Ultra-processed foods and cardiovascular disease: analysis of three large US prospective cohorts and a systematic review and meta-analysis of prospective cohort studies

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Summary

Background Prospective associations between total and groups of ultra-processed foods (UPF) and cardiovascular disease (CVD) remained to be characterised. Our aim was to assess the association of total and group-specific UPF intakes with CVD, coronary heart disease (CHD), and stroke in three large prospective cohorts of US adults. Additionally, we conducted a systematic review and meta-analyses on the existing evidence on the associations of total UPF intake with these outcomes.

Methods UPF intake was assessed through food frequency questionnaires in the Nurses' Health Study (NHS; n = 75,735), Nurses' Health Study II (NHSII; n = 90,813), and Health Professionals Follow-Up Study (HPFS; n = 40,409). Cox regression estimated cohort-specific associations of total and group-specific UPF intake with risk of CVD (cases = 16,800), CHD (cases = 10,401), and stroke (cases = 6758), subsequently pooled through fixed-effect models. Random-effects meta-analyses pooled existing prospective findings on the UPF-CVD association identified on Medline and Embase up to April 5, 2024, without language restrictions. Risk of bias was assessed with the Newcastle–Ottawa Scale, funnel plots, and Egger's tests, and meta-evidence was evaluated using NutriGrade.

Findings The baseline mean (SD) age was 50.8 years (7.2) for the NHS, 36.7 years (4.6) for the NHSII, and 53.4 years (9.6) for the HPFS. The proportion of participants of White race was 97.7% in the NHS, 96.4% in the NHSII, and 94.9% in the HPFS. Among the three cohorts, multivariable-adjusted hazard ratios [HRs (95% CIs)] for CVD, CHD, and stroke for the highest (vs. lowest) total UPF intake quintile were 1.11 (1.06–1.16), 1.16 (1.09–1.24), and 1.04 (0.96–1.12), respectively. UPF groups demonstrated divergent associations. Sugar-/artificially-sweetened drinks and processed meats were associated with higher CVD risk, whereas inverse associations were observed for bread/cold cereals, yoghurt/dairy desserts, and savoury snacks. Meta-analysing 22 prospective studies showed that total UPF intake at the highest category (vs. lowest) was associated with 17% (11%–24%), 23% (12%–34%), and 9% (3%–15%) higher CVD, CHD, and stroke risk. Meta-evidence quality was high for CHD, moderate for CVD, and low for stroke.

Interpretation Total UPF intake was adversely associated with CVD and CHD risk in US adults, corroborated by prospective studies from multiple countries, also suggesting a small excess stroke risk. Nutritional advice for cardiovascular health should consider differential consequences of group-specific UPF. Replication is needed in racially/ethnically-diverse populations.

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Research in context

Evidence before this study

We systematically searched Medline and Embase for prospective studies assessing the association between Nova-defined ultra-processed food consumption and the incidence of non-fatal myocardial infarction, fatal coronary heart disease, non-fatal/fatal stroke, and overall cardiovascular disease. For Medline, we used the following search terms: ("Cardiovascular Diseases" OR "Heart Diseases" OR "myocardial ischemia" OR "Coronary Disease" OR "Myocardial Infarction" OR "Cerebrovascular Disorders" OR "Stroke") AND ("ultra-processed" AND "food" OR "Nova"). For Embase, the terms were: ("ultra-processed" AND "food" OR "Nova") AND ("cardiovascular" AND "disease" OR "heart" AND "disease" OR "coronary" AND "heart" AND "disease" OR "cerebrovascular" AND "disease" OR "stroke"). We also screened the reference lists of eligible studies to identify additional publications. Eligible studies were limited to those published up to April 5, 2024, with no language restrictions. Our systematic search identified 19 cohort studies that reported adverse associations between total ultra-processed food intake and cardiovascular disease risk. Notably, a study revealed that the associations with cardiovascular risk varied based on the types of ultra-processed foods, showing differential directionality. While this evidence is consistent for diabetes and cancer-cardiometabolic multimorbidity, there are no other studies examining the associations of specific ultra-processed food groups with cardiovascular disease risk within the United States.

Added value of this study

Compared to published data, our study encompassed the longest follow-up duration with repeated dietary assessments spanning over three decades. Additionally, it captured a large number of disease cases, allowing us to account for long-term diet variations, control for time-varying confounding, and detect modest associations. We observed an adverse relationship between total ultra-processed food consumption and overall cardiovascular disease and coronary heart disease in three large prospective adult cohorts from the United States. We corroborated these findings with a systematic review and meta-analyses of similar studies from multiple countries, which also suggested a small significant higher stroke risk associated with the intake of these products. Furthermore, this study provides evidence on a divergent pattern of associations between ultra-processed food groups and cardiovascular risk. Sugar- and artificially sweetened beverages and processed meats were associated with higher cardiovascular disease risk, whereas inverse associations were observed for ultra-processed bread and cold cereals, yoghurt and dairy desserts, and savoury snacks.

Implications of all the available evidence

The diverse nutritional composition within these products warrants the need to deconstruct the ultra-processed food classification for a nuanced understanding of their impact on cardiovascular health. Our findings suggest that soft drinks and processed meats should be particularly discouraged, given their consistent adverse association with cardiovascular disease, coronary heart disease, and stroke. Reducing the content of sodium, saturated fats, added sugars, and cosmetic additives non-essential for human health in whole-grain bread, cold cereals, and some savoury snacks may enhance the cardioprotective benefits of the vitamins, minerals, and fibre found in some of these products. Replication in racially and ethnically diverse groups is necessary to determine these associations in other populations that may consume foods with distinctive composition.

Introduction

Ultra-processed foods (UPF) are edible products containing ingredients that extend palatability, profitability, and shelf-life. They encompass formulations with substances of rare culinary use and cosmetic additives, including stabilisers, colourants, flavour enhancers, emulsifiers, or sweeteners.[1] In the United States (US), UPF represent 57.0% of the adult population's energy intake.[2]

UPF may promote cardiovascular disease (CVD) through several mechanisms. Typical UPF contain excess calories, added sugars, sodium, and unhealthy fats[1] associated with higher CVD risk.[3–5] Beyond low nutritional quality, UPF are sources of compounds generated through production and packaging associated with glycometabolism disturbance,[6] microbiota alterations,[7] inflammation,[8] higher diabetes risk,[9] endothelial abnormalities,[10] pro-atherogenic apolipoproteins,[11] atherosclerosis,[12,13] and cardiac tissue damage.[14] These compounds are bisphenol-A,[6,9] emulsifiers,[7] thickeners,[8] advanced glycation end products,[10] sweeteners,[11] acrylamide,[12] monosodium glutamate,[13] and sulphites.[14] European and US cohort studies have consistently associated UPF consumption with higher CVD risk.[15–19] UPF are also associated with obesity, hypertension, and diabetes,[20–22] well-established CVD risk factors.[23]

Despite the accumulating evidence on UPF and CVD, a significant knowledge gap remains. UPF[1] encompass a

heterogeneous group of products ranging from mass-produced whole-grain vitamin-fortified breads,[24] to nutritionally devoid soft beverages associated with higher CVD.[25] Importantly, a US-based study showed that while artificially- and sugar-sweetened beverages, processed meats, and ready-to-eat dishes are associated with higher type 2 diabetes risk, ultra-processed whole-grain bread displays inverse associations.[22] Only one study in the US has examined whether contrasting associations by UPF groups also occur for CVD, documenting an adverse CVD risk with a higher intake of bread, processed meat, and low-calorie drinks, while a lower CVD risk with a higher breakfast cereals intake.[16]

To provide further evidence, we estimated the association of total and group-specific UPF intakes with CVD, coronary heart disease (CHD), and stroke in three large prospective cohorts of US adults. We also conducted a systematic review and meta-analyses to update the evidence of associations of total UPF intake with these outcomes.

Methods

Cohorts

Three prospective cohorts were included. The Nurses' Health Study (NHS) comprises 121,701 female nurses aged 30–55 years at recruitment (1976).[26] The Nurses' Health Study II (NHSII) recruited 116,340 women aged 25–42 years in 1989.[26] The Health Professionals Follow–up Study (HPFS) is composed of 51,529 men aged 40–75 years recruited in 1986.[27]

Exclusions applied to participants who returned only the baseline questionnaire, had prior CVD/cancer at baseline, or reported outlying energy intake (women: <500/>3500 kcal; men: <800/>4200 kcal). Participants with body mass index (BMI) < 15 kg/m^2/>50 kg/m^2 were excluded, as these values might be a proxy of cardiovascular pathophysiology[28,29] or dietary data misreport.[30] After exclusions, 75,735 NHS, 90,813 NHSII, and 40,409 HPFS participants remained in the analyses (Supplementary Fig. S1). Participants signed informed consent and the boards of the Brigham and Women's Hospital and the Harvard T.H. Chan School of Public Health approved the study.

Diet

Assessed every 2–4 years through validated food frequency questionnaires, dietary data were linked with the Harvard food frequency questionnaire items nutrient content database established in 1984.[26] This database is updated every four years with the US Department of Agriculture Nutrient Database for Standard Reference and the Food and Nutrients Database for Dietary Studies, manufacturers' data, and Harvard biochemical information.

Nova[1] was utilised to categorise foods into four groups: Unprocessed/minimally processed foods; processed culinary ingredients; processed foods; and UPF. Food frequency questionnaire items[31,32] categorisation[33] consisted of four iterative stages: creation of a list of all food frequency questionnaire items; assignment of items to Nova categories; cross-checking for consensus and shortlisting discordant items; discussion with experts supported by dieticians, cohort-specific documents, and grocery store websites scans.

UPF were divided into ten mutually exclusive groups (Supplementary Table S1) considering nutritional composition: 1) bread and cereals [sub-groups: breakfast cereals; dark/whole-grain bread; refined-grain bread]; 2) sauces, spreads, and condiments; 3) packaged sweet snacks and desserts; 4) packaged savoury snacks; 5) sugar-sweetened beverages; 6) processed red meat, poultry, and fish; 7) ready-to-eat/heat mixed dishes; 8) yoghurt/dairy-based desserts; 9) hard liquors; 10) artificially-sweetened beverages. Nine food frequency questionnaire items ("alternative" UPF), namely popcorn, soy milk, cream, pancakes/waffles, pie, chicken sandwich, beef, pork, or lamb sandwiches, tomato sauce, and potato/corn chips, had limited information on ingredient composition and were assigned to a non-UPF category in principal analyses and to UPF in sensitivity analyses.

Daily total energy and UPF intakes were calculated. UPF consumption was expressed as a percentage contribution to total energy intake and divided into quintiles. The original and a modified version of the Alternative Healthy Eating Index (AHEI)[34] were used to capture diet quality. To construct the modified score, whole grains from ultra-processed bread, and other items, namely soda, processed meats, hard liquors, fats, and sodium were removed from the AHEI; this modified score captures adherence to recommended intakes of unprocessed, minimally processed, or processed vegetables, fruits, whole grains, fruit juice, nuts, legumes, red meat, beer, and wine, which are associated with chronic disease.[34]

CVD

The outcomes were incident CHD (non-fatal myocardial infarction and fatal CHD), non-fatal and fatal stroke (ischemic and haemorrhagic), and a composite CVD outcome. Definite and probable (medical records or death certificate unavailable) cases were included; definite case-only analyses in the cohorts produced similar results.[35,36] Non-fatal cases were identified through self-reports at biennial questionnaires. Physicians blinded to the participants' dietary information confirmed or refuted cases by reviewing medical records. Myocardial infarction confirmation required symptoms and electrocardiographic abnormalities or elevated cardiac enzyme levels.[37,38] Stroke confirmation required neurological deficits of sudden or rapid onset lasting >24 h or until death, with thrombotic or embolic occlusion of a cerebral artery or clinical symptoms and signs of

spontaneous intracranial haemorrhage.[39] Fatal cases were identified through family member inquiry, the Postal Service, or the National Death Index.[40] Death certificates and medical/autopsy records further confirmed fatal events.

Covariates

Biennial questionnaires[26] inquired about information on age, race (White, African-American/Black, Asian, and others), and marital and working status. Data on smoking, physical activity, sleep duration, and use of multivitamins, aspirin, and non-steroidal anti-inflammatory drugs were collected. Participants provided information on CVD family history, menopausal hormone and oral contraceptive use (women only), body weight, height, and diagnosis status of hypertension, hypercholesterolemia, and diabetes. BMI was derived as kg/m^2.

Statistical analyses

Analyses were conducted in SAS (9.4) and Stata (17.0); statistical significance was set at $\alpha = 0.05$. To circumvent overreliance on significance testing, we integrated self-information values [*s-values* = $\log_2(p)$] when assessing primary associations. *s-values* represent the information of the data against the null hypothesis, facilitating the compatibility interpretation that is limited in *p*-values and their probability bounds; a higher *s-value* indicates stronger evidence against the null hypothesis.[41]

Cohort-specific baseline age-adjusted means, medians, or proportions of covariates were tabulated in the overall sample and across extreme UPF intake quintiles [quintile 1 (Q1) and quintile 5 (Q5)]. Dietary intakes were cumulatively averaged to account for within-person variability and long-term consumption. For example, for NHS, UPF intake data from the 1984 questionnaire were used to predict CVD incidence between June 1984 and 1986, the average of the 1984 and 1986 UPF intakes was used to predict CVD incidence between June 1986 and 1988, and so on. Generating a time-varying variable, this method uses all known UPF intake values prior to the occurrence of an event to investigate the development of CVD to best represent the participants' long-term dietary patterns during follow-up.[42,43] To alleviate potential reverse causation bias, diet updating was stopped upon cancer or diabetes diagnosis.[44] The proportion of missing data for UPF consumption at baseline was 0.0008% for NHS, 1.6% for NHSII, and 5.9% for HPFS (Supplementary Fig. S1). As these proportions were relatively immaterial to our cohort-specific final sample sizes (substantially lower than or close to 5%), we excluded them in the analyses and replaced missing intakes post-baseline with valid values from the preceding questionnaire. The missing covariate indicator method (MCIM) was implemented to deal with missingness in covariates. Analyses within our cohorts have shown that when missingness is not greater than 50%, MCIM yields estimates with relative bias greater than 10% in fewer than 5% of the cases, and then only when the covariate is a strong confounder.[45] The performance of MCIM to deal with missingness and prevent appreciable bias holds for our study, as our proportion of missing covariate values ranges from 0.1% to 13.3%. In previous analyses within our cohorts, MCIM produced results materially similar to those from the multiple imputation method.[45] For instance, in an analysis assessing the associations between a low-carbohydrate diet score and all-cause mortality, MCIM yielded a primary hazard ratio [(HR); 95% confidence interval (95% CI)] of 1.04 (0.96–1.12), and multiple imputation one of 1.06 (1.03–1.10)]. In another analysis estimating the association between skipping breakfast and incident coronary heart disease, MCIM produced a primary HR of 1.27 (1.06–1.53), and the multiple imputation method one of 1.29 (1.07–1.56). Similarly, in a study assessing the association between endometriosis and incident coronary heart disease, MCIM [HR: 1.62 (1.39–1.89)] yielded almost the same estimates as the multiple imputation method [1.63 (1.38–1.92)].[45]

The composite variable encompassing total UPF intake was utilized in our primary risk models. This approach is analogous to dietary pattern analyses, which are recommended for comprehensively considering various detrimental or beneficial dietary elements that may synergistically or antagonistically influence a specific outcome, such as the relationship between ultra-processed diets and CVD.[46,47] Age- and period-stratified Cox proportional hazards models estimated HRs and 95% CIs for the cohort-specific associations. The origin times for survival analyses are the study baselines, set to be 1984 (NHS), 1991 (NHSII), and 1986 (HPFS), when the first comprehensive food frequency questionnaire was administered. Participants' person-years were calculated from the point at which each participant returned the baseline questionnaire (start time for survival analysis) to the CVD diagnosis date, death date, date of last return of a biennial questionnaire, or the end of follow-up [June 2016 (NHS); June 2017 (NHSII); January 2016 (HPFS)], whichever happened first. We examined the possibly non-linear relation between UPF intake (continuous form) and our outcomes (risk of total CVD, CHD, and stroke) non-parametrically with restricted cubic splines.[48] We used four knots positioned at the cohort-specific 5th, 35th, 65th, and 95th percentiles of the distribution of the UPF intake variable, aimed at achieving a balance between model flexibility and simplicity. This approach ensures that the model can effectively capture non-linear relationships in both the central range and the tails of the distribution.[48] All selected confounders were included in this approach and tests for non-linearity used the likelihood ratio test, comparing the model with only the linear term to the model with the linear and the cubic spline terms (Supplementary Figs. S2–S10). The proportional

hazards assumption was assessed through separate cross-product terms between the quintile-specific median of UPF intake or each of all confounders and age in years (Supplementary Tables S2–S4).

Selection of confounders was determined by the modified disjunctive cause criterion,[49] guided by literature review. Model 1 was adjusted for energy intake (density model).[50] The principal coefficient in the density model represents the relationship between the UPF composition of the diet and CVD, holding total energy intake constant. This method entails an isocaloric approach, controls for confounding by energy intake, and accounts for imperfect dietary measurements associated with calorie intake.[50] The fully-adjusted model also included race (White and others),[51] marital (never married, married, divorced, separated, or widowed)[52] and working status (retired or not),[53] smoking status [never, past, or current smoker (1–14, 15–24, or ≥25 cigarettes/day)],[51] physical activity [quintiles of metabolic equivalents (METs)-hours/week],[51] sleep duration (≤5, six, seven, eight, nine, or ≥10 h/day),[54] family history of CVD (yes/no),[51] multivitamin,[55] aspirin[56] and non-steroidal anti-inflammatory drugs use (yes/no),[57] menopausal hormone (premenopausal, never, current, or former)[51] and oral contraceptive use (yes/no)[51]; only the baseline levels (not time-varying) of BMI (<25 kg/m^2, 25–29.9 kg/m^2, and ≥30 kg/m^2),[51] hypertension,[51] hypercholesterolemia,[51] and diabetes (yes/no)[51] were included in this model. The quintile-specific median of UPF intake was modelled as a continuous variable to obtain *p-values* for the trend through Wald tests.[58] The 10 UPF group intakes (quintiles) were simultaneously included in different models to assess their associations with CVD, CHD, and stroke risk, excluding total UPF intake to prevent collinearity. A distinct model, encompassing breakfast cereals, dark/whole-grain bread, refined-grain bread, and the remaining nine UPF groups (excluding total bread and cereals), was employed to derive estimates for the specified UPF sub-groups. Cohort estimates were pooled through fixed-effects models.

Sensitivity analyses were conducted. First, as some of the predictors exhibited non-proportional hazards, we introduced interaction terms between those covariates and a log-transformed age variable into the primary cohort risk models. This aimed to examine potential alterations in the primary estimates of the composite variable of CVD. Second, estimates were pooled through random-effects models. Third, modified definitions of total UPF were derived excluding hard liquors,[27] yoghurts,[59] and both items, given their inverse associations with cardiovascular risk. Furthermore, sugar-sweetened beverages and processed meats were excluded to evaluate an UPF pattern without products consistently adversely associated with CVD risk.[25,60] Fourth, the following analyses examined the robustness of our findings: incorporating the "alternative" UPF into the total UPF intake variable; further adjusting for the modified AHEI score; stratifying models by AHEI scores at or above the baseline median vs. below the median, and BMI ≥ 25 kg/m^2 vs. <25 kg/m^2. Cross-product terms between the quintile-specific UPF intake median and AHEI or BMI were used to evaluate interactions through Wald tests. We also conducted a four-year lagged analysis by excluding person-time and cases of the first four years of follow-up to account for potential reverse causation bias, and we fitted a model with time-varying BMI as a covariate. Three modified UPF group models were fitted to consider factors[61] potentially impacting artificially-sweetened beverages estimates: adjusting for time-varying BMI; adjusting for dieting and weight loss behaviours [self-report (yes/no) of intentional/unintentional weight loss, low-calorie diet adherence, fasting, increases in exercise, use of pills, following weight loss programs, and gastric bypass]; and adjusting for dieting and weight loss behaviours and time-varying BMI. Lastly, the original UPF group model was fitted in a four-year lagged analysis.

Systematic review and meta-analysis

Systematic review and meta-analysis were conducted to summarise existing evidence and current study findings (Supplementary Materials, Supplementary Materials for Systematic Review and Meta-analyses, Supplementary Methods). The report complies with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines.[62] The protocol was registered on the international prospective register of systematic reviews (PROSPERO CRD42023410448). Searches were conducted on Medline and Embase up to April 15, 2023. Updated searches were conducted until April 5, 2024, covering the time between the original searches and the peer review process. Search terms were entered into the search engines in English, but no language restrictions were applied when the actual searches were initiated. Risk of bias was assessed with the Newcastle–Ottawa Scale, funnel plots, and Egger's tests.

Exposure operationalisation-related heterogeneity was found in eligible studies. They utilised UPF servings/day or relative caloric or diet weight contributions. Hence, three separate random-effects meta-analyses were conducted to pool CVD, CHD, and stroke risk estimates, comparing the highest intake category vs. the lowest. Outcome-specific leave-one-out meta-analyses, stratified meta-analyses (CVD only), and random-effects meta-regressions (CVD only) explored heterogeneity. Meta-regression models used the log HR as the outcome variable and assumed a normal error distribution, except when the Knapp–Hartung adjustment (Sidik–Jonkman) was applied to models with covariate-specific strata with ≤5 studies. The quality of the meta-evidence was evaluated using NutriGrade.[63]

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Results

Cohorts

The baseline mean (SD) age was 50.8 years (7.2) for the NHS, 36.7 years (4.6) for the NHSII, and 53.4 years (9.6) for the HPFS. The proportion of participants of White race was 97.7% in the NHS, 96.4% in the NHSII, and 94.9% in the HPFS (Table 1). The mean total UPF caloric contribution ranged from 15.3–20.8% in Q1 and 42.8–49.6% in Q5, with NHSII having the highest intake [34.4% (10.3) of total energy intake]. Across cohorts, the top three UPF contributors to energy intake (median) were bread and cereals (6.4–7.4%), sweet snacks and desserts (4.5–6.3%), and ready-to-eat/heat mixed dishes (3.9–5.8%). Participants with the highest total UPF intake (vs. the lowest) had higher energy intake, lower AHEI scores, and higher prevalence of smoking and obesity.

The median [interquartile range (IQR)] of follow-up was 31.9 years (31.8, 32.0) for NHS, 26.0 (25.9, 26.1) for NHSII, and 29.7 (29.2, 29.8) for HPFS. The proportion of non-CVD deaths during the follow-up period was 20.3% for the NHS, 2.7% for the NHSII, and 24.3% for the HPFS; the proportion of loss to follow-up was 10.4% for NHS, 1.5% for NHSII, and 9.8% for HPFS. The cohort-specific and pooled HRs of incident cardiovascular outcomes are in Tables 2 and 3. Multivariable pooled HRs (95% CIs) comparing extreme total UPF intake quintiles were 1.11 (1.06–1.16; *s-value* > 13.3; *p-trend* < 0.0001) for CVD, 1.16 (1.09–1.24; *s-value* > 13.3; *p-trend* < 0.0001) for CHD, and 1.04 (0.96–1.12; *s-value* = 1.5; *p-trend* = 0.58) for stroke. NHSII participants had the highest HR for CVD [1.22 (95% CI: 1.05–1.42); *s-value* = 6.6; *p-trend* = 0.01] and CHD [1.28 (95% CI: 1.04–1.56); *s-value* = 5.8; *p-trend* = 0.01] compared with NHS and HPFS.

Sensitivity analyses showed that the cohort-specific associations between total UPF intake and CVD were the same in models with covariate-specific non-proportional hazards (Supplementary Table S5). Similarly, pooled associations of total UPF intake with CVD, CHD, and stroke were the same in random-effects models (Supplementary Table S6). The associations for total CVD and CHD persisted after removing hard liquors and yoghurt from the analysis (Fig. 1). Removing sugar-sweetened beverages and processed meats attenuated risk estimates (Q5 vs. Q1) for CVD [HR: 1.00 (95% CI: 0.96–1.05)] and CHD [HR: 1.06 (95% CI: 1.00–1.13)] and changed directionality of stroke estimates [HR: 0.92 (95% CI: 0.85–0.99)]. Associations were similar when including the nine "alternative" UPF. Adjustment for the modified AHEI scores produced attenuated HRs for CVD [1.03 (0.98–1.09)] and CHD [1.07 (1.00–1.14)]. Pooled HRs for CVD, CHD, and stroke did not substantially change after adjusting for time-varying BMI (Supplementary Table S7). Pooled HRs (95% CIs) comparing extreme total UPF intake quintiles remained statistically significant for CHD risk among participants with higher diet quality in AHEI-stratified models [1.12 (1.02–1.23; *p-trend* = 0.04)], although cross-product terms were not statistically significant. Risks for total CVD by total UPF were similar in both BMI strata; the association was higher for CHD among those with overweight/obesity [HR: 1.22 (95% CI: 1.12–1.33], but interaction terms were not significant (Supplementary Table S8). Associations between total UPF intake and CVD or CHD persisted in the four-year lagged analyses (Supplementary Table S9).

Among UPF groups (Fig. 2; Supplementary Table S10), processed meats and sugar-sweetened beverages (Q5 vs. Q1) were significantly associated with a higher risk of the three outcomes. A higher intake of artificially-sweetened beverages was associated with greater CVD and CHD risks when models were further adjusted for time-varying BMI and dieting and weight loss behaviours. Intakes of savoury snacks and yoghurt/dairy-based desserts were inversely associated with total CVD and CHD risks. A higher total intake of bread and cereals was associated with lower stroke risk. Cold cereal intake was associated with a lower risk of CVD and CHD; greater consumption of refined bread was only associated with lower stroke risk. Hard liquor intake was associated with lower CHD risk.

Systematic review and meta-analysis

Screening 2540 publications led to 19 cohort studies meeting inclusion criteria,[16–18,64–79] plus the NHS, NHSII, and HPFS (Supplementary Fig. S11 and Table S11). The studies comprise 1,261,040 adults and 63,666 CVD cases (Supplementary Table S12). Participants' age range was 18–91 years and follow-up duration was

	NHS, 1984 (n = 75,735) Total UPF intake			NHSII, 1991 (n = 90,813) Total UPF intake			HPFS, 1986 (n = 40,409) Total UPF intake		
	Overall	Total UPF Q1[a] (0.01–22.5)[b] n = 15,147	Total UPF Q5[a] (40.1–89.9)[b] n = 15,146	Overall	Total UPF Q1[a] (0.01–25.8)[b] n = 18,163	Total UPF Q5[a] (42.7–94.4)[b] n = 18,161	Overall	Total UPF Q1[a] (0.01–20.0)[b] n = 8082	Total UPF Q5[a] (36.3–86.4)[b] n = 8081
Age (years)[c], *mean (SD)*	50.8 (7.2)	52.4 (6.8)	49.5 (7.3)	36.7 (4.6)	37.3 (4.5)	36.1 (4.7)	53.4 (9.6)	55.6 (9.4)	51.3 (9.5)
Race/ethnicity, %									
White	97.7	96.4	98.4	96.4	94.1	97.1	94.9	93.5	95.4
African American	1.3	2.0	1.2	1.5	1.7	1.7	1.1	1.2	1.0
Asian	0.7	1.3	0.2	1.6	3.6	0.7	1.8	2.8	1.2
Other	0.2	0.3	0.2	0.5	0.7	0.4	2.3	2.4	2.4
% Energy[b] per day from total UPF, *mean (SD)*	31.5 (10.7)	17.3 (4.2)	47.0 (6.1)	34.4 (10.3)	20.8 (4.2)	49.6 (6.0)	28.3 (9.9)	15.3 (3.8)	42.8 (5.9)
UPF groups (%Energy[b]), *median (IQR)*									
Bread and breakfast cereals	7.4 (4.6, 10.9)	4.9 (2.9, 7.4)	9.4 (5.8, 13.6)	6.4 (4.0, 9.5)	4.9 (2.9, 7.0)	7.3 (4.3, 11.3)	6.7 (4.0, 9.8)	4.6 (2.6, 7.1)	8.5 (5.1, 12.7)
UP cold cereals	0.9 (0.1, 3.4)	0.6 (0.1, 2.6)	0.8 (0.0, 3.5)	1.4 (0.4, 3.1)	0.9 (0.3, 2.6)	1.0 (0.3, 3.0)	1.7 (0.3, 4.0)	0.8 (0.1, 3.1)	1.8 (0.3, 4.4)
UP dark bread and whole-grain breads	1.4 (0.3, 2.9)	1.4 (0.4, 2.7)	1.0 (0.2, 2.8)	1.3 (0.3, 2.6)	1.3 (0.4, 2.2)	1.0 (0.2, 2.6)	1.3 (0.3, 2.7)	1.2 (0.3, 2.3)	1.1 (0.2, 3.0)
Other UP refined bread	2.7 (1.1, 5.1)	1.3 (0.5, 2.8)	4.4 (2.0, 8.4)	2.3 (1.0, 4.3)	1.3 (0.6, 2.8)	3.2 (1.3, 6.2)	1.8 (0.6, 3.8)	0.9 (0.3, 2.1)	3.0 (1.1, 6.2)
Sweet snacks and desserts	6.3 (3.4, 10.5)	2.8 (1.2, 4.6)	12.2 (7.4, 18.7)	6.2 (3.7, 9.8)	3.4 (1.8, 5.2)	10.5 (6.3, 16.2)	4.5 (2.2, 7.7)	1.9 (0.7, 3.4)	8.8 (5.1, 13.5)
Savoury snacks	0.1 (0.01, 0.2)	0.1 (0.01, 0.2)	0.1 (0.01, 0.2)	0.3 (0.1, 0.6)	0.2 (0.1, 0.4)	0.3 (0.1, 0.8)	0.1 (0.01, 0.11)	0.1 (0.01, 0.11)	0.1 (0.01, 0.1)
Sauces, spreads, and condiments	3.4 (1.9, 5.4)	2.3 (1.1, 3.8)	4.1 (2.3, 6.5)	2.3 (1.3, 3.7)	1.6 (0.8, 2.7)	2.6 (1.4, 4.4)	2.0 (0.9, 3.4)	1.2 (0.5, 2.2)	2.5 (1.3, 4.3)
Processed red meat, poultry, and fish	1.7 (0.8, 3.1)	1.0 (0.1, 1.9)	2.3 (1.3, 4.1)	2.7 (1.6, 4.4)	2.1 (1.1, 3.4)	3.0 (1.7, 4.9)	1.4 (0.6, 2.8)	0.7 (0.1, 1.5)	2.0 (1.0, 3.8)
Ready-to-eat/heat mixed dishes	3.9 (1.9, 5.9)	2.1 (0.1, 3.9)	5.0 (3.0, 7.4)	5.8 (3.9, 8.2)	4.0 (2.5, 5.6)	7.5 (5.1, 11.9)	4.6 (2.6, 7.2)	2.7 (1.1, 4.3)	6.5 (3.9, 10.1)
Yoghurt and dairy-based desserts	0.9 (0.5, 2.1)	0.7 (0.1, 1.2)	1.1 (0.6, 3.1)	1.0 (0.5, 1.9)	0.7 (0.4, 1.3)	1.0 (0.6, 2.4)	1.0 (0.4, 2.3)	0.6 (0.1, 1.2)	1.4 (0.6, 3.2)
Sugar-sweetened beverages	0.8 (0.1, 2.9)	0.1 (0.01, 0.8)	2.7 (0.6, 8.3)	1.1 (0.1, 4.7)	0.1 (0.09, 1.4)	4.7 (0.6, 13.8)	0.9 (0.1, 3.3)	0.1 (0.01, 0.9)	3.1 (0.6, 7.5)
Artificially-sweetened beverages (servings/day)	0.1 (0.01, 0.9)	0.1 (0.01, 0.9)	0.1 (0.01, 0.9)	0.5 (0.1, 1.3)	0.3 (0.1, 1.0)	0.5 (0.1, 2.0)	0.1 (0.01, 0.6)	0.1 (0.01, 0.4)	0.1 (0.01, 0.9)
Hard liquors	0.1 (0.01,0.1)	0.1 (0.01, 0.2)	0.1 (0.01, 0.2)	0.1 (0.01, 0.11)	0.1 (0.01, 0.11)	0.1 (0.01, 0.11)	0.1 (0.01, 0.3)	0.1 (0.01, 0.3)	0.1 (0.01, 0.2)
Total energy intake (kcal/day), *mean (SD)*	1745.0 (531.0)	1589.0 (504.0)	1873.0 (572.0)	1788.0 (547.0)	1705.0 (521.0)	1860.0 (587.0)	1982.0 (616.0)	1883.0 (596.0)	2069.0 (661.0)
AHEI score (points), *mean (SD)*	48.3 (10.8)	54.7 (11.3)	42.5 (9.1)	48.6 (11.0)	55.1 (11.0)	42.1 (9.6)	52.8 (11.5)	59.1 (11.7)	46.8 (10.0)
Smoking status, %									
Never smoker	44.1	41.6	43.2	65.5	62.9	66.0	48.2	48.5	48.6
Past smoker	31.7	36.3	26.7	22.3	25.3	19.5	42.8	44.1	40.7
Current smoker, 1–14 cigarettes/day	7.5	7.4	8.4	5.5	5.7	5.4	2.8	2.6	2.7
15–24 cigarettes/day	9.7	8.7	11.6	4.7	4.4	6.1	3.3	2.9	3.6
25+ cigarettes/day	7.0	6.0	10.0	2.0	1.7	2.9	3.0	2.0	4.4
Family history of cardiovascular disease, %	19.5	20.1	19.1	49.8	48.8	50.7	12.2	12.4	12.7
Cardiovascular risk factors at baseline, %									
Body mass index (BMI), *mean (SD)*	25.0 (4.7)	24.6 (4.4)	25.4 (5.1)	24.6 (5.1)	24.0 (4.5)	25.1 (5.7)	25.4 (3.1)	25.1 (3.1)	25.7 (3.2)
Overweight (BMI 25–29.9 kg/m^2)	26.6	25.5	26.7	20.7	19.7	20.5	44.5	39.9	45.9
Obesity (BMI ≥ 30 kg/m^2)	13.3	10.7	15.8	13.4	9.8	17.6	7.6	6.2	8.9
Hypertension	8.1	8.4	7.9	3.3	3.1	3.9	20.4	21.3	20.5
Hypercholesterolemia	3.5	4.2	3.7	9.5	8.6	11.0	11.0	12.2	10.3
Diabetes	3.1	4.0	2.3	1.0	1.3	0.7	2.6	3.5	1.7
Multivitamin use, %	37.0	44.5	31.7	43.9	48.2	39.2	32.5	36.5	29.6
Aspirin use, %	71.1	67.3	71.7	11.3	10.7	12.1	27.0	24.8	28.1
Non-steroidal anti-inflammatory drugs use, %	36.3	33.4	37.1	19.3	18.1	21.1	5.4	4.7	6.1

UPF: Ultra-processed foods; AHEI, The Alternative Healthy Eating Index (AHEI). [a]Quintiles of energy proportion from UPF in the total calorie intake. [b]Energy proportion from UPF in the total calorie intake. [c]Not age-adjusted.

Table 1: **Age-standardised baseline characteristics of the Nurses' Health Study (NHS), NHSII, and the Health Professionals Follow-Up Study (HPFS) participants, according to total ultra-processed food intake.**

Nurses' Health Study (NHS)	Total UPF intake																	
	Q2[a]				Q3[a]				Q4[a]				Q5[a]					p for trend[b]
	HR	95% CI		p	HR	95% CI		p	HR	95% CI		p	HR	95% CI		p	s[d]	
Total CVD, 8446 cases/2104181 person-years																		
Age- and energy-adjusted	1.04	0.97	1.11	0.32	1.02	0.96	1.10	0.49	1.09	1.02	1.16	0.01	1.20	1.12	1.28	<0.0001	>13.3	<0.0001
Fully-adjusted model[c]	1.06	0.99	1.13	0.10	1.02	0.95	1.09	0.62	1.05	0.98	1.12	0.20	1.05	0.98	1.13	0.13	2.9	0.21
CHD, 4622 cases/2106706 person-years																		
Age- and energy-adjusted	1.05	0.95	1.15	0.33	1.05	0.96	1.15	0.30	1.14	1.04	1.25	0.01	1.29	1.18	1.41	<0.0001	>13.3	<0.0001
Fully-adjusted model[c]	1.09	0.99	1.19	0.08	1.05	0.96	1.16	0.29	1.09	0.99	1.20	0.07	1.11	1.01	1.22	0.03	5.1	0.04
Stroke, 4142 cases/2106517 person-year																		
Age- and energy-adjusted	1.01	0.92	1.11	0.78	1.00	0.91	1.11	0.93	1.05	0.95	1.15	0.34	1.12	1.01	1.23	0.03	5.3	0.02
Fully-adjusted model[c]	1.02	0.93	1.12	0.67	0.99	0.90	1.09	0.84	1.01	0.92	1.12	0.83	1.02	0.92	1.12	0.76	0.4	0.84
Nurses' Health Study II (NHSII)																		
Total CVD, 1668 cases/2309642 person-years																		
Age- and energy-adjusted	1.01	0.86	1.18	0.91	1.03	0.88	1.21	0.71	1.16	1.00	1.36	0.06	1.50	1.29	1.74	<0.0001	>13.3	<0.0001
Fully-adjusted model[c]	0.97	0.82	1.13	0.66	0.96	0.82	1.13	0.61	1.04	0.89	1.22	0.61	1.22	1.05	1.42	0.01	6.6	0.01
CHD, 889 cases/2310402 person-year																		
Age- and energy-adjusted	0.91	0.73	1.14	0.42	1.02	0.82	1.26	0.86	1.07	0.86	1.32	0.56	1.63	1.34	1.99	<0.0001	>13.3	<0.0001
Fully-adjusted model[c]	0.87	0.70	1.08	0.21	0.94	0.76	1.17	0.58	0.95	0.76	1.18	0.64	1.28	1.04	1.56	0.02	5.8	0.01
Stroke, 786 cases/2310399 person-years																		
Age- and energy-adjusted	1.13	0.90	1.41	0.31	1.04	0.82	1.31	0.74	1.29	1.03	1.61	0.03	1.36	1.09	1.70	0.01	7.2	0.01
Fully-adjusted model[c]	1.08	0.86	1.35	0.53	0.98	0.77	1.24	0.85	1.16	0.93	1.46	0.19	1.16	0.92	1.46	0.21	2.3	0.16
Health Professionals Follow-Up Study (HPFS)																		
Total CVD, 6686 cases/974073 person-years																		
Age- and energy-adjusted	1.03	0.96	1.11	0.39	1.05	0.98	1.13	0.18	1.03	0.95	1.11	0.48	1.17	1.08	1.26	<0.0001	>13.3	0.01
Fully-adjusted model[c]	1.06	0.98	1.14	0.15	1.08	1.01	1.17	0.04	1.05	0.97	1.13	0.22	1.15	1.07	1.24	0.01	11.7	0.01
CHD, 4890 cases/975454 person-year																		
Age- and energy-adjusted	1.01	0.93	1.10	0.78	1.03	0.94	1.12	0.54	1.05	0.96	1.15	0.30	1.19	1.09	1.30	<0.0001	>13.3	0.01
Fully-adjusted model[c]	1.04	0.96	1.14	0.35	1.07	0.98	1.17	0.14	1.08	0.99	1.19	0.08	1.19	1.09	1.30	0.01	13.3	0.01
Stroke, 1830 cases/976459 person-years																		
Age- and energy-adjusted	1.09	0.95	1.26	0.22	1.12	0.97	1.29	0.12	0.97	0.84	1.13	0.71	1.09	0.94	1.26	0.25	2.0	0.62
Fully-adjusted model[c]	1.10	0.95	1.26	0.19	1.12	0.97	1.29	0.13	0.96	0.83	1.12	0.59	1.04	0.90	1.21	0.60	0.7	0.87

UPF, Ultra-processed foods; CVD, cardiovascular disease; CHD, Coronary Heart Disease; NSAI, Non-steroidal-inflammatory drugs; BMI, body mass index. [a]Quintiles of energy proportion from total UPF intake in the total energy intake. Quintile one (not shown) was the reference category. [b]The median value of UPF intake within each quintile category was modelled as a continuous variable to calculate *p-value* for trend. [c]Multivariable Cox regression stratified by age in months and calendar year in two-year intervals was used to estimate the associations of cumulatively-averaged UPF intake quintiles with CVD risk. The model was adjusted for race/ethnicity, marital status, working status, smoking status, quintiles of physical activity (MET-hours/week), sleep patterns (hours/day), family history of CVD, multivitamin use, aspirin use, NSAID use, menopausal hormone use status (women only), oral contraceptive use (women only), energy intake, BMI at baseline, hypertension at baseline, hypercholesterolemia at baseline, and diabetes at baseline. We stopped updating the diet after the participant's diagnosis of cancer or diabetes. NHS and NHSII only included women, and HPFS only included men; therefore, cohort-specific models inherently controlled for sex. [d]*s-values*: $-\log_2(p)$. The *s-value* is the number of bits of information against the null hypothesis (HR = 1.0); a higher *s-value* indicates stronger evidence against the null hypothesis.

Table 2: **Hazard ratios and 95% confidence intervals for total cardiovascular disease, coronary heart disease, and stroke associated with total UPF intake in three US cohorts of women and men: the NHS (n = 75,735; 1984–2016), NHS II (n = 90,813; 1991–2017), and HPFS (n = 40,409; 1986–2016).**

5.2–32.0 years. Nine studies had UPF intake repeated measurements, nine were conducted in the US, and 13 utilised probabilistic sampling methods (vs. convenience sampling). UPF intake was operationalised as servings/frequency in 11 studies, diet weight percentage in seven, or percentage energy contribution in three studies. All studies used Cox regression to calculate risk estimates. The Newcastle–Ottawa Scale score was 7.2 (Supplementary Table S13). Funnel plots and Egger's tests revealed no risk of bias (Supplementary Figs. S12–S14).

In meta-analyses comparing the highest vs. lowest total UPF intake (Fig. 3), the pooled HRs for CVD, CHD, and stroke were 1.17 [95% CI: 1.11–1.24; I^2: 76.4%; *s-value* > 13.3], 1.23 [95% CI: 1.12–1.34; I^2: 79.8%; *s-value* > 13.3], and 1.09 [95% CI: 1.03–1.15; I^2: 9.8%; *s-value* > 13.3], respectively. Leave-one-out meta-analyses (Supplementary Figs. S15–S17) detected that excluding the Zhong et al. study decreased the pooled HRs for CVD and CHD to 1.13 (1.09–1.18) and 1.17 (1.12–1.22), respectively; the weight of this study in CVD and CHD meta-analyses was 7.2% and 10.6%, respectively (Fig. 3). Stratification (Supplementary Figs. S18–S22) displayed differences in the pooled HRs for total CVD in US vs. non-US studies, using probabilistic sampling vs. not, and in studies with

	Total UPF intake																		
	Q2[b]				Q3[b]				Q4[b]				Q5[b]						p for trend[d]
	HR	95% CI		p	HR	95% CI		p	HR	95% CI		p	HR	95% CI		p	s[f]	I^2, %[c]	
Total CVD, 16,800 cases/5387896 person-years																			
Age- and energy-adjusted model	1.03	0.98	1.08	0.20	1.04	0.99	1.09	0.15	1.07	1.02	1.12	0.01	1.21	1.16	1.27	<0.0001	>13.3	78.1	<0.0001
Fully-adjusted model[e]	1.05	1.00	1.10	0.05	1.04	0.99	1.09	0.13	1.05	1.00	1.10	0.07	1.11	1.06	1.16	<0.0001	>13.3	55.2	<0.0001
CHD, 10,401 cases/5392562 person-years																			
Age- and energy-adjusted model	1.02	0.96	1.08	0.54	1.04	0.98	1.10	0.25	1.09	1.02	1.16	0.01	1.27	1.20	1.35	<0.0001	>13.3	76.2	<0.0001
Fully-adjusted model[e]	1.05	0.99	1.11	0.14	1.05	0.99	1.12	0.12	1.08	1.01	1.14	0.02	1.16	1.09	1.24	<0.0001	>13.3	3.8	<0.0001
Stroke, 6758 cases/5393375 person-years																			
Age- and energy-adjusted model	1.05	0.97	1.13	0.23	1.04	0.96	1.12	0.31	1.05	0.98	1.14	0.19	1.13	1.05	1.22	0.01	10.0	31.2	0.01
Fully-adjusted model[e]	1.05	0.97	1.13	0.22	1.02	0.95	1.10	0.55	1.01	0.94	1.10	0.73	1.04	0.96	1.12	0.35	1.5	<0.1	0.58

NHS, Nurses' Health Study; HPFS, the Health Professionals Follow-Up Study; UPF, Ultra-processed foods; CVD, cardiovascular disease; CHD, Coronary Heart Disease; NSAI, Non-steroidal-inflammatory drugs; BMI, body mass index; I^2: the percentage of the total variability in the set of effect sizes due to heterogeneity (fixed effects models). [a]Cohort-specific estimates were meta-analysed with fixed-effects models. [b]Quintiles of energy proportion from total UPF intake in the total energy intake. Quintile one (not shown) was the reference category. [c]I^2 statistics were obtained for each pair of quintile comparisons (i.e., Q5 vs. Q1, Q4 vs. Q1, Q3 vs. Q1, and Q2 vs. Q1); only I^2 for Q5 vs. Q1 is shown. [d]The median value of UPF intake within each quintile category was modelled as a continuous variable to calculate the *p-value* for trend. [e]Multivariable Cox regression stratified by age in months and the calendar year in two-year intervals was used to estimate the associations of cumulatively-averaged UPF intake quintiles with CVD risk. The model was adjusted for race/ethnicity, marital status, working status, smoking status, quintiles of physical activity (MET-hours/week), sleep patterns (hours/day), family history of CVD, multivitamin use, aspirin use, NSAID use, menopausal hormone use status (women only), oral contraceptive use (women only), energy intake, BMI at baseline, hypertension at baseline, hypercholesterolemia at baseline, and diabetes at baseline. We stopped updating the diet after the participant's diagnosis of cancer or diabetes. NHS and NHSII only included women, and HPFS only included men; therefore, cohort-specific models inherently controlled for sex. [f]*s-values*: −log2(*p*). The *s-value* is the number of bits of information against the null hypothesis (HR = 1.0); a higher *s-value* indicates stronger evidence against the null hypothesis.

Table 3: **Pooled[a] hazard ratios and 95% confidence intervals for total cardiovascular disease, coronary heart disease, and stroke associated with total UPF intake in three large prospective cohorts in the US: the NHS (n = 75,735; 1984–2016), NHS II (n = 90,813; 1991–2017), and HPFS (n = 40,409; 1986–2016).**

different UPF intake operationalisations; however, meta-regression coefficients were not statistically significant (Supplementary Table S14). According to NutriGrade (Supplementary Table S15), the meta-evidence was high-quality (score: 8.0) for CHD, moderate-quality (6.9) for CVD, and low-quality (5.9) for stroke. Follow-up duration <10 years, insufficient studies (<10 only for stroke), between-study heterogeneity ≥ 40%, and small measures of association reduced the quality of meta-evidence.

Discussion

Higher total UPF intake was adversely associated with higher risk of CVD and CHD in the NHS, NHSII, and HPFS, robustly in multiple sensitivity analyses. Pooling findings from 19 cohort studies[16–18,64–79] provided a relevant amount of data (large *s*-values equivalent to small *p*-values) to strongly support evidence on adverse associations of total UPF intake with risk of CVD, CHD, and stroke. The quality of meta-evidence was deemed high for CHD, whose point estimate (1.23) and corresponding intervals (1.12–1.34) respectively surpassed or closely surrounded a clinically relevant measure of association (1.20).[63] Although meta-evidence quality was moderate for CVD and low for stroke, these quality scores were largely penalized by research methodology, and their homogeneous directionality reflects plausible biological harm. Of note, divergent associations were observed for specific UPF groups in our cohorts. Sugar-sweetened beverages, processed meats, and artificially-sweetened beverages were associated with higher CVD and CHD risk. Conversely, ultra-processed savoury snacks, cold cereals, and yoghurt/dairy-based desserts were inversely associated with CVD and CHD risk. Ultra-processed bread and cold cereals were associated with lower stroke risk, and hard liquors with lower CHD risk.

Our findings suggest that UPF groups have differential contributions to cardiovascular risk, consistent with a study in the US showing an inverse association of breakfast cereals and adverse associations of processed meat and artificially-sweetened beverages with CVD.[16] The divergent associations pattern may underlie the stronger associations of UPF consumption with CVD and CHD risk in the NHSII than in the other two cohorts. Indeed, the daily total calorie intake of NHSII participants had higher levels of sugar-sweetened beverages, processed meats, and artificially-sweetened beverages, and lower levels of yoghurt/dairy-based desserts and cold cereals, compared with the NHS and HPFS counterparts at the highest UPF intake category. Similar heterogeneous associations by UPF groups for diabetes[22] and cancer-cardiometabolic multimorbidity[79] have been observed in the US[22] and Europe.[79] These data suggest that UPF are not a homogeneous entity concerning their nutritional quality and role in cardiovascular risk.

Typical UPF (e.g., sugar-sweetened beverages, processed meats, fast foods) are energy-dense and high in added sugars, saturated fats, and sodium, established CVD risk factors.[3–5] Albeit not focused on food

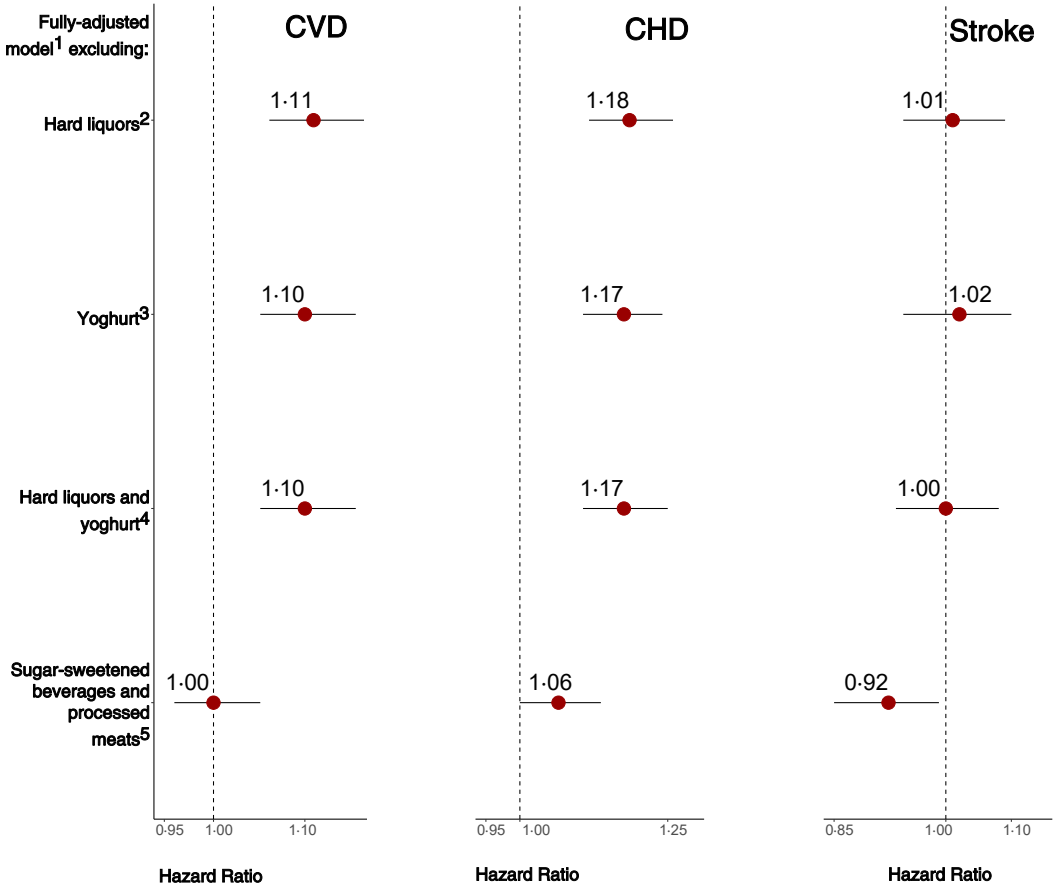

***Fig. 1:* Association between UPF intake (highest vs. lowest quintile) and cardiovascular disease in three US cohorts, excluding liquors, yoghurt, sugar-sweetened beverages, and processed meats.** Cohort-specific estimates from the NHS (n = 75,735; 1984–2016), NHS II (n = 90,813; 1991–2017), and HPFS (n = 40,409; 1986–2016) were meta-analysed with fixed-effects models. Pooled hazard ratios and 95% confidence intervals for total cardiovascular disease, coronary heart disease, and stroke are presented. [1]Multivariable Cox regression stratified by age in months and the calendar year in two-year intervals was used to estimate the associations between cumulatively-averaged UPF intake and CVD risk. The models were adjusted for race/ethnicity, marital status, working status, smoking status, quintiles of physical activity (MET-hours/week), sleep patterns (hours/day), family history of CVD, multivitamin use, aspirin use, NSAID use, menopausal hormone use status (women only), oral contraceptive use (women only), energy intake, BMI at baseline, hypertension at baseline, hypercholesterolemia at baseline, and diabetes at baseline. NHS and NHSII only included women, and HPFS only included men; therefore, cohort-specific models inherently controlled for sex. [2]Hard liquors (e.g., whiskey, vodka, brandy, rum) were removed from the variable reflecting total UPF intake. [3]Sugar-sweetened flavoured and artificially-sweetened yoghurt were removed from the variable reflecting total UPF intake. [4]Both yoghurt and hard liquors were removed from the variable reflecting total UPF intake (notice that dairy desserts were included). [5]Both ultra-processed sugar-sweetened beverages and meat were removed from the total UPF intake variable. Abbreviations: NHS, Nurses' Health Study; HPFS, the Health Professionals Follow-Up Study; UPF, ultra-processed foods; UP, ultra-processed; CVD, cardiovascular disease; CHD, Coronary Heart Disease; NSAID, Non-steroidal-inflammatory drugs; BMI, body mass index.

processing, a large body of literature[25,60] has consistently associated sugar-sweetened beverages and processed meats with CVD, similarly for artificially-sweetened beverages.[25] Compounds introduced into UPF during production and packaging may also elevate CVD risk. Bisphenol-A in plastic or metallic containers is linked to glycometabolism disturbance[6] and higher diabetes risk.[9] Advanced glycation end products in fried bacon and margarines are associated with endothelial disruption.[10] Acrylamide[12] in breakfast cereals and bread, and monosodium glutamate[13] in many UPF can promote atherosclerosis. Sulphites,[14] emulsifiers,[7] thickeners,[8] and sweeteners[11] are associated with cardiac tissue damage, metabolic syndrome-inducing microbiota alterations, inflammation, and pro-atherogenic apolipoproteins, respectively.

Conversely, the relatively high content of fibre, minerals, phenolic compounds, and other whole-grain ingredients in some ultra-processed bread, cereals,[24] and savoury snacks (e.g., popcorn)[24] may explain their

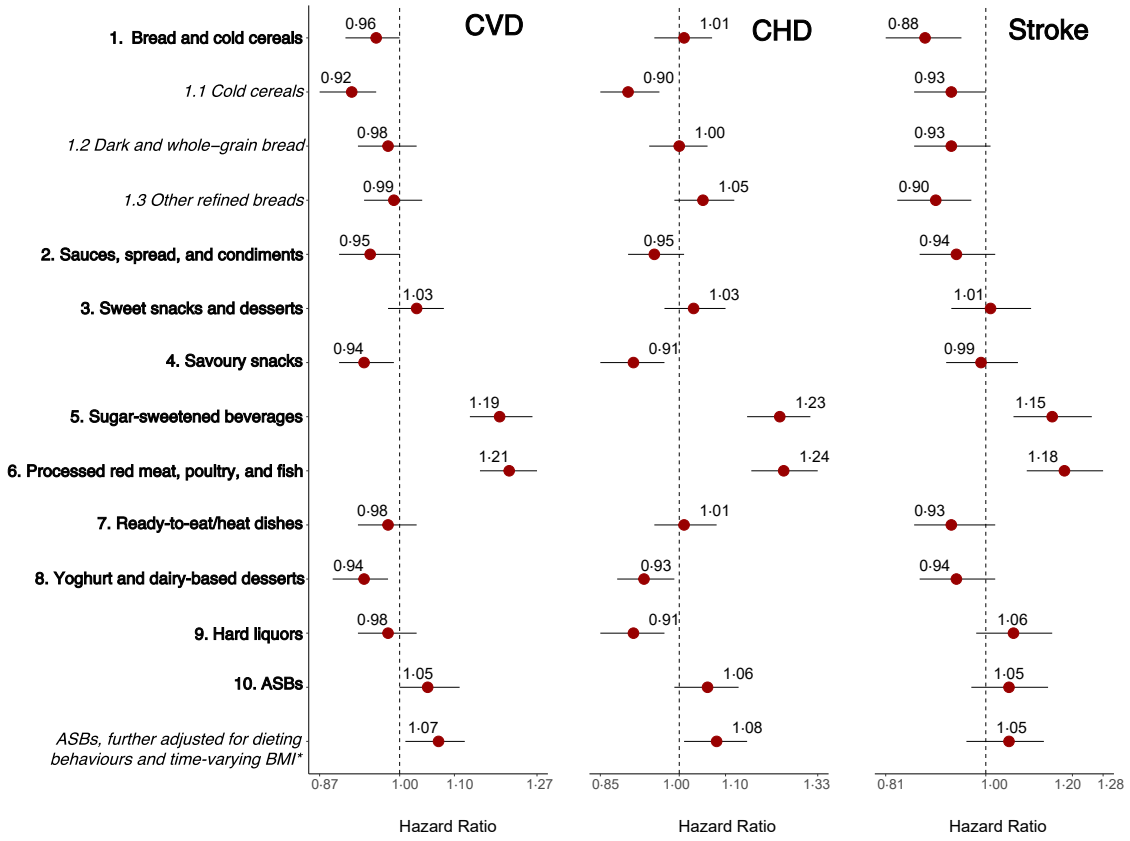

Fig. 2: **Association between group-specific UPF intake (highest vs. lowest quintile) and cardiovascular disease in three US cohorts.** Cohort-specific estimates from the NHS (n = 75,735; 1984–2016), NHS II (n = 90,813; 1991–2017), and HPFS (n = 40,409; 1986–2016) were meta-analysed with fixed-effects models. Pooled hazard ratios and 95% confidence intervals for total cardiovascular disease, coronary heart disease, and stroke are presented. Multivariable Cox regression stratified by age in months and the calendar year in two-year intervals was used to estimate the associations between cumulatively-averaged UPF group intake and CVD risk. All UPF groups were simultaneously included in the model as distinct covariables, adjusting for race/ethnicity, marital status, working status, smoking status, quintiles of physical activity (MET-hours/week), sleep patterns (hours/day), family history of CVD, multivitamin use, aspirin use, NSAID use, menopausal hormone use status (women only), oral contraceptive use (women only), energy intake, BMI at baseline, hypertension at baseline, hypercholesterolemia at baseline, and diabetes at baseline. NHS and NHSII only included women, and HPFS only included men; therefore, cohort-specific models inherently controlled for sex. *A separate model was fit to evaluate the effect of artificially-sweetened beverages, further adjusting for dieting and loss weight behaviours (i.e., self-report of intentional and unintentional weight loss, adherence to low-calorie diets, fasting, increases in exercise, use of pills, following weight loss programs, gastric bypass, and other methods) and time-varying BMI. Abbreviations: NHS, Nurses' Health Study; HPFS, the Health Professionals Follow-Up Study; UPF, ultra-processed foods; CVD, cardiovascular disease; CHD, Coronary Heart Disease; NSAID, Non-steroidal-inflammatory drugs; BMI, body mass index ASBs: artificially sweetened beverages.

inverse association with cardiovascular outcomes. Cold cereals are usually fortified with micronutrients, including B vitamins linked to lower homocysteine levels and stroke risk.[80] Our results of lower CVD risk for yoghurt/dairy-based desserts agree with evidence suggesting neutral or positive cardiovascular benefits from dairy products not always meeting UPF characteristics, especially fermented plain yoghurt.[81–84] Despite their usually high saturated fat and added sugar content, probiotic bacteria or odd-chain fatty acids in yoghurt/dairy-based desserts may contribute to lower cardiovascular risk.[59] Lastly, the inverse association of hard liquors with CHD aligns with existing evidence. Moderate alcohol consumption, regardless of beverage type [i.e., fermented (processed products: beer and wine) or distilled (UPF: spirits)], has been associated with lower CHD risk in some studies.[85–87] Also, modest ethanol[85] intake is associated with increased high-density lipoprotein-cholesterol, insulin sensitivity, and modulation of inflammation.[85]

Our analysis holds two significant advantages over existing literature. First, the repeated assessments of diet and covariates over three decades of follow-up (the longest duration in the reviewed studies) captured

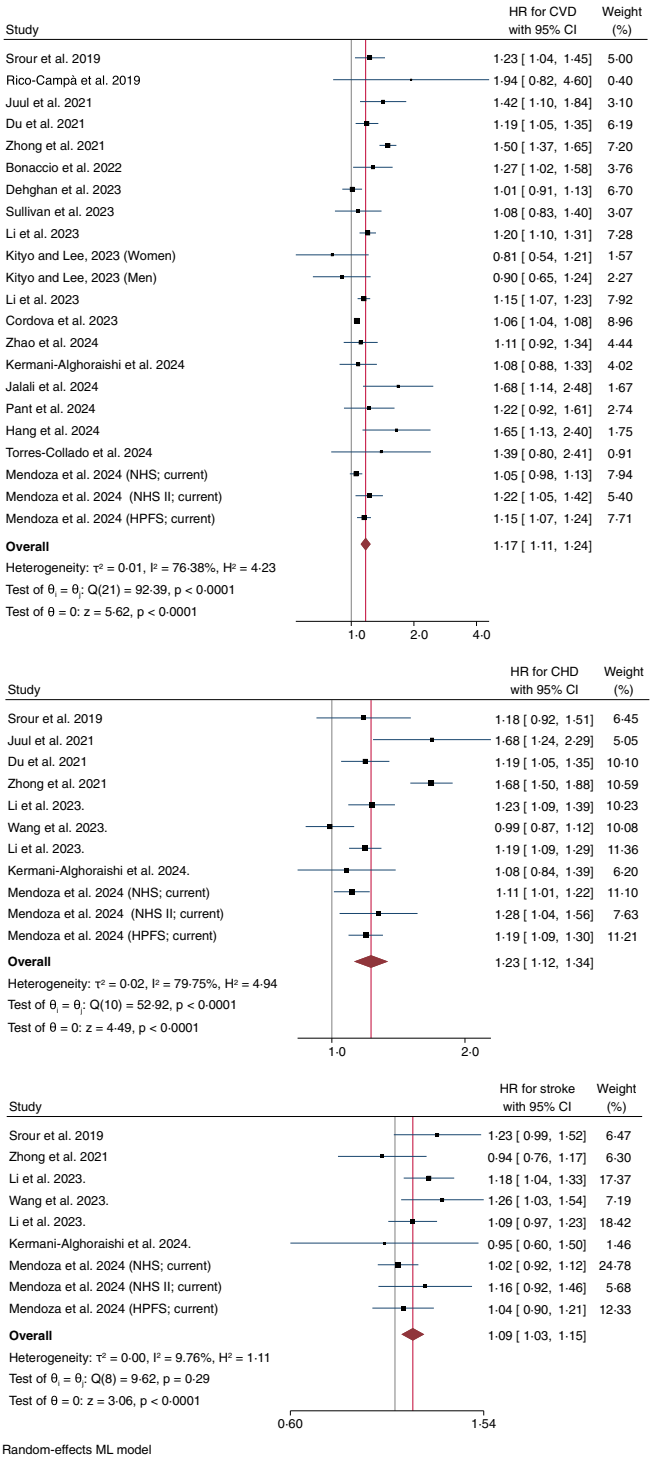

Fig. 3: **Random-effects meta-analyses of prospective cohort studies on the association of total UPF consumption (high vs. low) with CVD, CHD, and stroke risk.** Top: Association between UPF intake and fatal and non-fatal CVD events; 95% CI for I^2 = 64.5, 84.3; 95% CI for H^2 = 2.8, 6.4. Middle: Association between UPF intake and fatal and non-fatal CHD events; 95% CI for I^2 = 64.5, 88.4; 95% CI for H^2 = 2.8, 8.7. Bottom: Association between UPF intake and fatal and non-fatal stroke events; 95% CI for I^2 = 0.001, 68.2; 95% CI for H^2 = 0.4, 3.1. Abbreviations. HR, hazard ratio; ML, maximum likelihood; CVD, cardiovascular disease; CHD, coronary heart disease; NHS, the Nurses' Health Study; HPFS, the Health Professionals Follow-Up Study.

within-person variation in total UPF intake and UPF group intakes and allowed controlling for time-varying confounding. Second, a large number of CVD cases, as compared with previous studies, facilitated sufficient statistical power to detect small to modest associations, which are particularly expected when deconstructing the total UPF intake variable and evaluating the associations of UPF groups with CVD risk. Furthermore, our results on the divergent associations across UPF groups replicate findings from a single previous study conducted in the US,[16] strengthening the collective evidence. Of note, future research must undertake meticulously designed food-specific isocaloric replacement analyses[88–90] to scrutinize the associations between the displacement of specific equivalent non-UPF by UPF groups and their role on CVD. These analyses will address one of the proposed concepts for reducing UPF intake, which is enabling substitution with less processed and healthier options, such as fruits, vegetables, nuts, and fish.

Still, some limitations exist. First, our food frequency questionnaires were not designed to capture food processing information. However, our iterative UPF classification process involved several data sources,[33] only 4.4% of food frequency questionnaire items had an uncertain categorisation due to insufficient information,[33] and our findings are robust to the inclusion of these items. Furthermore, food frequency questionnaires not constructed to identify Nova groups validly rank UPF consumption.[91,92] Second, we were unable to assess the specific associations of ultra-processed yoghurt separately from dairy based-desserts throughout the entire follow-up as it was incorporated into food frequency questionnaires after the baseline, in 1994. Third, between-study heterogeneity regarding UPF operationalisation prevented us from conducting dose–response meta-analyses. Nevertheless, trend analyses in our cohorts provided data on the linear UPF-CVD association. Fourth, the generalizability of NHS, NHSII, and HPFS findings is limited, as the sample comprises health professionals mostly of white race and slightly higher socioeconomic status.[26] The low prevalence of non-White participants (2.3% to 5.1%) in our cohorts prevented us from conducting stratified analyses by race or ethnicity. The UPF contribution to total energy intake in these cohorts (28.3–34.4%) was lower than that of the US adult population aged over 19 years (57.0%)[2] in 2018. As UPF intake has been reportedly lower with increasing age[93] and in the previous decades,[2] these differences can be partially explained by the older age range of our cohorts, as well as by an earlier baseline period of statistical estimations (1984–1991). Furthermore, CVD rates differ by racial/ethnic groups in the US and several countries[94–97]; UPF in these populations might have a differential composition, necessitating further studies with UPF group analyses. Fifth, statistical software limitations precluded us from assessing additive interaction and calculating corresponding point estimates and standard errors. Assessing this type of heterogeneity in the UPF-CVD relationship can be preferred in terms of both causality and public health[98] and so should be assessed in future studies. Sixth, even with multivariable adjustments, unmeasured, measurement error-related, or residual confounding cannot be excluded in our observational design. Although we prevented overadjustment for major mediators via correct model specification and exposure operationalisation, other potential mediation effects of time-varying cofounders[99] specific to our cohorts may have affected our cohort estimates. Finally, as in other studies, our HRs inherently possess limitations that preclude causal interpretations.[100]

Data from three US cohorts and the existing evidence[16–18,64–79] suggest an adverse role of the consumption of total UPF as part of a dietary pattern in the risk of CVD, CHD, and stroke. Deconstructing the UPF classification provided more evidence to support the notion that the role of both food processing and nutritional quality in cardiovascular health shall be considered for individual UPF groups. Specifically, our findings suggest soft drinks and processed meats should be discouraged, given their consistent adverse association with CVD, CHD, and stroke. Reducing the content of sodium, saturated fats, added sugars, and cosmetic additives non-essential for human health in whole-grain bread, cold cereals, and some savoury snacks may enhance the otherwise nutritional value of these products in the US. Importantly, replication in racially/ethnically-diverse populations is needed to determine potential divergent associations in other populations, as they might reflect a differential quality of UPF that may need to be considered in nutritional advice and public health actions.

Contributors

The current study was conceptualized and designed by KM, JM, QS, and SAS-W. KM conducted data curation, formal analysis, wrote the original manuscript draft, and addressed editions suggested by the rest of the authors. QS, JM, WCW, and JEM oversaw all analyses, offering comprehensive insights to refine both principal and sensitivity analyses. KM and SLR directly accessed and verified the underlying data reported in the manuscript and conducted an internal technical review to ensure concordance between statistical software outputs and data presented in the manuscript, tables, and figures. JM and QS contributed equally and took primary responsibility for the final manuscript content, with JM coordinating the submission and peer review processes. All authors critically reviewed the manuscript, tables, and figures for pertinent subject matter knowledge content and approved the final version.

Data sharing statement

External investigators interested in accessing the resources of the studies need to submit a research plan as per the policies and guidelines for access to questionnaire data and other resources published on (https://nurseshealthstudy.org/researchers and https://www.hsph.harvard.edu/hpfs/for-collaborators/). The Nurses' Health Study (NHS), NHSII, and Health Professionals Follow-Up Study (HPFS) advisory committees will review the plan and data sharing will be facilitated by a data enclave or similar approaches.

Declaration of interests
The authors declare no conflict of interest.

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Appendix A. Supplementary data
Supplementary data related to this article can be found at https://doi.org/10.1016/j.lana.2024.100859.

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