Consumption of ultra-processed foods and risk of multimorbidity of cancer and cardiometabolic diseases: a multinational cohort study

Reynalda Cordova,[a,b] Vivian Viallon,[a] Emma Fontvieille,[a] Laia Peruchet-Noray,[a] Anna Jansana,[a] Karl-Heinz Wagner,[b] Cecilie Kyrø,[c] Anne Tjønneland,[c,d] Verena Katzke,[e] Rashmita Bajracharya,[e] Matthias B. Schulze,[f,g] Giovanna Masala,[h] Sabina Sieri,[i] Salvatore Panico,[j] Fulvio Ricceri,[k] Rosario Tumino,[l] Jolanda M. A. Boer,[m] W. M. Monique Verschuren,[m,n] Yvonne T. van der Schouw,[n] Paula Jakszyn,[o,p] Daniel Redondo-Sánchez,[q,r,s] Pilar Amiano,[s,t,u] José María Huerta,[s,v] Marcela Guevara,[s,w,x] Yan Borné,[y] Emily Sonestedt,[y] Konstantinos K. Tsilidis,[z,aa] Christopher Millett,[ab,ac] Alicia K. Heath,[aa] Elom K. Aglago,[aa] Dagfinn Aune,[aa,ad,ae] Marc J. Gunter,[a,aa] Pietro Ferrari,[a] Inge Huybrechts,[a] and Heinz Freisling[a,*]

[a]International Agency for Research on Cancer (IARC-WHO), Lyon, France
[b]Department of Nutritional Sciences, University of Vienna, Vienna, Austria
[c]Danish Cancer Institute Center, Copenhagen, Denmark
[d]Department of Public Health, University of Copenhagen, Copenhagen, Denmark
[e]Division of Cancer Epidemiology, German Cancer Research Center (DKFZ), Heidelberg, Germany
[f]Department of Molecular Epidemiology, German Institute of Human Nutrition Potsdam-Rehbruecke, Nuthetal, Germany
[g]Institute of Nutritional Science, University of Potsdam, Nuthetal, Germany
[h]Institute for Cancer Research, Prevention and Clinical Network (ISPRO), Florence, Italy
[i]Epidemiology and Prevention Unit, Fondazione IRCCS Istituto Nazionale dei Tumori di Milano, Milan, Italy
[j]Department of Clinical Medicine and Surgery, University of Naples Federico II, Naples, Italy
[k]Department of Clinical and Biological Sciences, Centre for Biostatistics, Epidemiology, and Public Health, University of Turin, Italy
[l]Hyblean Association for Epidemiological Research, AIRE ONLUS Ragusa, Italy
[m]Centre for Prevention, Lifestyle and Health, National Institute for Public Health and the Environment, Bilthoven, the Netherlands
[n]Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht University, Utrecht, the Netherlands
[o]Unit of Nutrition and Cancer, Cancer Epidemiology Research Programme, Catalan Institute of Oncology (ICO-IDIBELL), Barcelona, Spain
[p]Blanquerna School of Health Sciences, Ramon Llull University, Barcelona, Spain
[q]Escuela Andaluza de Salud Pública (EASP), Granada 18011, Spain
[r]Instituto de Investigación Biosanitaria ibs. Granada, Granada 18012, Spain
[s]Spanish Consortium for Research on Epidemiology and Public Health (CIBERESP), Instituto de Salud Carlos III, Madrid, Spain
[t]Ministry of Health of the Basque Government, Sub Directorate for Public Health and Addictions of Gipuzkoa, San Sebastian, Spain
[u]Bio Gipuzkoa Health Research Institute, Epidemiology of Chronic and Communicable Diseases Group, San Sebastián, Spain
[v]Department of Epidemiology, Murcia Regional Health Council-IMIB, Murcia, Spain
[w]Instituto de Salud Pública y Laboral de Navarra, Pamplona 31003, Spain
[x]Navarra Institute for Health Research (IdiSNA), Pamplona 31008, Spain
[y]Nutritional Epidemiology, Department of Clinical Sciences Malmö, The Faculty of Medicine, Lund University, Malmö, Sweden
[z]Department of Hygiene and Epidemiology, University of Ioannina School of Medicine, Ioannina, Greece
[aa]Department of Epidemiology and Biostatistics, School of Public Health, Imperial College London, London, United Kingdom
[ab]Public Health Policy Evaluation Unit, School of Public Health, Imperial College London, London, United Kingdom
[ac]NOVA National School of Public Health, Public Health Research Centre, Comprehensive Health Research Center, CHRC, NOVA University Lisbon, Lisbon, Portugal
[ad]Department of Nutrition, Oslo New University College, Oslo, Norway
[ae]Department of Research, The Cancer Registry of Norway, Oslo, Norway

Summary

Background **It is currently unknown whether ultra-processed foods (UPFs) consumption is associated with a higher incidence of multimorbidity. We examined the relationship of total and subgroup consumption of UPFs with the risk of multimorbidity defined as the co-occurrence of at least two chronic diseases in an individual among first cancer at any site, cardiovascular disease, and type 2 diabetes.**

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*Corresponding author. International Agency for Research on Cancer (IARC-WHO), 25 Avenue Tony Garnier, Lyon 69366 CEDEX 07, France.
E-mail address: freislingh@iarc.who.int (H. Freisling).

Methods This was a prospective cohort study including 266,666 participants (60% women) free of cancer, cardiovascular disease, and type 2 diabetes at recruitment from seven European countries in the European Prospective Investigation into Cancer and Nutrition (EPIC) study. Foods and drinks consumed over the previous 12 months were assessed at baseline by food-frequency questionnaires and classified according to their degree of processing using Nova classification. We used multistate modelling based on Cox regression to estimate cause-specific hazard ratios (HR) and their 95% confidence intervals (CI) for associations of total and subgroups of UPFs with the risk of multimorbidity of cancer and cardiometabolic diseases.

Findings After a median of 11.2 years of follow-up, 4461 participants (39% women) developed multimorbidity of cancer and cardiometabolic diseases. Higher UPF consumption (per 1 standard deviation increment, ~260 g/day without alcoholic drinks) was associated with an increased risk of multimorbidity of cancer and cardiometabolic diseases (HR: 1.09, 95% CI: 1.05, 1.12). Among UPF subgroups, associations were most notable for animal-based products (HR: 1.09, 95% CI: 1.05, 1.12), and artificially and sugar-sweetened beverages (HR: 1.09, 95% CI: 1.06, 1.12). Other subgroups such as ultra-processed breads and cereals (HR: 0.97, 95% CI: 0.94, 1.00) or plant-based alternatives (HR: 0.97, 95% CI: 0.91, 1.02) were not associated with risk.

Interpretation Our findings suggest that higher consumption of UPFs increases the risk of cancer and cardiometabolic multimorbidity.

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Keywords: Ultra-processed foods; Diet; Multimorbidity; Cardiovascular diseases; Diabetes; Cancer

Research in context

Evidence before this study

We searched PubMed without language restrictions for longitudinal or population-based published studies between database inception and 16th October 2023 using combinations of search terms such as "ultra-processed foods", "food processing", "type 2 diabetes", "cancer", "cardiovascular diseases", and "multimorbidity".

Several studies have investigated associations between ultra-processed food consumption and the incidence of single diseases including type 2 diabetes, cardiovascular diseases, or cancer. However, existing studies have not investigated the co-occurrence of these long-term conditions in an individual, defined as multimorbidity, and with few exceptions did not investigate consumption of subgroups of ultra-processed foods and its relationship with these disease outcomes.

Added value of this study

To our knowledge, this study is the first to examine in a multinational cohort with long-term follow-up the relationship between ultra-processed food consumption and the incidence of multimorbidity of cancer and cardiometabolic diseases. This study contributes to the evidence base suggesting a potential role of a higher consumption of ultra-processed foods in the accumulation of chronic morbidity and multimorbidity. Additionally, this study provides evidence of a differential relationship of subgroups of ultra-processed foods and multimorbidity of cancer and cardiometabolic diseases. Artificially and sugar-sweetened beverages, animal-based products and sauces, spreads and condiments, but not other subgroups, were associated with increased risk, suggesting that more nuanced subgroup analyses of ultra-processed foods are warranted.

Implications of all the available evidence

Multimorbidity is a growing health challenge not only in Europe, but in many regions of the world. Our study adds important evidence that can inform risk reduction of multimorbidity of cancer and cardiometabolic diseases through dietary recommendations, public health policies, and interventions. Lowering consumption of certain ultra-processed foods by replacing them with similar but less processed foods may be beneficial for the prevention of cancer and cardiometabolic multimorbidity.

Introduction

In the last two decades, the prevalence of people who developed more than one chronic disease has drastically increased,[1] especially in high-income countries,[2] with similar trends emerging in low- and middle-income countries.[3] In Europe alone, around 50 million people

are affected by multimorbidity, which is defined as the co-occurrence of at least two chronic diseases in an individual.[2]

Multimorbidity can result in reduced quality of life along with disability, functional decline, and substantial health care costs.[4] Therefore, identifying preventable risk factors of multimorbidity is crucial to reduce its burden.[2] Multimorbidity can include many different combinations of chronic diseases and given the heterogeneity of disease combinations, it has been suggested to initially focus on determinants of the most common clusters.[2] In our study, we included cancer, cardiovascular disease, and type 2 diabetes to define multimorbidity because these conditions are among the leading causes of morbidity and mortality worldwide,[1] and they share common preventable risk factors including poor diet.[5]

The availability and consumption of ultra-processed foods (UPFs) has increased worldwide and represents nowadays 50–60% of the daily energy intake in some high-income countries, and middle-income and low-income countries are following suit.[6,7] Fresh or minimally processed foods are being increasingly replaced by higher proportions of UPFs in the diet,[6] raising concerns about their long-term health effects.[8] According to the Nova food classification, UPFs are industrially manufactured products comprising deconstructed and modified food components recombined with a variety of additives.[6] Typically, UPFs are mass-produced packaged breakfast cereals, biscuits, reconstituted meat products, instant noodles, as well as soft and/or sweetened carbonated drinks.[9]

Several prospective and cross-sectional studies have shown positive associations between UPF consumption and the risk of cardiovascular disease, type 2 diabetes, and cancer.[8,10–12] We, and others,[12] previously reported that a higher proportion of UPFs in the diet was associated with greater weight gain and a greater risk to develop overweight or obesity,[13] which is a potential risk factor for multimorbidity.[14] However, studies investigating the role of UPF consumption in the co-occurrence of cancer and cardiometabolic diseases are lacking.

The aim of this study was to investigate the associations of total and subgroup intake of UPFs with the risk of multimorbidity defined as the co-occurrence of at least two chronic diseases in an individual among cancer at any site, cardiovascular disease, and type 2 diabetes. A secondary aim was to assess associations of total UPF consumption with a first disease among cancer, cardiovascular disease, and type 2 diabetes.

Methods

Study population and design

The European Prospective Investigation into Cancer and Nutrition (EPIC) is an ongoing prospective cohort study investigating the associations of diet, lifestyle, genetic, and environmental risk factors with the incidence of cancer and other diseases. From 1992 to 2000 close to 520,000 participants (around 70% female) were recruited across 23 centers in 10 European countries (Denmark, France, Germany, Greece, Italy, Norway, Spain, Sweden, the Netherlands, and the United Kingdom). The sample size was informed by estimations for the incidence of specific cancer sites including less common cancers (e.g., gall bladder). The study populations were samples of convenience of volunteers agreeing to participate, where the age limits were set between 35 and 74 years. Participants were recruited from the general population with a few exceptions. In France, Norway, Utrecht (Netherlands) and Naples (Italy), only women were recruited. Also, in France state-school employees were recruited. Centers in Utrecht and Florence (Italy) included women attending a local population-based breast cancer screening program. Some centers in Italy and Spain recruited members of local blood donor associations. In Oxford (United Kingdom), half of the cohort were participants following a lacto-ovo vegetarian or vegan diet. Participant eligibility within each center/country was determined by geographic or administrative criteria and source populations were identified according to age and self-reported sex and, in Denmark and Turin/Italy prevalent cancer was an exclusion criteria.[15] After enrolment, participants were contacted every 3–4 years to obtain information on any major diseases.[15]

Data from France, Greece, and Norway were excluded, because incident events of cardiovascular disease and/or type 2 diabetes were not ascertained in these countries. After further exclusion of participants with prevalent cancer, myocardial infarction, angina, stroke, or type 2 diabetes at baseline, as well as those with any missing information on diet or lifestyle at baseline, a total of 266,666 participants (60% women) was available for the analyses. Participants with missing information on diet (n = 12,780) did not differ in the distribution of age, sex, and body mass index (BMI). More details on exclusions are given in the Supplementary Appendix (Supplementary Fig. S1).

Ethics

The EPIC study was approved by the Ethical Review Boards of the IARC and the Institutional Review Board of each participating EPIC center. Written informed consent was obtained from all study participants. Withdrawal from the study was possible at any time during follow-up. The current study was approved by the IARC Ethics Committee (No. 21-47).

Dietary assessment and estimation of UPF consumption

In the EPIC study, usual food intake in the previous 12 months was assessed at baseline using country-specific

validated food-frequency questionnaires (FFQs). In brief, three types of dietary assessment methods were applied to examine the consumed food over the previous 12 months; a) quantitative dietary questionnaires in northern Italy, Ragusa in Italy, the Netherlands, Germany, Spain and France, b) semi-quantitative FFQs in Denmark, Norway, Naples in Italy, and Umeå in Sweden, and c) a combination of semi-quantitative FFQs and 7- and 14-day records in Malmö (Sweden) and the UK, respectively. The food items reported in each FFQ/dietary questionnaire were classified in respective harmonized food groups common across questionnaires. In addition, the frequency of consumption, the portion size consumed on each occasion, and the applied standard portion sizes were stored in a central database at IARC, from which the total quantity of each food was estimated as grams per day.

To estimate UPF consumption, the Nova food classification system was incorporated into the EPIC database containing more than 11,000 food items. Generic or multi-ingredient foods were decomposed into ingredients and were then classified according to the Nova classification. Nova classifies each food item (or ingredient) into one of four groups: 1) unprocessed or minimally processed foods (e.g., fresh, dry or frozen fruits or vegetables, grains, flours and pasta); 2) processed culinary ingredients (e.g., table sugar, oils, salt); 3) processed foods (e.g., cheese, simple breads, fruits in syrup, canned fish); and group 4) ultra-processed foods (e.g., soft drinks, sweet or savory packaged snacks, processed meat, and pre-prepared frozen or shelf-stable dishes). Our exposure of interest was the Nova group 4, which comprises for each participant the sum of all reported food items that were classified as Nova 4 (i.e., UPFs) and was calculated as a composite variable. We decided a *priori* to exclude alcoholic beverages from our UPF exposure because moderate alcohol consumption may show inverse associations with myocardial infarction, a subtype of our cardiovascular disease outcome, and positive associations with several common cancers such as of the breast, colorectum, head and neck, and liver.[16] Importantly, risk associations for cancer are irrespective of the type of alcoholic drink consumed, because ethanol is the cancer-causing compound.[16]

Since dietary assessment was conducted in the 1990s at recruitment of participants and the food environment has changed over the years of their follow-up, three likely scenarios of the degree of food processing were considered when classifying food items and ingredients according to Nova. The "middle-bound" scenario represented the most likely scenario of food processing during the period of recruitment in the different countries of this study and was used in the main analysis. In case a given food or ingredient could have been also less processed compared to the middle-bound scenario, it was assigned into a less processed Nova group in the lower-bound scenario. The same applied to foods or ingredients that could have been more processed, resulting in being classified into a more processed Nova group in the upper-bound scenario. This means that, depending on the foods an individual consumed, the proportion of UPFs in the diet was lower or higher and the ranking of individuals within the study population in terms of UPF consumption was altered accordingly.[17]

Assessment of covariates

Data on socio-demographic, lifestyle, such as smoking status (never, former, current), and other factors including educational level (none, primary completed, technical/professional, and longer education including university degree), menopausal status in women (premenopausal, perimenopausal, postmenopausal, and surgical), and use of hormones in postmenopausal women (no, yes) were collected at recruitment through validated lifestyle questionnaires. Adherence to a healthy diet was assessed by the modified relative Mediterranean Diet Score (mrMDS),[18] a variation of the original MDS substituting olive oil with vegetable oil. Physical activity was assessed by the four-level categorical Cambridge index (inactive, moderately inactive, moderately active, and active), which is based on the EPIC physical activity questionnaire and combines occupational physical activity with time participating in physical exercise.[19] Weight and height were measured at recruitment following standardized processes, except for part of the Oxford cohort where weight and height were self-reported. Body mass index (BMI) was then computed as weight/height^2 (kg/m^2).

Missing covariate data affected 4.7% of the participants eligible for study inclusion. We used complete case analysis because the overall level of missing data was low and a complete case analysis will be unbiased if, conditional on model covariates, missingness is independent of the outcome.[20]

Outcome assessment

Incident events among participants who developed cancer at any site (excluding non-melanoma skin cancer) were ascertained by linkage to population cancer registries in Denmark, the Netherlands, Spain, Sweden, the UK, and Italy, except in Naples, where active follow-up of participants and their next-of-kin was used. In Germany, a combination of methods was used including active follow-up of participants and their next-of-kin as well as the use of health insurance records and cancer pathology registries. Data on cancer incidence were coded according to the International Classification of Diseases for Oncology (ICD-O-3) and the 10th Edition of the International Classification of Diseases (ICD-10).

Incident cardiovascular disease diagnoses included ischemic heart diseases (ICD-10, I20–I25), atrial fibrillation (I48), and cerebrovascular diseases (I60–I69), and were ascertained by active follow-up through questionnaires, medical records, hospital morbidity registers,

contact with medical professionals, retrieving and assessing death certificates, or verbal autopsy.

The ascertainment of type 2 diabetes diagnoses (ICD-10, E11) involved multiple sources across the different centers including self-report, linkage to primary care registers, secondary care registers, medication use (drug registers), hospital admission, and mortality data.

Mortality data were also obtained at the regional or national level and used for censoring.

Any two diseases ascertained on the same day (n = 80) were arbitrarily separated by one day with the following temporal order: type 2 diabetes, cancer, cardiovascular disease.

All events of interest in this analysis were validated and loss to follow-up was low (e.g., less than 2% for cancer).

Statistical methods

Habitual consumption of energy adjusted UPFs was modelled on a continuous scale per 1 standard deviation (SD)/day increment (corresponding to ~260 g/day). For energy adjustment, we calculated standardized residuals by regressing the consumption of UPFs (g/day) on total energy intake and center. These standardized residuals of UPF consumption are uncorrelated with total energy intake and account for residual variation of estimated food consumption across centers that is due to different dietary assessment instruments used. Second, to reduce measurement error in dietary intake estimates we additionally corrected for total energy intake (kcal/day) in the multivariable-adjusted models. This is an efficient approach to improve validity of energy-adjusted dietary intake.[21]

We applied a multi-state framework[22] to construct transitions from baseline to any first of the three conditions, i.e., 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 (Fig. 1). Additionally, we modelled a direct transition from baseline to multimorbidity, where follow-up was until any second condition after any first condition among cancer, cardiovascular disease, and type 2 diabetes.

Multivariable Cox proportional hazard models were used to estimate cause-specific HRs and 95% CIs for associations between UPF consumption per 1 SD increment of energy adjusted g/day and the outcomes of interest. Entry time was age at recruitment and exit time was either age at diagnosis of the event of interest (defined by the last date of center- and event-specific ascertainment of cancer, cardiovascular disease, or type 2 diabetes), death, or censoring date (lost or end of follow-up), whichever occurred first. Based on subject knowledge, models were adjusted for the following variables: total energy intake (continuous, kcal/day), baseline alcohol intake (g/day), height (cm), smoking status, physical activity, educational level as a proxy for socio-economic position, the mrMDS (continuous score), and a categorical indicator for plausibility of dietary energy reporting (under-reporting, acceptable reporting, over-reporting) to minimize dietary misreporting bias based on Goldberg cut-offs.[23] In women, models were further adjusted for menopausal status, and use of post-menopause hormone therapy. All models were also stratified by sex, age at recruitment (1-year categories), center, and transitions in a clock forward multi-state analysis with age as primary time variable. For continuous variables, in case of non-linearity, we used restricted cubic splines to account for it. An additional model was further adjusted for BMI (continuous, kg/m^2) to explore a potential mediating role of BMI. Assessment of Schoenfeld residuals did not indicate violations of the proportional hazard assumption in the Cox proportional hazard regression models.

UPF subgroups analyses

We further created nine mutually exclusive UPF subgroups (Supplementary Table S1) and examined the associations between the nine UPF subgroups in the transition from baseline to multimorbidity. Subgroups were simultaneously added in the model as distinct covariables. The model was otherwise adjusted for the same variables as the main model.

Sensitivity analyses

We performed the following sensitivity analyses to assess robustness of our findings and address potential biases (Supplementary Table S2). First, we also modelled the UPF variable without energy adjustment (g/day), as a caloric proportion of UPFs (% kcal/day), as a proportion in grams of UPFs (% g/day), and energy adjusted UPFs (g/day) with alcoholic beverages. Second, we removed (ultra-processed) soft drinks from the total UPF exposure and adjusted for its consumption in the main model. The same approach was used to adjust for the consumption of animal-based products. Third, we used the lower or upper bound scenario of UPFs. Fourth, we excluded over- and under-reporters of energy intake. Fifth, we adjusted for smoking intensity in addition to smoking status. Sixth, we estimated HRs for each transition separately for men and women. Seventh, we assessed associations in the direct transition from baseline to multimorbidity in never smokers only and by geographical region (North: Sweden, Denmark; Central: the United Kingdom, the Netherlands, and Germany; South: Italy and Spain). Lastly, we modelled a transition from an intermediate state, where we combined any of the first events, to multimorbidity. Statistical tests were two-sided, and p-values <0.05 were considered statistically significant. All analyses were performed using R version 4.1.2 and using the Lexis class in the Epi R package.

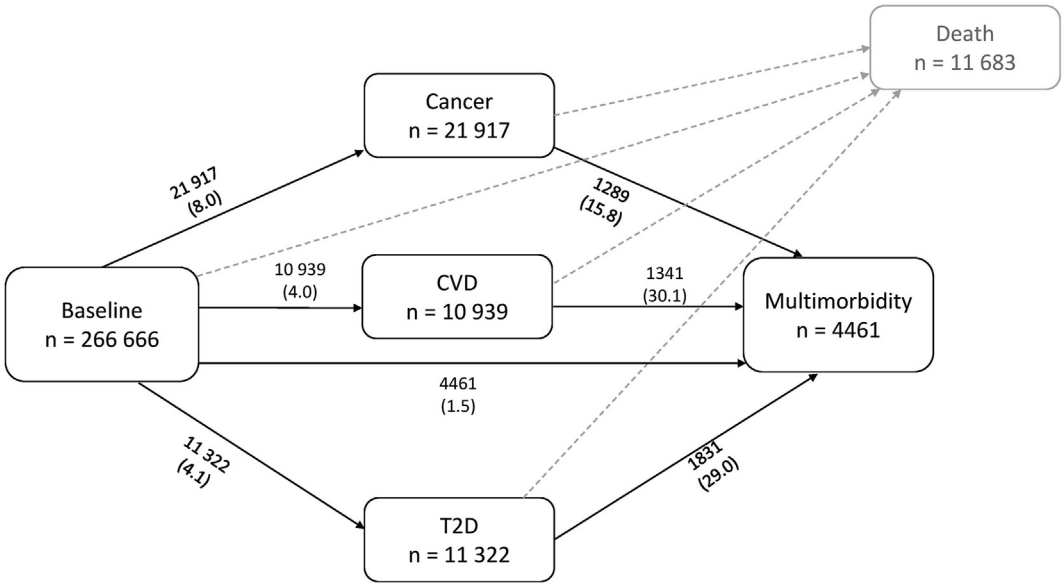


***Fig. 1:* Transitions from baseline to cancer, cardiovascular disease, type 2 diabetes, and subsequent cancer-cardiometabolic multimorbidity.** Cancer refers to first malignant tumour at any site excl. non-melanoma skin cancer. Deaths were censored and not modelled as a separate outcome. State-specific number of events is reported in boxes, and transition-specific number of events and incidence rates per 1000 person-years (within brackets) are reported on arrows. Abbreviations: CVD, cardiovascular disease; T2D, type 2 diabetes.

Patient and public involvement

This study used pseudo-anonymized data meaning that we had no means to contact study participants. Participants of this study were therefore not involved in setting the research question or the outcome measures, nor were they involved in developing plans for design, or implementation of the study, nor were they asked for advice on interpreting or writing up of results. However, we intend to engage the public to disseminate the results of our study.

Results

A total of 266,666 (60% women) participants were included in this study. Country- and sex-specific baseline characteristics of the study population are reported in Tables 1 and 2. The mean (SD) consumption of UPF (without alcoholic drinks) for men and women was 413 g/day (292) and 326 g/day (242), respectively. This corresponded to a proportion of 34% kcal and 32% kcal of UPFs in the daily diet among men and women, respectively. After a median follow-up time of 11.2 years (IQR 9.8–12.7), 4461 participants (39% women) developed multimorbidity of cancer and cardiometabolic diseases. The number of first incident events ascertained for each non-communicable disease (NCD) were 21,917 primary cancers, 10,939 cardiovascular events, and 11,322 type 2 diabetes events (Fig. 1). The most common multimorbidity pattern was cancer among persons with cardiovascular disease with a crude incidence rate of 17.1 events per 1000 person-years, followed by cancer among persons with type 2 diabetes (16.1/1000 person-years) and then type 2 diabetes among persons with cardiovascular disease (13.0/1000 person-years) (Supplementary Fig. S2).

Associations with multimorbidity of cancer and cardiometabolic diseases

In the multivariable-adjusted Cox model for the direct transition from baseline to multimorbidity, a positive association was observed between higher consumption of UPF (per 1 SD increment [~260 g/day]) and the risk of multimorbidity ($\text{Multimorbidity}_{\text{direct}}$ hazard ratio $(\text{HR})_{1\text{SD}}$ 1.09; 95% confidence interval (CI): 1.05–1.12) as well as after further adjustment for BMI ($\text{Multimorbidity}_{\text{direct}}$ $\text{HR}_{1\text{SD}}$ 1.06; 95% CI: 1.03–1.09) (Fig. 2).

The multivariable-adjusted HRs and 95% CIs for associations of the transitions from having developed a first NCD to multimorbidity of cancer and cardiometabolic diseases are displayed in Fig. 2. All transitions showed positive risk estimates between higher consumption of UPF (per 1 SD) and the risk of multimorbidity ($\text{Cancer}_{\text{MM}}$: $\text{HR}_{1\text{SD}}$ 1.05; 95% CI: 0.99–1.11, Cardiovascular $\text{disease}_{\text{MM}}$: $\text{HR}_{1\text{SD}}$ 1.02; 95% CI: 0.97–1.08, Type 2 $\text{diabetes}_{\text{MM}}$: $\text{HR}_{1\text{SD}}$ 1.02; 95% CI: 0.98–1.06, respectively), albeit associations included the null. These associations remained almost unchanged after controlling for BMI (Fig. 2).

Associations with first NCDs

Associations of the transitions from baseline UPF consumption and the risk of developing a first NCD are

	Italy	Spain	United Kingdom	The Netherlands	Germany	Sweden	Denmark	Overall
	(N = 29,239)	(N = 21,304)	(N = 17,925)	(N = 21,399)	(N = 24,042)	(N = 19,986)	(N = 26,655)	(N = 160,550)
UPF intake, g/day	183 (138)	144 (123)	479 (264)	378 (198)	417 (254)	297 (175)	424 (275)	326 (242)
UPF intake, % kcal/day	16.4 (7.9)	17.1 (9.9)	44.8 (11.1)	32.9 (8.0)	34.1 (10.5)	34.3 (9.8)	45.2 (10.0)	31.5 (14.6)
Cancer[a], n	1962	1361	1622	2111	1261	2093	2967	13,377
Cardiovascular disease[a], n	455	412	879	1168	238	950	913	5015
Type 2 diabetes[a], n	758	1127	340	499	540	828	1817	5909
Multimorbidity[b], n	147	203	222	235	87	305	526	1725
Age at recruitment, years	50.5 (8.1)	48.0 (8.3)	53.3 (11.7)	52.0 (11.2)	48.7 (8.9)	52.3 (11.2)	56.7 (4.4)	51.6 (9.6)
Follow-up, years	10.2 (2.1)	13.5 (1.3)	11.1 (1.7)	12.0 (1.8)	8.7 (1.7)	12.2 (2.1)	10.8 (1.7)	11.1 (2.3)
Alcohol at recruitment, g/day	8.6 (12.4)	4.3 (8.4)	6.7 (9.1)	8.7 (12.0)	9.5 (12.3)	5.3 (7.1)	13.8 (14.8)	8.4 (11.8)
Body mass index, kg/m^2	25.6 (4.2)	27.9 (4.6)	24.8 (4.1)	25.1 (4.0)	25.3 (4.4)	24.8 (4.2)	25.5 (4.3)	25.6 (4.4)
Smoking status, %								
Never	53.5	70.5	60.4	41.5	55.8	52.5	44.1	53.6
Former	20.2	10.2	30.4	31.8	25.8	23.3	24.5	23.5
Current	26.4	19.3	9.2	26.7	18.3	24.1	31.4	22.9
Education, %								
None	1.6	37.2	0	0	0.5	0.4	0	5.3
Primary school compl.	50.3	41.6	34.7	17.6	21.4	32.7	30.8	33.3
Tech/professional school	11.1	5.6	31.6	32.8	42.1	26.2	46.8	28.0
Secondary school	23.4	5.8	10.4	31.1	8.2	16.5	12.0	15.6
Longer education (incl. uni. deg.)	13.6	9.8	23.3	18.5	27.8	24.1	10.5	17.7
Physical activity, %								
Inactive	36.3	47.6	27.8	7.1	16.4	19.7	10.2	23.6
Moderately inactive	39.3	35.6	36.2	26.0	37.8	35.8	32.2	34.8
Moderately active	15.0	12.5	22.3	27.1	26.5	26.9	25.1	22.0
Active	9.4	4.3	13.7	39.8	19.3	17.7	32.5	19.6
mrMediterranean Diet Score	10.9 (2.4)	10.9 (2.2)	9.5 (2.5)	6.8 (2.5)	7.8 (2.5)	6.6 (2.4)	7.5 (2.7)	8.6 (3.0)
Dietary misreporting status[c], %								
Underreporting	6.3	18.2	13.4	15.4	21.4	19.6	12.9	14.9
Acceptable	74.4	75.1	76.9	81.8	73.2	74.6	79.8	76.5
Overreporting	19.3	6.7	9.7	2.9	5.4	5.8	7.2	8.6
Postmenopause hormone therapy, %								
No	93.1	94.8	81.0	89.7	76.4	85.5	70.8	84.4
Yes	6.9	5.2	19.0	10.3	23.6	14.5	29.2	15.6
Menopausal status, %								
Premenopausal	39.9	54.8	32.7	28.1	48.1	21.4	7.4	33.0
Postmenopausal	41.0	30.9	50.7	50.8	35.9	51.9	72.5	47.9
Perimenopausal	15.3	9.6	12.8	18.1	13.2	26.6	15.7	15.8
Surgical postmenopausal	3.7	4.8	3.7	3.0	2.8	0	4.4	3.3

Data are expressed as arithmetic mean ± standard deviation (SD) if not stated otherwise. Abbreviations: EPIC, European Prospective Investigation into Cancer and Nutrition; UPF, ultra-processed food; mr, modified relative. [a]Frequency of total incident events among first cancer at any site (excl. non-melanoma skin cancer), cardiovascular disease, and type 2 diabetes. [b]Frequency of participants developing at least two conditions among first cancer at any site, cardiovascular disease, and type 2 diabetes. [c]Plausibility of dietary intake reporting based on Goldberg's cut-off points to minimize dietary misreporting bias.

Table 1: **Country-specific characteristics of 160,550 women in the EPIC study.**

shown in Fig. 2. Higher consumption of UPF (per 1 SD) showed positive associations with each of the three NCDs (Cancer: HR_{1SD} 1.01; 95% CI: 1.00–1.03, Cardiovascular disease: HR_{1SD} 1.06; 95% CI: 1.04–1.08, Type 2 diabetes: HR_{1SD} 1.11; 95% CI: 1.10–1.13). After further adjustment for BMI, associations remained nearly unchanged, except for the transition to type 2 diabetes, which was attenuated (Type 2 diabetes: HR_{1SD} 1.07; 95% CI: 1.05–1.08) (Fig. 2).

UPF subgroup analyses

Among the nine UPF subgroups (Supplementary Table S1) after mutual adjustment, consumption of animal-based products, and artificially and sugar-sweetened beverages showed positive associations (HR_{1SD} 1.09; 95% CI: 1.05–1.12, HR_{1SD} 1.09; 95% CI: 1.06–1.12, respectively) in the direct transition from baseline to multimorbidity (Fig. 3). Sauces, spreads and condiments showed a positive association with the risk

	Italy (N = 12,892)	Spain (N = 13,156)	United Kingdom (N = 11,017)	The Netherlands (N = 6624)	Germany (N = 17,971)	Sweden (N = 20,354)	Denmark (N = 24,102)	Overall (N = 106,116)
UPF intake, g/day	207 (157)	163 (154)	522	544 (284)	522 (329)	382 (222)	517 (293)	413 (292)
UPF intake, % kcal/day	14.7 (7.1)	13.9 (8.4)	48.6 (11.0)	33.8 (8.0)	35.7 (10.0)	34.3 (9.2)	47.8 (9.5)	34.1 (15.7)
Cancer[a], n	891	1381	1241	369	1320	2480	2860	10,542
Cardiovascular disease[a], n	492	941	1301	455	541	1981	1825	7536
Type two diabetes[a], n	465	1247	418	122	824	1189	2350	6615
Multimorbidity[b], n	137	416	305	80	204	701	895	2738
Age at recruitment, years	49.9 (7.5)	50.4 (7.1)	56.8 (10.3)	43.0 (11.0)	51.8 (7.5)	51.3 (11.0)	56.5 (4.3)	52.3 (9.0)
Follow-up, years	10.3 (2.2)	13.5 (1.7)	10.7 (2.0)	11.7 (1.9)	8.74 (1.9)	12.1 (2.5)	10.7 (2.1)	11.0 (2.5)
Alcohol at recruitment, g/day	24.4 (22.5)	28.5 (28.7)	12.1 (14.9)	18.5 (21.0)	24.3 (24.2)	9.2 (11.4)	28.2 (24.9)	21.2 (23.1)
Body mass index, kg/m^2	26.3 (3.3)	28.4 (3.4)	25.7 (3.3)	25.4 (3.4)	26.7 (3.5)	25.5 (3.4)	26.5 (3.5)	26.4 (3.5)
Smoking status, %								
Never	27.6	30.1	39.0	31.1	33.8	45.7	26.4	33.6
Former	41.1	30.1	44.7	30.3	42.0	31.4	36.4	36.6
Current	31.3	39.8	16.3	38.6	24.2	22.9	37.3	29.8
Education, %								
None	0.4	25.1	0	0	0.5	0.3	0	3.3
Primary school compl.	41.6	38.1	30.6	9.5	22.3	35.2	33.8	31.8
Tech/professional school	14.9	13.4	35.8	41.6	27.4	21.7	29.4	25.3
Secondary school	28.9	8.1	9.8	20.7	5.4	21.9	7.8	13.7
Longer education (incl. uni. deg.)	14.1	15.2	23.9	28.2	44.4	20.8	28.9	25.9
Physical activity, %								
Inactive	12.9	20.7	30.7	8.3	15.1	20.4	10.9	16.8
Moderately inactive	35.5	29.8	28.5	22.5	35.0	35.1	28.8	31.6
Moderately active	23.8	27.7	21.8	24.7	27.0	26.3	23.9	25.2
Active	27.8	21.8	19.0	44.6	22.9	18.2	36.4	26.5
mrMediterranean Diet Score	10.8 (2.1)	11.5 (2.3)	8.50 (2.5)	6.2 (2.3)	7.3 (2.3)	5.6 (2.3)	6.4 (2.6)	7.8 (3.2)
Dietary misreporting status[c], %								
Underreporting	8.1	9.3	25.1	12.7	22.4	23.4	12.2	16.6
Acceptable	80.3	82.4	71.4	81.9	72.8	71.3	82.6	77.3
Overreporting	11.6	8.4	3.5	5.4	4.9	5.3	5.2	6.2

Data are expressed as arithmetic mean ± standard deviation (SD) if not stated otherwise. Abbreviations: EPIC, European Prospective Investigation into Cancer and Nutrition; UPF, ultra-processed food; mr, modified relative. [a]Frequency of total incident events among first cancer at any site (excl. non-melanoma skin cancer), cardiovascular disease, and type 2 diabetes. [b]Frequency of participants developing at least two conditions among first cancer at any site, cardiovascular disease, and type 2 diabetes. [c]Plausibility of dietary intake reporting based on Goldberg's cut-off points to minimize dietary misreporting bias.

Table 2: **Country-specific characteristics of 106,116 men in the EPIC study.**

of multimorbidity (HR_{1SD} 1.03; 95% CI: 1.00–1.06), although the CI reflected a borderline certainty. Ultra-processed breads and cereals were inversely associated with risk of multimorbidity (HR_{1SD} 0.97; 95% CI: 0.94–1.00) with similar uncertainty given the CI. The remaining groups—sweets and desserts, savory snacks, plant-based alternatives, ready-to-eat/heat mixed dishes and other unspecified ultra-processed foods—showed no association with the risk of multimorbidity (Fig. 3).

Sensitivity analyses

Our findings were robust among men and women, across geographic regions, and to a range of sensitivity analyses (Supplementary Table S2). For example, we observed similar results when using the proportion in grams of UPFs (% g/day), energy-adjusted UPFs (g/day) that included ultra-processed alcoholic beverages, or after adjusting for animal-based products. However, associations in all transitions were attenuated after adjusting for soft drinks or when using the daily caloric proportion of UPFs (% kcal/day). The results of all sensitivity analyses are shown in the Supplementary Table S2.

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Discussion

In this multinational European prospective cohort study, we found that higher consumption of UPF was associated with a higher risk of multimorbidity of cancer and

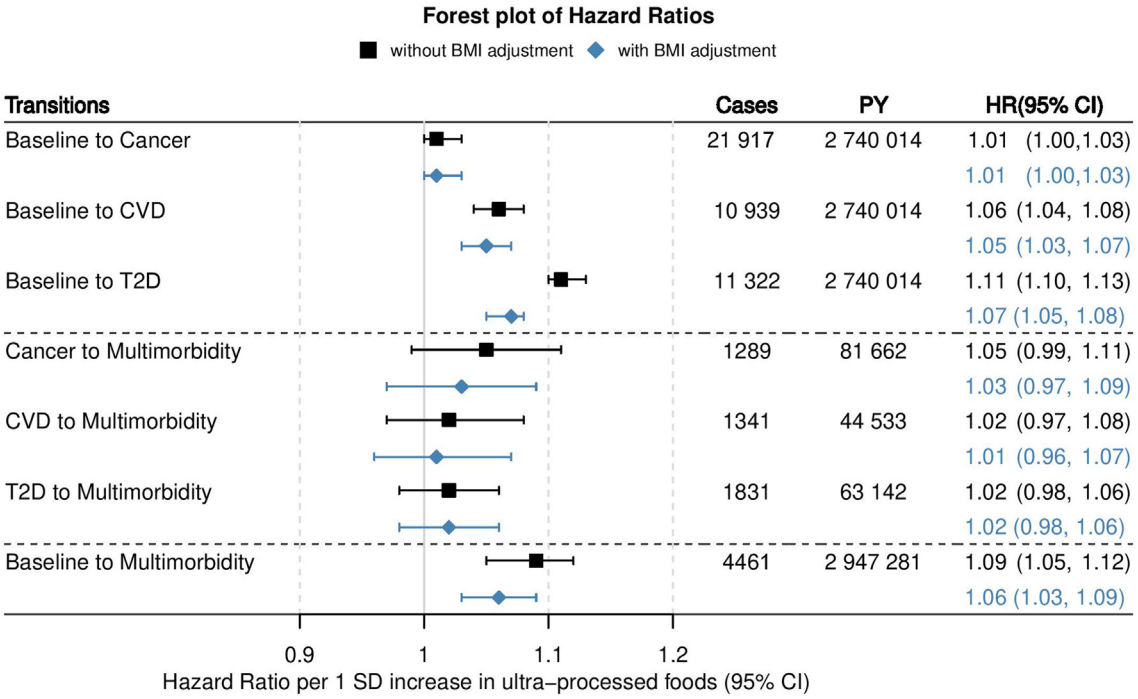


Fig. 2: **Associations between ultra-processed food consumption[a] and risk of cancer, cardiovascular disease, type 2 diabetes, and subsequent cancer-cardiometabolic multimorbidity.** Cancer refers to first malignant tumour at any site excl. non-melanoma skin cancer. [a]Energy-adjusted baseline UPF without alcoholic drinks (g/day) using residual method. Standardized residuals were computed by a linear regression of baseline UPF (g/day) adjusted for energy intake and center. Cox proportional hazard model, stratified by age at inclusion (1-year categories), sex, center, and transition in a clock forward multi-state analysis with age as primary time variable. Models were adjusted for total energy intake (continuous, kcal/day), baseline alcohol intake (g/day), height (cm), smoking status (never, former, current), the Cambridge physical activity index (inactive, moderately inactive, moderately active, active), highest attained educational level (none, primary completed, technical/professional, longer education including university degree), plausibility of dietary energy reporting (under-reporter, acceptable, over-reporter), and the modified relative Mediterranean Diet Score (mrMDS), post-menopause hormone therapy (yes, no), and menopausal status (premenopausal, perimenopausal, postmenopausal, surgical) in women. Abbreviations: CVD, cardiovascular disease; T2D, type 2 diabetes; BMI, body mass index; HR, hazard ratio; CI, confidence interval; SD, standard deviation.

cardiometabolic diseases. Among UPF subgroups, higher intakes of artificially and sugar-sweetened beverages, and animal-based products were associated with higher risk of multimorbidity, as was higher consumption of sauces, spreads and condiments, but with less certainty. In contrast, ultra-processed breads and cereals showed an inverse association with the risk of multimorbidity, but with a borderline certainty. Sweets and desserts, savory snacks, plant-based alternatives, ready-to eat/heat and mixed dishes were not associated with risk of multimorbidity.

Few studies to date investigated dietary exposures as determinants of multimorbidity.[2,24–27] The available evidence from prospective cohort studies suggests that adherence to a healthy dietary pattern such as the Mediterranean diet[27] or similar healthy eating patterns,[26] are associated with a reduced risk of different clusters of multimorbidity. While there is a lack of studies investigating the association between UPF consumption and multimorbidity of cancer and cardiometabolic diseases specifically, one prospective cohort study reported that a higher consumption of UPFs was associated with higher risk of multimorbidity of cardiovascular and respiratory diseases.[28]

Several more prospective studies assessed individually the associations between UPFs and the three major NCDs that defined our multimorbidity cluster, i.e., cancer, cardiovascular disease, and type 2 diabetes.[29–33] Three prospective cohort studies reported that higher consumption of UPFs was associated with an increased risk of cancer, overall, as well as for breast,[29] ovarian,[33] and head and neck[32] cancer, which is congruent with our findings for the transition from baseline to overall cancer. Further, in the French prospective population-based NutriNet-Santé cohort, higher consumption of UPFs was associated with higher risks of cardiovascular disease and type 2 diabetes.[30,31] Finally, a study using data from 3 large U.S. cohorts also reported that higher UPFs consumption was associated with a higher risk of type 2 diabetes.[11] These results are in line with our

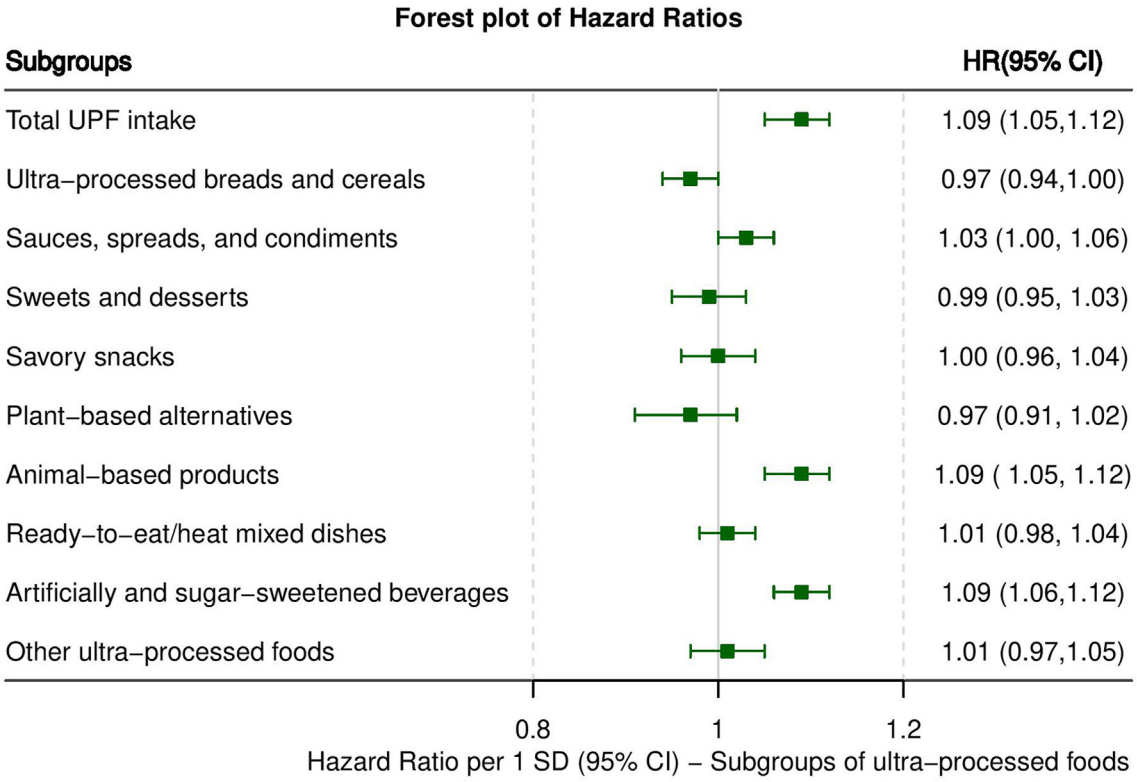


***Fig. 3*: Associations between subgroups of ultra-processed food consumption[a] and risk of cancer-cardiometabolic multimorbidity.** Cancer refers to first malignant tumour at any site excl. non-melanoma skin cancer. [a]Energy-adjusted subgroups of baseline UPF without alcoholic drinks (g/day) using residual method. Standardized residuals were computed by a linear regression of subgroups of baseline UPF (g/day) adjusted for energy intake and center. Cox proportional hazard model, stratified by age at inclusion (1-year categories), sex, center, and transition in a clock forward multi-state analysis with age as primary time variable. Subgroups were simultaneously added in the model as distinct covariables. Models were adjusted for total energy intake (continuous, kcal/day), baseline alcohol intake (g/day), height (cm), smoking status (never, former, current), the Cambridge physical activity index (inactive, moderately inactive, moderately active, active), highest attained educational level (none, primary completed, technical/professional, longer education including university degree), plausibility of dietary energy reporting (under-reporter, acceptable, over-reporter), and the modified relative Mediterranean Diet Score (mrMDS), post-menopause hormone therapy (yes, no), and menopausal status (premenopausal, perimenopausal, postmenopausal, surgical) in women. Abbreviations: HR, hazard ratio; CI, confidence interval; SD, standard deviation.

findings for the transitions from baseline to cardiovascular disease and type 2 diabetes.

These studies together with our findings that these NCDs can also co-occur in an individual, substantiate the hypothesis of common aetiological risk factors, from which cancer and cardiometabolic diseases originate. In the context of the role of UPF consumption in the aetiology of these NCDs, our study adds important evidence that can inform risk reduction of multimorbidity of cancer and cardiometabolic diseases through dietary recommendations, public health policies, and interventions.

We acknowledge that the Nova group 4 (i.e., UPFs) consists of very heterogeneous foods representing virtually all major food groups.[6] Although UPFs have on average a higher energy density compared to minimally processed foods,[34] they are not equally high in their energy-density, nutrition profile and intake rate,[6] raising the question about whether various types of UPFs contribute differently to the risk of developing a first NCD and multimorbidity. To explore this further we adjusted for the consumption of soft drinks in our main models for multimorbidity. Consuming sugar and artificially sweetened beverages is well-known for negative impacts on cardiometabolic diseases.[35] After accounting for soft drink consumption, the positive association with multimorbidity remained, although it was attenuated (Supplementary Table S2). Also, the analyses of nine different subgroups of UPFs in our main model indicated positive associations for the consumption of sugar sweetened and artificially sweetened beverages, and animal-based products with risk of multimorbidity. Conversely, consumption of ultra-processed breads and cereals was associated with lower risk, although with a

borderline certainty (Fig. 3), which might be explained by the fibre content of such products. Our findings regarding UPF subtypes are partly consistent with recent studies that showed some heterogeneity in the results for subtypes of UPFs, with positive associations observed between consumption of artificially and sugar-sweetened beverages,[11,36,37] animal-based products,[11,36–38] sauces spreads and condiments[11,36] and the risk of type 2 diabetes,[11] cardiovascular disease,[36] and/or certain cancers,[37,38] but inverse associations for UPF cereals and whole grain breads and type 2 diabetes.[11]

Mechanisms by which UPFs may influence the risk of chronic diseases and multimorbidity are not completely understood. One explanation would be their effect on increased weight gain.[13,39] Obesity represents an important risk factor for morbidity and may initiate and promote progression to multimorbidity.[13,40] Many UPFs have higher energy density (calories per weight or volume)[34] in combination with an altered food matrix which leads to a softer texture for less chewing and delays satiety signalling.[6,39] However, adjusting for BMI in our main model did attenuate but not annul the association between UPFs and multimorbidity implying additional mechanistic pathways. Diets with a high proportion of UPFs have been associated with a lower nutritional quality such as lower intake of dietary fiber and vitamins, and a higher intake of free sugars and saturated fat.[41] However, nutritional characteristics of UPFs may again only partially explain mechanistic pathways leading to health outcomes. For example, in a prospective cohort study from Italy, adjustment for nutritional composition of the diet using the Food Standards Agency Nutrient Profiling System (FSAm-NPS) did not attenuate associations between UPF consumption and all cause and cardiovascular mortality.[42] Similarly, the adjustment for diet quality in our study, using the Mediterranean diet score, suggests that UPF consumption plays a role in the development of cancer and cardiometabolic disease multimorbidity beyond the nutritional characteristics of UPFs. Furthermore, the Mediterranean diet score indirectly also accounted for red meat (and dairy) consumption because higher consumption of these leads to a lower Mediterranean diet score and vice versa.[18] The positive association of ultra-processed animal-based products with multimorbidity in our study are therefore likely explained by non-nutritional aspects of this subgroup of UPFs. Non-nutritional mechanisms through which UPFs could be hazardous for health include, but are not limited to, alteration of the food matrix, inclusion of certain food additives during processing (e.g., aspartame),[43] and contaminants from packaging material (e.g., bisphenol A).[44] Any of these may affect endocrine pathways or the gut microbiome,[8,39] and contribute to subsequent disease risk.

Strengths and limitations

Strengths of our study include access to individual-level data from a prospective cohort of adults from 7 European countries with validated assessments of cancer, cardiovascular disease, and type 2 diabetes. Second, the observed associations were modelled in a multi-state framework accounting for the sequence of incident chronic conditions. Furthermore, to the best of our knowledge, this is the first study that investigated the association between consumption of UPF and the risk of multimorbidity in a multinational setting.

The results of our study should be interpreted with the following limitations in mind. First, the Nova classification was implemented on dietary data captured more than 20 years ago at recruitment of participants into EPIC. However, three scenarios were considered when classifying food items and ingredients according to Nova to evaluate the impact of possible exposure misclassification, and results were similar. In addition, Nova misclassification might have occurred due to missing food processing information in the FFQs and assumptions were necessary while classifying the foods. However, data collected via 24-h dietary recalls in a subsample of individuals in all countries were used to inform assumptions and minimize misclassification.[32] Second, we collected diet and other lifestyle exposure data at recruitment, and potential changes in modifiable behaviors during follow-up, especially after the diagnosis of NCDs, were not possible to account for in our study. However, our results suggest that pre-diagnostic lifestyle habits are associated with the risk of NCDs and multimorbidity, assuming that exposure characteristics before the onset of a disease can influence subsequent health outcomes. Therefore, possible improvements in health behaviors after the diagnosis of a first NCD would most likely have resulted in an underestimation of the observed relative risks. Third, we were unable to account for treatment information after the first NCD. Among persons with type 2 diabetes, a common first-line medication is metformin, which is linked to a decreased risk of cardiovascular events and possibly some cancers.[45,46] In contrast, cancer therapy can increase the risk of cardiac diseases[47] and diabetes.[48] Nevertheless, if treatment alone does not influence diet habits, the observed result should not be affected by the lack of treatment information. Furthermore, we cannot exclude the possibility that unmeasured confounding, such as family history of (premature) cancer and cardiometabolic disease, could have affected the results. Lastly, our findings should be generalized with caution because study participants may not always be representative of the general population and only seven of the 10 countries in the EPIC study were included.

Conclusion

A higher consumption of UPFs was associated with a higher risk of multimorbidity of cancer and cardiometabolic diseases. Artificially and sugar-sweetened beverages, animal-based products and sauces, spreads and condiments, but not other items, were associated

with increased risk of multimorbidity, suggesting that more nuanced subgroup analyses of UPFs are warranted. Multimorbidity represents a continuum which starts when a healthy individual develops a chronic disease. Therefore, higher consumption of UPFs prior to a first NCD might contribute to unfavourable prognosis of these diseases by increasing the risk of multimorbidity.

Contributors

Conceived and designed the study: HF. Analysed the data: RC and HF. Supported data analysis: VV and EM. Wrote the manuscript: RC and HF. Has primary responsibility for the final content of the manuscript: HF. Had full access and verified all the data: RC, VV, and HF. Had final responsibility to submit for publication: HF. Critically reviewed the manuscript for important intellectual content and approved the final version: all authors.

Data sharing statement

Data access can be requested via https://epic.iarc.fr/access/index.php. The request will be assessed by the EPIC working groups and the EPIC Steering Committee. After approval by the EPIC Steering Committee, deidentified data will be made available. An agreement will be signed specifying the study protocol, variables, statistical analysis plan, researchers involved, and length of time that the data will be available.

Declaration of interests

None of the authors declared a competing interest.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lanepe.2023.100771.

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