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FULL RESEARCH PAPER
Nutrition/obesity (diet, alcohol)

Exposure to ultra-processed food and risk of cardiovascular mortality: a prospective cohort study

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Aims There has been a global shift from nutrient-dense diets to an ultra-processed food pattern, which is linked to adverse health outcomes, including cardiovascular mortality. However, there is limited evidence in an Australian setting. Furthermore, many people in Australia have emigrated from countries with heart-healthy diets. This study explored the association between ultra-processed food exposure and cardiovascular mortality in an Australian cohort.

Methods and results Data were derived from the Melbourne Collaborative Cohort Study. Food frequency questionnaire data collected at baseline were used to estimate ultra-processed food exposure according to the Nova classification system. Cardiovascular deaths were identified using data linkage between baseline (1990–94) and 31 March 2019. Fine and Gray competing risk models were fitted to assess the association between energy-adjusted ultra-processed food exposure and cardiovascular mortality, accounting for other types of mortality as competing risks. We included 39 544 participants (mean age 55.1 years at baseline, 60% female). During the follow-up period, which spanned 919 379 person-years and a median follow-up of 25.1 years, 4229 cardiovascular deaths occurred. After adjusting for sociodemographic, lifestyle, and health-related factors, participants with the highest relative intake of ultra-processed food had 19% higher risk of cardiovascular mortality (hazard ratio$_{\text{high (quartile 4) vs. low (quartile 1) category}}$ = 1.19, 95% confidence intervals: 1.09–1.29, *P*-value for trend < 0.001).

Conclusion Aligning with findings from the USA and Europe, higher exposure to the ultra-processed food pattern was prospectively associated with a higher risk of cardiovascular mortality.

Lay summary There is growing evidence that ultra-processed foods, foods that undergo extensive industrial processing and are often high in added sugars, unhealthy fats, and additives, may harm heart health. This study looked at the link between eating these foods and heart-related deaths in over 39 000 Australians followed over 25 years. We found that people eating and drinking higher amounts of ultra-processed food had a 19% higher risk of dying from heart disease compared to those who ate less. This relationship remained after considering factors like age, sociodemographic, lifestyle, and other health issues.

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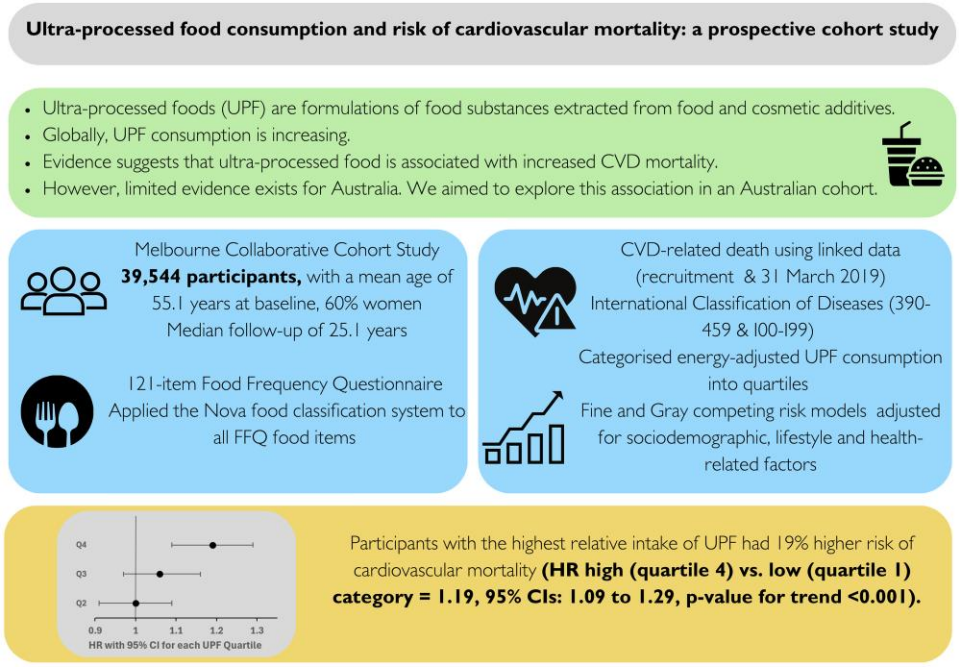
Graphical Abstract



Keywords Ultra-processed food • Nova food classification system • Dietary intake • Cardiovascular disease • Cardiovascular mortality

Introduction

It is well established that greater exposure to nutrient-dense dietary patterns, such as the Mediterranean diet, is effective for the primary and secondary prevention of cardiovascular disease (CVD).[1–3] In the Australian context, many people have emigrated from countries where there is a consumption of dietary patterns that are protective against CVD.[4] However, industrialization of the food supply in contemporary Australia and elsewhere has led to an increased proportion of people's dietary intake coming from ultra-processed foods.[5] As defined by the Nova food classification system, ultra-processed foods include a wide range of food products characterized by extensive industrial processing, usually including chemically modified substances extracted from foods, and additives to enhance taste, texture, appearance, and shelf life.[6] While there is substantial variation within and between countries and regions in the extent to which ultra-processed foods dominate dietary patterns, recent evidence shows that 42% of the total energy intake in Australia comes from ultra-processed foods—higher than in France (31%) but lower than in the USA (58%).[7,8] This is concerning as there is growing evidence that exposure to an ultra-processed food pattern is associated with a higher risk of cardiometabolic diseases and mortality.[9–11]

Our team recently led an umbrella review exploring the association between exposure to an ultra-processed food pattern and 32 adverse health outcomes.[9] In the pooled analysis for CVD, we found direct associations between greater ultra-processed food exposure and higher risk of CVD mortality as well as incident cardiovascular disease events, hypertension, hypertriglyceridaemia, and low HDL cholesterol. However, the association between ultra-processed food and CVD-related mortality was based on only four dose–response and five non-dose–response analyses, none of which were from an Australian cohort.[9] In the Framingham Offspring Study, each additional daily serving of ultra-processed food was associated with a 5% higher risk of CVD incidence and a 9% higher risk of CVD mortality.[11] Likewise, in the French NutriNet-Santé cohort study, compared to those with lower intake, those in the highest intake quartile of ultra-processed food had a higher risk of CVD.[10] Our umbrella review classed the quality of this evidence as very low using the GRADE criteria due to inconsistent or heterogeneous between-study effect estimates (I^2 value more than 50).[8] Therefore, given the substantial heterogeneity and low-quality meta-evidence, additional cohort studies are needed to strengthen the overall evidence base. This study thus aimed to expand the current evidence by prospectively determining the association between high exposure to the ultra-processed food dietary pattern and the risk of CVD mortality in a cohort of Australian men and women using data from the Melbourne Collaborative Cohort Study (MCCS). We hypothesized that higher exposure to the ultra-processed food pattern at baseline would be prospectively associated with CVD mortality.

Methods

Cohort profile

A detailed description of the MCCS cohort has been previously published.[12] In brief, 41 513 participants between the ages of 27 and 76 years were recruited from Melbourne and surrounding areas between 1990 and 1994. Of these, 59% were women, and 99% were aged between 40 and 69 years. Specific strategies were followed to recruit migrants from southern Europe, who constituted 24% of the sample. These participants have distinct dietary and lifestyle patterns from those born in Australia or New Zealand (69%) and Northern Europe (6%).[13] Self-reported

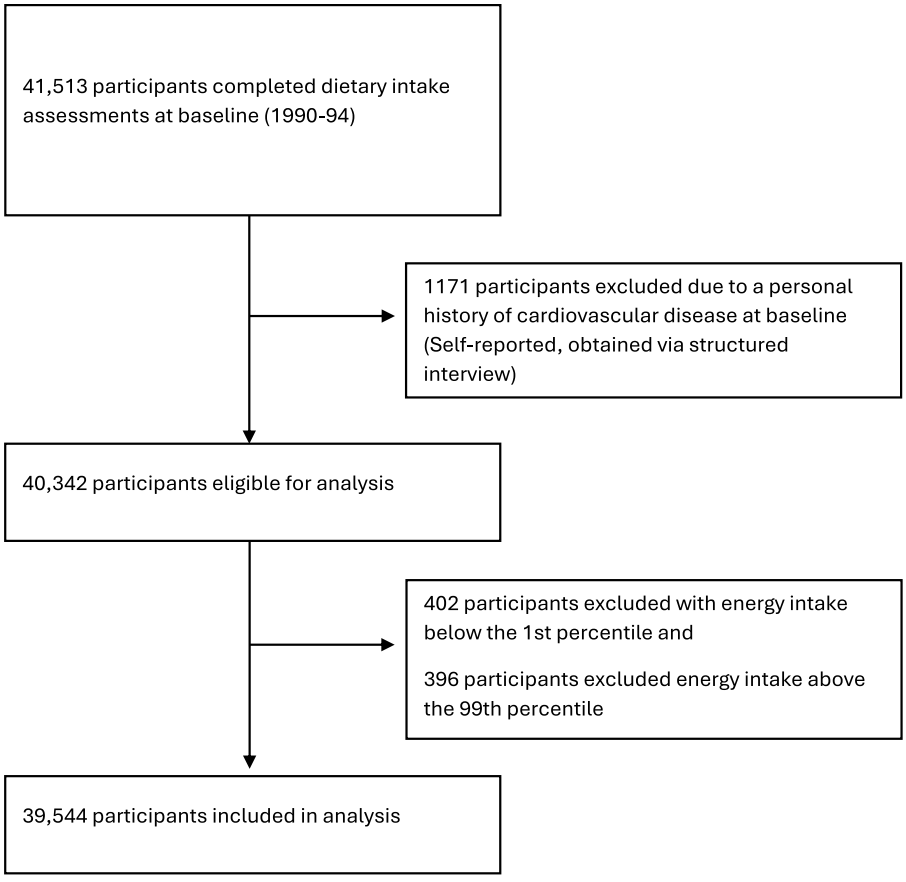


Figure 1 Flow-chart of participant selection. MCCS, Melbourne Collaborative Cohort Study.

demographics, lifestyle, health conditions, drug and medication information, dietary intake data, anthropometric measures, and blood samples were collected at baseline during face-to-face visits.

The MCCS cohort is regularly linked with the National Death Index, which provides data on mortality, including cause of death. Participants were eligible for inclusion in the present study if baseline dietary data and follow-up CVD mortality data linkage were complete (*Figure 1*).

Ethics approval and pre-registration

The MCCS is an Australian cohort study investigating associations between diet, lifestyle, and chronic non-communicable diseases.[12] The Cancer Council Victoria's Human Research Ethics Committee approved the original protocol for the MCCS. All participants provided written informed consent to participate and for researchers to access their medical records. The current study was approved for exemption from ethical review in accordance with the National Statement on Ethical Conduct in Human Research (2007, updated 2018) Section 5.1.22 by the Deakin University Human Research Ethics Committee (project number: 2023-185).

The current study was prospectively registered with the Open Science Framework (OSF) registry (https://osf.io/ryjuw) and reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement and checklist for cohort studies (see Supplementary material).

Exposure: dietary assessment

Participants completed a 121-item semi-quantitative Food Frequency Questionnaire (FFQ) at baseline, evaluating their dietary habits over the last 12 months. Using this dietary data, exposure to the ultra-processed food pattern was calculated using methods described in detail elsewhere[14] and in line with previous studies that have used this dataset.[15] In brief, we applied the Nova categorization system to place foods into one of four categories (Groups 1–3 are non-ultra-processed foods). Nova Group 1 includes unprocessed or minimally processed foods such as rice, meat, fish, and vegetables. Nova Group 2 includes processed culinary ingredients such as sugar, plant oils, and butter. Nova Group 3 includes processed foods such as processed bread, cheese, canned fruit, fish, and vegetables, and salted and smoked meats. Foods within Nova Group 4 are classified as ultra-processed foods, the category of interest in the current study; this includes soft drinks, sweet or savoury packaged snacks, confectionery, packaged bread and buns, margarine, reconstituted meat products, and pre-prepared frozen or shelf-stable dishes when these products are made up of food substances of no culinary use and/or contain classes of additives with cosmetic function. Two authors applied the Nova food classification system to all FFQ food items.[16]

The mean daily intake of ultra-processed foods was determined by converting frequencies into grams. This was based on sex-specific portion sizes of each food and multiplied by the daily equivalent frequency as per previous research.[17–19] Energy was estimated based on the Nutrient Data Table for Use in Australia 1995 (NUTTAB 95), a food composition database containing information for 1800 foods and beverages available in Australia.[20]

Outcome: cardiovascular disease mortality

Cardiovascular-related deaths were included in the analysis if occurring between the recruitment date and 31 March 2019, when data linkage was conducted. Mortality and specific causes were ascertained through linkage with

the Victorian Registry of Births, Deaths and Marriages, and the National Death Index. Deaths due to CVD were coded by the Australian Bureau of Statistics and defined based on underlying cause of death codes from the 9th and 10th revisions of the International Classification of Diseases (390–459 and I00–I99), respectively. Other types of mortality were considered as competing risk.

Assessment of covariates

Covariates were pre-identified based on prior research.[10,21] These covariates, assessed during baseline interviews, encompassed various sociodemographic factors, lifestyle, and health-related behaviours, and history of non-communicable diseases.

The sociodemographic factors considered included sex, age, education level, country of birth, marital status, household size, and the Socio-Economic Indexes for Areas (SEIFA), which measures the relative socioeconomic advantage or disadvantage within specific geographic areas based on postal code.[22] SEIFA scores were categorized into quintiles, with the lowest representing the most disadvantaged and the highest representing the least disadvantaged.

Additionally, lifestyle and health-related factors were considered, such as smoking status, alcohol consumption, and physical activity over the previous six months. These sociodemographic and lifestyle factors served as covariates in the main models. Physical activity was scored from 0 to 16, depending on the frequency and intensity of activities like walking and vigorous exercise. This score was then divided into categories ranging from 0 to ≥6, categorized as 0 [none], >0 and <4 [low], ≥4 and <6 [moderate], and ≥6 [high].[23]

Additional exploratory analyses were further adjusted to account for the potential mechanisms related to diet quality by using the Alternative Healthy Eating Index-2010 (AHEI-2010)[24] and FFQ estimated nutrient, fruit, and vegetable intakes.[19] The AHEI 2010 diet score ranges from 0 to 110; higher scores reflect 'healthier' diets.[24] These adjustments were made to determine whether any associations found with ultra-processed food were independent of overall diet quality.

Statistical analyses

Participant characteristics were summarized using the mean and standard deviation (SD) for continuous variables and frequency and percentage for categorical variables. To account for ultra-processed foods that offer little or no energy, such as artificially sweetened drinks, the total weight of ultra-processed foods [grams per day (g/d)] was used instead of energy.[10,15] This weight was adjusted for energy intake using Willett's residual method and used as the model exposure.[25] This approach considers the residuals from the regression, which represent the differences between participants' actual intake of ultra-processed food and the intake predicted by their total energy consumption.[25] To align with most observational studies on ultra-processed foods, which divide exposure into quantiles,[9] we categorized our exposure into quartiles based on its distribution in the dataset. Participants with a personal history of CVD at baseline were excluded ($n = 1171$), as well as those reporting energy intake above the 99th percentile or below the 1st percentile ($n = 798$).

We used Fine and Gray competing risk models to assess the association between energy-adjusted ultra-processed food consumption (as a categorical variable) and CVD mortality. A complete case analysis was performed. This primary analysis differed from the original analysis described in the pre-registration as this method accounts for other types of mortality as competing risk.[26] Quartile 1 was used as the reference, and hazard ratios (HRs) of quartiles 2 to 4, along with their 95% confidence intervals (HRs, 95% CIs) presented. Different sequential models were fitted to evaluate the association between energy-adjusted ultra-processed food consumption and CVD mortality. Model 1 was the unadjusted model. In Model 2, sociodemographic factors were incorporated. These factors included sex (male or female), age (as a continuous variable), education level (above or below high school), country of birth (with categories Australia/New Zealand, Southern Europe, or Northern Europe), marital status (married or in a relationship vs. not married or single), household size (with categories of 1, 2, 3–4, or 5+), and SEIFA scores (quintiles, Q1, Q2, Q3, Q4, or Q5), representing socioeconomic status. Model 3, the fully adjusted model, included lifestyle and health-related factors, smoking status (never smoked, current smoker, and former smoker), alcohol intake (categorized as lifetime abstainers, ex-drinkers, and current drinkers with subcategories for daily intake: 19, 20–29, 30–39, and 40+ g/d), and physical activity over the past six months. Model 3 was considered the main model. Trend was assessed by treating the quartiles of energy-adjusted ultra-processed food intake as a continuous, ordinal variable (Q1, Q2, Q3, or Q4). The proportional hazards assumption was assessed visually using Kaplan–Meier survival curves stratified by quartiles of energy-adjusted ultra-processed food intake.[27]

As an exploratory analysis to investigate whether potential mediators such as diet quality influenced the association between energy-adjusted ultra-processed food consumption and CVD mortality, models were additionally adjusted for the AHEI score (0–110) (Model 4); as well as for 'risk nutrients' linked to CVD, such as sugar (g/d), saturated fat (g/d), and sodium [milligrams per day (mg/d)] (Model 5); and fruit and vegetable intake [times per day (t/d)] (Model 6).

Furthermore, sensitivity analyses were designed to evaluate the robustness of the findings and reduce the potential impact of reverse causality by excluding participants with a personal history of type-2 diabetes ($n = 408$) or a body mass index (BMI) of 30 kg/m^2 or more at baseline ($n = 8052$). In addition, we conducted a *post hoc* analysis to determine the association between ultra-processed food consumption in energy [kilojoules per day (kJ/d)] and CVD mortality. We also conducted a *post hoc* analysis to determine the association between ultra-processed food consumption and coronary heart disease mortality, the most common form of CVD. Further exploratory analyses assessed potential effect modification by incorporating two-way interaction terms between energy-adjusted ultra-processed food consumption and sex (male vs. female), age (<55 years vs. ≥ 55 years), BMI (<30 kg/m^2 vs. ≥ 30 kg/m^2), and country of birth (Australia/New Zealand vs. Southern Europe and Northern Europe). Subsequently, stratified analyses were conducted if evidence of interaction was observed. Lastly, the shape of the dose–response association between the consumption of ultra-processed food and the risk of elevated cardiovascular mortality was estimated with restricted cubic spline analysis.[28]

All statistical tests were two-tailed. Although we defined statistical significance by a *P*-value of <0.05, we focused on point estimates, 95% CIs, and exact *P*-values to assess the strength of our findings rather than relying solely on this *P*-value threshold.[29] Analyses were undertaken using R version 4.2.1 (2022-06-23).[30]

Results

Participant characteristics

Table 1 describes the participants' sociodemographic and lifestyle characteristics at baseline (as well as age at baseline and follow-up) according to quartiles of ultra-processed food consumption. Participants in the highest two ultra-processed food quartiles were more likely to have tertiary education and less likely to be married. They were also more likely to be born in Australia or New Zealand, live alone and have a higher BMI.

Main analysis

During the follow-up period, which spanned 919 379 person-years and a median follow-up time of 25.1 years (interquartile range of 23.6–26.4 years), 4229 CVD deaths occurred. *Table 2* shows the associations between exposure to the energy-adjusted ultra-processed food pattern and the risk of CVD mortality. In Model 1, a higher intake was associated with 26% higher risk

Table 1 Descriptive characteristics of the study population at baseline according to ultra-processed food consumption

	Quartiles of energy-adjusted ultra-processed food intake (g/d)				
***n* (frequency)**	**Q1 (*N* = 9886)**	**Q2 (*N* = 9886)**	**Q3 (*N* = 9886)**	**Q4 (*N* = 9886)**	**Total (*N* = 39 544)**
Age (years) at baseline—mean (SD)	54.9 (8.5)	55.0 (8.6)	55.3 (8.7)	55.2 (8.8)	55.1 (8.7)
Female	5577 (56.4%)	6361 (64.3%)	6371 (64.4%)	5409 (54.7%)	23 718 (60.0%)
At least some tertiary education[a]	7368 (74.5%)	7982 (80.7%)	8343 (84.4%)	8347 (84.4%)	32 040 (81.0%)
Place of birth					
Born in Australian/New Zealand	5904 (59.7%)	6794 (68.7%)	7346 (74.3%)	7237 (73.2%)	27 281 (69.0%)
Northern Europe	634 (6.4%)	668 (6.8%)	658 (6.7%)	583 (5.9%)	2543 (6.4%)
Southern Europe	3348 (33.9%)	2424 (24.5%)	1882 (19.0%)	2066 (20.9%)	9720 (24.6%)
Top quintile of SEIFA index (least disadvantaged)[b]	2829 (28.8%)	2721 (27.7%)	2598 (26.4%)	2341 (23.8%)	10 489 (26.7%)
Married/*de facto*	7833 (79.2%)	7664 (77.5%)	7538 (76.2%)	7497 (75.8%)	30 532 (77.2%)
Lives alone	1242 (12.6%)	1406 (14.2%)	1549 (15.7%)	1541 (15.6%)	5738 (14.5%)
Smoking status					
Current smoker	1063 (10.8%)	1093 (11.1%)	1135 (11.5%)	1133 (11.5%)	4424 (11.2%)
Never smoked	5647 (57.1%)	5908 (59.8%)	5840 (59.1%)	5564 (56.3%)	22 959 (58.1%)
Former smoker	3176 (32.1%)	2885 (29.2%)	2911 (29.4%)	3188 (32.3%)	12 160 (30.8%)
High physical activity score[c] (≥6)	2387 (24.1%)	2170 (22.0%)	2095 (21.2%)	2199 (22.2%)	8851 (22.4%)
Alcohol intake of up to 19 g/d	4039 (41.7%)	4370 (44.8%)	4371 (44.8%)	4023 (41.5%)	16 803 (43.2%)
Body mass index					
Body mass index (kg/m^2)—mean (SD)	26.7 (4.2)	26.6 (4.4)	26.7 (4.4)	27.5 (4.6)	26.9 (4.4)
Body mass index (kg/m^2) ≥ 30	1850 (18.7%)	1881 (19.0%)	1913 (19.4%)	2408 (24.4%)	8052 (20.4%)
Personal history of diabetes	85 (0.9%)	107 (1.1%)	94 (1.0%)	122 (1.2%)	408 (1.0%)
Personal history of cancer	685 (6.9%)	729 (7.4%)	777 (7.9%)	802 (8.1%)	2993 (7.6%)
Diet/energy					
Proportion (%) of energy-adjusted ultra-processed food (g/d)—mean (SD)	15.6 (5.4)	20.7 (5.4)	26.9 (6.2)	37.8 (10.2)	25.2 (10.9)
Proportion (%) of ultra-processed food (kJ/d)—mean (SD)	30.0 (9.3)	37.9 (9.3)	44.4 (10.4)	47.4 (11.7)	39.9 (12.2)
Total energy-adjusted ultra-processed food (g/d)—mean (SD)	275.0 (120.8)	296.7 (125.0)	375.7 (134.1)	665.5 (325.0)	403.2 (250.6)
Total ultra-processed food (kJ/d)—mean (SD)	2709.7 (1369.7)	2848.8 (1402.9)	3366.3 (1567.8)	4007.5 (1852.2)	3233.1 (1641.0)
Total energy intake (kJ/d)—mean (SD)	8737.5 (2587.6)	7242.6 (2329.4)	7403.6 (2429.2)	8269.8 (2658.1)	7913.4 (2578.9)

[a]People who had some study towards a tertiary degree or diploma as well as people who had completed a tertiary degree or diploma.
[b]SEIFA = Socio-Economic Indexes for Areas.
[c]Ordinal score based on frequency of walking, plus frequency of less vigorous activity, plus twice the frequency of vigorous activity, and ranging from 0 to 16.

Table 2 Associations between energy-adjusted ultra-processed food intake (g/d) and cardiovascular mortality in the Melbourne Collaborative Cohort Study, 1990–2019: Fine and Gray competing risk models

	Q1 (275 g/d) HR (95% CI)	**Q2 (297 g/d) HR (95% CI)**	**Q3 (376 g/d) HR (95% CI)**	**Q4 (666 g/d) HR (95% CI)**	***P*-value for trend**
No. cases/non-cases	983/8903	972/8914	1058/8828	1216/8670	
Model 1[a]	1.0 (ref)	0.99 (0.91–1.08)	1.08 (0.99–1.18)	1.26 (1.15–1.37)	<0.001
Model 2[b]	1.0 (ref)	1.01 (0.93–1.11)	1.08 (0.99–1.18)	1.19 (1.09–1.30)	<0.001
Model 3[c]	1.0 (ref)	1.00 (0.91–1.09)	1.06 (0.97–1.16)	1.19 (1.09–1.29)	<0.001

[a]Model 1 = unadjusted.
[b]Model 2 = adjusted for sociodemographic characteristics: sex (male, female), age (continuous), education (above, below high school), country of birth (Australia/New Zealand, Southern Europe, Northern Europe), marital status (married or in a relationship, not married or single), number of people occupying household (1, 2, 3–4, 5+), and SEIFA quintiles (Q1–Q5).
[c]Model 3 = Model 2 + additionally adjusted for lifestyle and health-related behaviours: smoking status (never smoked, current smoker, former smoker), physical activity over the last 6 months (0 [none], >0 and <4 [low], ≥4 and <6 [moderate], ≥6 [high]), and alcohol intake (g/d) (lifetime abstainers, ex-drinkers, up to 19, 20–29, 30–39, 40+).

of CVD mortality ($HR_{\text{high (quartile 4) vs. low (quartile 1) category}} = 1.26$, 95% CIs: 1.15–1.37, *P*-value for trend < 0.001). Results remained significant after adjusting for sociodemographic characteristics and lifestyle and health-related behaviours in Models 2 and 3 ($HR_{\text{high (quartile 4) vs. low (quartile 1) category}} = 1.19$, 95% CIs: 1.09–1.30, *P*-value for trend < 0.001; $HR_{\text{high (quartile 4) vs. low (quartile 1) category}} = 1.19$,

95% CIs: 1.09–1.29, *P*-value for trend < 0.001, respectively). Further adjustment for several indicators of dietary quality, including the AHEI score, sugar, saturated fat, and sodium intakes, as well as fruit and vegetable intakes, did not alter the main findings (see Supplementary material online, *Table S1*, Models 4–6).

Sensitivity and *post hoc* analyses

Sensitivity analyses that excluded people with a history of diabetes or a BMI of 30 kg/m^2 or higher did not affect the results in terms of the direction and magnitude of effect estimates (see Supplementary material online, *Table S1*). The *post hoc* analysis using energy from ultra-processed food exposure instead of grams did not affect the direction of effect estimates (see Supplementary material online, *Table S2*). However, after adjustment for sociodemographic characteristics and lifestyle and health-related behaviours (Models 2 and 3), the 95% CIs crossed the null (see Supplementary material online, *Table S3*). The *post hoc* analysis examining the association between ultra-processed food consumption and coronary heart disease mortality was consistent with our primary finding (see Supplementary material online, *Table S4*). We found no evidence for an interaction of sex (male, female), age (<55 years, ≥55 years), BMI (BMI < 30, BMI ≥ 30), or country of birth (Australia/New Zealand, Southern Europe, Northern Europe) with ultra-processed food intake ($P > 0.05$). Thus, stratified analyses were not conducted. Additionally, restricted cubic spline analysis was used to assess the shape of the dose–response association, this showed that an increase in ultra-processed food consumption was associated with a higher risk of cardiovascular mortality; however, consistent with the main models (*Table 2*), participants in the top quartile (fourth) had a higher risk of cardiovascular mortality compared to participants in the first three quartiles (see Supplementary material online, *Figure S1*).

Discussion

In this study, higher exposure to the ultra-processed food pattern was associated with a 19% higher risk of CVD mortality over a median follow-up time of 25.1 years after adjusting for sociodemographic, lifestyle, and health-related behaviours. Additional adjustments for diet quality did not attenuate the association. To our knowledge, this is the first study to explore the association between ultra-processed food exposure and CVD mortality in a cohort of Australian women and men.

Our main findings are consistent with our recent umbrella review.[9] In the pooled analysis for CVD, we found direct associations between greater ultra-processed food pattern exposure and higher risk of CVD mortality [risk ratio = 1.50; 95% CIs: 1.37–1.24]. However, not all past studies have reported consistent results. In another study exploring all-cause and specific mortality ($n = 114\,064$), no association between ultra-processed food and CVD mortality was observed [odds ratio (OR) = 1.05, 95% CI: 0.99–1.11; *P*-value for trend = 0.164].[31] This null association may be explained by over-adjustment in the model; for example, Fang *et al.*[31] adjusted for BMI, which may be a potential mediator as opposed to a confounder in this association.

Potential mechanisms of action

Ultra-processed food has been suggested to affect CVD through direct and indirect pathways and mechanisms.[32] Ultra-processed foods tend to be higher in sodium, energy density, trans fat, and sugar and lower in fibre.[6] In addition, ultra-processed foods have minimal bioactive compounds, such as polyphenols, which have demonstrated anti-inflammatory properties in humans.[33] Such nutrient profiles (high in sodium, energy density, trans fat, and sugar and lower in fibre[6]) have been repeatedly shown to increase the risk of CVD[34,35] and may disrupt related metabolic pathways. For example, ultra-processed foods such as sugar-sweetened beverages have been implicated in disrupted glucose control and insulin dysregulation.[36] This increases the risk of CVD through increased weight gain, inflammation, oxidative stress, and endothelial dysfunction.[32,37] In the current study, the association remained robust after accounting for diet quality and specific nutrients (saturated fat, sodium, and sugar). This suggests that the nutritional composition of ultra-processed foods is not the only factor driving the association observed. The processing of ultra-processed foods can impact health through cosmetic additives, food contact materials, neoformed compounds, and the degradation of the food matrix.[38] Ultra-processed foods are thought to impact dietary behaviours by affecting satiety signalling and food reward systems,[32] resulting in overconsumption. For example, a cross-over randomized controlled trial demonstrated that a diet rich in ultra-processed food, compared to an unprocessed diet matched for presented calories, macronutrients, sugar, sodium, and fibre, resulted in increased energy intake and weight gain.[39]

There is also growing evidence that the gut microbiome may play an important role in the association between ultra-processed food and adverse health outcomes, including CVD.[32] Additives common within ultra-processed foods, such as emulsifiers and artificial sweeteners, are posited to influence gut microbiota composition, function, and bacteria–host interactions.[40] This can lead to increased inflammation, inducing immune responses, and weight gain, contributing to a higher risk of CVD.[32,41]

Strengths, limitations, and implications of this research

This study has several strengths. Firstly, the prospective nature of the study and large cohort of 39 544 Australian adults. Secondly, the associations found were supported by sensitivity analysis and the adjustment for important confounders. The results remained robust after accounting for overall diet quality and nutrient intakes such as salt, sugar, and fat, suggesting that the association may be due to specific characteristics of ultra-processed foods beyond the nutrient composition. Furthermore, while this is the first study exploring the association between ultra-processed food exposure and CVD mortality in Australia, it has a diverse population with a high proportion of people born overseas, which results in a wide range of dietary patterns. However, it would be of value for future studies to assess whether time lived in Australia could impact the association between ultra-processed food intake and cardiovascular mortality. The current study also has the following limitations. Firstly, although many possible confounders were adjusted for, due to its observational design, we cannot rule out residual confounding. Furthermore, the dietary data were self-reported and subsequently subject to recall error and bias to over- or under-reporting. While FFQs can adequately categorize foods based on the NOVA classification,[42] the FFQ used in this study was not specifically designed to distinguish different levels of food processing, meaning some misclassification may have occurred. To minimize misclassification, we followed best practices for applying the NOVA system in dietary assessments.[43] Two independent researchers with expertise in dietary assessment and the Australian food supply classified the FFQ, resolving discrepancies through group discussion and consensus. When a food item could belong to either ultra-processed foods or non-ultra-processed foods categories (e.g. pizza), we used Australian nationally representative data

from 1995–96 (unpublished) and 2011–12[14] to guide classification. For example, as most pizzas consumed in Australia were non-ultra-processed foods, they were classified accordingly. Details on FFQ classification in the MCCS are available elsewhere.[15,44] Furthermore, research following best practices[43] has shown that FFQs are sufficiently valid and reliable for classifying foods according to the Nova system.[45–47] Moreover, misclassification of food items with limited detail does not seem to impact the overall study findings.[48,14] The dietary data were also only assessed at one-time point. Therefore, the dietary habits of participants may have changed during the follow-up period.

This study has several implications for policy, practice, and future research. Our findings demonstrate that ultra-processed foods may contribute to the significant burden of cardiovascular diseases in Australia. Effective public health interventions, population, and clinical dietary guidance are necessary to support people to reduce the consumption of ultra-processed foods. The American Heart Association included a statement on ultra-processed food in their 2021 Dietary Guidance scientific statement, advising people to choose minimally processed foods instead of ultra-processed food.[49] In addition, many Latin American countries have public health regulations promoting the reduction of ultra-processed foods; these measures include warning labels on food packaging and taxes on ultra-processed foods, marketing restrictions.[50] Although future guidelines for heart-healthy diets should reflect the growing evidence demonstrating an association between ultra-processed food dietary pattern exposure and CVD mortality, and while numerous observational studies have demonstrated a link between ultra-processed food intake and poor cardiometabolic health, additional research is needed, including clinical trials and experimental studies to determine if limiting ultra-processed food consumption reduces CVD risk factors and to explore potential mechanisms of action, as well as to confirm these findings from other population groups. Future research could also examine the association of specific ultra-processed food groups and health outcomes using substitution analysis. This method would explore the potential impact of replacing specific subgroups of ultra-processed foods with different foods, either less processed alternatives or other types of ultra-processed foods, while keeping the total calorie intake constant. It aims to clarify associations with health outcomes and reduce the heterogeneity seen in studies focusing solely on individual food types.[51]

Conclusions

In this large Australian cohort, higher exposure to the ultra-processed food dietary pattern was associated with a higher risk of CVD mortality. This study contributes to the growing body of literature suggesting that ultra-processed food intake is associated with adverse health outcomes, collectively providing a rationale for more causal and mechanistic research and public health policies to reduce ultra-processed food consumption to promote heart health and potentially prevent cardiovascular-related deaths.

Supplementary material

Supplementary material is available at *European Journal of Preventive Cardiology*.

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Author contribution

S.G.: Conceptualization, Project administration, Writing—original draft, Writing—review & editing. M.L.: Data curation, Formal analysis, Writing—review & editing. M.M.L.: Conceptualization, Supervision, Data curation, Formal analysis, Writing—review & editing. W.M.: Conceptualization, Supervision, Writing—review & editing. All remaining authors were involved in Conceptualization and Writing—review & editing. All gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

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Data availability

The data underlying this article were provided by Cancer Council Victoria. Further details about using MCCS data can be found at the data administrators' website: https://www.pedigree.org.au/.

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