Associations between degree of food processing and all-cause and cause-specific mortality: a multicentre prospective cohort analysis in 9 European countries

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Summary

Background Ultra-processed food (UPF) consumption has been linked with higher risk of mortality. This multi-centre study investigated associations between food intake by degree of processing, using the Nova classification, and all-cause and cause-specific mortality.

Methods This study analyzed data from the European Prospective Investigation into Cancer and Nutrition. All-cause mortality and cause-specific mortality due to cancer, circulatory diseases, digestive diseases, Parkinson's disease, and Alzheimer's disease served as endpoints. Hazard ratios (HRs) and 95% CIs were estimated using multivariable Cox proportional hazards regression models. Substitution analyses were also performed.

Findings Overall, 428,728 (71.7% female) participants were included in the analysis and 40,016 deaths were documented after 15.9 years of follow-up. UPFs (in percentage grams per day [g/d]) were positively associated with all-cause mortality (HRs per 1-SD: 1.04; 95% CI: 1.02,1.05), as well as mortality from circulatory diseases (1.09; 95% CI: 1.07,1.12), cerebrovascular disease (1.11; 95% CI: 1.05,1.17), ischemic heart disease (1.10; 95% CI: 1.06,1.15), digestive diseases (1.12; 95% CI: 1.05,1.20), and Parkinson's disease (1.23; 95% CI: 1.06,1.42). No associations were found between UPFs and mortality from cancer or Alzheimer's disease. Replacing processed and UPFs with unprocessed/minimally processed foods was associated with lower mortality risk.

Interpretation In this pan-European analysis, higher UPF consumption was associated with greater mortality from circulatory diseases, digestive diseases, and Parkinson's disease. The results support growing evidence that higher consumption of UPFs and lower consumption of unprocessed foods may have a negative impact on health.

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Keywords: Nova classification; Unprocessed/minimally processed foods; Ultra-processed foods; Mortality; EPIC study

Research in context

Evidence before this study

We searched PubMed, Web of Science, and Google Scholar for English language publications on longitudinal studies from inception to June 2024 using combinations of search terms such as 'ultra-processed foods', 'food processing', 'Nova' and 'mortality'. Several studies have reported associations between ultra-processed food consumption and all-cause and cause-specific mortality. Ultra-processed food consumption has been linked to higher risk of all-cause and some specific causes of death, however, evidence from large-scale prospective cohort studies examining multiple causes of death, as well as other degrees of food processing, is limited.

Added value of this study

In this study, the largest of its kind to date, we report robust positive associations between consumption of processed and ultra-processed food with all-cause and cause-specific mortality, including mortality endpoints not previously assessed such as Parkinson's disease. Further, this is one of the first studies to evaluate unprocessed/minimally processed foods with mortality outcomes and showed that the substitution of 10% grams per day of processed and ultra-processed foods with an equal amount of unprocessed/minimally processed foods was associated with a lower risk of all-cause and cause-specific mortality.

Implications of all the available evidence

This study confirms a positive association between consumption of processed and ultra processed foods and all-cause mortality but also identifies novel associations with endpoints such as deaths from digestive diseases and Parkinson's disease. Additionally, it was found that substitution of 10% of processed and ultra-processed food with an equal amount of minimally processed food likely reduces mortality risk. Promoting the consumption of unprocessed/minimally processed foods while discouraging highly processed foods in dietary recommendations may be beneficial for public health.

Introduction

Ultra-processed food (UPF) consumption has been gradually displacing unprocessed and minimally processed foods and now represents between 25% and 60% of the population's total energy intake in high-income countries such as the United States (US),[1] United Kingdom (UK)[2] and Canada,[3] and around 20–40% of the energy intake in several middle-income countries.[4,5] Several longitudinal studies and meta-analyses[6,7] have reported positive associations between the consumption of UPFs and a higher risk of cancer,[8] cardiovascular diseases (CVD),[9] type 2 diabetes,[10] and premature mortality in some prospective studies.[11–13]

A combined analysis[14] including participants from three cohort studies (the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial [1993–2001], the UK Biobank [2006–2010], and the National Health and Nutrition Examination Survey [1999–2018]) showed that those in the highest quartile of UPF consumption had a higher risk of all-cause and CVD mortality compared to those in the lowest quartile. Similar results regarding the positive association of UPFs with CVD-related mortality or all-cause mortality have been observed in other studies.[13,15–17] Furthermore, a previous analysis within the UK Biobank showed that every 10% increment in grams per day (g/d) of UPF consumption was associated with an increased risk of all-cause, ovarian cancer-, and breast cancer-related mortality.[18] In addition, a recent multi-cohort analysis from the US found that those in the highest quartile of UPFs, compared with those in the lowest, showed a 9% higher mortality from causes other than cancer or cardiovascular diseases.[13] To date, no large-scale cohort study has systematically evaluated the association of degree of food processing with less common causes of mortality such as neurodegenerative disease subtypes and digestive diseases.

The aim of this study was to investigate the association between food consumption, by degree of industrial food processing, and mortality, including cause-specific mortality due to cancer, circulatory diseases (including cerebrovascular and ischemic heart disease), digestive diseases, Parkinson's disease, Alzheimer's disease, and suicide in the European Prospective Investigation into Cancer and Nutrition (EPIC) study, one of the world's largest multicenter prospective cohorts.

Methods

Study design and participants

The EPIC study is a multicenter prospective cohort that recruited 521,330 participants from 23 centers across 10 European countries - Denmark, France, Germany, Greece, Italy, the Netherlands, Norway, Spain, Sweden, and the U.K - between 1992 and 2000. The study populations included convenience samples 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. Several centers in Italy and Spain recruited members of local blood donor associations. 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 criterion. After enrollment, participants were contacted every 3–4 years to obtain information on any major diseases and mortality. The study design and procedures for EPIC have been published elsewhere.[19,20]

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

Study population and follow-up

The current analysis used data from all participating centers apart from Greece (data not available). Participants who reported a current or prior cancer diagnosis, ischemic heart disease, stroke, angina and/or diabetes at baseline or who were missing information on follow-up, or an extreme ranking energy intake/energy requirement ratio (top and bottom 1%) were excluded (flowchart, Fig. 1). The mean follow-up of participants was 15.9 years (standard deviation [SD] 3.05). Participants with the aforementioned diseases at baseline were excluded to minimize effects of reverse causality confounding and ensure that observed associations were more likely to be due to food consumption by level of food processing rather than being confounded by existing health issues.

Food intake and nova classification

Usual food intake was assessed at baseline using country-specific validated food-frequency questionnaires (FFQs). In brief, three types of FFQs were applied to examine the consumed food over the previous 12 months; 1) quantitative dietary questionnaires in Ragusa in Italy, the Netherlands, Germany, Spain and France, 2) semi-quantitative FFQs in Denmark, Norway, Naples in Italy, and Umeå in Sweden, and 3) a combination of semi-quantitative FFQs and 7- and 14-day records in Malmö (Sweden) and the UK, respectively.

EPIC food items were classified into four groups according to the Nova system[19,21] (Supplementary Table S1). In brief, foods were classified as

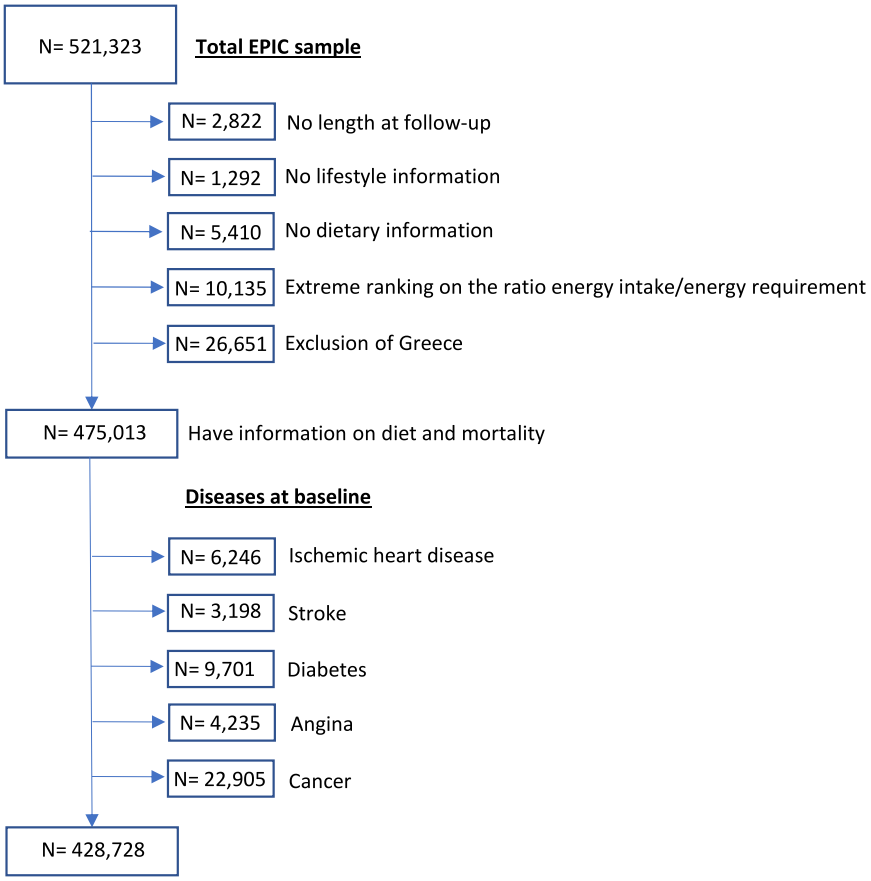

Fig. 1: Flowchart of the study sample.

unprocessed or minimally processed foods (Nova 1) if they were natural foods or foods altered by traditional methods such as freezing and that did not include additives. Processed culinary ingredients (Nova 2) were obtained from substances obtained from Nova 1 foods or from nature (e.g., oils, salt, fats). Processed foods (Nova 3) included food products made from a combination of Nova 1 and 2 foods, including those made using preservation methods (e.g., salting, curing, smoking, fermenting). UPFs (Nova 4) corresponded to industrial formulations containing substances derived from foods and industrial additives (e.g., sweeteners, colorants, flavorings, stabilizers, emulsifiers).

To account for potential changes in the prevalence of food processing over time, we considered: lower-, middle-, and upper-bound scenarios.[19] For example, if insufficient information was available for classifying a food item with sufficient certainty according to the Nova classification, then the most likely scenario of food processing for that food item was applied as the middle-bound scenario. For the lower-bound scenario, some foods were classified in a less processed Nova group compared to the middle-bound scenario when the food item may also have been prepared at home or in an artisanal setting instead of being industrially produced. For the upper-bound scenario, some food items were classified in a more processed Nova group compared to the middle-bound scenario when it was possible that the food item could be more processed than the most likely option assigned in the middle-bound scenario. The middle bound scenario showed higher associations with food processing biomarkers such as elaidic acid (industrial trans-fat) in validation analyses and was therefore used in the current analysis.

The dietary intake from each Nova food group was expressed as the absolute food quantity intake in grams per day (g/day) and the energy intake in kcal per day. The relative contribution of each Nova food group to the total daily dietary intake (% g/day) and energy intake (% kcal/day) was also calculated. Specifically, the intakes for baseline characteristics are presented in grams per day, as this unit is more suitable for comparing categories and aligns with how characteristics are typically reported in other epidemiological studies. The hazard ratios (HRs), however, are reported per 1 SD increment in the percentage of grams per day, as using 1 g per day or 1

percentage alone would reflect only a tiny increment/change compared to the 1 SD, making it challenging to capture associations with mortality effectively. Finally, the percentage of grams per day is used in quartiles and in substitution analyses to capture dietary patterns across different levels of food processing more precisely and the effect of a 10% substitution.

Assessment of mortality outcomes

Data on vital status as well as the cause and date of death were collected by EPIC centers through record linkages with cancer registries, boards of health, and death indices in Denmark, Italy, the Netherlands, Norway, Spain, Sweden, and the United Kingdom or through active follow-up (inquiries by mail or telephone to municipal registries or regional health departments or to physicians or hospitals) in Germany, Greece, and France. For the current study, follow-up of participants from baseline (1992–2000) occurred from December 2009 to December 2013. Data on causes of death were coded in accordance with the International Classification of Diseases, 10th Revision (ICD-10): cancer (ICD-10 codes C00 to D48), circulatory diseases (codes I00 to I99), which included ischemic heart diseases (codes I20 to I25) and cerebrovascular diseases (codes I60 to I69), digestive diseases (codes K00 to K93), Parkinson's disease (code G20), Alzheimer's disease (code G30), suicide (X60-X84), and transport accidents (V01–V99) as a negative control.

Covariates at recruitment

Body mass index (BMI), educational level and the marital status of the participants were recorded. The Cambridge physical activity index was derived from questionnaires. Alcohol intake in g/day, smoking duration and smoking intensity were also assessed. Finally, the total energy intake in kcal/day and the relative Mediterranean diet score (MedScore)[22] were calculated and included.

Statistical analysis

Baseline characteristics were examined according to sex-specific quartiles for the daily percentage intake in grams of each Nova food group. Descriptive analyses were performed per country and for each Nova category considering the absolute daily intake in calories and grams and the percentage intake.

Time at study entry was age at recruitment and exit time was age at death or age at end of follow-up in each EPIC centre. To assess food consumption, we used sex-specific quartiles of each Nova group expressed as percentage of g/day (categorical exposure) and as 1 SD increment of each Nova group in percentage of g/day (continuous exposure). Cox proportional hazard regression models were used to evaluate the associations between Nova category and all-cause and cause-specific mortality.

Model 1 was stratified by age (in 1-year categories), centre, and sex, and adjusted for smoking intensity, marital status, educational level, and physical activity. Model 2 included variables from Model 1 and was further adjusted for total energy intake, alcohol intake (g/day), smoking duration, BMI, and MedScore.

A leave-one-out substitution analysis was performed to assess the effect of replacing 10% of processed foods (Nova 3) and UPFs (Nova 4) with unprocessed/minimally processed foods (Nova 1) on mortality risk using Cox proportional hazards regression models. The models were stratified by age at recruitment (in 1-year categories), center and sex, and adjusted for the same covariates as the main models.

In these analyses, we model the effect of substituting 10% of energy intake from one food group (e.g., Nova 4) with another food group (e.g., Nova 1 or Nova 3), while keeping total energy intake constant. This approach allows us to evaluate the specific impact of replacing a portion of one type of food on mortality. They also help disentangle the specific contribution of each food processing category, enabling more precise interpretation of the results.

All analyses were repeated with the exclusion of alcoholic drinks from the Nova classification. Also, we performed extra sensitivity analyses removing those who died within 2 years of recruitment to limit potential impact of reverse causality. Additionally, we repeated the analysis considering the lower-bound and the upper-bound scenarios for food intake as exposures. Schoenfeld residuals for the main analyses per 1 SD increment in the percentage of grams per day and mortality are reported in Supplementary Table S11.

Statistical analyses were performed using the R software (v 4.1.3). All tests were two-sided and P value < 0.05 was considered statistically significant.

Role of the funding source

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

Results

After exclusions, 428,728 participants were included in the final analytic dataset. The baseline characteristics for all participants by sex-specific quartiles of percentage intake in grams of UPFs are detailed in Table 1. In addition, Supplementary Table S2 outlines both the percentage and absolute contributions of Nova groups to the total daily diet by mass and energy for the total cohort and individual countries. The mean consumption of UPFs in the cohort was 13.7% g/d, ranging from an intake of 8.06% g/d in Spain to 22.7% g/d in Norway.

In the multivariable model, higher intake of unprocessed/minimally processed foods (Nova 1 in % of grams per day per 1-SD increment) was associated with

	All participants N = 428,728	Nova 4			
		1st quartile	2nd quartile	3rd quartile	4th quartile
Proportion of grams					
Nova 1	71.5% (12.1)	77.6% (11.9)	74.7% (10.8)	71.4% (9.6)	62.5% (10.2)
Nova 2	1.2% (1.0)	1.6% (1.1)	1.2% (1.1)	1.1% (1.0)	0.9% (0.9)
Nova 3	13.6% (10.0)	16.0% (11.5)	14.4% (10.4)	12.9% (9.2)	10.9% (7.6)
Nova 4	13.7% (8.8)	4.9% (1.8)	9.7% (1.3)	14.6% (1.7)	25.7% (7.7)
Proportion of kcals					
Nova 1	36% (10.4)	41.7% (10.6)	37.1% (9.7)	34.4% (9.3)	30.7% (8.9)
Nova 2	7.4% (6.1)	11.1% (6.2)	7.7% (6.0)	6.1% (5.3)	4.8% (4.6)
Nova 3	24.6% (11.8)	30.8% (11.9)	26.2% (11.0)	22.7% (10.6)	18.6% (10.0)
Nova 4	32% (14.9)	16.4% (9.2)	29.0% (10.3)	36.8% (10.5)	45.8% (11.3)
Age, years	50.8 (9.7)	52.5 (7.7)	52.1 (8.9)	50.7 (10.1)	47.7 (11.0)
Height, cm	166.2 (8.8)	163.0 (7.9)	166.1 (8.8)	167.6 (9.0)	168.1 (8.7)
BMI, kg/m2	25.1 (4.1)	25.1 (4.2)	25.2 (4.0)	25.2 (4.0)	25.2 (4.2)
Normal weight	233,822 (54.5%)	58,906 (55.0%)	58,167 (54.3%)	57,856 (54.0%)	58,893 (54.9%)
Overweight	145,086 (33.8%)	35,069 (32.7%)	36,920 (34.4%)	37,562 (35.0%)	35,535 (33.2%)
Obese	49,820 (11.6%)	13,207 (12.3%)	12,095 (11.3%)	11,764 (11.0%)	12,754 (11.9%)
Sex					
Men	121,300 (28.3%)	20,854 (19.5%)	30,602 (28.6%)	36,428 (34.0%)	33,416 (31.2%)
Women	307,428 (71.7%)	86,328 (80.5%)	76,580 (71.4%)	70,754 (66.0%)	73,766 (68.8%)
Education					
Primary	117,497 (27.4%)	35,997 (33.6%)	29,974 (28.0%)	26,868 (25.1%)	24,658 (23.0%)
Secondary or technical school	109,158 (44.4%)	41,922 (39.1%)	46,521 (43.4%)	48,547 (45.3%)	53,141 (49.6%)
Longer education	105,470 (24.6%)	26,854 (25.1%)	27,620 (25.8%)	26,980 (25.2%)	24,016 (22.4%)
Not specified	15,603 (3.6%)	2409 (2.2%)	3067 (2.9%)	4760 (4.4%)	5367 (5.0%)
Physical activity					
Inactive	80,879 (18.9%)	26,072 (24.3%)	19,927 (18.6%)	18,418 (17.2%)	16,462 (15.4%)
Moderately inactive	142.956 (33.3%)	38,334 (35.8%)	37,245 (34.7%)	34,872 (32.5%)	32,505 (30.3%)
Moderately active	116,210 (27.1%)	26,687 (24.9%)	27,414 (25.6%)	28,840 (26.9%)	33,269 (31.0%)
Active	80,113 (18.7%)	15,678 (14.6%)	21,067 (19.7%)	22,089 (20.6%)	21,279 (19.9%)
Missing	8570 (2%)	411 (0.4%)	1529 (1.4%)	2963 (2.8%)	3667 (3.4%)
Alcohol					
No ethanol intake	53,630 (12.5%)	19,087 (17.8%)	11,257 (10.5%)	10,131 (9.5%)	13,155 (12.3%)
<5 g per day	150,328 (35.1%)	30,139 (28.1%)	34,296 (32.0%)	38,385 (35.8%)	47,508 (44.3%)
5–14.9 g per day	116,881 (27.3%)	25,574 (23.9%)	30,097 (28.1%)	32,082 (29.9%)	29,128 (27.2%)
15–29.9 g per day	59,219 (13.8%)	16,394 (15.3%)	16,663 (15.5%)	15,350 (14.3%)	10,812 (10.1%)
>30 g per day	48.670 (11.4%)	15,988 (14.9%)	14,869 (13.9%)	11,234 (10.5%)	6579 (6.1%)
Alcohol (g/day)	13.0 (18.0)	15.3 (21.3%)	14.9 (19.2%)	12,6 (16.5%)	9,1 (13.6%)
Smoke duration					
Non-smoker	183,422 (42.8%)	43,394 (40.7%)	44,154 (41.1%)	46,293 (43.2%)	49,581 (46.1%)
<10 years	30,923 (7.2%)	5378 (5.0%)	6946 (6.5%)	8359 (7.8%)	10,240 (9.5%)
11–20 years	51,812 (12.1%)	11,730 (11.0%)	13,287 (12.4%)	13,764 (12.8%)	13,031 (12.1%)
21–30 years	57,598 (13.4%)	13,945 (13.1%)	14,295 (13.3%)	14,354 (13.4%)	15,004 (14.0%)
31–40 years	42,770 (10%)	9890 (9.3%)	11,705 (10.9%)	11,430 (10.7%)	9745 (9.1%)
>40 years	16,678 (3.9%)	3553 (3.3%)	5072 (4.7%)	4666 (4.4%)	3387 (3.2%)
Unknown duration	45.525 (10.6%)	18.733 (17.6%)	11,946 (11.1%)	8342 (7.8%)	6504 (6.1%)
Smoking intensity					
Never	183,422 (42.8%)	43,394 (40.7%)	44,154 (41.1%)	46,293 (43.2%)	49,581 (46.1%)
Current, 1–15 cig per day	50,440 (11.8%)	10,807 (10.1%)	12,748 (11.9%)	12,886 (12.0%)	13,999 (13.0%)
Current, 16–25 cig per day	26,395 (6.2%)	6209 (5.8%)	6565 (6.1%)	6749 (6.3%)	6872 (6.4%)
Current, >26 cig per day	6194 (1.4%)	1804 (1.7%)	1651 (1.5%)	1373 (1.3%)	1366 (1.3%)
Former, quit ≤10 years	40,294 (9.4%)	9096 (8.5%)	10,075 (9.4%)	10,364 (9.7%)	10,759 (10.0%)
Former, quit 11–20 years	35,474 (8.3%)	8237 (7.7%)	9218 (8.6%)	9489 (8.9%)	8530 (7.9%)
Former, >20 years	34,350 (8.0%)	6903 (6.5%)	9191 (8.6%)	9745 (9.1%)	8511 (7.9%)

(Table 1 continues on next page)

	All participants N = 428,728	Nova 4			
		1st quartile	2nd quartile	3rd quartile	4th quartile
(Continued from previous page)					
Current: pipe, cigars.	38,372 (9.0%)	17,258 (16.2%)	10,779 (10.0%)	6681 (6.2%)	3654 (3.4%)
Current/former, missing	7286 (1.7%)	1464 (1.4%)	1823 (1.7%)	2059 (1.9%)	1940 (1.8%)
Unknown	6501 (1.5%)	1451 (1.4%)	1201 (1.1%)	1569 (1.5%)	2280 (2.1%)
Marital status					
Single	38,218 (8.9%)	9432 (8.8%)	8406 (7.8%)	8919 (8.3%)	11,461 (10.7%)
Married/living together	258,817 (60.4%)	59,462 (55.5%)	62,110 (57.9%)	67,265 (62.8%)	69,980 (65.3%)
Divorced/Separated	20,504 (4.8%)	3092 (2.9%)	5381 (5.0%)	6169 (5.8%)	5862 (5.5%)
Widowed	10,374 (2.4%)	1873 (1.7%)	2962 (2.8%)	3135 (2.9%)	2401 (2.2%)
No specified	100,815 (23.5%)	33,323 (31.1%)	28,320 (26.4%)	21,694 (20.2%)	17,478 (16.3%)
Mediterranean diet score	8.4 (3.0)	9.7 (2.9)	8.4 (2.9)	7.9 (2.8)	7.7 (2.9)
Total energy intake (Kcal/d)	2137.7 (624.9)	2064.6 (606.8)	2109.1 (597.7)	2165.1 (611.8)	2212.6 (670.6)

Table 1: **Baseline characteristics for all participants by sex-specific quartiles of percentage intake in grams of ultra processed food (Nova 4). Data are mean (SD) or n (%).**

a lower risk of all-cause mortality (hazard ratio (HR):0.92; 95% confidence interval (CI):0.90,0.93) and mortality from cancer (HR: 0.96; 95% CI:0.94,0.98), circulatory disease (HR: 0.89; 95% CI:0.87,0.92), cerebrovascular disease (HR: 0.88; 95% CI:0.83,0.93), ischemic heart disease (HR: 0.88; 95% CI 0.85,0.93), digestive diseases (HR: 0.70; 95% CI:0.65,0.75) and Parkinson's disease (HR:0.81; 95% CI:0.68,0.96) (Fig. 2a, Supplementary Table S3). No associations were observed between Nova 1 and mortality from Alzheimer's disease, suicide, and transport accidents (negative control). Similar associations were observed in the sex-specific quartile models (Supplementary Table S5). However, in sensitivity analyses that excluded alcohol from the Nova groups the statistical significance was lost for associations with cancer mortality (Supplementary Fig. S1 and Tables S4 and S6).

Nova 2 (processed culinary ingredients) was not associated with all-cause mortality (Fig. 2b, Supplementary Fig. S2 and Table S3). However, when comparing the highest vs the lowest quartile, consumption of Nova 2 was associated with a several mortality end-points (Supplementary Table S5). The associations for all-cause mortality ($HR_{Q4\ vs\ Q1}$, 0.96, 95% CI:0.92,0.99) and circulatory disease mortality ($HR_{Q4\ vs\ Q1}$, 0.91, 95% CI:0.84,0.98) remained after removing alcohol (Supplementary Table S6).

In the fully adjusted model, higher intake of Nova 3 (processed foods) in 1-SD increment of % of grams per day was associated with a higher risk of all-cause mortality (HR:1.08; 95% CI:1.06,1.09), and mortality from cancer (HR: 1.06; 95% CI:1.03,1.08), circulatory disease (HR:1.04; 95% CI:1.01,1.08), digestive disease (HR:1.41; 95% CI:1.32,1.52) and ischemic heart disease (HR:1.05; 95% CI:1.00,1.11), and suicide (HR:1.15; 95% CI:1.00,1.31) (Fig. 2c, Supplementary Table S3). However, no associations were observed in the sensitivity analyses when removing alcoholic beverages from the Nova groups (Supplementary Fig. S3 and Table S4). Results by quartiles did not show associations except for digestive diseases mortality ($HR_{Q4\ vs\ Q1}$, 1.36, 95% CI:1.06,1.75) (Supplementary Tables S5 and S6) but only when alcoholic beverages were included in the Nova groups (Supplementary Table S5).

For Nova 4 (UPFs), in the fully adjusted model (model 2), a 1 SD increment of % of grams per day higher intake was associated with higher risk of all-cause mortality (HR:1.04; 95% CI:1.02,1.05), and mortality from circulatory disease (HR:1.09; 95% CI:1.07,1.12), cerebrovascular diseases (HR:1.11; 95% CI:1.05,1.17), ischemic heart disease (HR: 1.10; 95% CI:1.06,1.15), digestive diseases (HR:1.12; 95% CI:1.05,1.20) and Parkinson's disease (HR: 1.23; 95% CI:1.06,1.42) (Fig. 2d, Supplementary Table S3). After removing alcoholic beverages from UPFs, all associations remained statistically significant (Supplementary Fig. S4 and Table S4). Similarly, in the fully adjusted model, sex-specific quartile results showed similar associations, but not for cerebrovascular and digestive diseases (Supplementary Table S5). When excluding alcohol from the Nova groups, results were similar while there was also an association between the highest quartile of Nova 4 with digestive diseases mortality when compared with the lowest quartile ($HR_{Q4\ vs\ Q1}$: 1.38; 95% CI:1.12,1.71).

Substitution analyses

Replacing 10% g/day of Nova 3 with Nova 1 was associated with a 9% lower all-cause mortality risk, and this association was similar after removing alcohol from Nova food groups (Table 2). On the other hand, replacing 10% of grams per day of Nova 4 with Nova 1 was associated with a reduced risk of all-cause mortality of 6% (9% when removing alcoholic beverages). For

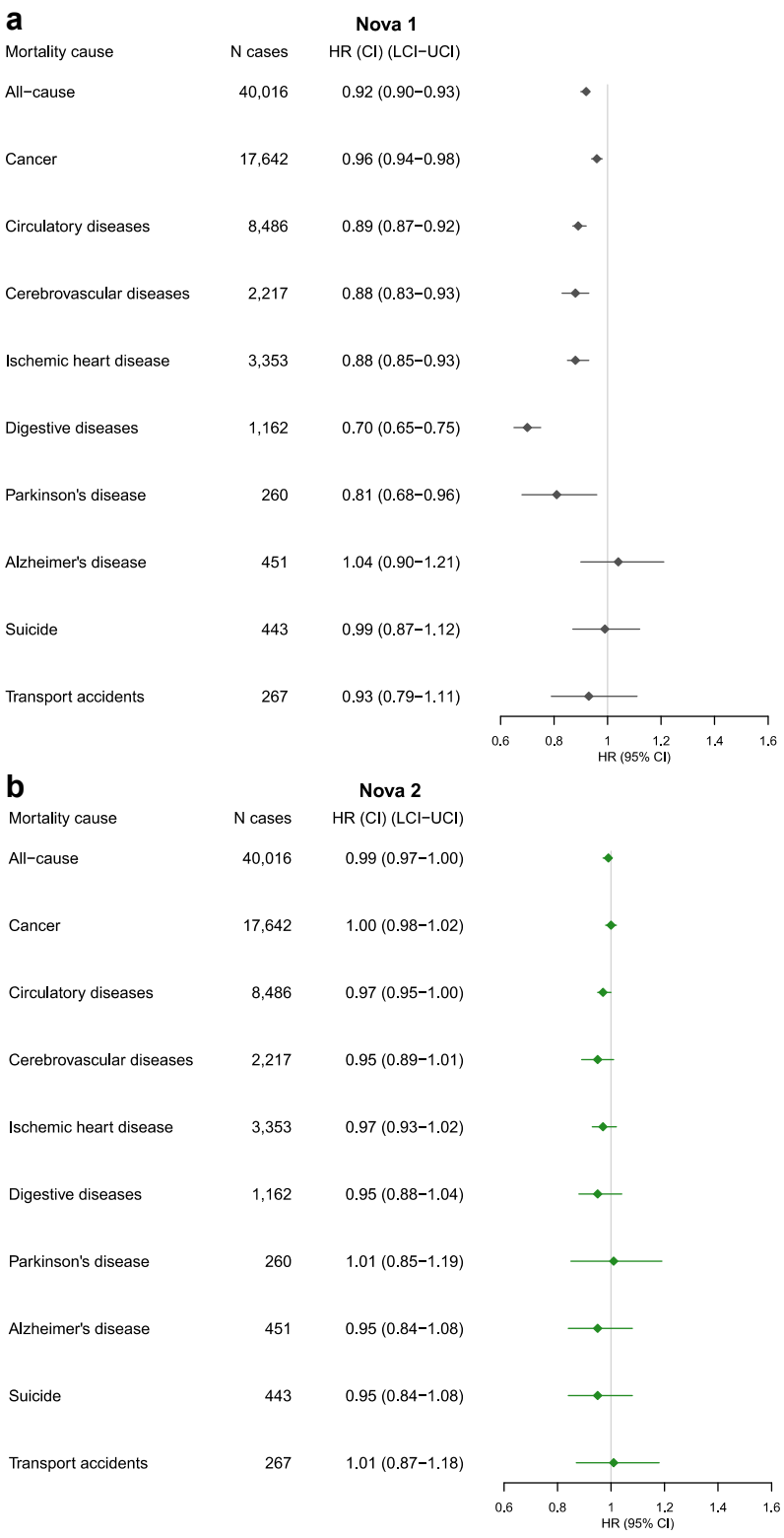

Fig. 2: Associations of consumption of unprocessed/minimally processed foods (Nova 1), culinary ingredients (Nova 2), processed foods (Nova 3) and ultra-processed foods (Nova 4) per 1SD increment of percentage of grams per day and all-Cause and cause specific mortality. Cox regression stratified by age (1-year categories), sex, centre and controlled by smoking intensity, smoking status, educational level, marital status, physical activity, total energy intake, alcohol intake, body mass index and MedScore. Total of subjects included in the analysis 428,728. HR: hazard ratio; LCI: lower confidence interval; UCI: upper confidence interval.

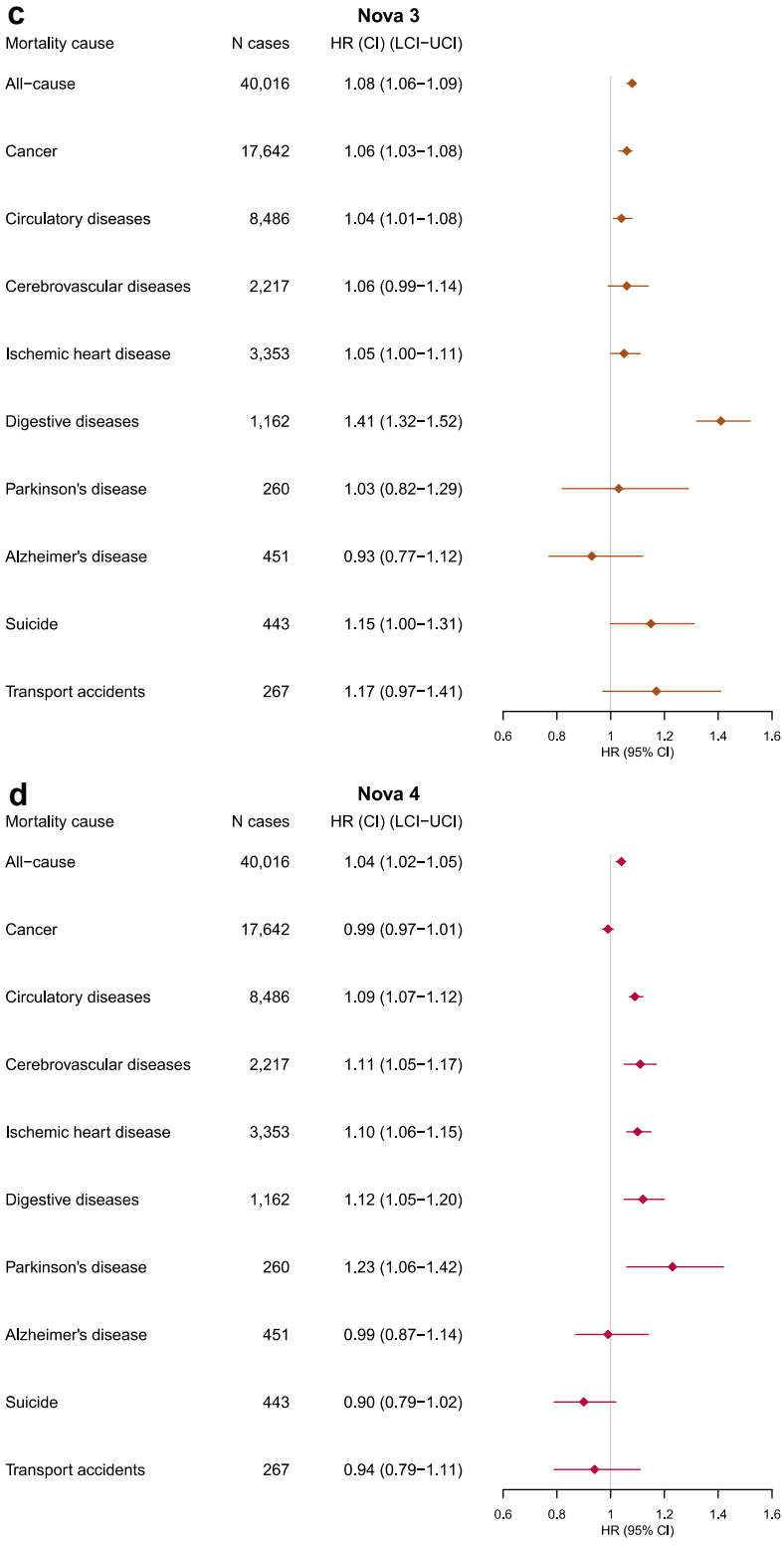

Fig. 2: Continued.

	Nova classification with alcoholic drinks		Nova classification without alcoholic drinks	
	Substitution of Nova 3 by Nova 1	Substitution of Nova 4 by Nova 1	Substitution of Nova 3 by Nova 1	Substitution of Nova 4 by Nova 1
All-cause				
Model 1	**0.93 (0.92–0.94)****	**0.93 (0.92–0.94)****	**0.94 (0.93–0.95)****	**0.91 (0.90–0.92)****
Model 2	**0.91 (0.90–0.93)** **	**0.94 (0.93–0.96)****	**0.92 (0.90–0.94)****	**0.91 (0.90–0.93)****
Cancer				
Model 1	**0.94 (0.92–0.96)** **	0.98 (0.96–1.01)	**0.94 (0.92–0.96)****	**0.95 (0.93–0.96)****
Model 2	**0.94 (0.92–0.96)** **	1.00 (0.98–1.02)	**0.94 (0.91–0.96)****	**0.96 (0.94–0.98)****
Circulatory diseases				
Model 1	0.98 (0.96–1.01)	**0.87 (0.85–0.90)****	1.00 (0.97–1.03)	**0.92 (0.90–0.94)****
Model 2	**0.94 (0.91–0.97)****	**0.89 (0.86–0.92)****	**0.95 (0.91–0.98)***	**0.90 (0.88–0.92)****
Cerebrovascular diseases				
Model 1	**0.91 (0.86–0.96)****	**0.86 (0.81–0.91)****	**0.93 (0.87–0.98)***	**0.87 (0.83–0.91)****
Model 2	**0.92 (0.85–0.99)***	**0.87 (0.82–0.93)****	0.94 (0.86–1.02)	**0.88 (0.83–0.92)****
Ischemic heart disease				
Model 1	1.03 (0.99–1.08)	**0.87 (0.83–0.91)****	**1.07 (1.02–1.12)***	0.96 (0.93–1.00)
Model 2	**0.93 (0.88–0.98)***	**0.88 (0.84–0.92)****	0.94 (0.88–1.00)	**0.90 (0.86–0.93)****
Digestive diseases				
Model 1	**0.67 (0.64–0.71)****	**0.80 (0.74–0.87)****	**0.66 (0.62–0.70)****	**0.69 (0.66–0.73)****
Model 2	**0.68 (0.63–0.73)****	**0.82 (0.75–0.89)****	**0.67 (0.61–0.73)****	**0.73 (0.68–0.77)****
Parkinson's disease				
Model 1	1.01 (0.85–1.20)	**0.76 (0.64–0.89)****	1.05 (0.86–1.27)	0.88 (0.77–1.00)
Model 2	0.94 (0.75–1.18)	**0.78 (0.66–0.93)***	0.97 (0.74–1.25)	**0.83 (0.71–0.97)***
Alzheimer's disease				
Model 1	1.08 (0.93–1.25)	0.99 (0.85–1.14)	1.10 (0.93–1.29)	1.03 (0.91–1.16)
Model 2	1.07 (0.88–1.29)	1.00 (0.86–1.17)	1.10 (0.88–1.33)	1.00 (0.87–1.15)
Suicide				
Model 1	0.97 (0.88–1.07)	1.08 (0.94–1.24)	0.96 (0.85–1.07)	1.02 (0.93–1.12)
Model 2	0.87 (0.76–1.00)	1.11 (0.96–1.28)	0.85 (0.72–1.00)	1.00 (0.89–1.12)
Transport accidents				
Model 1	0.94 (0.82–1.08)	1.00 (0.83–1.21)	0.94 (0.80–1.09)	0.99 (0.86–1.13)
Model 2	0.85 (0.70–1.03)	1.04 (0.86–1.27)	0.84 (0.68–1.03)	0.97 (0.83–1.15)

P < 0.05*, P < 0.001**. Bold font indicates statistical significance (P < 0.05). Model 1 stratified by sex, age, centre and controlled by smoke intensity, physical activity index, education, marital status. Model 2: Model 1 + Smoke duration, body mass index, total energy intake, alcohol and the mediterranean diet score.

Table 2: **Substitution models replacing 10% of percentage of grams of processed foods (Nova 3) and ultra-processed foods (Nova 4) with 10% of minimally processed foods (Nova 1) and their effect on mortality.**

cause-specific mortality, the replacement of 10% g/day of Nova 3 with Nova 1 was associated with lower risk of death due to cancer (HR:0.94; 95% CI:0.92,0.96), circulatory diseases (HR:0.94; 95% CI:0.91,0.97), cerebrovascular disease (HR: 0.92; 95% CI:0.85,0.99), ischemic heart disease (HR:0.93; 95% CI:0.88,0.98), and death due to digestive diseases (HR:0.68; 95% CI:0.63,0.73). Results were similar after removing alcoholic beverages from the Nova groups, except for cerebrovascular diseases. The substitution of 10% g/day of Nova 4 with Nova 1 was associated with lower all-cause mortality (HR:0.94; 95% CI:0.93,0.96) but also with circulatory diseases (HR: 0.89; 95% CI:0.86,0.92), cerebrovascular diseases (HR:0.87; 95% CI:0.82,0.93), ischemic heart disease (HR:0.88; 95% CI:0.84,0.92) digestive diseases (HR:0.82; 95% CI:0.75,0.89), and Parkinson's disease mortality (HR:0.78; 95% CI:0.66,0.93). Results were similar after excluding alcohol from the Nova groups, but an association was also revealed for cancer mortality (HR:0.96; 95% CI:0.94,0.98).

Removal of participants who died within 2 years of recruitment did not change the results appreciably (Supplementary Tables S7 and S8). Likewise, when we repeated the analyses considering the lower-bound and the upper-bound scenarios for food intake as the exposures, we found similar results to those obtained in the main analyses (Supplementary Tables S9 and S10).

Discussion

The results from this large-scale, multicenter, prospective study indicate that higher consumption of unprocessed/minimally processed foods is associated with lower risk of all-cause and multiple forms of cause-specific mortality, while greater consumption of UPFs raises risk of all-cause mortality and mortality from

circulatory diseases (including cerebrovascular or ischemic heart disease), digestive diseases, and Parkinson's disease, after controlling for education and lifestyle factors, including alcohol intake. Further, replacing 10% g/day of either processed or UPFs with an equal amount of unprocessed/minimally processed foods was inversely related to all-cause mortality and several cause-specific mortality endpoints.

In this study, we have categorized foods using the Nova classification, which distinguishes between processed (Nova 3) and ultra-processed (Nova 4) foods. However, it is important to clarify that while both categories involve some level of processing, they differ significantly in terms of their nutritional composition and potential health impacts. Processed foods (Nova 3) generally undergo preservation techniques such as canning or freezing and can include relatively healthier options such as canned vegetables, preserved fish, and homemade sauces. Also, they include the most commonly consumed alcoholic beverages - beer and wine, which can have harmful effects. On the other hand, ultra-processed foods (Nova 4) tend to contain artificial ingredients, additives, and highly processed substances, often associated with poorer health outcomes. In addition, spirits are also included in this group.

Previous studies have reported positive associations between consumption of UPFs with mortality.[13–15,23,24] There is robust evidence from meta-analyses and umbrella reviews that UPFs are positively associated with risk of mortality.[11] However, unlike in our analysis, previous studies have focused on all-cause mortality and the most common causes of death and had a relatively low number of participants. Our findings on the association of UPFs and circulatory diseases-related mortality, even when removing alcoholic beverages from the analyses, are consistent with those previously reported in other populations[17,23–25] including one study which investigated the mediating role of biomarkers on the association between UPFs and all-cause and cardiovascular mortality.[25] Results from that study suggested that inflammation mediates 29.2% of the association between UPF consumption and cardiovascular disease mortality. Other potential mediators have also been suggested, including the increase in energy intake associated with UPFs, changes in the gut microbiome, alterations in the gut–brain satiety signaling, and hormonal effects.[26] These exposures may also act as initiators of atherogenic processes, dysglycemia, dyslipidemia, hypertension, obesity, inflammation, endothelial dysfunction, and oxidative stress.

The current evidence linking UPFs and cancer mortality is inconsistent. Although UPF consumption was positively associated with cancer mortality in the UK Biobank,[18] our findings are in line with other studies where no association was found with overall cancer mortality.[13,14,17] Further research is needed to investigate associations with mortality from specific cancer types, particularly those cancers for which the incidence was associated with food processing.[8]

While prior large-scale studies have focused on circulatory-related disease mortality and cancer, we also explored the association of food processing with other causes of mortality, such as mortality related to digestive and neurodegenerative diseases. In our analysis, the association between consumption of UPFs and digestive disease-related mortality was found even when removing alcoholic beverages in the Nova groups. Another prospective cohort study found that greater intake of UPFs was associated with an increased risk of nonalcoholic fatty liver disease, liver fibrosis and cirrhosis, and severe liver disease, along with adverse levels of serum biomarkers such as c-reactive protein, alkaline phosphatase, gamma-glutamyl transferase, and triglycerides even when adjusting for alcohol intake.[27] These findings highlight the potential benefits of decreasing UPFs consumption as a means of enhancing liver health.[27]

Consumption of UPFs has been suggested to play a role in cognitive decline and risk of dementia,[28] however, there is a lack of studies evaluating the association of UPFs with neurodegenerative mortality. A single previous study that included overall neurodegenerative disease-related mortality found associations with UPFs.[13] Results from our study suggest that consumption of UPFs is associated with Parkinson's disease mortality but not Alzheimer's disease. This could be due to the potential underdiagnosis of Alzheimer's disease as symptoms are similar to other diseases. More studies are needed to confirm these results.

In addition, previous studies have suggested an association between UPF consumption and adverse mental health outcomes, including depression,[29,30] which may influence the risk of suicide. Therefore, we included suicide as a mortality endpoint in our analysis to capture the potential impact of UPF intake on mental health-related mortality but no associations were found.

In our study, consumption of processed foods (Nova 3) was associated with all-cause, cancer, circulatory disease, ischemic heart disease, digestive diseases, or suicide mortality; however, these associations disappeared when removing alcohol from the Nova groups. This suggests that alcohol likely drives the association between processed foods (Nova 3) and mortality and needs to be considered when evaluating the effects of processed foods on health outcomes. Additionally, some Nova 3 foods, such as preserved meats, fatty fish, cheese and homemade sauces, may also contain high levels of salt, preservatives, or unhealthy fats, which could contribute to digestive health risks.

The substitution of 10% of UPFs with 10% of unprocessed/minimally processed foods was associated with reduced risk of mortality and may be due to the double effect of removing the unhealthy components associated with UPFs and the beneficial effect of

increasing consumption of unprocessed/minimally processed foods and their associated compounds. UPFs are mostly energy-dense foods, high in sugar, in trans-fats, and low in protein and fiber[11] that contain chemical substances released by elevated cooking temperature, food manufacturing (e.g., food additives, oils hydrogenation) and packaging materials that may negatively impact the microbiota and induce inflammation.[11,31]

The Nova classification system, which categorizes foods based on the level of processing, places certain foods in Nova 3 and Nova 4 that dietary guidelines sometimes endorse for their nutritional benefits. In our analyses we aimed at using the Nova classification for its core purpose, which is classifying foods in terms of food processing rather than in terms of nutritious components or composition. Therefore, we do not consider it appropriate to investigate separate food groups and their harmful-beneficial effects on mortality in our study. However, it would be pertinent to investigate a further refinement of Nova to account for these complexities of the food items in order to investigate the potential health effects of certain UPF (e.g., high-fiber UPFs) in intervention studies or cohorts with more detailed food descriptions in further studies.

Strengths of this study include the large sample size, long-term follow-up and the inclusion of data from multiple European countries (large heterogeneity in food consumption). Also, we accounted for a large set of lifestyle- and socio-economic factors. Validation analyses for the Nova classification in EPIC have been conducted by comparing questionnaire-based consumption data and biomarker levels. Also, the inclusion of other endpoints beyond those reported previously, i.e., Alzheimer's or Parkinson's disease should be considered a relevant strength. Transport accidents were used as a negative control, and we found no associations between food consumption, categorized by level of processing, and mortality from these accidents.

The study also has limitations. The Nova classification is based on broad categories that can miss certain specificities of food processing. This is partly due to methodological issues in categorizing UPFs across EPIC centers, where variations in dietary questionnaires might affect the classification of foods according to the Nova system. The EPIC dietary questionnaires were not necessarily specifically designed to collect the information needed to link food to the Nova classification. Also, despite using a standardized coding protocol to disaggregate homemade recipes into ingredients, some commercially processed ingredients may have been classified as less processed (Nova groups 1 and 2) rather than as Nova groups 3 or 4. This misclassification could also result in an underrepresentation of ultra-processed items, potentially attenuating the observed associations with mortality. Additionally, recipes that were typically homemade in the 1990s may now be more likely to be industrially processed, contributing further to this underestimation. Moreover, changes in food processing techniques over time, such as the banning of trans fats in certain countries, were not accounted for in our data, as both dietary intake and food processing biomarkers were collected only at baseline. However, dietary data collected via 24-h dietary recalls in a subsample of individuals in all countries were used to inform assumptions and minimize misclassification.[32] Furthermore, dietary, and other lifestyle exposure measurements were collected at recruitment, and potential changes in modifiable behaviors likely occurred during follow-up. These limitations were mitigated by creating and evaluating different scenarios for the different Nova categories (e.g., lower, middle and upper bound scenario) finding similar results. However, the actual association between UPF intake and mortality risk in contemporary populations could be larger than observed in our findings.

Conclusion

In conclusion, this study provides new evidence on the potential impact of dietary intake according to degree of industrial food processing on mortality risk. In particular, UPFs consumption may increase the risk of mortality from circulatory disease, cerebrovascular disease, ischemic heart disease, digestive diseases, and Parkinson's disease. Promoting the consumption of unprocessed/minimally processed foods while discouraging highly processed foods in dietary recommendations may be beneficial for health.

Contributors

EMGG did the statistical analysis and drafted the manuscript. IH, MJG and MM made a substantial contribution to the concept of the article. MT, GN and IH, were involved in the acquisition and interpretation of data. IH and MJG were responsible for the study design. FMB, MC, GN, JB, NK, RB, FR, IJ, AAN, EKC, EPV, KC, YSG, CM, MT, MGMP, KKT, AKH, CML, VP, CMI, MSDM, CCD, NB, AO, AT, YTVS, PA, FJ, MBS, FM, CM, CC, CBB, DRS, KBB, MB, GS, JHG, AM, PF, LD, MJG, and IH critically assessed, edited, and approved the final manuscript. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. EMGG is the guarantor.

Data sharing statement

EPIC data are available for investigators who seek to answer important questions on health and disease in the context of research projects that are consistent with the legal and ethical standard practices of IARC/WHO and the EPIC centers. The primary responsibility for accessing the data belongs to IARC and the EPIC centers. For information on how to submit an application for gaining access to EPIC data and/or biospecimens, please follow the instructions at https://login.research4life.org/tacsgr0epic_iarc_fr/access/index.php. The research findings are disseminated to participants and public communities (https://epic.iarc.fr/).

Declaration of interests

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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.2024.101208.

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