 690 (20·8%)	9725 (20·5%)	8168 (19·7%)	7580 (18·5%)	36 163 (19·9%)
Q3	9950 (19·4%)	9593 (20·2%)	8457 (20·4%)	8588 (21·0%)	36 588 (20·2%)
Q4	9303 (18·1%)	9579 (20·2%)	8830 (21·3%)	9175 (22·4%)	36 887 (20·3%)
Q5	9029 (17·6%)	9166 (19·3%)	8670 (20·9%)	9686 (23·7%)	36 551 (20·2%)
Energy intake, kcal/d	1880 (545)	1980 (531)	2100 (510%)	2270 (478)	2050 (538)
Menopausal status					
No	9973/30 039 (33·2%)	6793/24 911 (27·3%)	5545/21 855 (25·4%)	5603/23 922 (23·4)	27 914/100 727 (27·7%)
Yes	15 312/30 039 (51·0%)	14 463/24 911 (58·1%)	13 175/21 855 (60·3%)	15 174/23 922 (63·4%)	58 124/100 727 (57·7%)
Not sure, had a hysterectomy	3197/30 039 (10·6%)	2523/24 911 (10·1%)	2156/21 855 (9·9%)	2192/23 922 (9·2%)	10 068/100 727 (10·0%)
Not sure, other reason	1557/30 039 (5·2%)	1132/24 911 (4·5%)	979/21 855 (4·5%)	953/23 922 (4·0%)	4621/100 727 (4·6%)
Postmenopausal hormones					
No	20 246/30 039 (67·4%)	15 949/24 911 (64·0%)	14 003/21 855 (64·1%)	15 213/23 922 (63·6%)	65 411/100 727 (64·9%)
Yes	9793/30 039 (32·6%)	8962/24 911 (36·0%)	7852/21 855 (35·9%)	8709/23 922 (36·4%)	35 316/100 727 (35·1%)

Data are n, n (%), n/N (%), median (IQR) or mean (SD). The proportion of missing values ranged from 0·1% to 2·1%, whereby a total of 2·8% of participants had at least one missing value in any of these baseline characteristics. hDPI=healthful plant-based diet index.

Table 2: **Baseline characteristics of the study population across quartiles of the hPDI score in UK Biobank**

Role of the funding source

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

Results

A total of 407 618 participants (226 324 from EPIC and 181 294 from UK Biobank) were included in this study (appendix pp 6–7). Baseline characteristics of the two study populations across quartiles of the hPDI are shown in table 1 and table 2. During a median follow-up time of 10·9 years (IQR 9·7–12·5) in EPIC and 11·4 years (IQR 10·9–12·2) in UK Biobank, 6604 cancer–cardiometabolic multimorbidity events (2377 [36·0%] among women and 4227 [64·0%] among men) occurred in both cohorts combined (3455 in EPIC and 3149 in UK Biobank). The number of events ascertained for each disease and corresponding incidence rates are shown in figure 1.

In both cohorts, higher adherence to a healthy plant-based diet was associated with a lower risk of cancer, cardiovascular disease, and type 2 diabetes. For example, the multivariable-adjusted HR for type 2 diabetes, per ten-point increase of the hPDI score, was 0·82 (95% CI 0·79–0·85) in EPIC and 0·74 (0·70–0·78) in UK Biobank (figure 2A). In contrast, higher adherence to an unhealthy plant-based diet (per ten-point increase of the uPDI score) was associated with a higher risk of these three diseases in both cohorts, except for the risk of type 2 diabetes in EPIC (HR 1·02, 95% CI 0·98–1·07; figure 2B). Additional adjustment for BMI did not change these associations except for cardiovascular disease risk, for which the association with hPDI was weaker and crossed the null after BMI adjustment (appendix pp 11–14).

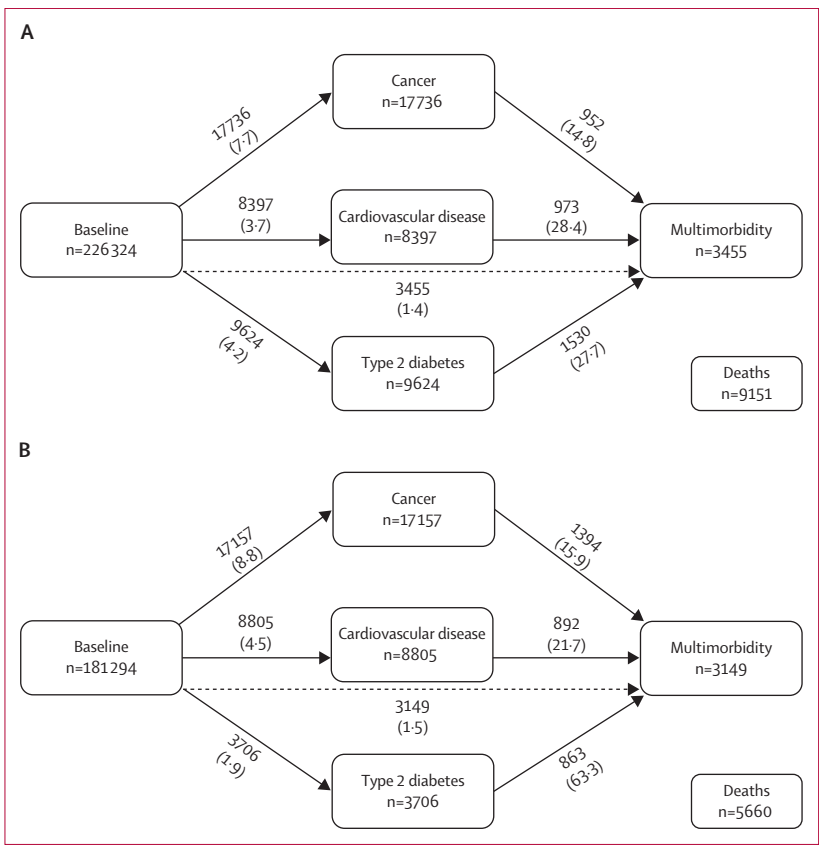

Figure 1: **Transitions from baseline to cancer, cardiovascular disease, and type 2 diabetes, and subsequent cancer-cardiometabolic multimorbidity**

Transitions are shown separately for the EPIC (A) and UK Biobank (B) cohorts. Cancer refers to first malignant tumour at any site excluding non-melanoma skin cancer. Deaths were censored and not modelled as a separate outcome. State-specific number of events are reported in boxes, and transition-specific number of events and incidence rates per 1000 person-years (within brackets) are reported on arrows. Dashed line indicates the direct transition from baseline to multimorbidity (at least two diseases in an individual). Censoring due to loss to follow-up was 1·5% (n=3395) in the EPIC cohort and 0·3% (n=544) in UK Biobank.

In the direct transition from baseline to multimorbidity, higher adherence to a healthy plant-based diet was associated with a lower risk of multimorbidity in both cohorts, with an HR of 0·89 (95% CI 0·83–0·96) in EPIC and 0·81 (0·76–0·86) in UK Biobank (figure 2A). In contrast, the association between higher adherence to an unhealthy plant-based diet and multimorbidity was positive in UK Biobank (HR 1·22, 95% CI 1·16–1·29) but not associated with risk of multimorbidity in EPIC (1·00, 0·94–1·08; figure 2B). For transitions to multimorbidity among participants who developed cancer, cardiovascular disease, or type 2 diabetes, higher adherence to a healthy plant-based diet was consistently inversely associated with the risk of multimorbidity across the two cohorts, albeit the CI often included the null. A suggestive positive association was noted after type 2 diabetes to multimorbidity in UK Biobank (1·08, 0·97–1·21; figure 2A). An unhealthy plant-based diet was positively associated with multimorbidity risk after cancer in UK Biobank and after type 2 diabetes in EPIC (figure 2B). There was little change after further BMI adjustment in these associations (appendix pp 11–14). Similar trends in associations were observed when the hPDI and uPDI scores were analysed as quartiles in both cohorts (appendix pp 18–21).

Adhering to a healthy plant-based diet was associated with a lower risk of multimorbidity in both middle-aged and older adults, although associations were more pronounced in those younger than 60 years (figure 3A). In the EPIC cohort, the association in people older than 60 years crossed the null and was no longer significant (95% CI 0·84–1·02, p=0·13; figure 3A). Adherence to an unhealthy plant-based diet was positively associated with the risk of multimorbidity in both age groups in UK Biobank, but no associations were observed in either age group in EPIC (figure 3B). The most pronounced additive interaction was observed in UK Biobank for the joint association of having an above median uPDI and being aged 60 years or older when compared with low uPDI and being younger than 60 years, with a HR of 3·58 (95% CI 3·19–4·03) and a RERI of 0·51 (0·21–0·82; appendix p 34).

The main results for both hPDI and uPDI were generally consistent after multiple imputation, in men and women, in never smokers, across European geographical regions, and when we further adjusted for overall diet quality (appendix pp 22–33). In UK Biobank, after accounting for the number of completed dietary assessments, ethnicity, education and/or Townsend deprivation index, polypharmacy, or in participants who completed at least two, and in turn, at least three 24-hour recalls, results did not materially differ from our main analyses (appendix pp 22–33).

Discussion

In two large European prospective cohorts, we found that higher adherence to a healthy plant-based diet was associated with a lower risk of multimorbidity of cancer and cardiometabolic diseases (baseline to multimorbidty). This finding was consistent in middle-aged (<60 years) and older adults (≥60 years). Higher adherence to a healthy plant-based diet was also associated with lower risks of a first disease of cancer, cardiovascular disease, or type 2 diabetes. In contrast, higher adherence to an unhealthy plant-based diet was associated with a higher risk of developing cancer or cardiovascular disease, but associations with type 2 diabetes or multimorbidity were inconsistent between the two cohorts (with either a positive or null association).

Unlike vegetarian or vegan diets, plant-based diets assess the healthfulness of a dietary pattern consisting of foods primarily from plants without completely neglecting animal products. From a practical perspective, it is probably easier to shift the diet of populations towards a higher proportion of plant-based foods without excluding animal products. Similarly to vegetarian or vegan diets, plant-based diets are also more environmentally sustainable than diets with a higher proportion of animal products; for example, they are associated with lower greenhouse gas emissions than diets high in animal products.[5]

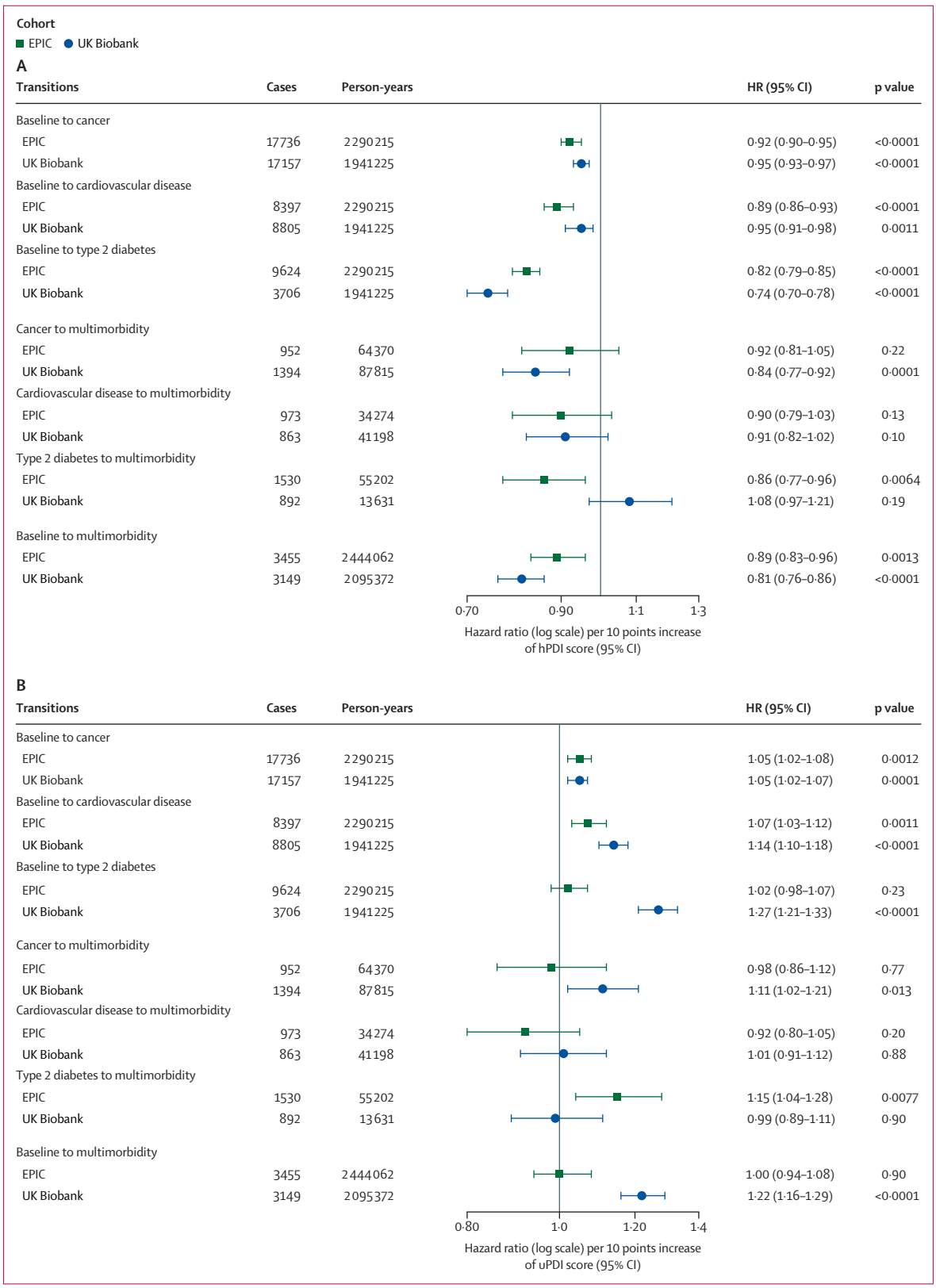

Figure 2: **Associations between a plant-based diet and risks of cancer, cardiovascular disease, type 2 diabetes, and subsequent cancer–cardiometabolic multimorbidity**
Data are from the EPIC (n=226 324) and UK Biobank (n=181 294) cohorts, and associations are with either the hPDI score (A) or the uPDI score (B). Cox proportional hazard regression models were stratified by age categories at recruitment, sex, centre (or geographical region of recruitment in UK Biobank), and transitions in a clock forward multistate analysis with age as primary time variable. Models were adjusted for physical activity, smoking status, alcohol intake, energy intake, an indicator for socioeconomic status, and in women further adjusted for menopausal status and use of menopausal hormone therapy. hPDI=healthy plant-based diet index. uPDI=unhealthy plant-based diet index.

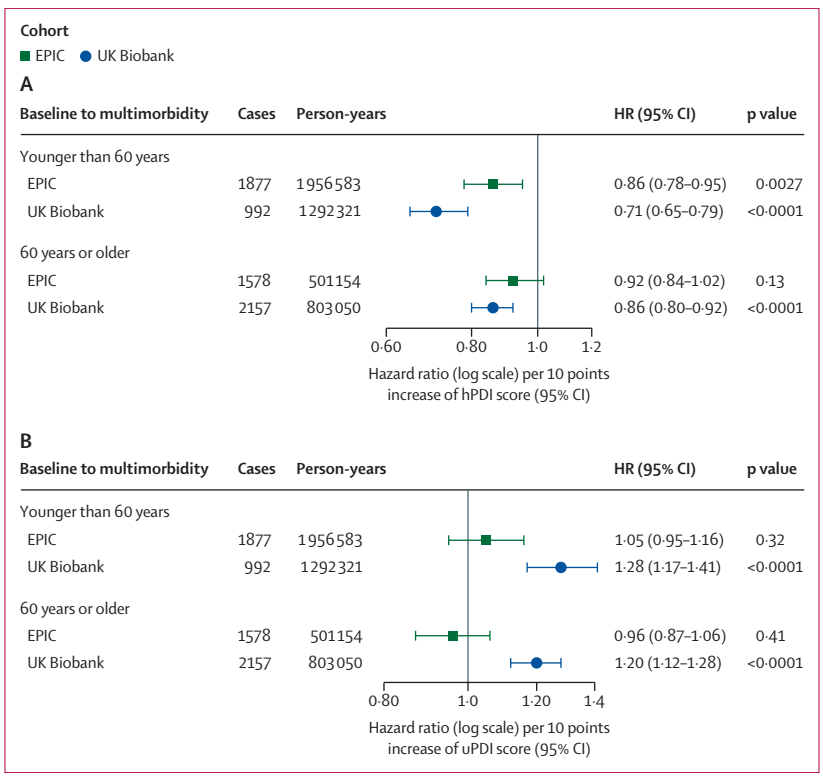

Figure 3: **Associations between a plant-based diet and risk of multimorbidity, stratified by age**
Data are from the EPIC (n=226 324) and UK Biobank (n=181 294) cohorts, and associations are with either the hPDI score (A) or the uPDI score (B). Cox proportional hazard regression models were stratified by age categories at recruitment, sex, centre (or geographical region of recruitment in UK Biobank), and transitions in a clock forward multistate analysis with age as primary time variable. Models were adjusted for physical activity, smoking status, alcohol intake, energy intake, an indicator for socioeconomic status, and in women further adjusted for menopausal status and use of menopausal hormone therapy. The risk difference (multiplicative interaction) for the hPDI score (A) in EPIC was 0·93 (95% CI 0·81–1·07, p value 0·32) and in UK Biobank was 0·83 (95% CI 0·74–0·93, p value 0·0016). The risk difference (multiplicative interaction) for the uPDI score (B) in EPIC was 1·10 (95% CI 0·96–1·26, p value 0·19) and in UK Biobank was 1·07 (95% CI 0·96–1·20, p value 0·23). hPDI=healthy plant-based diet index. uPDI=unhealthy plant-based diet index.

One previous study investigated associations between plant-based diets and the risk of multimorbidity defined from eight self-reported conditions: hypertension, diabetes, cancer, chronic lung disease, heart disease, stroke, arthritis, and depression.[15] In their study, a healthy plant-based diet was inversely associated with the risk of multimorbidity, although an unhealthy plant-based diet was not associated with risk.[15] Our findings regarding a healthy plant-based diet are congruent and add new insights by investigating disease transitions to multimorbidity in diverse European populations and provide specific evidence for older adults, who are usually most affected by multimorbidity burden. Our findings about associations between an unhealthy plant-based diet and transitions to multimorbidity were inconclusive, as depending on the disease transition either a null association or a positive association was observed in one of the two cohorts.

Our findings regarding developing a first disease (either cancer, cardiovascular disease, or type 2 diabetes) are in line with previous studies.[6–11] In three large, prospective, US cohorts, adherence to a healthy plant-based diet, was associated with a lower risk of coronary heart disease,[11] type 2 diabetes,[10] and some cancers including digestive system cancers,[7] prostate cancer,[8] and breast cancer.[9] In the Multiethnic Cohort Study, a higher adherence to a healthy plant-based diet was also associated with a lower risk of colorectal cancer than a lower adherence.[6] The same studies reported that higher adherence to an unhealthy plant-based diet was associated with a higher risk of coronary heart disease, type 2 diabetes, and specific cancers.[7,10,11] Except for type 2 diabetes risk in EPIC, for which we observed a null association, our findings align with these studies.

Mechanistically, a higher adherence to a healthy plant-based diet is associated with lower bodyweight, lower inflammation, and better insulin sensitivity than a lower adherence to a healthy plant-based diet,[24] all of which have a role in the development of type 2 diabetes, cardiovascular disease, and cancer.[25,26] Moreover, many nutrients and food constituents that are abundant in a healthy plant-based diet are known for favourable health effects.[24] For example, dietary fibre improves immune function and reduces intestinal inflammation by modulating the composition and function of the gut microbiome,[27] promotes the production of short-chain fatty acids by intestinal bacteria, and reduces the production of potentially harmful metabolites such as trimethylamine N-oxide or secondary bile acids.[27] In contrast, greater adherence to an unhealthy plant-based diet is characterised by higher added sugar consumption and lower intake of dietary fibre or antioxidants, which could result in higher disease risk through compromised insulin sensitivity and oxidative stress.[25,26] Understanding how different components of the plant-based diet index scores contribute to the risk of multimorbidity and individual diseases, and exploring variations in scoring or use of a weighted outcome-specific index,[28] could inform mechanistic investigations and refine public health recommendations.

Strengths of this study include the multinational setting across six European countries and the replication of results in two independent cohorts. Additionally, associations were modelled in a multistate framework, accounting for the sequence of incident chronic diseases.

Several limitations should be considered in the interpretation of this study. First, information on diet and other lifestyle factors was collected at baseline, probably with some measurement error leading to an overestimation or underestimation of risk estimates. In addition, we could not account for potential changes in these modifiable behaviours during follow-up. However, we have previously shown that the hPDI and uPDI scores have very good reliability over time in a subsample of the UK Biobank cohort.[14] Second, potential improvements in the adherence to a healthy plant-based diet after diagnosis of a first disease would most likely have led to an underestimation of observed risks. Third, associations between risk factors and the risk of multimorbidity after the occurrence of a first disease could be affected by selection bias, which tends to

weaken observed associations. However, in our study risk estimates were in the expected direction and magnitude after conditioning on the first disease, except for multimorbidity risk after type 2 diabetes in the UK Biobank cohort, suggesting that collider bias was of little concern in our study. Fourth, we did not have specific treatment data. If treatment was independent of diet, then our observed associations should be unaffected. This assumption is supported by the weak correlation between PDI scores and medication use at baseline (Spearman's $\rho<0{\cdot}03$). However, the estimated risk from a first disease to multimorbidity could also reflect a concomitant dietary and treatment effect (ie, confounding by treatment). To test which of the two scenarios is more probable, we provided estimates with and without adjustment for polypharmacy. Unfortunately, such data were only available in UK Biobank at baseline, but not in EPIC. Given that the risk estimates did not materially change after adjusting for available treatment information in UK Biobank (appendix pp 24–33), we assume that confounding by medication was not substantial. Fifth, our cause-specific hazard model relied on assumptions such as conceivable elimination of the competing event and no unmeasured risk factors common to the outcome and competing event.[22] Although we adjusted for many common risk factors, unmeasured confounding or residual confounding due to measurement error in confounders cannot be ruled out. Information on ethnicity was not collected in EPIC. HRs could also be susceptible to selection bias if there was a differential depletion of participants, who are more susceptible to the investigated disease.[29] Sixth, we noted pronounced heterogeneity in results across the two cohorts for type 2 diabetes risk and in the progression from its onset to multimorbidity. Differences in type 2 diabetes ascertainment could potentially explain this heterogeneity. Whether or not undiagnosed diabetes is differential with respect to the exposure, results for type 2 diabetes could be either attenuated or inflated. Seventh, a limitation of UK Biobank is its low response rate to recruitment invitations (~5%). UK Biobank participants were less socioeconomically deprived, had fewer risk factors, and had a lower prevalence of long-term conditions than the general UK population.[30] We partly addressed this concern by replicating results in the independent EPIC cohort. Nevertheless, our findings should be generalised with caution because study participants in EPIC might not be representative of the general population and only six of the ten countries in the EPIC study were included.

In conclusion, adherence to a healthy plant-based diet was associated with a reduced risk of multimorbidity of cancer, cardiovascular disease, and type 2 diabetes. This finding was consistent in adults younger than 60 years and those 60 years or older. Emphasising plant-based diets composed of healthy plant foods and small amounts of animal-based foods could be beneficial to reducing the burden of cancer and cardiometabolic multimorbidity among middle-aged and older adults.

Contributors

JK and HF had full access to all data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis. JK, RC, TK, AST, and HF designed the study. RC performed the statistical analyses. JK wrote the manuscript with the support of RC, AST, TK, HN, SS, and HF. Centre coauthors were invited based on the contribution of data of the centres. All authors critically reviewed and revised the manuscript. JK and HF supervised the data analysis. JK and HF had primary responsibility for the final content. All authors approved the final draft for submission for publication.

Declaration of interests

We declare no competing interests.

Data sharing

Data described in the paper, code book, and analytical code will be made available upon request. For information on how to submit an application for gaining access to EPIC data and/or biospecimens, please follow the instructions at http://epic.iarc.fr/access/index.php. 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/.

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