RESEARCH ARTICLE

Molecular Nutrition & Food Research
www.mnf-journal.com

Association of Ultraprocessed Food Consumption with Risk of Cardiovascular Disease Among Individuals with Type 2 Diabetes: Findings from the UK Biobank

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Scope: **Among patients with diabetes, who have modified nutritional behavior and a higher risk of cardiovascular disease (CVD), the influence of ultraprocessed foods (UPFs) on CVD remains unknown. The study aims to evaluate the association between UPF intake and the risk of CVD among individuals with type 2 diabetes (T2D) and further examine the potential biological pathways linking the association.**

Methods and results: **This study includes 5405 participants with T2D who provided at least one 24-h dietary recall from the UK Biobank study. In the fully adjusted models, a 10% increase in the proportion of UPFs is associated with higher hazards of overall CVD (hazard ratio [HR]: 1.10; 95% confidence interval [CI]: 1.04, 1.15), coronary heart disease (HR: 1.10; 95% CI: 1.04, 1.16), heart failure (HR: 1.14; 95% CI: 1.05, 1.25), but not stroke (HR: 1.01; 95% CI: 0.90, 1.12). Cystatin C, high-density lipoprotein cholesterol (HDL-C), apolipoprotein A, C-reactive protein, and body mass index collectively explain 26.9% (12.8%, 48.5%) of the association between UPF intake and the risk of overall CVD.**

Conclusion: **Higher UPF intakes are associated with increased hazards of CVD among individuals with T2D, and the association is partly mediated through worsening biomarkers of renal function, lipid metabolism, inflammation, and body weight.**

1. Introduction

Type 2 diabetes (T2D) is a serious public health problem, bringing a substantial health and economic burden. The number of people with diabetes is expected to increase to 783 million in 2045.[1] Cardiovascular disease (CVD) is the major cause of death among individuals with diabetes.[2]

Dietary factors play an important role in the primary prevention of CVD in patients with diabetes.[3] The consumption of ultraprocessed foods (UPFs) has been increasing worldwide over the past decades.[4] The proportion of UPFs in total daily energy intake has reached more than 50% in some high-income countries.[4–6] UPFs are foods generally with five or more ingredients, which include substances not commonly used in kitchens and additives to disguise undesirable sensory properties.[7] Generally, UPFs are produced by a series of industrial processing and contain few whole foods.[7]

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The ORCID identification number(s) for the author(s) of this article can be found under https://doi.org/10.1002/mnfr.202300314

DOI: 10.1002/mnfr.202300314

Previous studies have linked diets rich in UPFs with a higher risk of CVD in general populations.[8–11] However, individuals with diabetes, compared with those without diabetes, seemed to have different characteristics of UPF intake. They tended to avoid sugar-containing foods such as cakes and sugar-sweetened beverages but had high intakes of foods rich in protein and fat like processed meat.[12,13] Besides, the diabetic state is more sensitive to some of the attributes of UPFs compared to the nondiabetic state, such as newly formed molecules by food processing (e.g., acrylamide) and plasticizers migrated from packaging (e.g., phthalates),[14,15] which are widely postulated to play important roles in the hazard effect.[8–10] To our knowledge, no study has examined the association between UPF intake and the risk of CVD among patients with T2D. In addition, higher UPF intakes have been reported to be associated with increased risks of metabolic abnormalities, such as obesity, hypertension, dyslipidemia,[16] and renal function decline[17]; however, it remains unclear whether and the extent to which these pathways could relate UPFs to CVD among individuals with T2D.

To fill these knowledge gaps, we examined the association between UPF consumption and the risk of CVD among individuals with T2D using data from the UK Biobank. Furthermore, we tested potential biological pathways (e.g., lipid profile, inflammation, and renal function) linking UPFs and CVD.

2. Results

2.1. Characteristics of the Study Population

Of the 5405 participants with T2D included in this study, the mean age was 59.4 ± 6.9 years and 3313 (61.3%) were male. The mean number of dietary recalls for each participant within 36 months of their baseline assessments was 1.9 ± 1.1; 2813 (52.0%) participants had one dietary recall. Compared with T2D patients without valid dietary recalls, those with dietary recalls had similar distributions of age, sex, ethnicity, body mass index (BMI), and disease history. However, they tended to be higher educated, less deprived, current drinkers, and physically active, and were less likely to be current smokers, have a longer duration of diabetes, and have multiple medications for diabetes (Supporting Information Table S4).

The baseline characteristics of participants according to quartiles of the proportion of UPFs in the diet are shown in **Table 1**. Participants with higher UPF intakes tended to be younger, less educated, more deprived, Black or Black British, physically inactive, never smokers, and never drinkers, and were more likely to have a higher BMI and a history of hypertension. They also tended to have an unhealthier diet, and have higher intakes of energy, saturated fat, sugar, and sodium, but lower intakes of fruit, vegetables, and fiber. For dietary intake, compared to participants without T2D, those with T2D were more likely to have higher intakes of UPFs, processed meat, unprocessed meat, and sodium, and tended to consume less sugar-sweetened beverages and sugar (Supporting Information Table S5). The mean weight ratio of UPFs in the diet was 18.6%. The main food groups contributing to UPF consumption were beverages (53%), followed by cereals and starchy food (21%), dairy based products (9%), and sugary products (6%) (Supporting Information Figure S3).

2.2. Associations between UPF Intake and CVD Risk

During 57 840 person-years of follow-up (median follow-up time 11.7 years), a total of 1089 incident CVD events occurred, including 829 coronary heart disease (CHD), 225 stroke, and 310 heart failure events. In the fully adjusted model, compared with the least quartile of UPF intake, the hazard ratios (HRs) (95% confidence intervals [CIs]) for the highest quartile of UPF intake were 1.28 (1.08–1.51) for overall CVD, 1.28 (1.06–1.56) for CHD, and 1.46 (1.07–2.00) for heart failure (**Table 2**). Furthermore, the HRs (95% CIs) for a 10% increment in the proportion of UPF consumption were 1.10 (1.04–1.15) for overall CVD, 1.10 (1.04–1.16) for CHD, and 1.14 (1.05–1.25) for heart failure. However, there was no significant association for stroke risk. The restricted cubic spline (RCS) curves confirmed the linear relationship between the proportion of UPFs in the diet and risk of overall CVD, CHD, and heart failure (p values for the overall association: <0.001, 0.003, and 0.01, respectively; respective p values for nonlinearity: 0.26, 0.61, and 0.98, respectively) (**Figure** 1A–D).

2.3. Mediation Analyses

Five biomarkers significantly mediated the associations of UPF intake with overall CVD and CHD, including cystatin C, high-density lipoprotein cholesterol (HDL-C), apolipoprotein A, C-reactive protein, and BMI (**Table 3**). The mediated proportion ranged from 6.8% to 18.4% among the five mediators. The C-reactive protein and BMI respectively explained 5.7% and 22.2% of the relation between UPF intake and heart failure. Collectively, all explanatory factors explained 26.9%, 26.7%, and 28.7% of the associations of UPF consumption with overall CVD, CHD, and heart failure, respectively.

2.4. Stratified Analyses

Largely consistent results were observed between UPF intake and overall CVD when analyses were stratified by age, sex, BMI, leisure-time physical activity, dietary pattern, the number of dietary recalls, and diabetes duration (Supporting Information Table S6). No significant interactions were found considering multiple testing.

2.5. Sensitivity Analyses

In the sensitivity analyses, the results were not substantially changed when excluding participants who developed CVD within 2 or 3 years of follow-up and excluding participants who had diabetes within 1 year or 2 years of the completion of 24-h dietary recalls (Supporting Information Table S7). Further adjustment of BMI, consumption of food groups (fruits and vegetables), intake of nutrients (saturated fat, sugar, fiber, and sodium), healthy diet score, or the average time interval between baseline and completion of 24-h recalls did not modify the results. Similar estimates were observed when considering the absolute daily intake (g day^{-1}) as the consumption of UPFs (Supporting Information Table S8). Additionally, the results were not materially altered when using competing risk models (Supporting Information Table S9).

Table 1. Baseline characteristics according to quartiles of ultraprocessed food consumption among individuals with type 2 diabetes in the UK Biobank ($n = 5405$).

	Quartiles of ultraprocessed food consumption[a]				
	Q1	Q2	Q3	Q4	*p* value[b]
Weight ratio	6.0 ± 2.4	12.7 ± 1.8	20.0 ± 2.5	35.6 ± 10.5	–
Number of subjects	1351 (25.0)	1351 (25.0)	1352 (25.0)	1351 (25.0)	–
Age [years]	59.8 ± 6.5	60.1 ± 6.7	59.6 ± 6.8	58.2 ± 7.4	<0.001
Number of dietary recalls	1.6 ± 1.0	2.0 ± 1.2	2.1 ± 1.2	1.9 ± 1.1	<0.001
Male	828 (61.3)	828 (61.3)	829 (61.3)	828 (61.3)	–
Ethnicity					<0.001
White	1210 (89.8)	1191 (88.8)	1197 (89.1)	1172 (87.4)	
Mixed	19 (1.4)	33 (2.5)	27 (2.0)	35 (2.6)	
Asian or Asian British	89 (6.6)	82 (6.1)	70 (5.2)	64 (4.8)	
Black or Black British	30 (2.2)	36 (2.7)	50 (3.7)	70 (5.2)	
College	498 (37.2)	463 (34.7)	472 (35.2)	390 (29.2)	<0.001
Townsend Deprivation Index	−1.03 ± 3.17	−1.13 ± 3.00	−0.98 ± 3.08	−0.49 ± 3.20	<0.001
Smoking status					0.003
Never	583 (43.3)	636 (47.4)	668 (49.6)	670 (49.8)	
Past	635 (47.1)	593 (44.2)	587 (43.6)	553 (41.1)	
Current	129 (9.6)	112 (8.4)	92 (6.8)	122 (9.1)	
Drinking status					<0.001
Never	64 (4.7)	74 (5.5)	81 (6.0)	107 (7.9)	
Past	62 (4.6)	58 (4.3)	71 (5.3)	97 (7.2)	
Current	1223 (90.7)	1219 (90.2)	1199 (88.8)	1146 (84.9)	
Leisure-time physical activity, MET-min/week	596.0 ± 846.4	559.3 ± 838.8	527.8 ±715.6	469.2 ±763.7	<0.001
Body mass index [kg m^{-2}]	30.4 (5.6)	30.5 (5.6)	31.2 (5.7)	32.5 (6.4)	<0.001
Family history of CVD	818 (60.6)	824 (61.0)	822 (60.8)	812 (60.1)	0.97
History of hypertension	992 (73.4)	968 (71.7)	1002 (74.1)	1036 (76.7)	0.03
History of hyperlipidemia	1054 (78.0)	1045 (77.4)	1026 (75.9)	1076 (79.6)	0.13
History of cancer	174 (12.9)	156 (11.6)	177 (13.1)	152 (11.3)	0.35
Duration of diabetes	6.3 ± 6.8	6.0 ± 6.6	6.3 ± 6.6	6.5 ± 6.2	0.37
Medication for diabetes					0.08
None	451 (33.4)	454 (33.6)	425 (31.4)	392 (29.0)	
Only oral drugs	718 (53.2)	700 (51.8)	744 (55.0)	745 (55.1)	
Insulin and others	182 (13.5)	197 (14.6)	183 (13.5)	214 (15.8)	
Dietary factors					
Total energy intake [kcal day^{-1}]	1917.9 ±569.6	2034.8 ±581.0	2063.2 ±556.3	2095.7 ±612.3	<0.001
Healthy diet score	19.6 ± 2.9	19.9 ± 2.9	19.5 ± 3.0	18.9 ± 3.0	<0.001
Fruit [g day^{-1}]	243.6 ± 195.8	238.6 ± 180.5	230.6 ± 179.5	205.9 ± 173.2	<0.001
Vegetable [g day^{-1}]	343.6 ± 267.3	324.3 ± 224.1	294.8 ± 209.7	266.4 ± 215.5	<0.001
Saturated fat [g day^{-1}]	23.8 ± 11.9	26.4 ± 11.9	27.1 ± 11.7	28.2 ± 13.4	<0.001
Sugar [g day^{-1}]	94.8 ± 38.5	108.3 ± 40.9	116.5 ± 44.0	129.0 ± 54.6	<0.001
Fiber [g day^{-1}]	18.0 ± 7.4	18.7 ± 6.8	18.3 ± 6.7	17.8 ± 6.8	0.006
Sodium [g day^{-1}]	1838.5 ± 800.3	2042.5 ± 847.3	2113.6 ± 817.5	2194.2 ± 903.1	<0.001

Values are *n* (%) for categorical variables and means ± standard deviations for continuous variables. CVD, cardiovascular disease; MET, metabolic equivalent. [a] Quartiles of the weight ratio of ultraprocessed food intake in the total food consumed (%). Sex-specific cut-offs for quartiles of ultraprocessed weight ratio were 9.7, 16.1, and 24.9 in men and 9.5, 15.7, and 24.6 in women; [b] *p* values were calculated by variance or χ^2 test where appropriate.

In the secondary analyses assessing the associations of each UPF subgroup with the risk of CVD, intake of beverages was associated with increased risks of overall CVD, CHD, and heart failure (Supporting Information Table S10). Sugary products were associated with increased risks of overall CVD and CHD.

Table 2. Hazard ratios (95% confidence intervals) for associations of ultraprocessed food intake with overall cardiovascular disease, coronary heart disease, stroke, and heart failure among individuals with type 2 diabetes in the UK Biobank ($n = 5405$).

	Quartiles of ultraprocessed food consumption [%]						
	Q1	Q2	Q3	Q4	*p* trend	Continuous[a)]	*p* value
Mean, standard deviation	6.0 (2.4)	12.7 (1.8)	20.0 (2.5)	35.6 (10.5)			
Overall cardiovascular disease							
Cases/person-years	276/14 778	247/14 574	264/14 462	302/14 026			
Model 1[b)]	1 (ref)	0.91 (0.77–1.08)	1.01 (0.86–1.20)	1.28 (1.08–1.51)	<0.001	1.10 (1.05–1.16)	<0.001
Model 2[c)]	1 (ref)	0.95 (0.80–1.14)	1.07 (0.90–1.27)	1.28 (1.08–1.51)	<0.001	1.10 (1.04–1.15)	<0.001
Coronary heart disease							
Cases/person-years	208/15 037	190/14 805	200/14 694	231/14 280			
Model 1[b)]	1 (ref)	0.93 (0.77–1.14)	1.02 (0.84–1.24)	1.29 (1.06–1.55)	0.002	1.10 (1.04–1.16)	<0.001
Model 2[c)]	1 (ref)	0.97 (0.80–1.18)	1.06 (0.87–1.29)	1.28 (1.06–1.56)	0.004	1.10 (1.04–1.16)	0.001
Stroke							
Cases/person-years	64/15 823	53/15 507	52/15 416	56/15 153			
Model 1[b)]	1 (ref)	0.86 (0.59–1.23)	0.87 (0.60–1.26)	1.02 (0.71–1.46)	0.79	1.03 (0.92–1.14)	0.65
Model 2[c)]	1 (ref)	0.91 (0.63–1.31)	0.92 (0.63–1.34)	0.99 (0.68–1.43)	0.97	1.01 (0.90–1.12)	0.90
Heart failure							
Cases/person-years	75/15 803	65/15 474	77/15 391	93/15 098			
Model 1[b)]	1 (ref)	0.88 (0.63–1.23)	1.10 (0.80–1.52)	1.52 (1.12–2.07)	0.001	1.18 (1.08–1.29)	<0.001
Model 2[c)]	1 (ref)	0.91 (0.65–1.28)	1.14 (0.83–1.58)	1.46 (1.07–2.00)	0.004	1.14 (1.05–1.25)	0.003

[a)] Hazard ratio for per increase of 10% in the proportion of ultraprocessed food intake; [b)] Model 1: adjusted for age, sex, and total energy intake; [c)] Model 2: Model 1 + the number of 24-h dietary recalls, ethnicity, education attainment, smoking status, drinking status, leisure-time physical activity, Townsend Deprivation Index, history of hypertension, history of hyperlipidemia, history of cancer, family history of cardiovascular disease, duration of diabetes, and medication for diabetes.

3. Discussion

To the best of our knowledge, this is among the first studies to provide evidence that higher consumption of UPFs was associated with higher risks of overall CVD, CHD, and heart failure among individuals with T2D. Regarding potential mechanisms, worsening biomarkers of renal function, lipid metabolism, inflammation, and body weight partly explained the association between UPF intake and overall CVD risk.

Previous studies conducted in the general populations have observed UPF intake was associated with higher risks of overall CVD, CHD, or cerebrovascular diseases among the Framingham Offspring Study,[8] the French NutriNet-Santé cohort,[9] and the UK biobank.[10,11] Similar associations linking UPF intake to overall CVD and CHD were observed among patients with T2D in our study, but we did not observe an association between UPF consumption and stroke. Limited stroke events and different characteristics of UPF intake among individuals with T2D (lower intakes of sugar products and higher intakes of processed meat) may explain the nonsignificant result in our study. Future large-scale studies are needed to confirm the association between UPF intake and stroke in T2D patients. In addition to the three CVD outcomes investigated in the above studies, we observed higher UPF intakes were associated with a higher risk of heart failure. Heart failure has been acknowledged as a common complication of diabetes with a prevalence of 22% among patients with T2D.[18] The result extends evidence to support the adverse effects of UPF intake in individuals with diabetes, especially in diabetes-related cardiac dysfunction. Considering that an appropriate diet represents the cornerstone of diabetes management and therapy,[19] intaking less processed food may serve as an additional dimension for nutrition therapy. Indeed, the American Diabetes Association has advised choosing whole food rather than highly processed food in their 2022 guidelines.[20]

Among a seriesof putative biological mechanisms proposed to explain the association between UPF intake and CVD risk,[16] altered renal function was similarly proved in the mediation analyses based on current evidence.[21–23] Specifically, in the Moli-sani Study, altered renal function explained 12.0%–21.8% of excess CVD mortality associated with higher UPF intakes among the general populations or individuals with CVD.[21–23] In T2D patients, our study also identified altered renal function partly accounted for the higher risk of overall CVD and CHD associated with diets rich in UPFs. The consistent pathway further supports the biological plausibility of the epidemiology evidence. Our data also showed inflammation and excess body weight might explain the associations of UPF intake with overall CVD, CHD, and heart failure, with dyslipidemia reflected by decreasing HDL-C levels might additionally explain UPF intake related to overall CVD and CHD. We firstly observed that HDL-C could be a potential pathway linking UPF intake and CVD, and the result is in line with a systematic review which showed the highest UPF consumption was associated with a 102% increased risk of low HDL-C levels.[24] Given that one of the hallmarks of dyslipidemia in T2D is low HDL-C,[25] UPF intake may further worsen the situation.

Several attributes of UPFs may contribute to the observed association between UPF intake and CVD risk among individuals with T2D, and some of them could also link with the pathways identified in our study. First, we observed that T2D patients eating higher amounts of UPFs showed lower nutritional

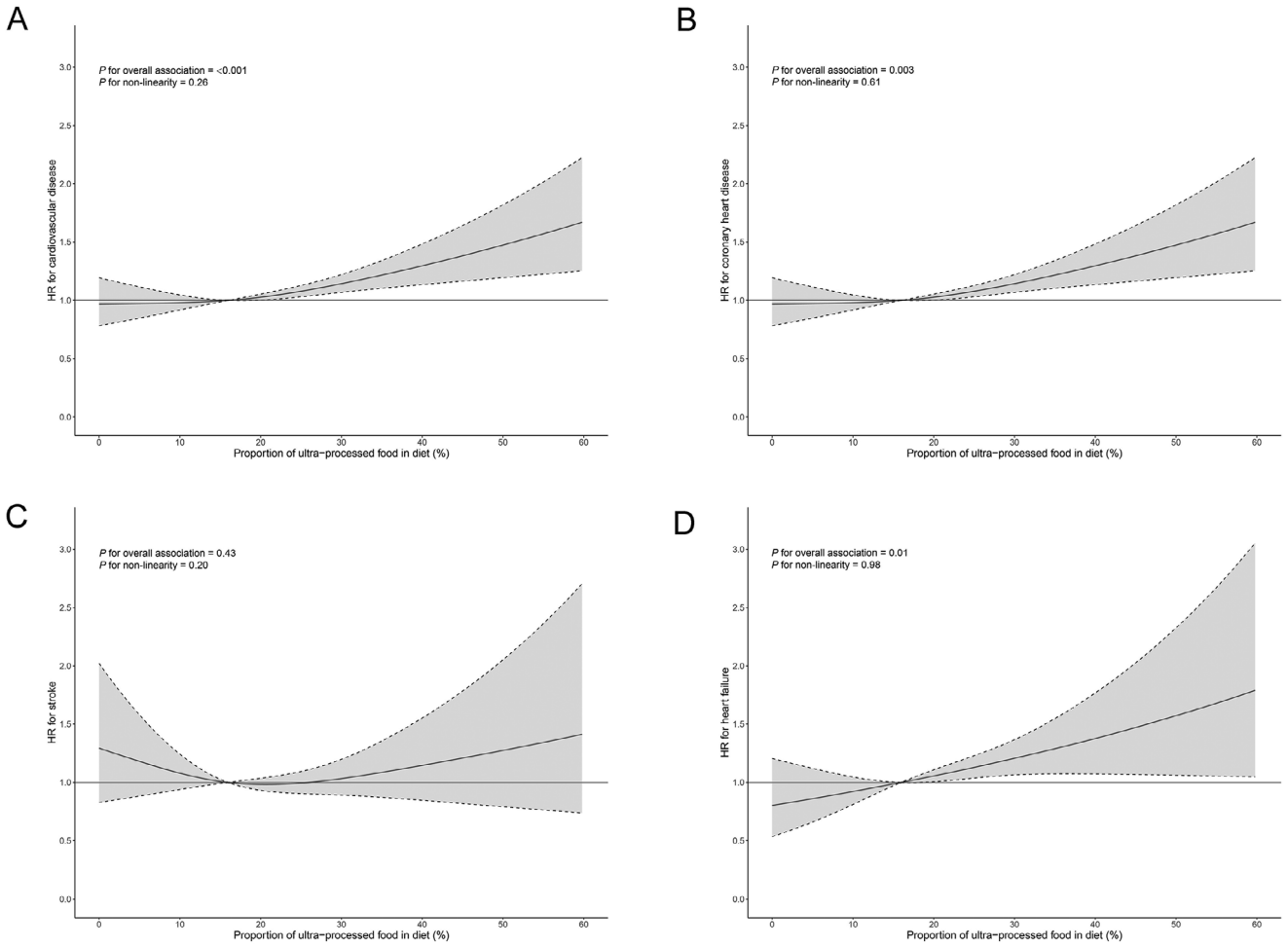

Figure 1. Multivariable adjusted hazard ratios (HRs) for associations of ultraprocessed food intake with overall cardiovascular disease, coronary heart disease, stroke, and heart failure among individuals with type 2 diabetes in the UK Biobank. The study included 5405 participants with type 2 diabetes. *p* values were placed on the figure and tested by Wald χ^2 tests. HRs with 95% confidence intervals (CIs) were calculated based on the multivariable model adjusted for age, the number of 24-h dietary recalls, sex, ethnicity, education attainment, smoking status, drinking status, leisure-time physical activity, Townsend Deprivation Index, history of hypertension, history of hyperlipidemia, history of cancer, family history of cardiovascular disease, duration of diabetes, medication for diabetes, and total energy intake. The reference values for HRs were set as 16.0% (the median value of the proportion of ultraprocessed food intake). Three knots were located at the 10th, 50th, and 90th percentiles of the exposure. The gray zones indicated 95% CIs. The first imputed dataset was used since other imputed datasets were similar.

quality. The poor nutrient profiles of UPFs are known risk factors for CVD.[26] However, in our analyses, the consumption of UPFs was associated with CVD outcomes independently of food groups, nutrients, or the healthy diet score. Hence, additional attributes of UPFs beyond nutritional quality may contribute to the observed relations. Second, UPFs commonly contain food additives to make the product palatable and more appealing. For instance, low-calorie sweeteners, which are typically consumed by individuals with metabolic conditions,[27] could disrupt the gut microbiota and cause insulin resistance.[28] Third, food processing, especially heat treatment, could produce new contaminants, such as acrylamide in cookies, bread, and French fries. An animal study showed that compared with healthy mice, diabetic mice could be more susceptible to acrylamide toxicity, which is reflected by histopathological alterations in the kidney, increased oxidative stress and inflammation, as well as disturbed glucose and lipid metabolism.[15] Finally, contaminants including bisphenol A might migrate from the plastic packaging to UPFs. Bisphenol A was associated with renal impairment, immune-inflammatory response, and remodeling of the diabetic kidney–heart axis in male diabetic rats.[29]

The strengths of our study include the prospective study design, the exploration of mediators represented by different pathways, and careful adjustments of covariates to minimize confounding. Yet several limitations should be considered. First, the 24-h dietary questionnaire used in the UK biobank was not specifically designed to collect dietary data based on the NOVA category, thus misclassification of UPFs may not be ruled out. However, the misclassification is likely to bias the results toward the null. Second, compared with participants who did not complete the dietary assessments, those with at least one 24-h dietary recall had similar distributions of demographic characteristics, BMI, and disease history, but they were more likely to have higher socioeconomic characteristics, a healthier lifestyle, and a mild form of

Table 3. Biomarkers of cardiovascular risk as mediators of associations of ultraprocessed food intake with overall cardiovascular disease, coronary heart disease, and heart failure among individuals with type 2 diabetes in the UK Biobank ($n = 5405$).

	Overall cardiovascular disease		Coronary heart disease		Heart failure	
	Proportion mediated (95% CI)[a]	*p* value	Proportion mediated (95% CI)[a]	*p* value	Proportion mediated (95% CI)[a]	*p* value
Cystatin C [mg L^{-1}][b]	10.5% (3.9%–25.4%)	0.01	9.2% (3.2%–23.3%)	0.009	9.8% (2.1%–35.1%)	0.08
TC [mmol L^{-1}]	NM	NM	NM	NM	–	–
HDL-C [mmol L^{-1}]	11.8% (5.0%–25.1%)	<0.001	12.6% (4.9%–28.8%)	<0.001	–	–
Apolipoprotein A [g L^{-1}]	9.2% (3.8%–20.5%)	<0.001	10.0% (3.8%–23.9%)	0.001	–	–
C-reactive protein [mg L^{-1}][b]	6.8% (2.7%–16.0%)	0.005	6.9% (2.6%–17.1%)	0.005	5.7% (1.7%–17.9%)	0.03
White blood cell count [x10^9 L^{-1}][b]	1.4% (0.1%–13.1%)	0.19	1.5% (0.1%–15.2%)	0.20	NM	NM
HbA_{1c} [mmol mol^{-1}]	–	–	–	–	2.5% (0.5%–12.4%)	0.10
Body mass index [kg m^{-2}]	18.4% (9.2%–33.4%)	<0.001	18.4% (8.2%–36.2%)	<0.001	22.2% (9.5%–43.6%)	<0.001
All explanatory factors	26.9% (12.8%–48.0%)	<0.001	26.7% (11.4%–50.8%)	<0.001	28.7% (10.5%–58.0%)	0.001

CI, confidence intervals; HbA_{1c}, glycated hemoglobin A_{1c}; HDL-C, high-density lipoprotein cholesterol; NM, not mediating; TC, total cholesterol. –, The proportion of mediation effect could not be calculated since the biomarkers were not associated with both the exposure and the outcome. [a] Proportion of effect explained by mediators with 95% CI and *p* value as produced by %MEDIATE macro in SAS are reported, in multivariable models adjusted for age, the number of 24-h dietary recalls, sex, ethnicity, education attainment, smoking status, drinking status, leisure-time physical activity, Townsend Deprivation Index, history of hypertension, history of hyperlipidemia, history of cancer, family history of cardiovascular disease, duration of diabetes, medication for diabetes and total energy intake. Proportion refers to per 10% increase in the proportion of ultraprocessed food. Mediation analyses were generated using the first imputed dataset. Other imputed datasets were omitted since they were similar to the first imputed dataset; [b] The variables were log-transformed.

diabetes. Therefore, selection bias may still exist. Third, about half of the participants had one dietary recall, which could not capture the long-term dietary intake. Nevertheless, we have adjusted the number of dietary recalls in fully adjusted models, and the subgroup analysis stratified by the number of dietary recalls showed similar results. Fourth, the diet data and biomarkers reflected the baseline level, and potential changes over time might modify the strength of the results. However, previous studies showed that diets are likely to remain stable in adulthood,[30] and most of the biomarkers examined here did not change substantially over time.[31] Fifth, the possibility of residual confounding could not be ruled out. Finally, because our study was observational design, causality cannot be established.

4. Conclusion

In this prospective cohort of individuals with T2D, higher UPF intakes were associated with an increased risk of overall CVD, CHD, and heart failure. The higher risk of overall CVD associated with higher UPF consumption possibly went through pathways that include renal function, lipid metabolism, inflammation, and body weight. Our study supports the need to stress the importance of decreasing UPF intake in dietary guidelines for T2D patients. Future studies are needed to confirm our findings.

5. Experimental Section

Study Population: The UK Biobank is a large population-based prospective cohort study recruiting more than 500 000 participants aged 37–73 years from 22 assessment centers across England, Scotland, and Wales between 2006 and 2010. At baseline, participants completed a touchscreen questionnaire and a verbal interview, took anthropometric measurements, and provided biological samples.[32]

Participants with prevalent T2D at recruitment were identified through a UK Biobank algorithm or electronic health records (ICD-10 code: E11). The UK Biobank algorithm identified T2D cases based on self-reported, trained staff queried medical and medication history, with 96% accuracy.[33] After the exclusion of those without valid baseline dietary data, with implausible total energy intake (men with <800 or >4200 kcal day^{-1} or women with <600 or >3500 kcal day^{-1}), or existing CVD at baseline, 5405 participants with T2D were included in the final analysis (Supporting Information Figure S1).

The UK Biobank received ethics approval from the North West Multicentre Research Ethics Committee (21/NW/0157). All participants gave written informed consent.

Dietary Assessment: The Oxford WebQ, a web-based 24-h dietary questionnaire that aims to record the consumption of 206 food and 32 beverage items in the previous 24 h period, was used to assess dietary intake during 2009–2012. The questionnaire was first introduced as a part of the baseline assessments for 70 724 participants between 2009 and 2010. Subsequently, participants who provided their e-mail addresses were also invited to complete the Oxford WebQ via e-mail on four separate occasions between February 2011 and June 2012. The Oxford WebQ showed similarity of food types and quantities, estimated energy, and daily nutrient intakes compared with a traditional interviewer-administered 24-h dietary recall,[34] and showed high validity against the urinary biomarkers for protein, sugar, and potassium.[35]

Due to the inconsistency in the timing of assessment center visits and completion of 24-h dietary recalls, 24-h recalls within 36 months of their baseline assessments were considered relevant to the baseline dietary intake.[36] Dietary intake was averaged among participants with more than one 24-h dietary recall within 36 months of baseline assessments. Since the UK Biobank only provided the number of portions for each food and beverage item consumed a day, it assigned a revised standard portion size based on a previous study.[37] Total energy and nutrient intakes were also derived using the same portion size and published by UK Biobank. The quantity of each food or beverage consumed was calculated by multiplying the amounts consumed by the portion size in grams.

The consumption of UPFs was derived from their 24-h dietary recalls. The study allocated each food and beverage item into one of the four food groups according to the extent and purpose of food processing as described by the NOVA food classification system: 1) unprocessed or minimally processed foods (e.g., fresh fruits, vegetables, and milk); 2) processed culinary ingredients, (e.g., table salt, butter, and sugar); 3) processed foods (e.g., cheese, fruits in syrup, and canned fish); and 4) UPFs (e.g., soft drinks, savory snacks, and sauce).[7] Detailed definitions

of the NOVA classification can be found elsewhere.[7] This study primarily focused on the UPF group, and the details along with some examples are presented in Supporting Information Table S1. For each participant, UPF consumption (g day^{-1}) was calculated by summing up the amounts of each food group item from the fourth category of the NOVA classification. The study calculated the proportion (%) of UPFs by dividing the UPF consumption by the total weight of food consumed (g day^{-1}). Creating a weight ratio rather than an energy ratio was to account for non-nutritional factors related to food processing (e.g., additives and altered structure of raw foods).[9]

Outcome Ascertainment: The primary outcomes of the study were incident overall CVD and its three component endpoints—CHD, stroke, and heart failure. Cases were ascertained through multiple sources including primary care data, hospital admission data, death register records, and self-reported medical condition. Health records data were available up to October 13, 2021; November 12, 2021; and October 7, 2021 for centers in England, Wales, and Scotland, respectively. The ICD10 code was used to define CVD events: CHD (I20–I25), stroke (I60–I64), and heart failure (I50).

Covariate Assessment: Information on age, sex, ethnicity, education attainment, smoking status, drinking status, leisure-time physical activity, and family history of CVD was obtained through a touch-screen questionnaire at the baseline assessment. Townsend Deprivation Index (TDI) was derived from national census data according to postcodes of residence, which considered car and home ownership, household overcrowding, and unemployment.[38] Leisure-time physical activity was assessed using the long-form International Physical Activity Questionnaire, and weekly metabolic equivalent minutes (MET-min/week) were calculated. Height and body-weight measurements were taken by trained nurses. BMI (kg m^{-2}) was calculated as body weight in kilograms divided by the square of height in meters. A healthy diet score was computed to reflect the overall dietary quality based on a previous UK Biobank study,[39] which considered adequate consumption of healthy food categories (fruit, vegetables, whole grains, seafood, dairy, and vegetable oils) and reduced consumption of unhealthy food (refined grains, processed meats, unprocessed meats, and sugar-sweetened beverages). For the healthy food, the point was given based on tertiles (from 3 points in the highest tertile to 1 point in the lowest tertile) while the unhealthy food was inversely scored. Data on the medical history of hypertension, hyperlipidemia, and cancer, and duration of T2D were collected through questionnaires, verbal interviews, and electronic health records. Medication for T2D was ascertained through questionnaires and verbal interviews.

Selection of Cardiovascular Risk Factors: Potential biological mechanisms linking UPF intake and adverse health outcomes include renal function decline, obesity, dyslipidemia, dysglycemia, inflammation, and hypertension.[16,17] In the context of biological mechanisms, biomarkers reflecting different potential pathways and relating to cardiovascular complications among individuals with diabetes in epidemiologic studies[40,41] were selected as potential mediators between UPF intake and cardiovascular complications. Specifically, chosen biomarkers included renal function (cystatin C and creatinine), lipid profile (total cholesterol [TC], low-density lipoprotein cholesterol [LDL-C], HDL-C, triglycerides, apolipoprotein A, and apolipoprotein B), inflammation (C-reactive protein and white blood cell count), blood pressure (systolic blood pressure and diastolic blood pressure), glycated hemoglobin A_{1c} (HbA_{1c}), and BMI. The details of the assessment of biomarkers in the UK biobank are described in the Supporting Information. A causal diagram for the adjusted covariates and mediated variables is shown in Supporting Information Figure S2.

Statistical Analysis: Baseline characteristics are presented as the mean ± standard deviations (SDs) for continuous variables and the number (percentage) for categorical variables according to sex-specific quartiles of UPF consumption. Differences among groups were tested by analysis of variance or χ^2 test when appropriate. Each participant's person-years were calculated from the date of recruitment to the date of CVD diagnosis, death, or the end of follow-up, whichever occurred first.

This study used Cox proportional hazard regression models to estimate the HRs and 95% CIs for the associations between the proportion of UPFs in the diet (sex-specific quartiles or a continuous variable) and risks of overall CVD, CHD, stroke, and heart failure. The proportional hazards assumption was examined by creating a product term of follow-up time and UPF intake, and it found no significant deviation from the assumption. This study tested linear trends by coding median values to each quartile of the proportion of UPFs in the regression models. RCS analysis with three knots (10th, 50th, and 90th percentiles) was used to examine the relationship between UPF intake and risks of overall CVD, CHD, stroke, and heart failure, and the linearity was tested by Wald χ^2 tests.

Two models were fitted: Model 1 including age (continuous, years), sex (male, female), and total energy intake (continuous, kcal day^{-1}); Model 2 including covariates in Model 1 plus the number of 24-h dietary recalls (continuous), ethnicity (White, Mixed, Asian, Black), education attainment (college/university degree, other degrees), smoking status (never, past, current), drinking status (never, past, current), leisure-time physical activity (continuous, MET-min/week), TDI (continuous), history of hypertension (yes, no), history of hyperlipidemia (yes, no), history of cancer (yes, no), family history of CVD (yes, no), duration of T2D (continuous, years), and medication for T2D (none, only oral medicine, insulin, and others). Missing values (Supporting Information Figure S1) were handled using multiple imputations to maximize data availability ($n = 10$ imputed datasets).

According to the predefined mediation principle,[42] the biomarkers that are selected as potential mediators should be associated with both the exposure and the outcome. These criteria were tested in the multivariable linear regression models for each potential mediator individually (Supporting Information Table S2) and then in Cox models including UPF consumption (continuous) as a covariate (Supporting Information Table S3). The mediation analyses used the %MEDIATE macro in SAS which calculates the point and interval estimates of the percentage of exposure effect explained by ≥1 intermediate variables, with 95% CIs and p values.

This study also conducted stratified analyses by age (≤60, >60 years), sex (male, female), BMI (<30, ≥30 kg m^{-2}), leisure-time physical activity level (<500, ≥500 MET-min/week), dietary patterns (less healthy and healthy pattern) categorized by the median of the healthy diet score, the number of dietary recalls (1, ≥2), and diabetes duration (≤5, >5 years). The multiplicative interactions between UPF consumption and the stratified factors on the risk of overall CVD were tested using the Wald test by including an interaction term in Model 2. To test the robustness of findings, the study performed a number of sensitivity analyses. First, the study excluded participants who had CVD events within 2 or 3 years of follow-up to minimize the possibility of reverse causality. Second, considering a short time interval between diabetes onset and the 24-h dietary recalls may not consider the impact of diabetes status on nutritional behavior, the study excluded participants who had diabetes within 1 or 2 years of the completion of 24-h dietary recalls. Third, since BMI could serve as both a mediator and a confounder, the study additionally adjusted for BMI. Fourth, to test for the potential influence of diet quality, the study further adjusted for the consumption of fruits and vegetables, intakes of saturated fat, sugar, fiber, and sodium, or the healthy diet score. Fifth, the study additionally adjusted for the time interval between baseline recruitment into the study and the completion of 24-h dietary recall (for participants with more than one 24-h dietary recall, the time interval was averaged as time intervals between baseline recruitment and each dietary recall). Sixth, the study explored the association between the quantity (g day^{-1}) (rather than the proportion) of UPF intake and the risk of CVD. Seventh, considering the competing risk of death, the study also conducted Fine and Gray competing risk analyses. Moreover, as a secondary analysis, the study tested the associations between each UPF subgroup and CVD risk.

All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC) and R software (version 4.2.2). Two-sided $p < 0.05$ was considered to be statistically significant.

Supporting Information

Supporting Information is available from the Wiley Online Library or from the author.

Acknowledgements

The authors would like to express their gratitude to the participants and staff involved in data collection and management in the UK Biobank. This research has been conducted using the UK Biobank Resource under Application Number 68307. An Pan was funded by grants from National Natural Science Foundation of China (81930124, 82192902, and 82021005), and the National Key Research and Development Program of China (2022YFC3600600). Gang Liu was supported by grants from National Nature Science Foundation of China (82073554 and 82273623), the Hubei Province Science Fund for Distinguished Young Scholars (2021CFA048), and the Fundamental Research Funds for the Central Universities (2021GCRC076). The funding agencies play no role in the design or conduct of the study; collection, management, analysis, or interpretation of the data; preparation, review, or approval of the manuscript; or decision to submit the manuscript for publication.

Conflict of Interest

The authors declare no conflict of interest.

Author Contributions

Y.L. and Y.W.L. contributed equally to this work. Y.L., Y.W.L., Y.-F.L., A.P., and G.L. conceived the study design. Y.L. and Y.W.L. conducted analyses and wrote the first draft of the paper. A.P. and G.L. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors contributed to the interpretation of the results and critical revision of the manuscript for important intellectual content, and approved the final version of the manuscript.

Data Availability Statement

Data from UK Biobank are available on application at www.ukbiobank.ac.uk/register-apply. This research has been conducted using the UK Biobank Resource under Application Number 68307.

Keywords

cardiovascular disease, mediation, metabolic biomarkers, type 2 diabetes, ultraprocessed foods

Received: May 13, 2023
Revised: February 28, 2024
Published online: April 19, 2024

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