Association of Ultra-processed Food Consumption With Cardiovascular Mortality in the US Population: Long-term Results From a Large Prospective Multicenter Study

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Abstract

Background

Ultra-processed foods have now become dominant in the global food system. Whether their consumption is associated with cardiovascular mortality remains controversial. Moreover, data on ultra-processed foods and cardiovascular outcomes are scarce in the US population. We aimed to examine the association of ultra-processed food consumption with cardiovascular mortality in a US population.

Methods

A population-based cohort of 91891 participants was identified from the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial. Dietary data were collected through a validated 137-item food frequency questionnaire. Ultra-processed foods were defined by the NOVA classification. Cox regression was used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) for cardiovascular mortality. Restricted cubic spline regression was used to test nonlinearity. Subgroup analyses were conducted to identify the potential effect modifiers.

Results

After an average follow-up of 13.5 years (1236049.2 person-years), 5490 cardiovascular deaths were documented, including 3985 heart disease deaths and 1126 cerebrovascular deaths. In the fully adjusted model, participants in the highest *vs.* the lowest quintiles of ultra-processed food consumption had higher risks of death from cardiovascular disease ($HR_{quintile\ 5\ vs.\ 1}$, 1.52; 95% CI, 1.39–1.67) and heart disease ($HR_{quintile\ 5\ vs.\ 1}$, 1.70; 95% CI, 1.52–1.89) but not cerebrovascular disease ($HR_{quintile\ 5\ vs.\ 1}$, 1.00; 95% CI, 0.80–1.23). A nonlinear dose–response pattern was observed for overall cardiovascular and heart disease mortality (all $P_{nonlinearity}<0.05$), with a threshold effect observed at ultra-processed food consumption of 2.5 servings/day and 2.4 servings/day, respectively; below the thresholds, no significant associations were observed for these two outcomes. Subgroup analyses showed that the increased risks of mortality from ultra-processed foods were significantly higher in women than in men (all $P_{interaction}<0.05$).

Conclusions

High consumption of ultra-processed foods is associated with increased risks of overall cardiovascular and heart disease mortality. These harmful associations may be more pronounced in women. Our findings are needed to be confirmed in other populations and settings.

Background

Cardiovascular disease (CVD) is the most common cause of death in the US and worldwide, with an estimated 0.84 million and 17.90 million cardiovascular deaths in 2016, respectively [1, 2]. The American Heart Association has released the 2030 Impact Goal for improving cardiovascular health and preventing CVD, and one of approaches achieving this goal may be through targeting modifiable CVD risk factors [3]. It is now well known that diet can directly and strongly affect the occurrence and development of CVD [4, 5].

Ultra-processed foods are industrial formulations mostly or entirely made from substances derived from additives and foods, with little or even no whole foods [6]. They are usually ready-to-eat, highly affordable, hyper-palatable, and energy-dense, and are marketed intensively and packaged attractively. Ultra-processed foods have now become dominant in the global food system [7]. In the US, the percentage of energy from ultra-processed foods has reached as high as 58.5% in the period 2007–2012 [8].

Several observational studies have showed that higher consumption of ultra-processed foods is associated with higher incidences of coronary heart and cerebrovascular diseases [9] as well as CVD risk factors (hypertension, type 2 diabetes, and obesity) [10–12]. However, whether ultra-processed food consumption is a predictor of cardiovascular mortality remains controversial. Specifically, modelling studies showed that decreasing consumption of ultra-processed foods would lead to a significant reduction in cardiovascular mortality [13, 14], whereas observational studies on this subject showed a null association [15, 16]. Importantly, these two observational studies observed limited cardiovascular deaths, so a significant association between ultra-processed food consumption and cardiovascular mortality could have been missed due to insufficient power. Additionally, to our knowledge, the above-mentioned study (ref.16) is the only one investigating the association of ultra-processed food consumption with cardiovascular outcomes in the US population to date.

Considering the need for data from large studies on this topic in the US population, we performed a prospective multicenter study of 91891 American adults with long-term follow-up to examine the association of ultra-processed food consumption with cardiovascular mortality.

Methods

We reported this study in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology statement.

Study population

Between November 1993 and September 2001, nearly 155000 American adults aged 55 to 74 years were enrolled to the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial, a multicenter randomized controlled trial for investigating whether screening for prostate, lung, colorectal, and ovarian cancer could decrease the risk of mortality from these cancers. Study design of this trial has been reported elsewhere [17]. The PLCO Cancer Screening Trial was approved by the Institutional Review

Boards of the US National Cancer Institute and each recruitment center. All participants provided written informed consent.

The following subjects were excluded in the present study: (1) subjects receiving a diagnosis of any cancer before completing a baseline questionnaire or a diet history questionnaire (DHQ; n = 11882); (2) subjects with an invalid DHQ, which is defined as the presence of extreme values of energy intake (i.e., the first or last percentile), the date of DHQ completion prior to the date of death, missing the date of DHQ completion, or ≥ 8 missing DHQ items (n = 4841); (3) subjects with an incomplete DHQ (n = 34401); (4) subject with a history of stroke or heart attack at baseline (n = 9932); and (5) subjects failing to return the baseline questionnaire (n = 1940). After exclusions, a total of 91891 subjects were included (Figure S1). Of note, a comparison of baseline characteristics of included (n = 91891) and excluded (n = 62966) subjects showed that there were no significant differences in age, sex, race, educational level, body mass index (BMI), smoking status, history of diabetes, and history of hypertension between two groups (all *P* for difference > 0.05), suggesting that the potential for nonparticipation biases was low in our study. For all eligible subjects, follow-up time was calculated from the date of DHQ completion to the date of death, study dropout, or the end of follow-up (i.e., December 31, 2015), whichever came first (Fig. 1).

Data collection

Baseline data, including sex, marital status, race, height, body weight, educational level, history of diabetes or hypertension, and smoking status, were collected with a self-administrated baseline questionnaire. BMI was calculated as body weight (kg) divided by height squared (m^2). Age at DHQ completion, alcohol intake, food consumption, nutrient intake, and energy intake from diet were collected with a DHQ (version 1.0, National Cancer Institute, 2007). The DHQ is a self-administered 137-item food frequency questionnaire, which is designed to assess the frequency and portion size of food consumption and nutrient intake during the past year. The Eating at America's Table Study had validated the DHQ performance in a nationally representative sample of 1640 subjects against four 24-hour dietary recalls, indicating that the DHQ had good performance in the estimation of dietary intakes [18]. Daily consumption of each food in the DHQ was estimated by multiplying food frequency by portion size; daily intake of each nutrient was estimated using the approach described by Subar *et al.* [19] based on the USDA's 1994-96 Continuing Survey of Food Intakes by Individuals [20] and the Nutrition Data Systems for Research [21]. Healthy Eating Index-2005, a measure of diet quality, was calculated using the method described in the literature [22]. Physical activity level was estimated based on the frequency and duration of moderate and strenuous activities that were collected with a self-administrated supplemental questionnaire.

Assessment of ultra-processed food consumption

Two dietitians classified all food and drink items of the DHQ into one of the four food groups defined by the NOVA classification [23]. Based on the purpose, nature, and degree of food processing, the NOVA classification outlines four food groups: unprocessed or minimally processed foods, processed culinary ingredients, processed foods, and ultra-processed foods. The detailed description, including definition and

example, for each group is available elsewhere [23]. In the present study, we focused on ultra-processed foods, which include sour cream, cream cheese, ice cream, frozen yogurt, fried foods, breads, cookies, cakes, pastries, salty snacks, breakfast cereals, instant noodles and soups, sauces, oils and fats, candy, soft drinks, fruit drinks, restaurant/industrial hamburgers, hot dogs, and pizza. Based on a reported categorization method [24], all ultra-processed foods were further categorized into nine food groups for relevant analyses, namely soft drinks, cereals, ultra-processed fruits and vegetables, ultra-processed dairy products, meat and fish, sauces and dressings, salty snacks, sugary products, and oils and fats. Table S1 shows the full list of ultra-processed foods in each food group.

The amount consumed of each food item (78 items, see Table S1) was summed together to calculate an individual's overall consumption of ultra-processed foods. Similarly, the energy content (kcal) of each food item, which was estimated based on the USDA Food and Nutrient Database for Dietary Studies 2015–2016 [25], was summed together to calculate total energy from ultra-processed foods. Importantly, ultra-processed food consumption used for all analyses was adjusted for energy intake from diet using the residual method [26].

Outcome assessment

Vital status was ascertained primarily through a mailed annual study update form. Individuals who did not return the form were contacted repeatedly via telephone or e-mail. Additionally, information on vital status was supplemented by periodic linkage to the US National Death Index to increase its completeness. The *International Classification of Diseases, ninth Revision (ICD-9)* was used to define the underlying causes of mortality obtained from death certificates: CVD (codes: 390–459), heart disease (codes 390–398, 402, 404, and 410–429), and cerebrovascular disease (codes 430–438).

Statistical analysis

As there were seven covariates with missing data (see Table S2), for increasing statistical power and reducing potential biases, multiple imputation by chained equations was applied to impute missing data (the number of imputations = 25) [27], with the assumption that the above-mentioned data were missing at random. All variables involved in statistical analyses were employed to yield the imputed data sets. Main analyses were repeated in participants with complete data for comparison.

Cox proportional hazards regression was applied to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between ultra-processed food consumption and cardiovascular mortality, with person-year as the underlying time metric. Ultra-processed food consumption was divided into quintiles, with the lowest quintile as the reference group. To test linear trends across quintiles of ultra-processed food consumption, the median value of each quintile was assigned to each participant in the quintile and then regarded as a continuous variable in regression models. In multivariable analyses, covariate selection was based on the change-in-estimate approach [28] and the existing literature. Specially, model 1 was adjusted for age, sex, race, educational level, marital status, and study center; model 2 was further adjusted for aspirin use, history of hypertension, history of diabetes, smoking status, alcohol consumption, BMI, physical activity level, and energy intake from diet. To assess how robust our

results were to the potential unmeasured confounding, we calculated the E-value through an online calculator (https://mmathur.shinyapps.io/evalue/) [29], with an assumption of outcome prevelence less than 15%. The E-value represents what the minimum HR would have to be for an unmeasured confounder, conditional on the measured covariates, to negate the observed association of ultra-processed food consumption with cardiovascular mortality. No violation of the proportional hazards assumption was found using Schoenfeld residuals method (all $P > 0.05$). We expressed ultra-processed food consumption as the serving daily in all main analyses based on the USDA Pyramid Servings Database [30]. Meanwhile, we expressed ultra-processed food consumption as serving per day/kilogram body weight in supplementary analyses to examine the potential impacts of body size. For comparison with the published data, we also tested the association between the proportion of energy from ultra-processed foods to total daily energy intake (% energy) and cardiovascular mortality.

Prespecified subgroup analyses were conducted to assess whether the observed association of ultra-processed food consumption with cardiovascular mortality was modified by age (≥ 65 *vs.* <65 years), sex (male *vs.* female), BMI (≥ 25 *vs.* <25 kg/m^2), smoking status (current or former *vs.* never), and alcohol consumption (no, light, or moderate *vs.* heavy). Here, light, moderate, and heavy alcohol consumption were defined as ≤ 6 g/day, > 6–28 g/day for male and > 6–14 g/day for female, and > 28 g/day for male and > 14 g/day for female, respectively [31]. A $P_{interaction}$ was obtained through a likelihood ratio test, which compares the models with and without interaction terms.

Restricted cubic spline regression [32] with four knots at the 5th, 35th, 65th, and 95th percentiles was used to explore the potential dose–response relationship between ultra-processed consumption and cardiovascular mortality. The reference level was set at 0 serving/day. A $P_{nonlinearity}$ was obtained by testing the null hypothesis that regression coefficients of the second and third splines are equal to zero [32].

Sensitivity analyses were performed to evaluate the robustness of our results: (1) excluding deaths occurring within the first five years of follow-up to determine the potential effects of reverse causation; (2) excluding subjects with extreme values of energy intake, which are defined as < 800 or > 4 000 kcal/day and < 500 or > 3500 kcal/day for men and women, respectively [33]; (3) including subjects with history of cancer at baseline; (4) including subjects with history of heart attack or stroke at baseline; (5) repeating main analyses with competing risk regression [34] to assess the potential effects of competing risk bias, with non-CVD causes of death as competing events; (6) adjustment for propensity score on unadjusted model (all covariates in model 2 were used to calculate propensity score); and (7) additional adjustment for several indicators of diet quality, including Healthy Eating Index-2005, intakes of sodium, added sugars, and saturated fatty acids, and consumption of red meat, processed meat, whole grain, fruit, vegetable, dietary fiber, and dairy.

We calculated the proportion of each food group in total amounts of ultra-processed foods to quantify their contributions to ultra-processed food consumption. In addition, we tested the association between ultra-processed food consumption by food group and cardiovascular mortality.

As cancer is most common cause of death in this study population, we also performed a supplementary analysis to examine the association between ultra-processed food consumption and overall cancer mortality. To validate our study design and methods, we used all-cause mortality as a positive control outcome, given the well-established association of ultra-processed food consumption with all-cause mortality [15, 16, 24, 35]. The statistical significance level was set at $P < 0.05$ under a two-tailed test. Statistical analyses were performed using STATA version 12.0 (StataCorp, College Station, TX).

Results

Participant characteristics

In the entire study population, the average consumption of ultra-processed foods (without adjustment for energy intake) was 2.9 servings/day; the average energy contribution of ultra-processed foods in the diet was up to 38%. Compared with participants in the lowest quintile of ultra-processed food consumption, those in the highest quintile had higher consumption of red meat but lower consumption of fruit, vegetable, dietary fiber, and dairy, and higher intakes of energy, cholesterol, saturated fatty acids, polyunsaturated fatty acids, carbohydrate, fat, added sugar, and sodium but lower intakes of magnesium, potassium, and calcium (Table 1).

Ultra-processed foods and cardiovascular mortality

During an average follow-up of 13.5 ± 3.3 years (1236049.2 person-years), a total of 5490 cardiovascular deaths were documented, of which 3985 (72.6%) and 1126 (20.5%) were classified as deaths from heart disease and cerebrovascular disease, respectively. Crude mortality rates of CVD, heart disease, and cerebrovascular disease were 44.42, 32.24, and 9.11 per 10000 person-years, respectively. After the full adjustment for confounders, participants in the highest *vs.* the lowest quintiles of ultra-processed food consumption were found to be at increased risks of overall cardiovascular ($HR_{\text{quintile 5 } vs. \text{ 1}}$, 1.52; 95% CI, 1.39–1.67; P_{trend}<0.001;E-value, 2.41) and heart disease mortality ($HR_{\text{quintile 5 } vs. \text{ 1}}$, 1.70; 95% CI, 1.52–1.89; P_{trend}<0.001; E-value, 2.79) (Table 2). No significant association was observed for cerebrovascular mortality. When the above-mentioned analyses were performed in participants with complete data, similar results were obtained (Table S3). When ultra-processed food consumption was expressed as serving per day/kilogram body weight or % energy, the initial results did not alter substantially (Tables S4 and S5).

Table 2
Association between ultra-processed food consumption (serving daily) and cardiovascular mortality

Causes of mortality	Quintiles of energy-adjusted ultra-processed food consumption, range (mean), servings/day					P_{trend}
	< 0.6 (0.2)	0.6–1.2 (0.9)	1.3–2.2 (1.7)	2.3–4.2 (3.1)	> 4.2 (8.3)	
No. of participants	18378	18378	18379	18377	18379	
Person-years	247441.4	247110.6	247344.6	247556.6	246596.1	
Cardiovascular disease						
No. of deaths	1007	959	1009	1144	1371	
Death rate [a]	40.70	38.81	40.79	46.21	55.60	
Model 1 [b]	1.00 (reference)	0.97 (0.88, 1.06)	1.03 (0.94, 1.13)	1.23 (1.13, 1.34)	1.63 (1.49, 1.77)	< 0.001
Model 2 [c]	1.00 (reference)	0.96 (0.88, 1.06)	1.02 (0.94, 1.12)	1.20 (1.10, 1.31)	1.52 (1.39, 1.67)	< 0.001
Heart disease						
No. of deaths	681	664	678	850	1112	
Death rate [a]	27.52	26.87	27.41	34.34	45.09	
Model 1 [b]	1.00 (reference)	0.98 (0.88, 1.10)	1.01 (0.91, 1.12)	1.32 (1.19, 1.46)	1.87 (1.70, 2.07)	< 0.001
Model 2 [c]	1.00 (reference)	0.98 (0.87, 1.09)	0.99 (0.88, 1.10)	1.26 (1.13, 1.40)	1.70 (1.52, 1.89)	< 0.001
Cerebrovascular disease						
No. of deaths	257	217	259	214	179	
Death rate [a]	10.39	8.78	10.47	8.64	7.26	

Values are hazard ratios (95% confidence intervals).

[a] Crude death rate per 10000 person-years.

[b] Adjusted for age (years), sex (male, female), race (non-Hispanic white, non-Hispanic black, Hispanic, others), educational level (college below, college graduate, postgraduate), marital status (married, widowed, divorced, separated, never married), and study center (10 categories).

[c] Adjusted for model 1 plus aspirin use (yes, no), history of hypertension (yes, no), history of diabetes (yes, no), smoking status (current, former, never), alcohol consumption (g/day), body mass index (< 18.5, 18.5–24.9, 25.0–30.0, > 30.0), physical activity (min/week), and energy intake from diet (kcal/day).

Causes of mortality	Quintiles of energy-adjusted ultra-processed food consumption, range (mean), servings/day					P_{trend}
	< 0.6 (0.2)	0.6–1.2 (0.9)	1.3–2.2 (1.7)	2.3–4.2 (3.1)	> 4.2 (8.3)	
Model 1 [b]	1.00 (reference)	0.87 (0.72, 1.04)	1.07 (0.90, 1.28)	0.96 (0.80, 1.16)	0.93 (0.76, 1.13)	0.681
Model 2 [c]	1.00 (reference)	0.88 (0.73, 1.06)	1.13 (0.94, 1.36)	1.02 (0.84, 1.24)	1.00 (0.80, 1.23)	0.860

Values are hazard ratios (95% confidence intervals).

[a] Crude death rate per 10000 person-years.

[b] Adjusted for age (years), sex (male, female), race (non-Hispanic white, non-Hispanic black, Hispanic, others), educational level (college below, college graduate, postgraduate), marital status (married, widowed, divorced, separated, never married), and study center (10 categories).

[c] Adjusted for model 1 plus aspirin use (yes, no), history of hypertension (yes, no), history of diabetes (yes, no), smoking status (current, former, never), alcohol consumption (g/day), body mass index (< 18.5, 18.5–24.9, 25.0–30.0, > 30.0), physical activity (min/week), and energy intake from diet (kcal/day).

Subgroup analyses

A significant interaction between ultra-processed food consumption and sex was detected for overall cardiovascular ($P_{interaction}$=0.008) and heart disease mortality ($P_{interaction}$=0.004) but not for cerebrovascular mortality (Table 3). Specifically, the highest fifth of ultra-processed food consumption was found to be associated with higher risks of death from CVD and heart disease in women (CVD: HR $_{quintile\ 5\ vs.\ 1}$, 1.92; 95% CI, 1.68–2.21; heart disease: HR $_{quintile\ 5\ vs.\ 1}$, 2.18; 95% CI, 1.85–2.56) than in men (CVD: HR $_{quintile\ 5\ vs.\ 1}$, 1.26; 95% CI, 1.11–1.43; heart disease: HR $_{quintile\ 5\ vs.\ 1}$, 1.41; 95% CI, 1.22–1.63). No significant interaction was found for remaining predefined factors.

Table 3
Subgroup analyses on the association between ultra-processed food consumption (serving daily) and cardiovascular mortality

Subgroup variable	Overall cardiovascular mortality		Heart disease mortality		Cerebrovascular disease mortality	
	$HR_{quintile\ 5\ vs.\ 1}$ (95% CI) [a]	$P_{interaction}$	$HR_{quintile\ 5\ vs.\ 1}$ (95% CI) [a]	$P_{interaction}$	$HR_{quintile\ 5\ vs.\ 1}$ (95% CI) [a]	$P_{interaction}$
Age (years)						
≥ 65	1.52 (1.21, 1.90)	0.523	1.66 (1.48, 1.87)	0.420	0.96 (0.75, 1.24)	0.685
< 65	1.49 (1.34, 1.65)		1.74 (1.32, 2.27)		0.96 (0.63, 1.48)	
Sex						
Male	1.26 (1.11, 1.43)	0.008	1.41 (1.22, 1.63)	0.004	0.83 (0.61, 1.13)	0.203
Female	1.92 (1.68, 2.21)		2.18 (1.85, 2.56)		1.16 (0.85, 1.58)	
Body mass index (kg/m^2)						
≥ 25	1.50 (1.35, 1.66)	0.876	1.65 (1.46, 1.86)	0.195	1.04 (0.81, 1.34)	0.251
< 25	1.61 (1.32, 1.96)		1.90 (1.50, 2.40)		0.83 (0.53, 1.30)	
Smoking status						
Current or former	1.47 (1.30, 1.66)	0.805	1.60 (1.39, 1.84)	0.730	1.07 (0.81, 1.41)	0.875
Never	1.60 (1.39, 1.85)		1.83 (1.55, 2.17)		0.90 (0.65, 1.26)	
Alcohol consumption (g/day) [b]						

[a] Adjusted for age (years), sex (male, female), race (non-Hispanic white, non-Hispanic black, Hispanic, others), educational level (college below, college graduate, postgraduate), marital status (married, widowed, divorced, separated, never married), study center (10 categories), aspirin use (yes, no), history of hypertension (yes, no), history of diabetes (yes, no), smoking status (current, former, never), alcohol consumption (g/day), body mass index (< 18.5, 18.5–24.9, 25.0–30.0, > 30.0), physical activity (min/week), and energy intake from diet (kcal/day). In subgroup analyses stratified by sex and smoking status, hazard ratios were not adjusted for the stratification factor.

[b] Light, moderate, and heavy alcohol consumption are defined as ≤ 6 g/day, > 6–28 g/day for male and > 6–14 g/day for female, and > 28 g/day for male and > 14 g/day for female, respectively.

Subgroup variable	Overall cardiovascular mortality		Heart disease mortality		Cerebrovascular disease mortality	
	$HR_{quintile\ 5\ vs.\ 1}$ (95% CI) [a]	$P_{interaction}$	$HR_{quintile\ 5\ vs.\ 1}$ (95% CI) [a]	$P_{interaction}$	$HR_{quintile\ 5\ vs.\ 1}$ (95% CI) [a]	$P_{interaction}$
No, light or moderate	1.58 (1.43, 1.74)	0.070	1.74 (1.55, 1.96)	0.118	1.06 (0.85, 1.34)	0.167
Heavy	1.16 (0.90 1.48)		1.36 (1.02, 1.81)		0.63 (0.34, 1.16)	

[a] Adjusted for age (years), sex (male, female), race (non-Hispanic white, non-Hispanic black, Hispanic, others), educational level (college below, college graduate, postgraduate), marital status (married, widowed, divorced, separated, never married), study center (10 categories), aspirin use (yes, no), history of hypertension (yes, no), history of diabetes (yes, no), smoking status (current, former, never), alcohol consumption (g/day), body mass index (< 18.5, 18.5–24.9, 25.0–30.0, > 30.0), physical activity (min/week), and energy intake from diet (kcal/day). In subgroup analyses stratified by sex and smoking status, hazard ratios were not adjusted for the stratification factor.

[b] Light, moderate, and heavy alcohol consumption are defined as ≤ 6 g/day, > 6–28 g/day for male and > 6–14 g/day for female, and > 28 g/day for male and > 14 g/day for female, respectively.

Dose–response analyses

In the whole study population, ultra-processed food consumption was found to be associated with risks of death from CVD ($P_{nonlinearity}$<0.001) and heart disease ($P_{nonlinearity}$<0.001) in a nonlinear dose–response manner (Fig. 2); furthermore, a threshold effect was observed at ultra-processed food consumption of 2.5 servings/day for overall cardiovascular mortality and 2.4 servings/day for heart disease mortality, below which there was no significant associations with two outcomes. Considering the above-mentioned significant interaction between ultra-processed food consumption and sex, we performed sex-specific dose–response analyses (Figures S2 and S3 for women and men, respectively). The nonlinear dose–response relationship of ultra-processed food consumption to overall cardiovascular and heart disease mortality was seen in both men and women (all $P_{nonlinearity}$<0.001), but the thresholds for increased overall cardiovascular and heart disease mortality were lower in women than in men (women: 1.8 and 2.1 servings/day for overall cardiovascular and heart disease mortality, respectively; men: 4.2 and 3.6 servings/day for overall cardiovascular and heart disease mortality, respectively). No significant dose–response relationship was observed for cerebrovascular mortality in the whole study population and in men or women.

Sensitivity analyses

The initial associations between ultra-processed food consumption and risks of death from CVD, heart disease, and cerebrovascular disease persisted in a large range of sensitivity analyses (Table S6).

Contributions of and associations by ultra-processed food groups

Main food groups contributing to ultra-processed food consumption were cereals (35.6%) followed by soft drinks (14.6%), sauces and dressings (8.1%), and meat and fish (8.0%) (Fig. 3). The highest *vs.* the lowest quintiles of consumption of soft drinks, salty snacks, and sugary products was found to be significantly associated with increased risks of overall cardiovascular and heart disease mortality (all P_{trend}<0.05) (Table S7). For sauces and dressings, the associations with these two outcomes were in the same direction (CVD: HR $_{quintile\ 5\ vs.\ 1}$, 1.10; 95% CI, 1.01–1.23; heart disease: HR $_{quintile\ 5\ vs.\ 1}$, 1.11; 95% CI, 1.00–1.23), but the marginal significance was detected for linear trend test (CVD: P_{trend}=0.054; heart disease: P_{trend}=0.065).

Supplementary analysis: ultra-processed foods and overall cancer mortality

A total of 6175 cancer deaths were identified over an average follow-up of 13.5 ± 3.3 years. After the full adjustment for confounders, no significant association was found for ultra-processed food consumption and overall cancer mortality (HR$_{quintile\ 5\ vs.\ 1}$, 1.03; 95% CI, 0.94–1.12; P_{trend}=0.243) (Table S8).

Positive control outcome: all-cause mortality

A total of 19586 all-cause deaths were documented during follow-up, with the overall mortality rate of 158.46 per 10000 person-years. In the fully adjusted model, participants in the highest quintile of ultra-processed food consumption had a higher risk of all-cause mortality than those in the lowest quintile (HR $_{quintile\ 5\ vs.\ 1}$, 1.20; 95% CI, 1.14–1.26; P_{trend}<0.001) (Table S9).

Discussion

Based on prospective data from a large multicenter trial, our study, for the first time, revealed significant harmful associations of ultra-processed foods with risks of death from CVD and heart disease, with a threshold for harm above consumption of 2.5 servings/day for overall cardiovascular mortality and 2.4 servings/day for heart disease mortality. Sex-specific analyses further showed that these harmful associations were more pronounced in women than in men. No significant association was observed for cerebrovascular mortality.

Interpretation and comparison with other studies

Several studies have examined the association of ultra-processed food consumption with all-cause mortality [15, 16, 24, 35], but few studies focus on cause-specific mortality that may be more biologically relevant to ultra-processed food consumption [15, 16]. In this study, we revealed a positive association of ultra-processed food consumption with cardiovascular mortality, which is inconsistent with previous studies on this topic [15, 16]. Specifically, with similar study design and methods, previous studies on this subject failed to detect a significant association [15, 16]. The inconsistency may result from the significant difference in the power. Of note, previous studies documented a small number of cardiovascular deaths (71 in Spanish study [15] and 648 in American study [16]), which results in the

limited power. The inconsistency could be also due to the differences in characteristics of study population. For example, the age of participants in previous studies was significantly lower than that in our study (the average age: 37.6 [15] *vs.* 65.3 years and 41.0 [16] *vs.* 65.3 years). However, such an explanation seems to be not supported by our observation that there was no significant difference in risk estimates between subgroups stratified by age.

The harmful association of ultra-processed foods with cardiovascular mortality could be accounted by several factors. First, unfavorable nutritional composition of ultra-processed foods may be a key factor driving the observed associations. It has been found that ultra-processed food consumption is positively associated with added sugar intake and inversely associated with dietary fiber intake [36], both of which are shown to be predictive of cardiovascular mortality [37, 38]. Second, chemicals may transfer from packaging materials to food contents, some of which may have detrimental impacts on cardiometabolic health [39]. Indeed, a cross-sectional study showed that ultra-processed food consumption could increase exposure to phthalates (the synthetic chemicals widely used in food packaging) [40]; a recent Cochrane review further showed a significant association between exposure to phthalates and cardiometabolic risk factors [41]. Third, food additives were frequently used in the production of ultra-processed foods [6], and some studies have reported their adverse effects on cardiovascular outcomes. For example, observational studies found that a high serum level of phosphate, a commonly used food additive, was a risk factor for cardiovascular event [42, 43]. Additionally, a cell study indicated that long-term use of artificial sweeteners might exacerbate atherosclerosis [44]. Fourth, ultra-processed foods may contain some neo-formed contaminants formed during industrial processes that ultra-processed foods undergo, such as acrolein. Importantly, both *in vitro* and *in vivo* studies have suggested that acrolein has toxic effects on cardiovascular tissues [45]; observational studies further showed that exposure to acrolein was associated with an increased risk of CVD [45, 46].

Explanations for sex difference in cardiovascular mortality

Interestingly, our study found that the increased risks of death from CVD and heart disease were more pronounced in women. Similarly, previous studies also observed that consumption of soft drinks and processed meat was positively associated with higher CVD incidence and mortality in women than in men [47–49]. In fact, sex difference in cardiovascular outcomes has long been recognized [50]. We propose several possible explanations for this phenomenon.

First, biologically, such a phenomenon may result from the hormonal differences between men and women. As almost all women in our study had experienced menopause, thus one would not expect estrogen level difference between sexes to be a major driver for the sex-specific association of ultra-processed food consumption with cardiovascular mortality. Instead, testosterone may be involved in the relevant mechanisms. Indeed, testosterone signaling has been suggested to play an important role in maintaining cardiovascular health [51]; moreover, observational studies have observed inverse associations of endogenous testosterone levels with CVD incidence and mortality [52–54]. Thus, the fact that women have lower testosterone levels than men may explain, at least partly, the observed sex difference in cardiovascular mortality.

Second, sex disparities in the prevention, diagnosis, and treatment of CVD should be considered. Generally, women are less likely to receive preventive guidance or therapy, be diagnosed appropriately, and be treated aggressively compared with their male counterparts [55, 56]. A registry study of 82196 patients with acute coronary syndrome found that women received medical strategies and acute treatments for secondary prevention less frequently than did men [57]. Additionally, compared with men, women have a poorer adherence to the use of chronic medication [58]. In fact, even with a comparable adherence, women always benefit less from medication use than do men, considering the low enrollment of women in clinical trials of CVD [59], resulting in that current diagnostic and therapeutic methods primarily target men [60]. Therefore, sex disparities in access to health care possibly mediate sex difference in cardiovascular mortality owing to ultra-processed food consumption.

Third, compared with men, women possibly have a poorer risk factor profile, suggesting that individual risk factors, such as high consumption of ultra-processed foods, could lead to greater deleterious effects in women. Indeed, a meta-analysis of 2.4 million subjects showed that smoking conferred a 25% higher risk of coronary heart disease in women than in men [61]. Similar phenomena can be seen for other CVD risk factors, such as heavy alcohol intake [62] and overweight and obesity [63]. However, this explanation seems to be not supported by the fact that our primary results remained after adjustment for traditional CVD risk factors.

Fourth, ultra-processed foods may specifically promote proneurotensin synthesis and endothelial mineralocorticoid receptor activation, both of which have been suggested to play a critical role in sex difference in cardiovascular outcomes [50, 60]. A prospective study showed that increasing fasting proneurotensin levels in plasma were associated with increased risks of CVD incidence and mortality in women but not in men [64]. Likewise, both clinical and animal studies have demonstrated that activation of endothelial mineralocorticoid receptor contributes to CVD pathogenesis in a sex-specific manner [50].

Importantly, we cannot exclude the possibility that sex difference in cardiovascular mortality observed in our study is a chance finding, although this phenomenon could be explained by the above-mentioned points. Hence, the stronger associations with cardiovascular mortality in women compared to men should be treated with caution, and needs to be confirmed by future studies.

Conclusions

In the US population, high consumption of ultra-processed foods is associated with increased risks of death from CVD and heart disease. These harmful associations may be more pronounced in women than in men. Our findings suggest that reducing ultra-processed food consumption may be beneficial in reducing cardiovascular mortality, especially in women. However, these findings are needed to be confirmed in other populations and settings, considering the aforementioned limitations and the modest changes in mortality from CVD and heart disease even with large differences in ultra-processed food consumption. If confirmed, given the increasing dominance of ultra-processed foods in the global food system, limiting ultra-processed food consumption would represent an attractive strategy to reduce the

global burden of CVD. Future studies should explore the relevant mechanisms and deepen the understanding of sex differences in the observed associations.

Limitations

Our study has several limitations. First, misclassification bias might occur when we categorized food items, as the DHQ did not provide enough information needed to correct categorization for some food items. However, this bias is nondifferential (because it was not expected to be associated with future cardiovascular mortality), and potentially biases risk estimates toward the null. Moreover, we observed an expected association between ultra-processed food consumption and positive control outcome, indicating the validity of our study methods. Second, we had fully adjusted for confounders, but our results were still subject to residual confounding due to unrecognized or unmeasured confounders. For example, individuals with higher consumption of ultra-processed foods are found to have a poorer overall diet [65]; hence, it is possible that high ultra-processed food consumption is only a simple marker of poor diet quality, reminding us that the observed associations with cardiovascular mortality may be mediated by diet quality. However, this seems to be not the case in our study, as the initial results persisted after we adjusted for several indicators of diet quality (Supplementary Table 6). Moreover, the E-value for overall cardiovascular mortality was 2.41 in our study setting, indicating that an unmeasured confounder with a HR $\geq$ 2.41 can explain away the observed association; the possibility of existing such an unmeasured confounder seems to be low, as the HR for history of hypertension, a strong CVD risk factor, was only 1.52 in our study. Third, food consumption was assessed once at baseline in our study. Considering that diet habits can change with time, the assessment of food consumption at one time point may result in non-differential bias. Nonetheless, one would not expect an adult's diet habits to change drastically during several years; furthermore, it has been found that the approach using only baseline diet generally yields a weaker association than that using the cumulative averages [66]. Fourth, we chose serving daily as an indicator for ultra-processed food consumption. However, this measure may not precisely reflect the contribution of ultra-processed foods in the diet, and possibly produces inaccurate results. Nonetheless, our initial results remained in analyses where ultra-processed food consumption was expressed as serving per day/kilogram body weight or % energy, which alleviates this concern to some extent. Finally, our study could not examine the association of ultra-processed food consumption with CVD incidence, as this outcome was not available in the PLCO Cancer Screening Trial. Nonetheless, our study had revealed its harmful association with cardiovascular mortality, a primary outcome in the cardiology research.

Conclusions

In the US population, high consumption of ultra-processed foods is associated with increased risks of death from CVD and heart disease. These harmful associations may be more pronounced in women than in men. Our findings suggest that reducing ultra-processed food consumption may be beneficial in reducing cardiovascular mortality, especially in women. However, these findings are needed to be confirmed in other populations and settings, considering the aforementioned limitations and the modest changes in mortality from CVD and heart disease even with large differences in ultra-processed food

consumption. If confirmed, given the increasing dominance of ultra-processed foods in the global food system, limiting ultra-processed food consumption would represent an attractive strategy to reduce the global burden of CVD. Future studies should explore the relevant mechanisms and deepen the understanding of sex differences in the observed associations.

Abbreviations

HR
hazard ratio; CVD = cardiovascular disease; PLCO = Prostate, Lung, Colorectal, and Ovarian; DHQ = diet history questionnaire; BMI = body mass index; ICD = International Classification of Diseases; CI = confidence interval

Declarations

Ethics approval and consent to participate

The PLCO Screening Trial concept was approved by the Institutional Review Board of the National Cancer Institute and each screening center. Written informed consent was obtained from all individuals. The study was conducted in accordance with the Declaration of Helsinki.

Consent for publication

Not applicable.

Availability of data and materials

Original data used in this study are not freely available to the public because of US NCI's data policy. These original data can be accessible upon the reasonable request and the final approval by US NCI.

Competing interests

None declared.

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Authors' contributions

Guo-Chao Zhong and Hai-Tao Gu conceived the study idea. Guo-Chao Zhong drafted the study protocol and the initial manuscript. You-Qi-Le Wu categorized food items according to the NOVA classification

system. Feng-Chuang Jing and Yang Peng made critical comments and revisions for the initial manuscript. Kang Wang was responsible for statistical analyses. Guo-Chao Zhong and Kang Wang interpreted the results of statistical analyses together. All authors approved the final version of the article, including the authorship list.

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Tables

Table 1. Baseline characteristics of study population according to energy-adjusted ultra-processed food consumption in 91891 participants

Characteristics	Quintiles of energy-adjusted ultra-processed food consumption, range (mean), servings/day				
	<0.6 (0.2)	0.6–1.2 (0.9)	1.3–2.2 (1.7)	2.3–4.2 (3.1)	>4.2 (8.3)
No. of participants	18378	18378	18379	18377	18379
Age (years)	66.3 ± 5.7	66.0 ± 5.7	65.6 ± 5.7	64.9 ± 5.6	63.7 ± 5.3
Male	5868 (31.9)	7382 (40.2)	9039 (49.2)	9662 (52.6)	10592 (57.6)
Married	13504 (73.5)	14483 (78.8)	14825 (80.7)	14841 (80.8)	14493 (78.9)
History of diabetes	824 (4.5)	805 (4.4)	903 (4.9)	1076 (5.9)	1716 (9.3)
History of hypertension	5111 (27.8)	5349 (29.1)	5488 (29.9)	5716 (31.1)	6275 (34.1)
Alcohol consumption (g/day)	13.8 ± 38.6	8.7 ± 19.7	8.4 ± 18.7	8.4 ± 19.1	8.5 ± 23.8
Energy intake from diet (kcal/day)	1415.0 ± 636.5	1525.6 ± 545.8	1725.4 ± 630.0	1886.8 ± 724.6	2130.0 ± 870.3
Physical activity (min/week) [a]	130.1 ± 125.7	125.2 ± 122.0	123.5 ± 121.5	123.9 ± 124.0	124.1 ± 127.5
Healthy Eating Index-2005	63.1 ± 11.6	61.4 ± 10.7	59.7 ± 10.7	58.8 ± 10.7	56.9 ± 10.9
Race					
Non-Hispanic white	17257 (93.9)	17097 (93.0)	16483 (89.7)	16354 (89.0)	16357 (89.0)
Non-Hispanic black	474 (2.6)	419 (2.3)	578 (3.1)	674 (3.7)	836 (4.5)
Hispanic	341 (1.9)	228 (1.2)	255 (1.4)	252 (1.4)	284 (1.5)
Others [b]	306 (1.7)	634 (3.4)	1063 (5.8)	1097 (6.0)	902 (4.9)
Educational level					
College below	11236 (61.1)	11363 (61.8)	11583 (63.0)	11764 (64.0)	12194 (66.3)

College graduate	3493 (19.0)	3373 (18.4)	3286 (17.9)	3212 (17.5)	3003 (16.3)
Postgraduate	3649 (19.9)	3642 (19.8)	3510 (19.1)	3401 (18.5)	3182 (17.3)
Smoking status					
Current	1507 (8.2)	1524 (8.3)	1617 (8.8)	1678 (9.1)	2085 (11.3)
Former	7754 (42.2)	7454 (40.6)	7524 (40.9)	7592 (41.3)	8055 (43.8)
Never	9117 (49.6)	9400 (51.1)	9238 (50.3)	9107 (49.6)	8239 (44.8)
Body mass index (kg/m2)					
<18.5	201 (1.1)	144 (0.8)	92 (0.5)	99 (0.5)	82 (0.5)
18.5–24.9	8249 (45.5)	6964 (38.4)	6188 (34.1)	5578 (30.7)	4263 (23.6)
25.0–30.0	6772 (37.4)	7604 (41.9)	7978 (43.9)	8116 (44.7)	7917 (43.8)
>30	2906 (16.0)	3436 (18.9)	3895 (21.5)	4362 (24.0)	5834 (32.2)
Food consumption					
Red meat (g/day)	44.4 ± 42.1	58.9 ± 50.6	65.7 ± 53.5	69.6 ± 55.5	67.8 ± 54.2
Fruit (g/day)	363.6 ± 281.9	302.3 ± 217.0	269.3 ± 193.1	238.4 ± 171.7	194.6 ± 158.1
Vegetable (g/day)	330.6 ± 230.8	301.1 ± 185.5	283.9 ± 172.3	267.7 ± 163.3	233.5 ± 150.0
Dietary fiber (g/day)	20.3 ± 10.0	18.8 ± 8.5	18.0 ± 8.0	17.2 ± 7.6	15.5 ± 7.2
Whole grain (servings/day)	1.2 ± 0.9	1.2 ± 0.8	1.2 ± 0.8	1.1 ± 0.8	1.0 ± 0.8
Dairy (cups/day)	1.6 ± 1.4	1.5 ± 1.2	1.4 ± 1.1	1.3 ± 1.0	1.1 ± 0.9
Nutrient intake					
Cholesterol (mg/day)	136.0 ± 88.2	177.7 ± 97.6	212.9 ± 116.4	240.3 ± 135.6	277.8 ± 169.7
Saturated fatty acids (g/day)	12.2 ± 5.9	16.7 ± 7.5	20.4 ± 9.4	23.5 ± 11.9	27.3 ± 15.2
Polyunsaturated	9.5 ± 4.9	12.3 ±	14.5 ±	16.2 ±	18.2 ±

fatty acids (g/day)		5.5	6.5	7.7	9.5
Carbohydrate (g/day)	160.6 ± 61.3	194.5 ± 64.4	221.1 ± 71.3	245.9 ± 83.6	281.6 ± 113.6
Fat (g/day)	39.6 ± 18.0	53.1 ± 21.5	64.0 ± 26.6	72.9 ± 33.6	83.7 ± 43.0
Protein (g/day)	65.2 ± 29.1	67.7 ± 30.3	68.5 ± 30.8	67.9 ± 30.8	63.3 ± 29.9
Added sugar (tsp/day)	6.5 ± 3.4	9.2 ± 4.1	11.6 ± 5.2	14.4 ± 7.1	20.4 ± 14.1
Sodium (mg/day)	1874.7 ± 703.8	2385.1 ± 798.6	2774.7 ± 962.0	3090.4 ± 1181.9	3484.8 ± 1520.9
Magnesium (mg/day)	353.7 ± 143.5	335.3 ± 127.4	325.1 ± 122.9	312.8 ± 119.2	284.1 ± 114.8
Potassium (mg/day)	3562.7 ± 1359.1	3403.3 ± 1251.0	3288.5 ± 1217.0	3153.8 ± 1182.6	2816.6 ± 1134.1
Calcium (mg/day)	815.4 ± 457.8	785.4 ± 420.7	756.3 ± 397.1	727.0 ± 377.9	663.1 ± 350.6

Values are mean (standard deviation) or counts (percentage) as indicated.

[a] Total time of moderate to vigorous physical activities per week.

[b] “Others” refers to Asian, Pacific Islander, or American Indian.

Table 2. Association between ultra-processed food consumption (serving daily) and cardiovascular mortality

Causes of mortality	Quintiles of energy-adjusted ultra-processed food consumption, range (mean), servings/day					P_{trend}
	<0.6 (0.2)	0.6–1.2 (0.9)	1.3–2.2 (1.7)	2.3–4.2 (3.1)	>4.2 (8.3)	
No. of participants	18378	18378	18379	18377	18379	
Person-years	247441.4	247110.6	247344.6	247556.6	246596.1	
Cardiovascular disease						
No. of deaths	1007	959	1009	1144	1371	
Death rate [a]	40.70	38.81	40.79	46.21	55.60	
Model 1 [b]	1.00 (reference)	0.97 (0.88, 1.06)	1.03 (0.94, 1.13)	1.23 (1.13, 1.34)	1.63 (1.49, 1.77)	<0.001
Model 2 [c]	1.00 (reference)	0.96 (0.88, 1.06)	1.02 (0.94, 1.12)	1.20 (1.10, 1.31)	1.52 (1.39, 1.67)	<0.001
Heart disease						
No. of deaths	681	664	678	850	1112	
Death rate [a]	27.52	26.87	27.41	34.34	45.09	
Model 1 [b]	1.00 (reference)	0.98 (0.88, 1.10)	1.01 (0.91, 1.12)	1.32 (1.19, 1.46)	1.87 (1.70, 2.07)	<0.001
Model 2 [c]	1.00 (reference)	0.98 (0.87, 1.09)	0.99 (0.88, 1.10)	1.26 (1.13, 1.40)	1.70 (1.52, 1.89)	<0.001
Cerebrovascular disease						
No. of deaths	257	217	259	214	179	
Death rate [a]	10.39	8.78	10.47	8.64	7.26	
Model 1 [b]	1.00 (reference)	0.87 (0.72, 1.04)	1.07 (0.90, 1.28)	0.96 (0.80, 1.16)	0.93 (0.76, 1.13)	0.681
Model 2 [c]	1.00 (reference)	0.88 (0.73, 1.06)	1.13 (0.94, 1.36)	1.02 (0.84, 1.24)	1.00 (0.80, 1.23)	0.860

Values are hazard ratios (95% confidence intervals).

[a] Crude death rate per 10000 person-years.

[b] Adjusted for age (years), sex (male, female), race (non-Hispanic white, non-Hispanic black, Hispanic, others), educational level (college below, college graduate, postgraduate), marital status (married, widowed, divorced, separated, never married), and study center (10 categories).

[c] Adjusted for model 1 plus aspirin use (yes, no), history of hypertension (yes, no), history of diabetes (yes, no), smoking status (current, former, never), alcohol consumption (g/day), body mass index (<18.5, 18.5–24.9, 25.0–30.0, >30.0), physical activity (min/week), and energy intake from diet (kcal/day).

Table 3. Subgroup analyses on the association between ultra-processed food consumption (serving daily) and cardiovascular mortality

Subgroup variable	Overall cardiovascular mortality		Heart disease mortality		Cerebrovascular disease mortality	
	$HR_{quintile\ 5\ vs.\ 1}$ (95% CI) [a]	$P_{interaction}$	$HR_{quintile\ 5\ vs.\ 1}$ (95% CI) [a]	$P_{interaction}$	$HR_{quintile\ 5\ vs.\ 1}$ (95% CI) [a]	$P_{interaction}$
Age (years)						
≥65	1.52 (1.21, 1.90)	0.523	1.66 (1.48, 1.87)	0.420	0.96 (0.75, 1.24)	0.685
<65	1.49 (1.34, 1.65)		1.74 (1.32, 2.27)		0.96 (0.63, 1.48)	
Sex						
Male	1.26 (1.11, 1.43)	0.008	1.41 (1.22, 1.63)	0.004	0.83 (0.61, 1.13)	0.203
Female	1.92 (1.68, 2.21)		2.18 (1.85, 2.56)		1.16 (0.85, 1.58)	
Body mass index (kg/m^2)						
≥25	1.50 (1.35, 1.66)	0.876	1.65 (1.46, 1.86)	0.195	1.04 (0.81, 1.34)	0.251
<25	1.61 (1.32, 1.96)		1.90 (1.50, 2.40)		0.83 (0.53, 1.30)	
Smoking status						
Current or former	1.47 (1.30, 1.66)	0.805	1.60 (1.39, 1.84)	0.730	1.07 (0.81, 1.41)	0.875
Never	1.60 (1.39, 1.85)		1.83 (1.55, 2.17)		0.90 (0.65, 1.26)	
Alcohol consumption (g/day) [b]						
No, light or moderate	1.58 (1.43, 1.74)	0.070	1.74 (1.55, 1.96)	0.118	1.06 (0.85, 1.34)	0.167
Heavy	1.16 (0.90 1.48)		1.36 (1.02, 1.81)		0.63 (0.34, 1.16)	

[a] Adjusted for age (years), sex (male, female), race (non-Hispanic white, non-Hispanic black, Hispanic, others), educational level (college below, college graduate, postgraduate), marital status (married, widowed, divorced, separated, never married), study center (10 categories), aspirin use (yes, no), history of hypertension (yes, no), history of diabetes (yes, no), smoking status (current, former, never), alcohol

consumption (g/day), body mass index (<18.5, 18.5–24.9, 25.0–30.0, >30.0), physical activity (min/week), and energy intake from diet (kcal/day). In subgroup analyses stratified by sex and smoking status, hazard ratios were not adjusted for the stratification factor.

[b] Light, moderate, and heavy alcohol consumption are defined as ≤6 g/day, >6–28 g/day for male and >6–14 g/day for female, and >28 g/day for male and >14 g/day for female, respectively.

Figures

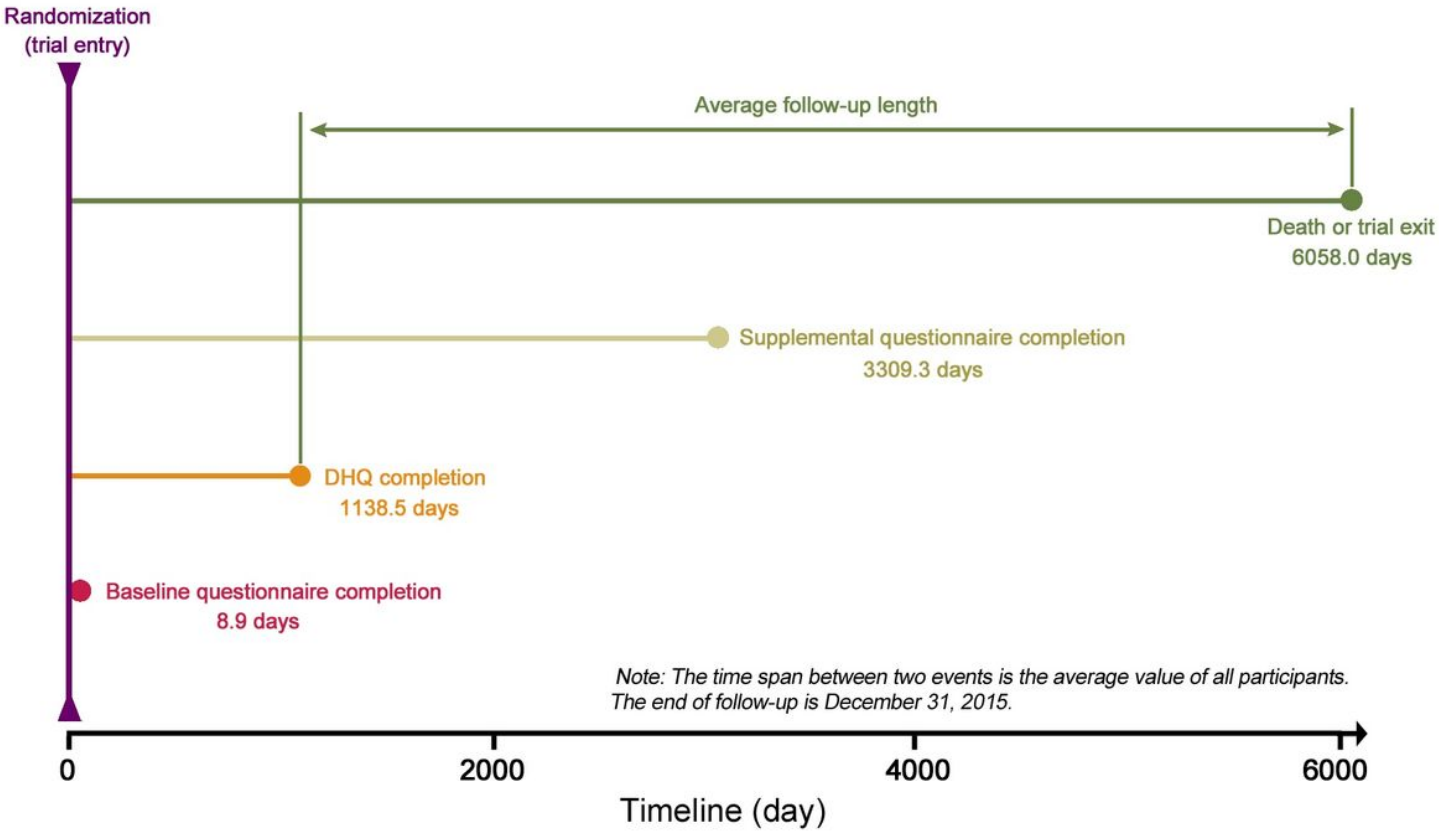

Figure 1

The timeline and follow-up scheme of the present study. DHQ, diet history questionnaire.

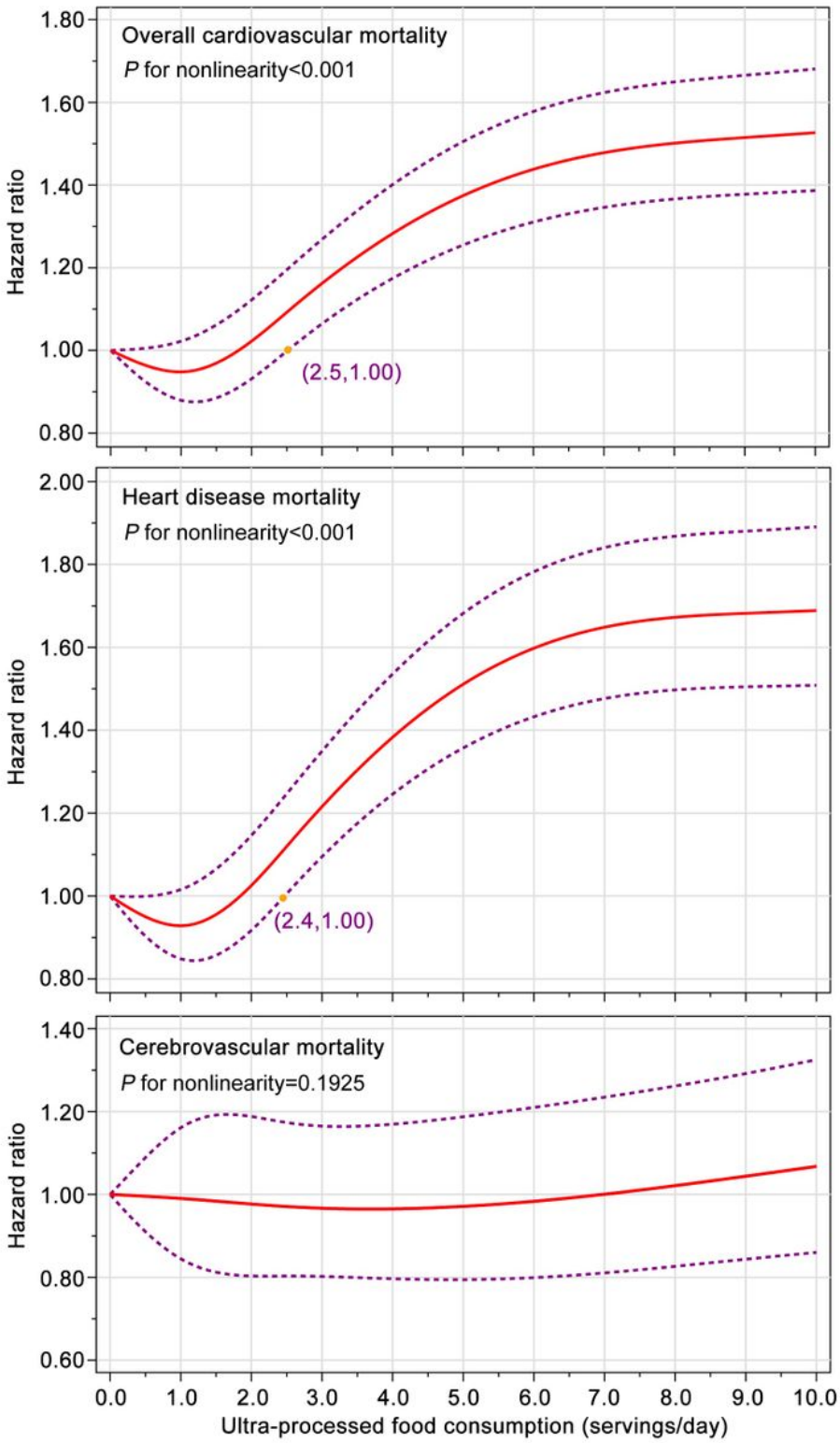

Figure 2

Nonlinear dose–response analyses on ultra-processed food consumption and cardiovascular mortality in the whole study population. The reference level was set at 0 serving/day. Hazard ratio was adjusted for age, sex, race, educational level, marital status, study center, aspirin use, history of hypertension, history of diabetes, smoking status, alcohol consumption, body mass index, physical activity level, and energy

intake from diet. The red solid line represents the fitted nonlinear trend, and the purple short-dash line represents corresponding 95% confidence interval.

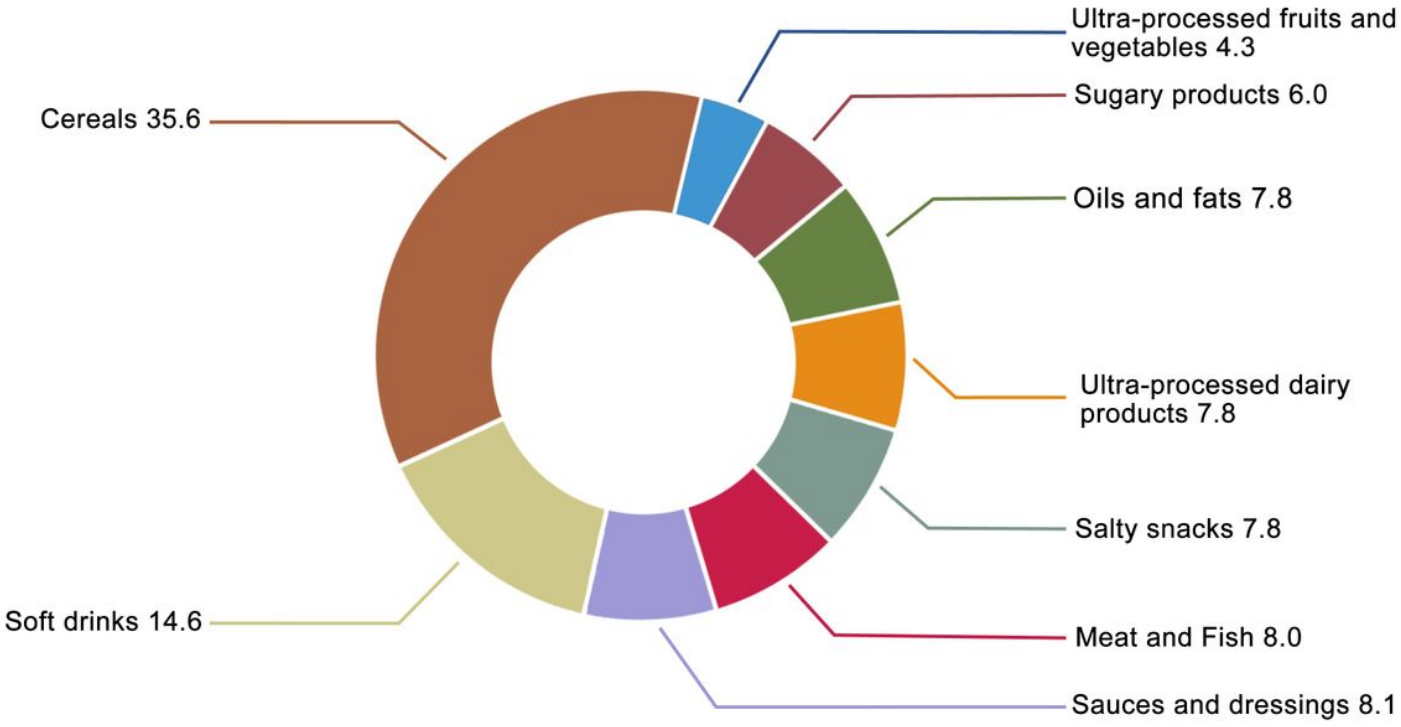

Figure 3

Proportion (%) of each food group in total amounts of ultra-processed foods in the whole study population.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- STROBEchecklistcohort.doc
- Additionalfiles.doc