Association of ultra-processed food consumption with all cause and cause specific mortality: population based cohort study

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ABSTRACT

OBJECTIVE

To examine the association of ultra-processed food consumption with all cause mortality and cause specific mortality.

DESIGN

Population based cohort study.

SETTING

Female registered nurses from 11 US states in the Nurses' Health Study (1984-2018) and male health professionals from all 50 US states in the Health Professionals Follow-up Study (1986-2018).

PARTICIPANTS

74 563 women and 39 501 men with no history of cancer, cardiovascular diseases, or diabetes at baseline.

MAIN OUTCOME MEASURES

Multivariable Cox proportional hazard models were used to estimate hazard ratios and 95% confidence intervals for the association of ultra-processed food intake measured by semiquantitative food frequency questionnaire every four years with all cause mortality and cause specific mortality due to cancer, cardiovascular, and other causes (including respiratory and neurodegenerative causes).

RESULTS

30 188 deaths of women and 18 005 deaths of men were documented during a median of 34 and 31 years of follow-up, respectively. Compared with those in the lowest quarter of ultra-processed food consumption, participants in the highest quarter had a 4% higher all cause mortality (hazard ratio 1.04, 95% confidence interval 1.01 to 1.07) and 9% higher mortality from causes other than cancer or cardiovascular diseases (1.09, 1.05 to 1.13). The all cause mortality rate among participants in the lowest and highest quarter was 1472 and 1536 per 100 000 person years, respectively. No associations were found for cancer or cardiovascular mortality. Meat/poultry/seafood based ready-to-eat products (for example, processed meat) consistently showed strong associations with mortality outcomes (hazard ratios ranged from 1.06 to 1.43). Sugar sweetened and artificially sweetened beverages (1.09, 1.07 to 1.12), dairy based desserts (1.07, 1.04 to 1.10), and ultra-processed breakfast food (1.04, 1.02 to 1.07) were also associated with higher all cause mortality. No consistent associations between ultra-processed foods and mortality were observed within each quarter of dietary quality assessed by the Alternative Healthy Eating Index-2010 score, whereas better dietary quality showed an inverse association with mortality within each quarter of ultra-processed foods.

CONCLUSIONS

This study found that a higher intake of ultra-processed foods was associated with slightly higher all cause mortality, driven by causes other than cancer and cardiovascular diseases. The associations varied across subgroups of ultra-processed foods, with meat/poultry/seafood based ready-to-eat products showing particularly strong associations with mortality.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Ultra-processed foods have been suggested to have adverse health effects

Evidence is limited on the influence of ultra-processed food consumption on mortality outcomes in large cohorts with long term follow-up and repeated dietary assessment

WHAT THIS STUDY ADDS

A higher intake of ultra-processed foods was associated with slightly higher all cause mortality, driven by causes other than cancer and cardiovascular diseases

The positive associations were mainly driven by meat/poultry/seafood based ready-to-eat products, sugar and artificially sweetened beverages, dairy based desserts, and ultra-processed breakfast foods

Dietary quality was observed to have a more predominant influence on mortality outcomes than ultra-processed food consumption

Introduction

Ultra-processed foods are ready-to-eat/heat industrial formulations made mostly or entirely from substances derived from foods, including flavors, colors, texturizers, and other additives, with little if any intact whole food.[1] Ultra-processed foods, which are typically of low nutritional quality and high energy density, have been dominating the food supply of high income countries, and their consumption is markedly increasing in middle income countries.[2] Ultra-processed food consumption accounts for 57% of daily energy intake among adults and 67% among youths in the US according to the National Health and Nutrition Examination Survey (NHANES).[3 4]

Ultra-processed foods usually disproportionately contribute added sugars, sodium, saturated fats and trans fats, and refined carbohydrates to the diet together with low fiber.[5 6] As well as having low nutritional quality, ultra-processed foods may contain harmful substances, such as additives and contaminants formed during the processing.[7-10] Growing evidence from large prospective cohorts show that ultra-processed food is associated with adverse health outcomes, such as overweight/obesity, cardiovascular diseases, type 2 diabetes, and colorectal cancer.[11-14] A systematic review showed that high ultra-processed food consumption was associated with increased risk of all cause mortality, cardiovascular diseases, metabolic syndrome, depression, and postmenopausal breast

cancer.[15] However, few prospective cohort studies with a follow-up longer than 20 years have examined the association for all cause mortality or cause specific mortality, especially mortality due to cancer. High quality evidence from cohorts with a long follow-up is critical to inform dietary recommendations and food policies.

Leveraging the rich data obtained through repeated assessments for more than 30 years in two large US prospective cohorts, we examined the associations of total ultra-processed food and subgroups of ultra-processed food with mortality from all causes and major individual causes.

Methods

Study population

We used data from two large prospective cohorts in the US: the Nurses' Health Study (NHS) began in 1976 and included 121 700 female registered nurses aged 30-55 years from 11 states; the Health Professionals Follow-up Study (HPFS) began in 1986 and enrolled 51 529 male health professionals aged 40-75 years from all 50 states. Every two years participants completed a mailed questionnaire enquiring about medical and lifestyle information. The baseline of this study was set to 1984 for the NHS and 1986 for the HPFS when the ultra-processed food data were first available. We excluded participants at baseline if they had reported a history of cancer, cardiovascular diseases, or diabetes; left more than 70 food items blank in the food frequency questionnaire or had implausible caloric intakes (<800 or >4200 kcal/d for men; <600 or >3500 kcal/d for women); or had missing data on ultra-processed food intakes. After exclusions, we included 74 563 women from the NHS and 39 501 men from the HPFS (supplementary figure A).

Assessment of ultra-processed food intake

Diet was assessed using a validated semiquantitative food frequency questionnaire administered every four years.[16] We grouped all foods into four categories of the Nova classification: unprocessed or minimally processed foods, processed culinary ingredients, processed foods, and ultra-processed foods, which has been described in detail elsewhere.[17] we further categorized ultra-processed foods into nine mutually exclusive subgroups (supplementary table B; supplementary figure B): ultra-processed breads and breakfast foods; fats, condiments, and sauces; packaged sweet snacks and desserts; sugar sweetened and artificially sweetened beverages; ready-to-eat/heat mixed dishes; meat/poultry/seafood based ready-to-eat products (for example, processed meat); packaged savory snacks; dairy based desserts; and other. Because alcohol is a well studied risk factor for premature death and a distinct factor in diet, we did not consider alcohol in ultra-processed foods in the primary analysis. Moreover, as wholegrain foods have established benefit for lowering all cause mortality,[18] we removed whole grains from ultra-processed foods in the primary analysis. We measured ultra-processed food intake as servings per day and adjusted it for total energy intake by using the residual method.[19]

Ascertainment of outcomes

Death of a cohort member was notified by the next of kin via the post office when questionnaires or newsletters were returned or was identified through searches of the vital records of states and of the National Death Index. Study investigators blinded to the exposure status reviewed death certificates and extracted information from medical records to confirm the cause of death according to ICD-8 (international classification of diseases, 8th revision). The primary outcome of this study was all cause mortality. The secondary outcomes included deaths from cancer (ICD-8 codes 140-207), cardiovascular diseases (ICD-8 codes 390-459), and other causes (including respiratory diseases (ICD-8 codes 460-519) and neurodegenerative diseases (ICD-8 codes 290, 332, 340, 342, and 348)).

Assessment of covariates

Biennial follow-up questionnaires were used to collect self-reported information on body weight, marital status, smoking status and pack years, physical activity, family history of cancer/cardiovascular diseases/diabetes, and physical examination for screening purposes, as well as menopausal status and postmenopausal hormone use for women. We calculated body mass index as weight in kilograms divided by height squared in meters. Physical activity was assessed with a validated questionnaire and converted into metabolic equivalent task hours.[20] Alcohol drinking was measured by food frequency questionnaires as the number of drinks per week (considering one drink as one glass, bottle, or can of beer; one 4 ounce glass of wine; or one shot of liquor) and then converted into grams per day. We assessed overall dietary quality by using the Alternative Healthy Eating Index-2010 (AHEI) score.[21]

Statistical analysis

Follow-up time accrued from the date of return of the baseline questionnaire to the date of death or the end of follow-up (30 June 2018 for NHS; 31 January 2018 for HPFS), whichever came first. To better represent long term dietary habits and to minimize within person variation, we calculated cumulative averages of ultra-processed food consumption as the primary exposure. We did primary analyses in pooled cohorts and a secondary analysis in each cohort separately. We used time varying Cox proportional hazards models stratified by age (months), questionnaire cycle (two year interval), and cohort (in pooled analyses) with the counting process data structure to estimate the hazard ratios and 95% confidence intervals according to quarters of ultra-processed food consumption. We calculated P for trend on the basis of the Wald test by assigning the median intake to each quarter and modeling it as a continuous variable. In the multivariable model, we adjusted for race/ethnicity, marital status, physical activity, body mass index,

smoking status and pack years, alcohol consumption, physical examination performed for screening purposes, family history of diabetes mellitus, myocardial infarction, or cancer, and menopausal status and hormone use (women only). We carried forward non-missing values from the previous survey cycle to replace missing data. If the value remained missing, we created missing indicators. The percentage of missing data is shown in supplementary table A. We also tested for the dose-response relation by using the restricted cubic spline regression.[22]

In secondary analyses, we further categorized ultra-processed foods into mutually exclusive subgroups (supplementary tables B and C) to investigate whether the associations were driven by specific food groups.[13] Furthermore, to assess the independent and combined association of ultra-processed food consumption and overall dietary quality with mortality, we categorized individuals jointly according to quarters of AHEI score and quarters of ultra-processed food intake and estimated the hazard ratios by using participants with the highest quarter of AHEI score and lowest quarter of ultra-processed food intake as the reference.

We did several sensitivity analyses to test the robustness of the results. Firstly, given that people are likely to change their dietary habits after the diagnosis of certain chronic diseases, we stopped updating ultra-processed food consumption after the diagnosis of cardiovascular diseases, cancer, or diabetes during follow-up. Secondly, because of the uncertainty of the etiological time window, we introduced an eight to 12 year lag period between assessment of ultra-processed food intake and each follow-up period (for example, we used ultra-processed food intake from the 1986 questionnaire to assess the mortality risk in the period of 1994 to 1998). Thirdly, we added back to total ultra-processed food whole grains and distilled alcohol individually and in combination (that is, using the standard Nova definition) and repeated the analysis. Finally, we removed from the multivariable model pack years of smoking, which was not adjusted for in most previous studies, and further adjusted for AHEI score, to assess the confounding by smoking and dietary quality, respectively. We also removed from the multivariable model body mass index, which might be a mediator. Furthermore, we did the stratified analysis by major risk factors and repeated the primary analysis with ultra-processed food intake measured by percentage of energy.

We used SAS statistical package (version 9.4) for all the statistical analyses. We considered a P value <0.05 (two sided) to be statistically significant unless otherwise specified.

Patient and public involvement

The public was concerned about the health effects of ultra-processed foods, and their concerns informed our research question. Although participants were not involved in the study design, they played a central role in the conduct of the study by completing the biennial questionnaires in our cohorts, and we appreciate their contributions. We could not directly involve members of the public in this study, as no funding was available or set aside for patient and public involvement and our study team was not trained to work directly with the public.

Results

During a median of 34 years of follow-up, we documented 48 193 deaths (30 188 deaths of women and 18 005 deaths of men), including 13 557 deaths due to cancer, 11 416 deaths due to cardiovascular diseases, 3926 deaths due to respiratory diseases, and 6343 deaths due to neurodegenerative diseases. Table 1 shows the characteristics of participants according to quarters of energy adjusted ultra-processed food consumption throughout follow-up. Participants with higher ultra-processed food consumption were younger, more physically inactive, and more likely to smoke and had higher body mass index, lower consumption of alcohol, whole fruits and vegetables, and whole grains, and lower AHEI score.

Table 2 shows the hazard ratios of mortality according to quarters of ultra-processed food consumption. In the age, sex, and total calorie adjusted analysis, we observed strong positive associations between ultra-processed food and mortality outcomes. The associations became substantially attenuated in the multivariable analysis (table 2; supplementary figure C). Compared with participants in the lowest quarter (median 3.0 servings/day), those in the highest quarter (median 7.4 servings/day) had a 4% higher risk of total deaths (multivariable adjusted hazard ratio 1.04, 95% confidence interval 1.01 to 1.07; P for trend=0.005) and a 9% higher risk of other deaths (1.09, 1.05 to 1.13; P for trend<0.001), including an 8% higher risk of neurodegenerative deaths (1.08, 1.01 to 1.17; P for trend=0.1). We found no associations for deaths due to cardiovascular diseases, cancer, or respiratory diseases. The all cause mortality rate among participants in the lowest and highest quarter of ultra-processed food consumption was 1472 and 1536 per 100 000 person years, respectively.

Table 3 shows the associations for nine subgroups of ultra-processed foods. Meat/poultry/seafood based ready-to-eat products (for example, processed meat) showed the strongest association with higher all cause mortality (hazard ratio 1.13 (1.10 to 1.16) comparing highest versus lowest quarter) and mortality due to individual causes other than cardiovascular diseases and neurodegenerative diseases (hazard ratios ranged from 1.06 to 1.43). Other subgroups also showed an association with higher all cause mortality, including sugar sweetened and artificially sweetened beverages (1.09, 1.07 to 1.12), other ultra-processed foods (mainly composed of artificial sweeteners) (1.08, 1.05 to 1.11), dairy based desserts (1.07, 1.04 to 1.10), and ultra-processed breakfast foods excluding whole grains (1.04, 1.02 to 1.07). When further separating sugar sweetened and artificially sweetened beverages, we found a generally stronger association for sugar sweetened than artificially sweetened

Table 1 | Age standardized characteristics of study participants according to quarters of ultra-processed food (UPF) consumption across entire follow-up period. Values are number (percentage) of person years unless stated otherwise

	Health Professionals Follow-up Study (n=39 501)				Nurses' Health Study (n=74 563)			
Characteristics*	Quarter 1	Quarter 2	Quarter 3	Quarter 4	Quarter 1	Quarter 2	Quarter 3	Quarter 4
Mean (SD) age, years	66.1 (11.6)	65.4 (11.8)	65.2 (11.9)	64.7 (11.7)	65.7 (11.2)	64.7 (11.5)	64.3 (11.6)	64.1 (11.6)
White	232 540 (89)	238 259 (91)	238 262 (91)	240 763 (92)	540 359 (97)	546 475 (98)	546 242 (98)	545 722 (98)
Married	175 058 (67)	183 276 (70)	183 278 (70)	177 955 (68)	373 238 (67)	379 187 (68)	37 3451 (67)	356 390 (64)
Mean (SD) BMI	25.1 (3.2)	25.7 (3.3)	26.0 (3.3)	26.5 (3.7)	24.1 (3.8)	24.9 (4.1)	25.4 (4.4)	26.0 (4.8)
Mean (SD) total activity, MET-h/week	32.9 (26.3)	29.9 (24.2)	28.1 (23)	25.3 (22.3)	20.4 (20.6)	17.3 (17)	15.6 (16)	14.0 (15.3)
Mean (SD) alcohol drinking, g/day	13.3 (15.8)	12.0 (13.6)	10.6 (12.8)	8.6 (11.4)	7.7 (11.1)	6.3 (9.4)	5.5 (8.5)	4.6 (7.7)
Mean (SD) AHEI score†	52.8 (10.1)	47.5 (9.5)	45.1 (9.5)	43.5 (9.7)	51.2 (9.5)	47.1 (8.5)	45.1 (8.4)	43.7 (8.4)
Smoking status:								
Never smoking	143 705 (55)	133 530 (51)	130 913 (50)	117 765 (45)	272 965 (49)	262 085 (47)	256 399 (46)	23 3881 (42)
Former smoking	104 512 (40)	112 584 (43)	115 203 (44)	122 999 (47)	228 399 (41)	234 204 (42)	239 678 (43)	250 587 (45)
Current smoking	13 064 (5)	15 709 (6)	15 710 (6)	20 936 (8)	55 707 (10)	61 339 (11)	61 313 (11)	72 392 (13)
Mean (SD) pack years of smoking	9.2 (15.2)	10.6 (16.4)	11.8 (17.6)	14.5 (19.6)	11.1 (18)	11.8 (18.3)	12.9 (19.2)	15.6 (21.1)
Physical examination for screening	138 479 (53)	146 621 (56)	144 004 (55)	138 700 (53)	384 379 (69)	390 340 (70)	384 599 (69)	373 096 (67)
Family history of cancer	91 448 (35)	94 256 (36)	94 257 (36)	94 212 (36)	233 970 (42)	228 627 (41)	228 530 (41)	233 881 (42)
Family history of myocardial infarction	91 448 (35)	91 638 (35)	94 257 (36)	96 829 (37)	133 697 (24)	139 407 (25)	144 921 (26)	144 783 (26)
Family history of diabetes	62 707 (24)	68 074 (26)	70 693 (27)	73 276 (28)	150 409 (27)	156 136 (28)	161 643 (29)	167 058 (30)
Menopause and hormone use:								
Premenopausal	NA	NA	NA	NA	55 707 (10)	61 339 (11)	61 313 (11)	61 254 (11)
Never user, postmenopausal	NA	NA	NA	NA	139 268 (25)	133 831 (24)	133 774 (24)	133 646 (24)
Current user, postmenopausal	NA	NA	NA	NA	133 697 (24)	133 831 (24)	123 200 (23)	122 509 (22)
Past user, postmenopausal	NA	NA	NA	NA	172 692 (31)	178 441 (32)	183 939 (33)	183 763 (33)
Missing	NA	NA	NA	NA	55 707 (10)	50 187 (9)	50 165 (9)	55 686 (10)
Mean (SD) UPF intake, servings/week:								
Total UPF	22.1 (7.5)	32.2 (4.3)	41.3 (5.2)	56.2 (14.2)	20.7 (6.1)	29.1 (3.6)	36.9 (4.4)	49.5 (11.7)
Ultra-processed breads and breakfast foods‡	2.1 (2.1)	3.5 (3.5)	4.9 (4.2)	7.7 (7)	2.1 (2.1)	3.5 (2.8)	4.9 (3.5)	7.0 (5.6)
Fats, condiments, and sauces	4.9 (3.5)	8.4 (4.2)	10.5 (5.6)	16.8 (11.2)	5.6 (3.5)	8.4 (4.2)	10.5 (5.6)	16.8 (10.5)
Packaged sweet snacks and desserts§	4.9 (3.5)	7.7 (4.2)	9.1 (5.6)	11.9 (8.4)	4.2 (2.8)	6.3 (3.5)	7 (4.2)	9.1 (6.3)
Sugar and artificially sweetened beverages	2.8 (2.8)	4.9 (3.5)	6.3 (4.9)	11.2 (10.5)	2.1 (2.1)	4.2 (3.5)	5.6 (4.2)	9.8 (9.1)
Ready-to-eat/heat mixed dishes	2.1 (1.4)	2.1 (1.4)	2.8 (1.4)	2.8 (2.1)	0.7 (0.7)	1.4 (0.7)	1.4 (0.7)	1.4 (0.7)
Meat/poultry/seafood based ready-to-eat products	1.4 (1.4)	2.1 (2.1)	2.8 (2.1)	2.8 (2.8)	1.4 (0.7)	1.4 (1.4)	2.1 (1.4)	2.1 (1.4)
Packaged savory snacks	1.4 (1.4)	1.4 (2.1)	2.1 (2.8)	2.8 (4.9)	1.4 (1.4)	2.1 (2.1)	2.1 (2.8)	3.5 (5.6)
Dairy based desserts	1.4 (1.4)	2.1 (1.4)	2.1 (2.1)	2.1 (2.1)	1.4 (1.4)	1.4 (1.4)	2.1 (1.4)	2.1 (2.1)
Other	0 (0.7)	0.7 (1.4)	0.7 (2.1)	2.1 (4.9)	0 (0.7)	0.7 (1.4)	0.7 (2.1)	2.1 (3.5)
Mean (SD) intake of major non-UPFs: servings/week:								
Whole fruits	14.7 (10.5)	11.9 (7.7)	10.5 (7)	9.1 (6.3)	14 (7.7)	11.9 (6.3)	10.5 (6.3)	9.1 (5.6)
Whole vegetables	30.8 (16.8)	26.6 (13.3)	24.5 (12.6)	22.4 (11.9)	24.5 (11.9)	21.7 (9.8)	20.3 (9.8)	18.2 (9.1)
Whole grains‡	5.6 (6.3)	4.2 (4.9)	3.5 (4.2)	2.8 (4.2)	3.5 (4.2)	2.8 (2.8)	2.1 (2.8)	2.1 (2.1)
Tea and coffee	12.6 (11.2)	14 (11.2)	14.7 (11.2)	16.1 (11.9)	19.6 (12.6)	20.3 (12.6)	21 (12.6)	21.7 (13.3)
Nuts and legumes	7.0 (5.6)	6.3 (4.9)	6.3 (4.9)	5.6 (4.2)	4.2 (2.8)	4.2 (2.1)	3.5 (2.1)	3.5 (2.1)
Red meat	3.5 (2.8)	4.2 (2.8)	4.2 (2.8)	4.2 (2.8)	4.2 (2.8)	4.9 (2.8)	4.9 (2.8)	4.9 (2.8)
Fish	2.8 (2.1)	2.1 (2.1)	2.1 (1.4)	2.1 (1.4)	2.8 (2.1)	2.1 (2.1)	2.1 (2.1)	2.1 (1.4)
Poultry	2.8 (2.1)	2.8 (2.1)	2.8 (1.4)	2.8 (1.4)	3.5 (2.8)	3.5 (2.1)	3.5 (2.1)	3.5 (2.1)

AHEI=Alternative Healthy Eating Index-2010; BMI=body mass index; IQR=interquartile range; MET=metabolic equivalent of task; NA=not applicable; SD=standard deviation.
*All values other than age were directly standardized to age distribution of participants.
†Alcohol was removed from calculation of AHEI score.
‡Ultra-processed whole grains were not counted in UPF intake in primary analysis.
§Major ingredients are not dairy.

beverages; we present these results and those for other selected individual ultra-processed food categories in supplementary table D.

When we examined ultra-processed food intake and AHEI score together (fig 1), we did not observe a consistent association of ultra-processed foods with mortality within each quarter of the AHEI score, whereas AHEI score generally showed an inverse association with mortality within each of the quarters of ultra-processed food consumption.

We found similar results in men and women (supplementary table E). The results of sensitivity analyses are summarized in supplementary table F. The lagged analysis showed similar results to the primary analysis. The associations were attenuated when we stopped updating the information on ultra-processed food intake at a diagnosis of chronic disease, likely owing to the increased intake of ultra-processed foods over time (supplementary figures D and E). Unsurprisingly, including wholegrain products in ultra-processed foods weakened the associations, whereas including distilled alcohol strengthened the associations. Removing pack years of smoking from the multivariable model led to a much stronger positive association, whereas adjusting for the AHEI score attenuated the association toward null.

Table 2 | Hazard ratios and 95% confidence intervals for mortality according to quarters of ultra-processed food (UPF) consumption

	Energy adjusted ultra-processed food consumption—median (IQR) servings/day					
	Quarter 1—3.0 (2.5-3.4)	Quarter 2—4.3 (4.0-4.6)	Quarter 3—5.5 (5.1-5.8)	Quarter 4—7.4 (6.7-8.6)	P for trend	Per difference in medians between quarters 4 and 1
Total mortality						
No of cases	11 862	11 682	12 168	12 481		
Incidence rate per 100 000 person years*	1472	1404	1472	1536		
Model 1†	1	1.06 (1.03 to 1.08)	1.12 (1.09 to 1.15)	1.22 (1.18 to 1.25)	<0.001	1.23 (1.19 to 1.26)
Model 2‡	1	1.04 (1.02 to 1.07)	1.07 (1.04 to 1.10)	1.04 (1.01 to 1.07)	0.005	1.04 (1.01 to 1.07)
Cancer mortality						
No of cases	3427	3260	3476	3394		
Incidence rate per 100 000 person years*	430	402	414	410		
Model 1†	1	1.01 (0.96 to 1.06)	1.09 (1.04 to 1.15)	1.10 (1.05 to 1.16)	<0.001	1.12 (1.07 to 1.17)
Model 2‡	1	1.00 (0.95 to 1.04)	1.04 (0.99 to 1.09)	0.95 (0.91 to 1.00)	0.08	0.96 (0.91 to 1.00)
Cardiovascular mortality						
No of cases	2817	2773	2799	3027		
Incidence rate per 100 000 person years*	348	334	341	370		
Model 1†	1	1.07 (1.01 to 1.12)	1.09 (1.04 to 1.15)	1.28 (1.22 to 1.35)	<0.001	1.29 (1.22 to 1.36)
Model 2‡	1	1.03 (0.98 to 1.09)	1.01 (0.96 to 1.07)	1.05 (0.99 to 1.11)	0.14	1.04 (0.99 to 1.10)
Other mortality						
No of cases	5618	5649	5893	6060		
Incidence rate per 100 000 person years*	694	668	717	757		
Model 1†	1	1.08 (1.04 to 1.12)	1.14 (1.10 to 1.19)	1.25 (1.21 to 1.30)	<0.001	1.40 (1.34 to 1.47)
Model 2‡	1	1.08 (1.04 to 1.12)	1.11 (1.07 to 1.16)	1.09 (1.05 to 1.13)	<0.001	1.12 (1.06 to 1.17)
Respiratory mortality						
No of cases	880	922	1011	1113		
Incidence rate per 100 000 person years*	121	111	118	130		
Model 1†	1	1.13 (1.03 to 1.24)	1.25 (1.14 to 1.37)	1.49 (1.36 to 1.63)	<0.001	1.80 (1.60 to 2.01)
Model 2‡	1	1.05 (0.95 to 1.15)	1.10 (1.01 to 1.21)	1.09 (0.99 to 1.20)	0.06	1.12 (1.00 to 1.27)
Neurodegenerative mortality						
No of cases	1633	1653	1575	1482		
Incidence rate per 100 000 person years*	181	188	204	202		
Model 1†	1	1.10 (1.03 to 1.18)	1.08 (1.00 to 1.15)	1.10 (1.02 to 1.18)	0.03	1.15 (1.05 to 1.26)
Model 2‡	1	1.16 (1.08 to 1.25)	1.14 (1.06 to 1.22)	1.08 (1.01 to 1.17)	0.10	1.09 (0.99 to 1.20)

IQR=interquartile range.
*Multivariable adjusted incidence rate was calculated via several steps: firstly, regression of total UPF intake on full set of covariates in linear regression stratified by cohort and questionnaire cycle to calculate residuals of total UPF intake; secondly, categorization of residuals into quarters; finally, calculation of incidence rate on basis of number of cases and person years across quarters.
†Stratified by age (months), questionnaire cycle (two year interval), and cohort and adjusted for total energy intake.
‡Further adjusted for categorical covariates including race, marital status, physical activity, body mass index, smoking status and pack years, alcohol consumption, physical examination performed for screening purposes, and family history of diabetes mellitus, myocardial infarction, or cancer; for women, also menopausal status and hormone use.

In the stratified analysis by major risk factors, the associations between ultra-processed food intake and all cause mortality seemed to be stronger in participants consuming less alcohol (P for interaction=0.005) and not currently smoking (P for interaction<0.001), but we found no interaction by body mass index or physical activity (supplementary table G). We repeated the primary analysis using percentage of energy to measure ultra-processed food intake and observed similar results (supplementary table H).

Discussion

In two large prospective cohorts with up to 34 years of follow-up, we found that higher consumption of ultra-processed foods was associated with modestly higher all cause mortality. We found no associations for mortality due to cancer or cardiovascular diseases. The associations varied across subgroups of ultra-processed foods, with meat/poultry/seafood based ready-to-eat products consistently showing associations with higher all cause mortality and cause specific mortality. The associations between ultra-processed food consumption and mortality were attenuated after we accounted for overall dietary quality.

Comparison with other studies and possible explanations

Existing evidence suggests a relation between ultra-processed food consumption and mortality. A meta-analysis of prospective cohorts reported that the highest ultra-processed food consumption was associated with higher all cause mortality compared with the lowest consumption (hazard ratio 1.21, 1.13 to 1.30).[23] Two studies were conducted in the US,[24 25] whereas the other six were conducted in Spain,[26-28] France,[29] Italy,[30] and the UK.[31] Unlike our study, which excluded alcohol from ultra-processed foods and carefully controlled for smoking status and pack years, all the above studies included alcohol in ultra-processed foods and adjusted for smoking status (never, former, and current) only. As noted in our sensitivity analysis, pack years of smoking strongly confounded the association—additionally adjusting for smoking pack years remarkably attenuated the

Table 3 | Multivariable hazard ratios and 95% confidence intervals for mortality according to quarters of subgroups of ultra-processed food consumption*

	Energy adjusted ultra-processed food consumption†				P for trend	Per difference in medians between quarters 4 and 1
	Quarter 1	Quarter 2	Quarter 3	Quarter 4		
Total mortality						
Ultra-processed breads and breakfast foods	1	1.05 (1.02 to 1.07)	1.06 (1.03 to 1.09)	1.04 (1.02 to 1.07)	0.01	1.03 (1.01 to 1.06)
Fats, condiments, and sauces	1	1.01 (0.98 to 1.04)	1.03 (1.01 to 1.06)	1.00 (0.98 to 1.03)	0.86	1.00 (0.98 to 1.03)
Packaged sweet snacks and desserts	1	1.02 (0.99 to 1.05)	0.99 (0.97 to 1.02)	0.99 (0.97 to 1.02)	0.17	0.98 (0.96 to 1.01)
Sugar and artificially sweetened beverages	1	1.03 (1.01 to 1.06)	1.06 (1.03 to 1.08)	1.09 (1.07 to 1.12)	<0.001	1.09 (1.06 to 1.12)
Ready-to-eat/heat mixed dishes	1	1.02 (1.00 to 1.05)	1.05 (1.03 to 1.08)	1.02 (0.99 to 1.05)	0.03	1.03 (1.00 to 1.06)
Meat/poultry/seafood based ready-to-eat products	1	1.06 (1.03 to 1.09)	1.10 (1.07 to 1.13)	1.13 (1.10 to 1.16)	<0.001	1.13 (1.10 to 1.16)
Packaged savory snacks	1	1.05 (1.02 to 1.08)	1.05 (1.02 to 1.08)	1.01 (0.99 to 1.04)	0.47	0.99 (0.97 to 1.02)
Dairy based desserts	1	1.06 (1.03 to 1.08)	1.06 (1.03 to 1.09)	1.07 (1.04 to 1.10)	<0.001	1.06 (1.03 to 1.08)
Other	1	1.00 (0.98 to 1.03)	1.07 (1.05 to 1.10)	1.08 (1.05 to 1.11)	<0.001	1.04 (1.03 to 1.06)
Cancer mortality						
Ultra-processed breads and breakfast foods	1	1.03 (0.98 to 1.08)	1.05 (1.00 to 1.10)	1.05 (1.00 to 1.10)	0.08	1.04 (0.99 to 1.09)
Fats, condiments, and sauces	1	1.00 (0.96 to 1.05)	1.03 (0.98 to 1.08)	0.99 (0.94 to 1.04)	0.62	0.99 (0.94 to 1.04)
Packaged sweet snacks and desserts	1	1.01 (0.97 to 1.06)	1.00 (0.95 to 1.05)	0.95 (0.90 to 0.99)	0.01	0.94 (0.89 to 0.98)
Sugar and artificially sweetened beverages	1	1.00 (0.95 to 1.04)	1.03 (0.98 to 1.08)	0.99 (0.95 to 1.05)	0.92	1.00 (0.95 to 1.05)
Ready-to-eat/heat mixed dishes	1	1.02 (0.98 to 1.07)	1.04 (0.99 to 1.09)	0.99 (0.94 to 1.04)	0.85	1.00 (0.95 to 1.05)
Meat/poultry/seafood based ready-to-eat products	1	1.02 (0.97 to 1.07)	1.04 (0.99 to 1.10)	1.06 (1.00 to 1.11)	0.02	1.06 (1.01 to 1.11)
Packaged savory snacks	1	1.03 (0.98 to 1.08)	1.03 (0.98 to 1.09)	1.01 (0.97 to 1.06)	0.99	1.00 (0.96 to 1.05)
Dairy based desserts	1	1.04 (0.99 to 1.09)	1.03 (0.98 to 1.08)	1.04 (0.99 to 1.09)	0.16	1.03 (0.99 to 1.08)
Other	1	0.96 (0.91 to 1.00)	1.07 (1.02 to 1.13)	1.02 (0.97 to 1.07)	0.02	1.03 (1.01 to 1.07)
Cardiovascular mortality						
Ultra-processed breads and breakfast foods	1	1.04 (0.99 to 1.10)	1.05 (1.00 to 1.11)	1.02 (0.97 to 1.08)	0.62	1.01 (0.96 to 1.07)
Fats, condiments, and sauces	1	1.01 (0.96 to 1.07)	1.01 (0.96 to 1.06)	1.02 (0.97 to 1.08)	0.33	1.03 (0.97 to 1.08)
Packaged sweet snacks and desserts	1	0.99 (0.94 to 1.05)	0.96 (0.91 to 1.01)	0.94 (0.89 to 0.99)	0.005	0.93 (0.88 to 0.98)
Sugar and artificially sweetened beverages	1	1.03 (0.98 to 1.09)	1.05 (1.00 to 1.11)	1.13 (1.07 to 1.19)	<0.001	1.13 (1.06 to 1.19)
Ready-to-eat/heat mixed dishes	1	0.99 (0.94 to 1.04)	1.01 (0.96 to 1.07)	0.96 (0.91 to 1.02)	0.32	0.97 (0.91 to 1.03)
Meat/poultry/seafood based ready-to-eat products	1	1.07 (1.01 to 1.13)	1.14 (1.08 to 1.20)	1.15 (1.09 to 1.21)	<0.001	1.14 (1.09 to 1.21)
Packaged savory snacks	1	1.08 (1.03 to 1.14)	1.09 (1.03 to 1.15)	1.02 (0.97 to 1.08)	0.72	0.99 (0.94 to 1.04)
Dairy based desserts	1	1.04 (0.98 to 1.10)	1.01 (0.96 to 1.07)	0.97 (0.92 to 1.02)	0.07	0.95 (0.91 to 1.00)
Other	1	1.04 (0.98 to 1.09)	1.12 (1.06 to 1.19)	1.16 (1.09 to 1.22)	<0.001	1.07 (1.04 to 1.09)
Other mortality						
Ultra-processed breads and breakfast foods	1	1.05 (1.01 to 1.09)	1.07 (1.03 to 1.11)	1.04 (1.01 to 1.08)	0.09	1.03 (0.99 to 1.07)
Fats, condiments, and sauces	1	1.01 (0.98 to 1.05)	1.05 (1.01 to 1.09)	1.00 (0.97 to 1.04)	0.99	1.00 (0.96 to 1.04)
Packaged sweet snacks and desserts	1	1.04 (1.00 to 1.08)	1.00 (0.97 to 1.04)	1.05 (1.01 to 1.09)	0.04	1.04 (1.00 to 1.08)
Sugar and artificially sweetened beverages	1	1.05 (1.01 to 1.09)	1.07 (1.03 to 1.11)	1.14 (1.10 to 1.19)	<0.001	1.14 (1.09 to 1.18)
Ready-to-eat/heat mixed dishes	1	1.04 (1.00 to 1.08)	1.08 (1.04 to 1.12)	1.07 (1.03 to 1.11)	<0.001	1.09 (1.04 to 1.14)
Meat/poultry/seafood based ready-to-eat products	1	1.08 (1.04 to 1.13)	1.11 (1.07 to 1.16)	1.17 (1.13 to 1.21)	<0.001	1.17 (1.13 to 1.21)
Packaged savory snacks	1	1.05 (1.01 to 1.09)	1.04 (1.01 to 1.08)	1.01 (0.97 to 1.04)	0.44	0.99 (0.95 to 1.02)
Dairy based desserts	1	1.07 (1.03 to 1.12)	1.10 (1.06 to 1.14)	1.15 (1.11 to 1.19)	<0.001	1.13 (1.09 to 1.17)
Other	1	1.05 (1.01 to 1.09)	1.07 (1.03 to 1.11)	1.09 (1.05 to 1.13)	<0.001	1.04 (1.02 to 1.06)
Respiratory mortality						
Ultra-processed breads and breakfast foods	1	1.11 (1.01 to 1.22)	1.11 (1.01 to 1.22)	1.12 (1.02 to 1.22)	0.03	1.11 (1.01 to 1.21)
Fats, condiments, and sauces	1	0.96 (0.87 to 1.05)	1.08 (0.99 to 1.18)	1.02 (0.94 to 1.12)	0.39	1.04 (0.95 to 1.14)
Packaged sweet snacks and desserts	1	1.03 (0.93 to 1.13)	0.95 (0.87 to 1.05)	0.99 (0.91 to 1.09)	0.70	0.98 (0.90 to 1.07)
Sugar and artificially sweetened beverages	1	0.97 (0.89 to 1.06)	1.01 (0.92 to 1.10)	1.00 (0.91 to 1.10)	0.86	1.01 (0.91 to 1.11)
Ready-to-eat/heat mixed dishes	1	1.08 (0.99 to 1.18)	1.15 (1.05 to 1.25)	1.13 (1.03 to 1.24)	0.003	1.17 (1.05 to 1.29)
Meat/poultry/seafood based ready-to-eat products	1	1.15 (1.04 to 1.28)	1.26 (1.14 to 1.39)	1.43 (1.30 to 1.57)	<0.001	1.42 (1.30 to 1.56)
Packaged savory snacks	1	1.03 (0.94 to 1.13)	1.04 (0.95 to 1.14)	1.03 (0.94 to 1.12)	0.71	1.02 (0.93 to 1.11)
Dairy based desserts	1	1.09 (1.00 to 1.20)	1.07 (0.98 to 1.18)	1.16 (1.06 to 1.27)	0.003	1.14 (1.04 to 1.24)
Other	1	1.03 (0.94 to 1.13)	0.96 (0.87 to 1.06)	1.01 (0.92 to 1.11)	0.19	1.03 (0.98 to 1.08)
Neurodegenerative mortality						
Ultra-processed breads and breakfast foods	1	1.13 (1.05 to 1.21)	1.12 (1.04 to 1.20)	0.99 (0.93 to 1.06)	0.27	0.96 (0.89 to 1.03)
Fats, condiments, and sauces	1	1.03 (0.96 to 1.11)	1.09 (1.01 to 1.17)	0.97 (0.90 to 1.04)	0.33	0.96 (0.89 to 1.04)
Packaged sweet snacks and desserts	1	1.17 (1.08 to 1.26)	1.15 (1.06 to 1.24)	1.21 (1.13 to 1.30)	<0.001	1.18 (1.09 to 1.26)
Sugar and artificially sweetened beverages	1	1.09 (1.02 to 1.16)	1.08 (1.01 to 1.16)	1.15 (1.07 to 1.25)	0.002	1.14 (1.05 to 1.23)
Ready-to-eat/heat mixed dishes	1	1.09 (1.02 to 1.16)	1.06 (0.98 to 1.13)	1.03 (0.95 to 1.11)	0.58	1.02 (0.94 to 1.11)
Meat/poultry/seafood based ready-to-eat products	1	1.04 (0.97 to 1.12)	1.05 (0.97 to 1.12)	1.02 (0.95 to 1.10)	0.57	1.02 (0.95 to 1.10)
Packaged savory snacks	1	1.11 (1.03 to 1.20)	1.10 (1.02 to 1.18)	1.10 (1.03 to 1.18)	0.05	1.07 (1.00 to 1.15)
Dairy based desserts	1	1.17 (1.08 to 1.26)	1.36 (1.26 to 1.46)	1.45 (1.35 to 1.56)	<0.001	1.41 (1.32 to 1.50)
Other	1	1.04 (0.97 to 1.12)	1.08 (1.00 to 1.16)	1.04 (0.96 to 1.13)	0.50	1.01 (0.98 to 1.05)

*Results from Cox proportional hazards model stratified by age (months), questionnaire cycle (two year interval), and cohort and adjusted for total energy intake, race, marital status, physical activity, body mass index, smoking status and pack years, alcohol consumption, physical examination performed for screening purposes, and family history of diabetes mellitus, myocardial infarction, or cancer; for women, also menopausal status and hormone use.
†Quarter specific medians (servings/day) for each subgroup: ultra-processed breads and breakfast foods 0.1, 0.3, 0.6, 1.3; fats, condiments, and sauces 0.5, 1.0, 1.5, 2.5; packaged sweet snacks and desserts 0.4, 0,7, 1.1, 1.8; sugar sweetened and artificially sweetened beverages 0.09, 0.4, 0.8, 1.7; ready-to-eat/heat mixed dishes 0.07, 0.1, 0.2, 0.4; meat/poultry/seafood based ready-to-eat products 0.06, 0.2, 0.3, 0.5; packaged savory snacks 0.04, 0.1, 0.3, 0.6; dairy based desserts, 0.06, 0.1, 0.3, 0.5; other 0.009, 0.01, 0.01, 0.4.

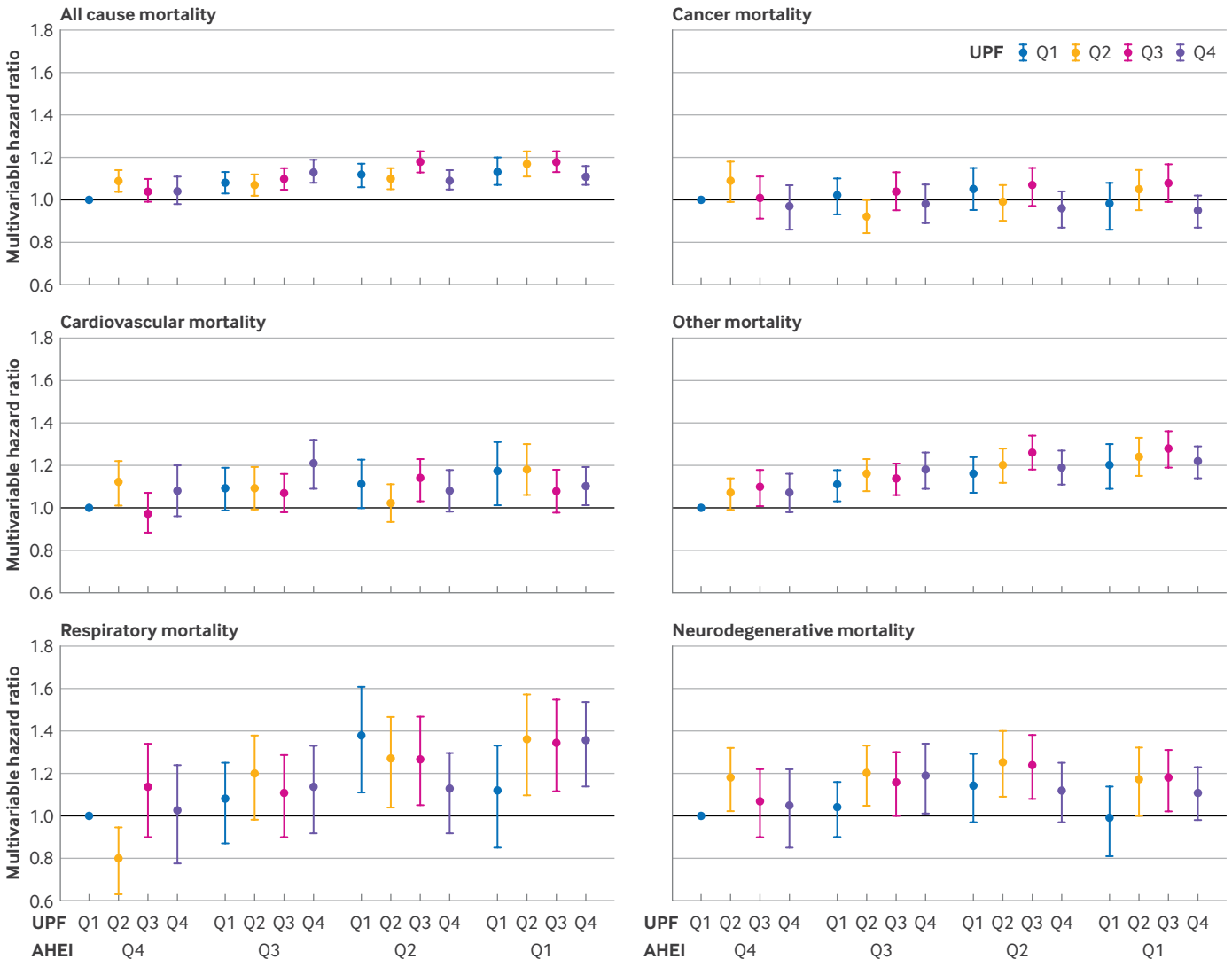

Fig 1 | Joint analysis for mortality according to quarters of ultra-processed food (UPF) consumption and quarters of Alternative Healthy Eating Index-2010 (AHEI) score. Alcohol was removed from calculation of AHEI score. Each participant was categorized according to their quarter of UPF intake and their quarter of AHEI score, resulting in 16 distinct groups. Using this combined variable as exposure, its association with mortality outcomes was assessed, with reference group being participants in highest quarter of AHEI score (Q4) and lowest quarter of UPF intake (Q1). Results were from multivariable Cox proportional hazards model stratified by age (months), questionnaire cycle (two year interval), and cohort and adjusted for total energy intake, race, marital status, physical activity, body mass index, smoking status and pack years, alcohol consumption, physical examination performed for screening purposes, and family history of diabetes mellitus, myocardial infarction, or cancer; for women, also menopausal status and hormone use. Markers denote point estimates of hazard ratios and error bars indicate 95% confidence intervals

hazard ratios toward the null. That may partly explain why the associations found in our study were weaker than those in previous studies. Another possible reason could be tighter control for socioeconomic status because our participants were all health professionals and had similar levels of education.

The evidence on mortality due to cancer is relatively sparse. Consistently, the Moli-sani Study did not observe a statistically significant association but reported a positive association with other mortality.[30] An analysis of three cohorts including the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO), NHANES (1999-2018), and UK Biobank reported null findings for mortality due to cancer in the PLCO and NHANES (1999-2018).[32] By contrast, the UK Biobank study found that every 10% increment in ultra-processed food consumption was associated with a 6% higher cancer mortality.[33] Diet was assessed in the UK Biobank through multiple 24 hour recalls between 2009 and 2012, and 40% of the participants had only one 24 hour recall, thus limiting the ability to capture long term dietary intake.

In agreement with our study, the Prospective Urban and Rural Epidemiology study from 25 high income, middle income, and low income countries in America, Europe, Africa, and Asia observed a null association with mortality due to cardiovascular diseases but a positive association with non-cardiovascular disease

mortality.[34] Our findings on the relation between ultra-processed foods and mortality due to cardiovascular diseases are inconsistent with previous evidence from Europe but consistent with the null finding in the US NHANES III (1988-94).[24 25 30] Moreover, a much stronger positive association was reported in the UK Biobank (1.28, 1.13 to 1.45) compared with the two US cohorts (1.12, 1.05 to 1.09; 1.11, 0.92 to 1.34).[32] In addition to the methodological differences mentioned above, different study populations, ultra-processed food compositions, and eating patterns may also contribute. Ultra-processed food intake in our two US cohorts is mainly contributed by "sauces, spreads, and condiments" and "sweet snacks and desserts," which together accounted for nearly 50% (supplementary figure B), but neither of the two subgroups was associated with increased mortality due to cardiovascular diseases. On the other hand, compelling evidence shows that nuts and (dark) chocolate, common constituents of "sweet snacks and desserts," are inversely associated with cardiovascular diseases.[35 36] We observed that dark chocolate in the subgroup "packaged sweet snacks and desserts" was associated with decreased mortality (supplementary table D). Therefore, the diverse array of constituents contained in ultra-processed foods with heterogeneous health effects may have contributed to the discrepant findings. Our findings suggest that meat/poultry/seafood based ready-to-eat products and sugar sweetened and artificially sweetened beverages are major factors contributing to the harmful influence of ultra-processed foods on mortality, which is in accordance with previous studies.[13 37-39]

Few studies have investigated the relation with cause specific mortality other than that due to cancer and cardiovascular diseases. We found that ultra-processed food intake was associated with higher neurodegenerative mortality. Increasing evidence suggests that ultra-processed food is linked to higher risk of central nervous system demyelination (a precursor of multiple sclerosis),[40] lower cognitive function,[41] and dementia.[42] Studies have shown that a diet rich in ultra-processed foods may drive neuroinflammation and impairment of the blood-brain barrier, leading to neurodegeneration.[43 44] Of note, among ultra-processed food subgroups, diary based desserts showed the strongest association with neurodegenerative mortality. Earlier finding from the HPFS and NHS cohorts showed that intake of sherbet/frozen yogurt was associated with an increased risk of Parkinson's disease.[45] Furthermore, we found a positive association between ultra-processed food intake measured by percentage of energy and respiratory mortality. Emerging evidence suggests that higher ultra-processed food intake is associated with increased risk of respiratory multimorbidity.[46] The increased respiratory mortality associated with processed red meat may be partly due to heme iron and nitrate/nitrite.[47]

An important question not answered by previous studies is whether and how food processing level and nutritional quality jointly influence health. We observed that in the joint analysis, the AHEI score but not ultra-processed food intake showed a consistent association with mortality and that further adjustment for the AHEI score attenuated the association of ultra-processed food intake with mortality. Although including AHEI in the multivariable model for ultra-processed food may represent an overadjustment because common foods are included in both the AHEI and ultra-processed food, our data together suggest that dietary quality has a predominant influence on long term health, whereas the additional effect of food processing is likely to be limited. Furthermore, foods may have dual attributes according to their processing level and nutritional quality, and these two features may have quantitatively and even qualitatively different effects on health. Another added value of our study is the exclusion of wholegrain products that fall in the ultra-processed foods from the primary exposure, based on the well established health benefits associated with whole grains. By taking this approach, we aim to rectify the potential misperception that all ultra-processed food products should be universally restricted and to avoid oversimplification when formulating dietary recommendations.

Besides neglecting overall nutritional quality, the ultra-processed food classification system has other limitations. The Nova classification is based on broad categories that do not capture the full complexity of food processing,[48] leading to potential misclassification. Further work is needed to improve the assessment and categorization of ultra-processed foods. On the other hand, dietary guidelines should provide clear and sound food selections that are available, actionable, attainable, and affordable for the largest proportion of the population. Thus, careful deliberation is necessary when considering incorporation of ultra-processed foods into dietary guidelines.[49 50] Again, on the basis of our data, limiting total ultra-processed food consumption may not have a substantial influence on premature death, whereas reducing consumption of certain ultra-processed food subgroups (for example, processed meat) can be beneficial.

We note that mortality is a more complicated endpoint than disease incidence and is also influenced by several factors including early detection, treatment, and individuals' overall health status. The findings for mortality should not be regarded as synonymous with those pertaining to disease incidence but rather considered as more comprehensive assessment of the health impact of risk factors.

Strengths and limitations of study

The strengths of the study include the prospective study design, large sample size, long follow-up, and detailed, validated, and repeated measurements. In addition, we rigorously controlled for confounding, did thorough sensitivity analyses, explored major specific causes of mortality, and examined individual ultra-processed food subgroups. Several limitations should also be noted. Firstly, we cannot rule out unmeasured and residual confounding due to the nature of the

observational study. Secondly, our participants are health professionals and predominantly non-Hispanic white, limiting the generalizability of our findings. Thirdly, as the food frequency questionnaires collected intake of only a limited number of pre-defined items representing the primary source of energy and nutrients in the US population and were not designed to classify foods by processing level, they may not capture the full spectrum of ultra-processed foods. Although the food frequency questionnaires used in our cohorts have been validated for foods and nutrients, they were not specifically validated for ultra-processed foods. Moreover, we classified ultra-processed foods by using the same algorithm throughout follow-up that did not account for changes in the grade of food processing over time. These factors may have introduced non-differential misclassification, likely biasing our results toward the null.

Conclusions

Higher ultra-processed food intake was associated with slightly increased all cause mortality. The mortality associations for ultra-processed food consumption were more modest than those for dietary quality and varied across ultra-processed food subgroups, with meat/poultry/seafood based ready-to-eat products generally showing the strongest and most consistent associations with mortality. The findings provide support for limiting consumption of certain types of ultra-processed food for long term health. Future studies are warranted to improve the classification of ultra-processed foods and confirm our findings in other populations.

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Contributors: ZF did the statistical analysis and drafted the manuscript. SLR and NK made a substantial contribution to the concept of the article. DH, WK, CHL, WCW, and ELG were involved in the acquisition and interpretation of data. MS was responsible for the study design. All authors 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. MS is the guarantor.

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Competing interests: All authors have completed the ICMJE uniform disclosure form at https://www.icmje.org/disclosure-of-interest/ and declare: support from the National Institutes of Health for the submitted work; NK received a consulting fee from the Pan American Health Organization for three months on the topic of nutrition disclosure initiatives and nutrient profiling models; no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval: The Nurses' Health Study I and the Health Professionals Follow-up Study were approved by the Institutional Review Board at the Brigham and Women's Hospital, the Harvard T.H. Chan School of Public Health (IRB protocol number: 1999-P-011114 and 10162). The completion of the self-administered questionnaire was considered to imply informed consent.

Data sharing: Data can be shared through mechanisms detailed at https://www.nurseshealthstudy.org and https://www.hsph.harvard.edu/hpfs/.

Transparency: The manuscript's guarantor affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Dissemination to participants and related patient and public communities: The research findings are disseminated to participants through periodic newsletters and study websites at https://www.nurseshealthstudy.org and https://www.hsph.harvard.edu/hpfs/. The manuscript will be disseminated to the general public through press releases.

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1 Monteiro CA, Cannon G, Levy RB, et al. Ultra-processed foods: what they are and how to identify them. *Public Health Nutr* 2019;22:936-41. doi:10.1017/S1368980018003762

2 Monteiro CA, Moubarac JC, Cannon G, Ng SW, Popkin B. Ultra-processed products are becoming dominant in the global food system. *Obes Rev* 2013;14(Suppl 2):21-8. doi:10.1111/obr.12107

3 Juul F, Parekh N, Martinez-Steele E, Monteiro CA, Chang VW. Ultra-processed food consumption among US adults from 2001 to 2018. *Am J Clin Nutr* 2022;115:211-21. doi:10.1093/ajcn/nqab305

4 Wang L, Martínez Steele E, Du M, et al. Trends in Consumption of Ultraprocessed Foods Among US Youths Aged 2-19 Years, 1999-2018. *JAMA* 2021;326:519-30. doi:10.1001/jama.2021.10238

5 Poti JM, Mendez MA, Ng SW, Popkin BM. Is the degree of food processing and convenience linked with the nutritional quality of foods purchased by US households?*Am J Clin Nutr* 2015;101:1251-62. doi:10.3945/ajcn.114.100925

6 Monteiro CA, Cannon G, Moubarac JC, Levy RB, Louzada MLC, Jaime PC. The UN Decade of Nutrition, the NOVA food classification and the trouble with ultra-processing. *Public Health Nutr* 2018;21:5-17. doi:10.1017/S1368980017000234

7 Zani F, Blagih J, Gruber T, et al. The dietary sweetener sucralose is a negative modulator of T cell-mediated responses. *Nature* 2023;615:705-11. doi:10.1038/s41586-023-05801-6
8 Sellem L, Srour B, Javaux G, et al. Food additive emulsifiers and risk of cardiovascular disease in the NutriNet-Santé cohort: prospective cohort study. *BMJ* 2023;382:e076058. doi:10.1136/bmj-2023-076058
9 Buckley JP, Kim H, Wong E, Rebholz CM. Ultra-processed food consumption and exposure to phthalates and bisphenols in the US National Health and Nutrition Examination Survey, 2013-2014. *Environ Int* 2019;131:105057. doi:10.1016/j.envint.2019.105057
10 Martínez Steele E, Monteiro CA. Association between Dietary Share of Ultra-Processed Foods and Urinary Concentrations of Phytoestrogens in the US. *Nutrients* 2017;9:209. doi:10.3390/nu9030209
11 Srour B, Fezeu LK, Kesse-Guyot E, et al. Ultra-processed food intake and risk of cardiovascular disease: prospective cohort study (NutriNet-Santé). *BMJ* 2019;365:l1451. doi:10.1136/bmj.l1451
12 Beslay M, Srour B, Méjean C, et al. Ultra-processed food intake in association with BMI change and risk of overweight and obesity: A prospective analysis of the French NutriNet-Santé cohort. *PLoS Med* 2020;17:e1003256. doi:10.1371/journal.pmed.1003256
13 Wang L, Du M, Wang K, et al. Association of ultra-processed food consumption with colorectal cancer risk among men and women: results from three prospective US cohort studies. *BMJ* 2022;378:e068921. doi:10.1136/bmj-2021-068921
14 Chen Z, Khandpur N, Desjardins C, et al. Ultra-Processed Food Consumption and Risk of Type 2 Diabetes: Three Large Prospective U.S. Cohort Studies. *Diabetes Care* 2023;46:1335-44. doi:10.2337/dc22-1993
15 Chen X, Zhang Z, Yang H, et al. Consumption of ultra-processed foods and health outcomes: a systematic review of epidemiological studies. *Nutr J* 2020;19:86. doi:10.1186/s12937-020-00604-1
16 Rimm EB, Giovannucci EL, Stampfer MJ, Colditz GA, Litin LB, Willett WC. Reproducibility and validity of an expanded self-administered semiquantitative food frequency questionnaire among male health professionals. *Am J Epidemiol* 1992;135:1114-26, discussion 1127-36. doi:10.1093/oxfordjournals.aje.a116211
17 Khandpur N, Rossato S, Drouin-Chartier JP, et al. Categorising ultra-processed foods in large-scale cohort studies: evidence from the Nurses' Health Studies, the Health Professionals Follow-up Study, and the Growing Up Today Study. *J Nutr Sci* 2021;10:e77. doi:10.1017/jns.2021.72
18 Aune D, Keum N, Giovannucci E, et al. Whole grain consumption and risk of cardiovascular disease, cancer, and all cause and cause specific mortality: systematic review and dose-response meta-analysis of prospective studies. *BMJ* 2016;353:i2716. doi:10.1136/bmj.i2716
19 Willett W. *Nutritional Epidemiology.* Oxford University Press, 2012. doi:10.1093/acprof:oso/9780199754038.001.0001
20 Chasan-Taber S, Rimm EB, Stampfer MJ, et al. Reproducibility and validity of a self-administered physical activity questionnaire for male health professionals. *Epidemiology* 1996;7:81-6. doi:10.1097/00001648-199601000-00014
21 Fung TT, McCullough ML, Newby PK, et al. Diet-quality scores and plasma concentrations of markers of inflammation and endothelial dysfunction. *Am J Clin Nutr* 2005;82:163-73. doi:10.1093/ajcn/82.1.163
22 Gauthier J, Wu QV, Gooley TA. Cubic splines to model relationships between continuous variables and outcomes: a guide for clinicians. *Bone Marrow Transplant* 2020;55:675-80. doi:10.1038/s41409-019-0679-x
23 Suksatan W, Moradi S, Naeini F, et al. Ultra-Processed Food Consumption and Adult Mortality Risk: A Systematic Review and Dose-Response Meta-Analysis of 207,291 Participants. *Nutrients* 2021;14:174. doi:10.3390/nu14010174
24 Kim H, Hu EA, Rebholz CM. Ultra-processed food intake and mortality in the USA: results from the Third National Health and Nutrition Examination Survey (NHANES III, 1988-1994). *Public Health Nutr* 2019;22:1777-85. doi:10.1017/S1368980018003890
25 Zhong GC, Gu HT, Peng Y, et al. Association of ultra-processed food consumption with cardiovascular mortality in the US population: long-term results from a large prospective multicenter study. *Int J Behav Nutr Phys Act* 2021;18:21. doi:10.1186/s12966-021-01081-3
26 Rico-Campà A, Martínez-González MA, Alvarez-Alvarez I, et al. Association between consumption of ultra-processed foods and all cause mortality: SUN prospective cohort study. *BMJ* 2019;365:l1949. doi:10.1136/bmj.l1949
27 Blanco-Rojo R, Sandoval-Insausti H, López-Garcia E, et al. Consumption of Ultra-Processed Foods and Mortality: A National Prospective Cohort in Spain. *Mayo Clin Proc* 2019;94:2178-88. doi:10.1016/j.mayocp.2019.03.035
28 Romero Ferreiro C, Martín-Arriscado Arroba C, Cancelas Navia P, Lora Pablos D, Gómez de la Cámara A. Ultra-processed food intake and all-cause mortality: DRECE cohort study. *Public Health Nutr* 2021;25:1-10.
29 Schnabel L, Kesse-Guyot E, Allès B, et al. Association Between Ultraprocessed Food Consumption and Risk of Mortality Among Middle-aged Adults in France. *JAMA Intern Med* 2019;179:490-8. doi:10.1001/jamainternmed.2018.7289
30 Bonaccio M, Di Castelnuovo A, Costanzo S, et al. Ultra-processed food consumption is associated with increased risk of all-cause and cardiovascular mortality in the Moli-sani Study. *Am J Clin Nutr* 2021;113:446-55. doi:10.1093/ajcn/nqaa299
31 Chen X, Chu J, Hu W, et al. Associations of ultra-processed food consumption with cardiovascular disease and all-cause mortality: UK Biobank. *Eur J Public Health* 2022;32:779-85. doi:10.1093/eurpub/ckac104
32 Zhao Y, Chen W, Li J, et al. Ultra-Processed Food Consumption and Mortality: Three Cohort Studies in the United States and United Kingdom. *Am J Prev Med* 2024;66:315-23. doi:10.1016/j.amepre.2023.09.005
33 Chang K, Gunter MJ, Rauber F, et al. Ultra-processed food consumption, cancer risk and cancer mortality: a large-scale prospective analysis within the UK Biobank. *EClinicalMedicine* 2023;56:101840. doi:10.1016/j.eclinm.2023.101840
34 Dehghan M, Mente A, Rangarajan S, et al, Prospective Urban Rural Epidemiology (PURE) study investigators. Ultra-processed foods and mortality: analysis from the Prospective Urban and Rural Epidemiology study. *Am J Clin Nutr* 2023;117:55-63. doi:10.1016/j.ajcnut.2022.10.014
35 Guasch-Ferré M, Liu X, Malik VS, et al. Nut Consumption and Risk of Cardiovascular Disease. *J Am Coll Cardiol* 2017;70:2519-32. doi:10.1016/j.jacc.2017.09.035
36 Morze J, Schwedhelm C, Bencic A, et al. Chocolate and risk of chronic disease: a systematic review and dose-response meta-analysis. *Eur J Nutr* 2020;59:389-97. doi:10.1007/s00394-019-01914-9
37 Du S, Kim H, Crews DC, White K, Rebholz CM. Association Between Ultraprocessed Food Consumption and Risk of Incident CKD: A Prospective Cohort Study. *Am J Kidney Dis* 2022;80:589-598.e1. doi:10.1053/j.ajkd.2022.03.016
38 Canhada SL, Vigo Á, Levy R, et al. Association between ultra-processed food consumption and the incidence of type 2 diabetes: the ELSA-Brasil cohort. *Diabetol Metab Syndr* 2023;15:233. doi:10.1186/s13098-023-01162-2
39 Cordova R, Viallon V, Fontvieille E, et al. Consumption of ultra-processed foods and risk of multimorbidity of cancer and cardiometabolic diseases: a multinational cohort study. *Lancet Reg Health Eur* 2023;35:100771. doi:10.1016/j.lanepe.2023.100771
40 Mannino A, Daly A, Dunlop E, et al, Ausimmune Investigator Group. Higher consumption of ultra-processed foods and increased likelihood of central nervous system demyelination in a case-control study of Australian adults. *Eur J Clin Nutr* 2023;77:611-4. doi:10.1038/s41430-023-01271-1
41 R Cardoso B, Machado P, Steele EM. Association between ultra-processed food consumption and cognitive performance in US older adults: a cross-sectional analysis of the NHANES 2011-2014. *Eur J Nutr* 2022;61:3975-85. doi:10.1007/s00394-022-02911-1
42 Li H, Li S, Yang H, et al. Association of Ultraprocessed Food Consumption With Risk of Dementia: A Prospective Cohort Study. *Neurology* 2022;99:e1056-66. doi:10.1212/WNL.0000000000200871
43 Więckowska-Gacek A, Mietelska-Porowska A, Wydrych M, Wojda U. Western diet as a trigger of Alzheimer's disease: From metabolic syndrome and systemic inflammation to neuroinflammation and neurodegeneration. *Ageing Res Rev* 2021;70:101397. doi:10.1016/j.arr.2021.101397
44 Martínez Leo EE, Segura Campos MR. Effect of ultra-processed diet on gut microbiota and thus its role in neurodegenerative diseases. *Nutrition* 2020;71:110609. doi:10.1016/j.nut.2019.110609
45 Hughes KC, Gao X, Kim IY, et al. Intake of dairy foods and risk of Parkinson disease. *Neurology* 2017;89:46-52. doi:10.1212/WNL.0000000000004057
46 Li H, Li S, Yang H, et al. Association of Ultra-Processed Food Intake with Cardiovascular and Respiratory Disease Multimorbidity: A Prospective Cohort Study. *Mol Nutr Food Res* 2023;67:e2200628. doi:10.1002/mnfr.202200628
47 Etemadi A, Sinha R, Ward MH, et al. Mortality from different causes associated with meat, heme iron, nitrates, and nitrites in the NIH-AARP Diet and Health Study: population based cohort study. *BMJ* 2017;357:j1957. doi:10.1136/bmj.j1957
48 Petrus RR, do Amaral Sobral PJ, Tadini CC, et al. The NOVA classification system: A critical perspective in food science. *Trends Food Sci Technol* 2021;116:603-8doi:10.1016/j.tifs.2021.08.010.
49 Vadiveloo MK, Gardner CD. Not All Ultra-Processed Foods Are Created Equal: A Case for Advancing Research and Policy That Balances Health and Nutrition Security. *Diabetes Care* 2023;46:1327-9. doi:10.2337/dci23-0018
50 Hess JM, Comeau ME, Casperson S, et al. Dietary Guidelines Meet NOVA: Developing a Menu for A Healthy Dietary Pattern Using Ultra-Processed Foods. *J Nutr* 2023;153:2472-81. doi:10.1016/j.tjnut.2023.06.028

Web appendix: Supplementary materials