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The association between ultra-processed foods and conventional markers of cardiovascular risk in an adult Iranian population

The Association between Ultra-Processed Foods and Conventional Markers of Cardiovascular Risk in an Adult Iranian Population.

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Abstract:

Background and Aims: Ultra-processed foods (UPFs) are associated with cardiovascular disease (CVD); however, few studies have investigated UPFs in Middle Eastern populations, despite high consumption in this region. Our study aimed to address this.

Materials and Results: The food intake of Iranian adults participating in the Prospective Epidemiological Research Studies in Iran was assessed using a food frequency questionnaire and the data was categorized into tertiles of UPF consumption using the NOVA system. ANCOVA and logistic regression analysis was used to assess differences between tertiles, and associations between UPFs and conventional markers of CVD respectively. Consumption of UPFs was associated with higher intakes of energy, fat, fiber, cholesterol, unsaturated fats, non-dairy beverages, cookies and cakes, processed meat and fast food, margarine, and sauces and sweets, but lower intake of protein, carbohydrate, and dairy products ($P < 0.001$ for all). Logistic regression showed that after adjustment for potential confounders, significant positive relationships existed between intake of UPFs and waist circumference (OR; 1.42, 95% CI; 1.19-1.69), LDL-C (OR; 1.28, 95% CI; 1.12-1.46), HDL-C (OR; 1.15, 95% CI; 1.02-1.30), non-HDL (OR; 1.25, 95% CI; 1.10-1.41) and LDL-C to HDL-c ratio (OR; 1.24, 95% CI; 1.10-1.41).

Conclusion: The consumption of UPFs is positively associated with waist circumference and atherogenic blood lipids and several dietary abnormalities. However, positive relationships between UPF consumption and increased HDL-C and intakes of unsaturated fats and fiber were also revealed. These findings offer insights into an understudied population and warrant further research in this area.

Key words: ultra-processed food, cardiovascular disease, risk factors, adult, Iranian

Introduction

Foods can be prepared in myriad ways, ranging from minimum processing techniques, such as freezing, pasteurization, and fermentation, through to ultra-processing techniques which may involve chemical modification, extrusion, or the use of multiple treatments employed in tandem [1]. Examples of ultra-processed foods (UPFs) include soft drinks, ice-cream, and pre-prepared items such as pizzas and pies and can also consist of food products sometimes regarded as healthy, including flavored yoghurts and breakfast cereals [2]. Given the heterogeneity of UPFs the NOVA classification system has been developed to enable food items to be categorized into four groups based upon the level of processing they have undergone [3]. However, research using this system to investigate the consumption and health impact of UPFs in ethnically diverse population's remains in its infancy.

This is concerning when considering that findings from the National Health and Nutrition Examination Survey (NHANES) and the Spanish Seguimiento Universidad de Navarra (SUN) cohort study have both demonstrated that the consumption of UPFs is associated with an increased risk of all-cause mortality [4, 5]. Furthermore, a recent dose-response meta-analysis which attempted to quantify the magnitude of response to UPFs revealed that for every 10% increase in UPF consumption, there is a 15% increase in all-cause mortality risk and a positive linear association with CVD-cause mortality [6]. These links with UPFs and increased risks of CVD have also been shown in several other large-scale cohort studies. Examples being the NutriNet-Santé cohort study, which found that the consumption of UPFs is significantly associated with increased cardiovascular, cerebrovascular, and coronary heart diseases, even after adjustment for known risk factors [7]. Similarly, the Framingham Offspring Study showed that each additional serving of UPFs consumed per day increased the likelihood of hard CVD (i.e. sudden and non-sudden coronary death, myocardial infarction, and fatal/nonfatal stroke), hard coronary heart disease and overall CVD and CVD mortality by 7%, 9% and 5% respectively [8]. The Italian Moli-Sani study also revealed that consuming UPFs is associated with an increased risk of CVD and all-cause mortality in individuals with a history of CVD, and for the first time highlighted the public health implications of UPFs specifically regarding secondary CVD prevention [9].

Due to these relationships, several biological mechanisms have been proposed. These include dyslipidemia and insulin resistance resulting from the excess energy, fat, sugar, and refined carbohydrates which are often present in UPFs [1]. High levels of sodium and additives may also promote hypertension and oxidative stress respectively, and changes to the matrix of UPFs may render them more readily absorbed, negatively impacting upon glycemic responses and the gut microbiota, contributing to increased CVD risk [1]. Furthermore, indirect effects resulting from inadequate fruit, vegetable, and fiber intake in those who consume UPFs may also be a contributing factor [1]. Consequently, organizations such as the American Heart Association have recommended individuals choose minimally processed foods as opposed to UPFs and in Latin America the avoidance of UPFs has been promoted as a 'Golden Rule' for dietary guidelines [2, 10].

Despite this progress little research regarding the impact of UPFs upon health has been conducted in the Middle East. This is particularly concerning since a global assessment of UPF consumption has shown increasing rates in the region [11] and a prospective cohort study of 21 countries highlighted that the Middle East had the second highest consumption of refined sweetened foods [12]. Also, a systematic review and meta-analysis of Iranian children showed high levels of sugar and fat consumption [13]. In terms of disease, a study of 139 healthy Iranian adolescents revealed increased DNA damage (as determined by 8-hydroxy-2 0-deoxyguanosine concentration) with increased UPF intake [14]. The relationship with UPFs and adiposity is unclear, despite Iranians consuming a fifth of energy from UPF the relationship may be sex specific, with males showing a positive association [15]. However, this is not in agreement with data from a multi-national European cohort study, with similar positive associations between UPF consumption and weight gain being observed regardless of sex [16]. Paradoxical findings such as these suggest further work needs to be conducted in more ethnically diverse populations to account for cultural differences and unique dietary intakes. More broadly, the dearth of research investigating the impact of UPFs upon CVD in the Middle East warrants urgent attention.

Method

Study Design, Study Population & Covariates

This cross-sectional study was conducted on a total of 10663 subjects aged 40–70 years who participated in the Prospective Epidemiological Research Studies in Iran (PERSIAN) [17], Kharameh cohort carried out between 2014 and 2017 [18]. Eligible individuals were included in the study by census method. As part of the PERSIAN cohort study, demographic information, physical activity, smoking status, and medical history were collected. In addition, weight, height, waist circumference (WC), hip circumference (HC), systolic blood pressure, and diastolic blood pressure, biochemical assessments including fasting blood glucose (FBS), total cholesterol (TC), triglyceride (TG), high-density lipoprotein (HDL), low-density lipoprotein (LDL) and diet were measured.

Among the participants of Kharameh cohort, those who had one or more types of cardiovascular diseases (CVDs) [19], hypertension, diabetes, other diseases, and an energy intake of less than 800 kcal or more than 4200 kcal were excluded (Figure 1). The study was approved by the ethics committee of Shiraz University of Medical Sciences, Fars, Iran (code: IR.SUMS.REC.1399.1115).

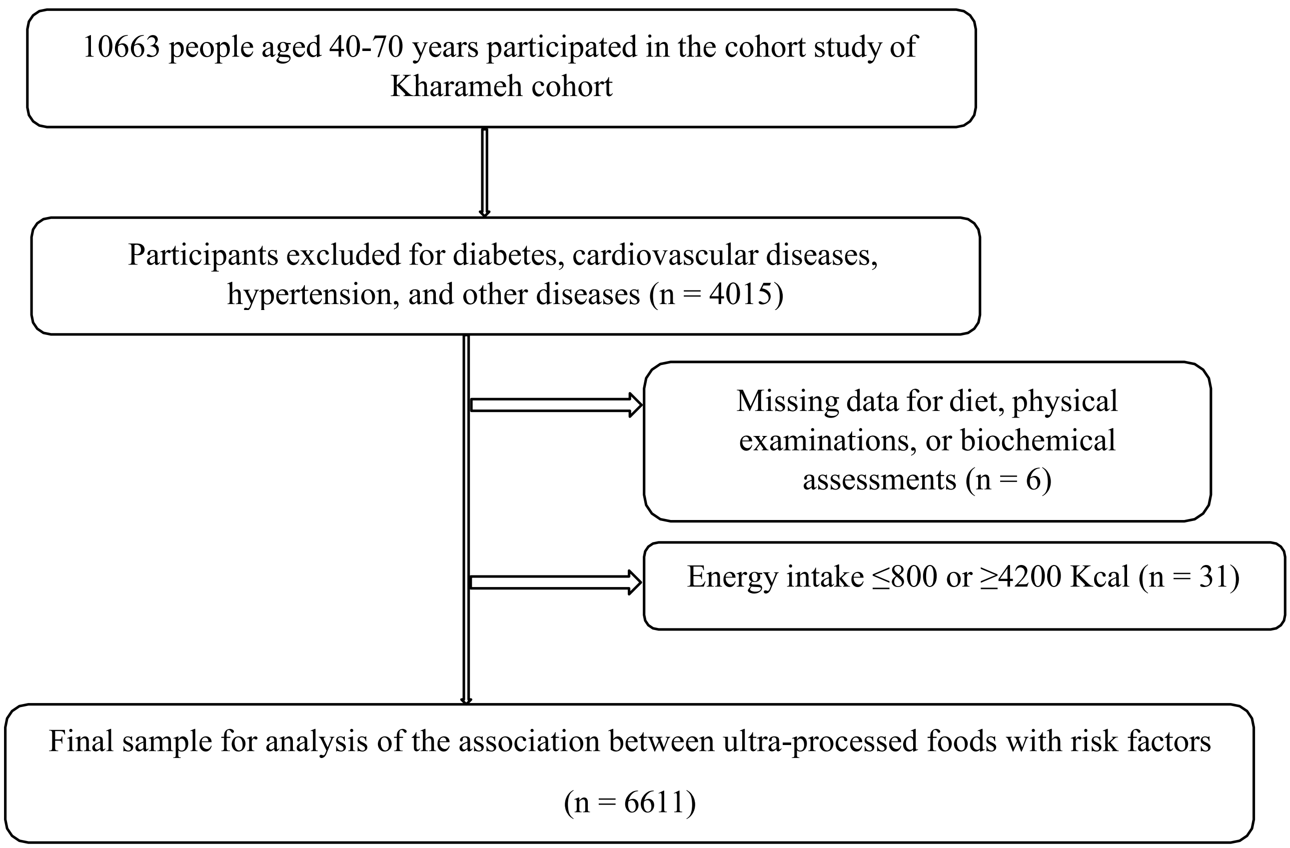

Figure1. Flow diagram of the study.

Dietary Intake Assessment

Food intake was collected using a 130-question food frequency questionnaire (FFQ) [20]. Based on home scales, the recorded values of each food item in the FFQ were converted to grams. Nutritionist IV software for Iranians (version 7.0; N-Squared Computing, Salem, OR, USA) was used to calculate energy, macro- and micronutrients. Finally, to calculate the ultra-processed foods index, based on the NOVA classification, the total daily consumption of 21 foods and beverages in 8 subgroups (gram per day) was calculated. To understand the contribution of each food group to the total intake of highly processed foods, the average daily intake of each of the 8 subgroups of UPFs (non-dairy beverages, cakes and cookies, dairy beverages, fast food and processed meats, oil and sauce, sweets, breads and others) was divided by the total daily intake of UPFs and multiplied by 100 [2, 21].

Anthropometric and Biochemical Assessments

Height, weight, WC, HC, and blood pressure of the participants were measured by trained experts. Weight was measured while wearing light clothing and height was measured without shoes. The accuracy of weight, HC and WC measurements were all within 0.1 cm accuracy. BMI was calculated by dividing weight by the square of height. Blood pressure was measured after 10 minutes of rest in a sitting position using a calibrated German standard Reiser model sphygmomanometer. For laboratory evaluations, after 10-14 hours fasting, a 20 ml blood sample was taken from each participant and stored at -80°C until further analysis. Glucose, TG, and blood cholesterol were measured using the Mindray device (Japan) by the Pars test kit. HDL-C, TG and TC levels were determined using an enzymatic method. Friedwald's formula was used to calculate LDL-C levels [22]. WC ≥ 88 cm for women and 102 for men, FBS ≥ 126 mg/dL, TG ≥ 150 mg/dL, TC ≥ 200 mg/dL L, LDL-C ≥ 130 mg/dL, HDL-C < 40 mg/dL for men and 50 mg/dL for women, and non-HDL ratio ≥ 130 were considered as abnormalities [23-26].

Statistical Analysis

In the study, age, gender, physical activity, and education level status were used as covariates. Demographic characteristics including age, gender, education level and smoking status of the participants were collected using a questionnaire. The educational level of the participants was determined by asking about the number of years of education. Physical activity was evaluated using a questionnaire that included the time spent on various activities such as exercise, work, sleep, and eating during the day [19]. The metabolic equivalent of task [27] was calculated for each activity. Finally, the total amount of metabolic equivalent of task (MET) (hours/day) was calculated for each participant [19].

All data were analyzed using SPSS software (version 20.0) and a p-value less than 0.05 was considered significant. The normality distribution of the variables was checked and determined by the Kolmogorov-Smirnov test. First, we obtained energy-adjusted intakes of all food items by residual methods [28]. To compare the baseline characteristics of participants one-way ANOVA or Chi-square tests were used for continuous and categorical variables respectively. Kruskal–Wallis tests were used to compare the intake of nutrients and food groups across tertiles of UPF intake. Two different multivariate logistic regression models were used to evaluate the relationship between the ultra-processed foods index and the odds of risk factors. Gender, age, physical activity, education, and BMI status were the confounding factors of the regression models.

Results

Baseline characteristic of the study population are shown in **Table 1**. There was significant associations with gender (P <0.001), age (P <0.001), weight (P <0.001), BMI (P = 0.001), WC (P = 0.001), HC (P <0.001), education (P <0.001), systolic blood pressure (P = 0.043), TG (P = 0.023), LDL-C (P = 0.004), HDL-C (P <0.001), non-HDL-C (P = 0.001) and LDL-C to HDL-C ratio (P <0.001) between tertiles of UPFs.

Higher consumption of UPFs was associated with higher intake of energy, fat, fibre, cholesterol, MUFA, PUFA, non-dairy beverages, cookies and cakes, processed meat and fast food, margarine, and sauces and sweets, but lower intake of protein, carbohydrate and dairy products (P <0.001 for all) (Table 2).

Multivariable-adjusted odd’s ratio (OR) and 95% confidence intervals (CIs) for outcomes through UPFs tertiles are displayed in **Table 3**. In the crude model, the population in the last tertile of UPFs were more likely to have higher odds of WC (OR; 1.23, 95% CI; 1.09-1.39, P <0.001), TG (OR; 1.18, 95% CI; 1.03-1.36, P = 0.014), LDL-C (OR; 1.23, 95% CI; 1.08-1.40, P = 0.001), HDL-C (OR; 1.25, 95% CI; 1.11-1.41, P <0.001), non-HDL (OR; 1.24, 95% CI; 1.10-1.40, P <0.001) and LDL-C to HDL-C ratio (OR; 1.29, 95% CI; 1.15-1.46, P <0.001) abnormalities compared to those in the first tertile. In addition, after adjustment for potential confounders, the positive relationship among intakes of UPFs and WC (Model 1: OR; 1.31, 95% CI; 1.15-1.48, P <0.001, and Model 2: OR; 1.42, 95% CI; 1.19-1.69, P <0.001), LDL-C (Adjusted model: OR; 1.28, 95% CI; 1.12-1.46, P <0.001), HDL-C (Adjusted model: OR; 1.15, 95% CI; 1.02-1.30, P = 0.022), non-HDL (Adjusted model: OR; 1.25, 95% CI; 1.10-1.41, P <0.001) and LDL-C to HDL-

C ratio (Adjusted model: OR; 1.24, 95% CI; 1.10-1.41, P <0.001) abnormalities remained significant.

Discussion

Our study aimed to address the dearth of literature concerning the impact of UPF consumption upon markers of CVD in a Middle Eastern population. We showed an increased intake of UPF was positively associated with WC and increased odds of a poorer overall blood lipid profile. These are findings which, although being described by others [29], have not been widely reported in a Middle Eastern population. We also found several dietary abnormalities, but no evidence to support a relationship between UPF consumption and glycemic control.

The positive relationship between UPF consumption and WC partially agrees with the literature. For example, several studies have failed to show an association between UPFs and numerous measures of adiposity, including ectopic fat, subcutaneous adipose tissue, total fat [30] and BMI, even after adjusting for physical activity [31]. Furthermore, a recent study conducted in Iranian children also revealed no associations between UPFs and measures of overweight and obesity [32]. These findings contrast with ours and the work of others, with one recent meta-analysis showing that the consumption of UPFs is associated with a 39% increased risk of overweight/obesity and greater waist circumference [33] and another showing an increased risk of overweight, obesity, and abdominal obesity [34]. A cross-sectional analysis of baseline data from the PREDIMED-PLUS trial also revealed direct associations between UPF consumption and weight using four different UPF classification systems and BMI when using the NOVA system [35]. Despite these contrary findings, it is important to note that most available evidence is observational. Currently only one randomized controlled trial (RCT) (metabolic ward setting) has been conducted, which found that UPF intakes causally increased energy intake and weight gain when compared with whole foods [36]. The author's recommended UPF intake should be limited in the context of obesity prevention and treatment.

With respect to other risk factors, our findings showed UPF intake increased the odds of higher LDL-C, non-HDL and LDL-C to HDL-C ratio abnormalities. The potential for increased levels of LDL-C and other apolipoprotein B-containing lipoprotein particles is concerning, especially given their clear role in cardiovascular disease [37]. In this context, our findings agree with previous studies. For example, a cohort study of Brazilian children showed that after 3-4 years of follow-up, UPF consumption was a predictor of LDL-C and total cholesterol levels [38]. A more recent extension of this work also highlighted other changes to blood lipids and showed that after 3 years of follow-up children in the highest tertile of UPF consumption had higher concentrations of blood TG; a finding reflected in our own data [39]. These longitudinal trends are suggestive of the ability of UPFs to modulate blood lipids after exposure and is a cause for concern given that dietary patterns adopted earlier in life can persist into adulthood [40].

Similarly, evidence shows UPFs are negatively associated with HDL-C [33]; as found in our study, with those in the third tertile having the lowest concentrations. This occurred despite significantly higher proportions of MUFA and PUFA in tertile 3 compared to the first tertile, although there is the possibility that some of these unsaturated fatty acids may be trans fats which are still present in the Iranian diet despite government interventions [41]. This suggests that the impact of food processing may eclipse that of fat composition and may perhaps explain our findings. Despite this, our logistic regression analysis showed a significant positive relationship between UPF consumption and HDL-C which is more difficult to explain.

The results from our logistic regression analysis also showed no significant association between UPF consumption and FBS; a finding which is not concordant with the literature. Several large-scale European studies have demonstrated a significant positive relationship between UPFs and risk of Type 2 diabetes [42-44]. Potential mechanisms have also been proposed, which include the production of and exposure to endocrine disruptors which have been associated with diabetes and increased intakes of fructose contributing to the promotion of hepatic and whole-body insulin resistance [44-46]. The reason for this lack of agreement with the wider literature is unknown; however, the authors speculate that although those in the third tertile consumed higher levels of all UPF items apart from dairy products, many of which are likely to be high in sugar and fat, significantly higher levels of fiber were being consumed too. This finding was unexpected but given the ability of dietary fiber to regulate blood glucose and other markers of glycemic control provides a plausible rationale for the lack of association [47, 48]. Furthermore, this may be a finding unique to Iran due to the regional dietary pattern, elements of which are known to be rich in fiber [49].

Limitations and Strengths

Our study has several strengths, including the large sample size and adjustments were made for a variety of potentially limiting confounding factors. Despite these aspects there are several limitations which should be mentioned. These include that the study is a cross-sectional, observational design and therefore does not offer any insights into the temporal effects of consuming UPFs. Furthermore, the study only recruited participants from Kharameh County and may not be nationally representative [50]. Similarly, although several confounding variables were accounted for there may be others which were not acknowledged that may have influenced the findings. Furthermore, although diet was assessed using a FFQ these instruments have been known to suffer from recall bias. Similarly, there are also issues with the NOVA classification system regarding misclassification of food items by evaluators, which may have affected the findings [51, 52].

Conclusions

In summary, our findings show that the consumption of UPFs is associated with several physiological and dietary abnormalities which are in turn associated with CVD. More specifically, these include positive associations with waist circumference and atherogenic blood lipids. However, several unexpected findings were revealed, including a positive relationship between UPF consumption and HDL-C, and increased consumption of unsaturated fats and fiber in those consuming higher levels of UPFs, which is perhaps an artefact of a unique regional dietary pattern. These findings offer insights into an understudied population and highlight a need for further evidence, particularly of a longitudinal nature, to determine the impact of UPFs on markers of CVD.

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Disclosure statement

All authors declare that they have no conflict of interest.

Availability of data and materials

Data is available on request from the authors.

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Table 1. Baseline characteristics of study participants.

	Ultra-processed Foods			
Variables	**T_1 (n=2295)**	**T_2 (n=2206)**	**T_3 (n=2110)**	**P-value**
Gender, male (%)	45.1	49.9	52.3	**<0.001**
Age (year)	51.16 ± 7.97	49.86 ± 7.60	49.08 ± 7.52	**<0.001**
Weight (kg)	67.40 ± 12.30	68.86 ± 12.04	69.11 ± 12.07	**<0.001**
BMI (kg/m^2)	25.27 ± 4.40	25.74 ± 4.41	25.64 ± 4.42	**0.001**
WC (cm)	92.89 ± 11.89	94.10 ± 11.93	94.08 ± 12.05	**0.001**
HC (cm)	99.85 ± 8.27	100.79 ± 8.26	100.65 ± 8.15	**<0.001**
Education (year)	4.21 ± 4.33	5.23 ± 4.61	5.49 ± 4.57	**<0.001**
Physical Activity (met/day)	39.15 ± 6.34	38.77 ± 6.07	39.17 ± 6.61	0.062
Systolic Blood Pressure (mmHg)	111.15 ± 15.28	111.06 ± 15.06	110.11 ± 14.71	**0.043**
Diastolic Blood Pressure (mmHg)	70.42 ± 9.39	70.58 ± 9.46	70.18 ± 9.16	0.359
FBS (mg/dL)	91.43 ± 16.84	91.33 ± 15.61	90.68 ± 17.07	0.266
TG (mg/dL)	121.88 ± 80.54	122.97 ± 69.21	127.99 ± 83.59	**0.023**
TC (mg/dL)	186.54 ± 40.32	188.81 ± 39.60	189.00 ± 41.06	0.078
LDL-C (mg/dL)	113.52 ± 33.49	116.48 ± 33.37	116.39 ± 34.67	**0.004**
HDL-C (mg/dL)	48.80 ± 12.99	47.89 ± 12.58	47.24 ± 12.39	**<0.001**
Non-HDL-C	137.71 ± 38.71	140.94 ± 38.04	141.79 ± 39.63	**0.001**
LDL-C to HDL-C ratio	2.46 ± 0.91	2.56 ± 0.91	2.59 ± 0.91	**<0.001**

BMI, body mass index; WC, waist circumference; HC, hip circumference; FBS, fasting blood sugar; TG, triglyceride; TC, total cholesterol; LDL-C, low density lipoprotein-cholesterol; HDL-C, high density lipoprotein-cholesterol.
Values are mean (SD) for continuous and percentage for categorical variables.
Using one-way ANOVA for continuous and Chi-square test for categorical variables.

Table 2. Nutrients and food intakes between tertiles of UPFs.

	Ultra-processed Foods			
Variables	**T_1 (n=2295)**	**T_2 (n=2206)**	**T_3 (n=2110)**	**P-value**
Nutrients	**Median (25-75)**	**Median (25-75)**	**Median (25-75)**	
Energy (kcal/d)	2331.28 (1870.4-2858.2)	2395.79 (1944.1-2886.1)	2507.79 (2053.7-2998.1)	**<0.001**
Protein (%Energy)	12.86 (10.35-16.11)	12.57 (10.10-15.51)	11.87 (9.56-14.46)	**<0.001**
Carbohydrate ((%Energy)	67.76 (55.45-84.61)	65.87 (53.95-80.15)	62.39 (50.73-75.83)	**<0.001**
Fat ((%Energy)	9.99 (7.59-12.81)	10.12 (7.98-12.83)	10.33 (8.39-12.55)	**<0.001**
Fiber (g/day)	22.69 (19.68-26.69)	24.21 (20.98-28.18)	24.60 (21.10-28.69)	**<0.001**
Cholesterol (g/day)	216.29 (166.60-276.23)	237.26 (179.20-288.87)	242.19 (192.88-305.54)	**<0.001**
SFA ((%Energy)	8.03 (5.89-10.65)	8.07 (6.11-10.35)	8.10 (6.33-10.28)	0.587
MUFA ((%Energy)	6.19 (4.40-8.32)	6.62 (4.97-8.49)	6.96 (5.46-8.66)	**<0.001**
PUFA ((%Energy)	3.28 (2.16-4.54)	3.65 (2.61-4.87)	4.04 (3.07-5.18)	**<0.001**
Food Items				
Non-dairy Beverage (%Energy)	4.70 (1.34-11.67)	7.01 (2.26-15.64)	8.36 (3.12-18.16)	**<0.001**
Cookies and cakes (%Energy)	14.55 (6.50-26.21)	20.48 (11.80-32.41)	28.72 (16.95-42.19)	**<0.001**
Dairy products (%Energy)	47.75 (30.72-63.66)	35.28 (24.40-46.30)	23.52 (15.26-33.71)	**<0.001**
Processed meat and fast food (%)	0.00 (0.00-3.17)	0.97 (0.00-4.71)	2.37 (0.00-8.52)	**<0.001**
Margarine and sauces (%Energy)	6.33 (2.11-13.80)	8.40 (3.51-16.67)	8.36 (3.53-16.35)	**<0.001**
Sweets (%Energy)	4.22 (1.15-9.02)	5.92 (2.57-10.95)	5.28 (2.59-9.56)	**<0.001**
Bread (%Energy)	0.33 (0.00-2.37)	0.82 (0.00-2.77)	0.80 (0.00-3.07)	**<0.001**
Others (%Energy)	1.61 (0.23-4.94)	1.92 (0.46-4.95)	1.65 (0.40-4.27)	0.007

UPFs, ultra-processed foods; SFA, saturated fatty acid; PUFA, polyunsaturated fatty acid; MUFA, monounsaturated fatty acid.

Using Kruskal–Wallis test.

Table 3. Crude and multivariable-adjusted odds ratios and 95% CIs across tertile of UPFs.

	Ultra-processed Foods			
Variables	**T_1 (n=2295)**	**T_2 (n=2206)**	**T_3 (n=2110)**	**P_{trend}**
WC (cm)				
Crude Model	Ref.	1.25 (1.11, 1.40)	1.23 (1.09, 1.39)	**<0.001**
Adjusted Model[a]	Ref.	1.29 (1.14, 1.46)	1.31 (1.15, 1.48)	**<0.001**
Adjusted Model[b]	Ref.	1.35 (1.14, 1.60)	1.42 (1.19, 1.69)	**<0.001**
FBS (mg/dL)				
Crude Model	Ref.	0.81 (0.49, 1.32)	0.82 (0.50, 1.34)	0.415
Adjusted Model[c]	Ref.	0.83 (0.51, 1.37)	0.87 (0.53, 1.44)	0.579
TG (mg/dL)				
Crude Model	Ref.	1.11 (0.97, 1.27)	1.18 (1.03, 1.36)	**0.014**
Adjusted Model[c]	Ref.	1.04 (0.90, 1.20)	1.12 (0.97, 1.29)	0.116
LDL-C (mg/dL)				
Crude Model	Ref.	1.20 (1.05, 1.37)	1.23 (1.08, 1.40)	**0.001**
Adjusted Model[c]	Ref.	1.21 (1.06, 1.38)	1.28 (1.12, 1.46)	**<0.001**
HDL-C (mg/dL)				
Crude Model	Ref.	1.16 (1.03, 1.31)	1.25 (1.11, 1.41)	**<0.001**
Adjusted Model[b]	Ref.	1.08 (0.95, 1.22)	1.15 (1.02, 1.30)	**0.022**
Non-HDL-C				
Crude Model	Ref.	1.25 (1.10, 1.40)	1.24 (1.10, 1.40)	**<0.001**
Adjusted Model[c]	Ref.	1.22 (1.08, 1.38)	1.25 (1.10, 1.41)	**<0.001**
LDL-C to HDL-C Ratio				
Crude Model	Ref.	1.22 (1.08, 1.37)	1.29 (1.15, 1.46)	**<0.001**
Adjusted Model[c]	Ref.	1.18 (1.04, 1.33)	1.24 (1.10, 1.41)	**<0.001**

UPFs, ultra-processed foods; WC, waist circumference; FBS, fasting blood sugar; TG, triglyceride; LDL-C, low density lipoprotein-cholesterol; HDL-C, high density lipoprotein-cholesterol.

Adjusted Model[a]: adjusted for age, physical activity and education.

Adjusted Model[b]: adjusted for age, physical activity, education and BMI.

Adjusted Model[c]: adjusted for gender, age, physical activity, education and BMI.

These values are odd ratio (95% CIs).

Obtained from logistic regression.

The Association between Ultra-Processed Foods and Conventional Markers of Cardiovascular Risk in an Adult Iranian Population.

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Abstract:

Background and Aims: According to the NOVA classification system, ultra-processed foods result from extensive industrial processing and use ingredients derived from food and non-food products, which can negatively impact on cardiovascular disease risk factors. Despite this, few studies have investigated UPFs in Middle Eastern populations regardless of high consumption in this region.

Methods and Results: This cross-sectional study was conducted on data from the Prospective Epidemiological Research Studies in Iran Kharemeh cohort (n = 6611). Food frequency questionnaires were assessed and the ratio of total UPFs energy/total energy intake was calculated. Data was categorized into tertiles of UPF consumption using the NOVA classification system. Kruskal–Wallis tests were used to assess differences in nutrient and food intakes between tertiles and logistic regression analysis was applied to assess the associations between UPFs and CVD risk factors. After adjustment for potential confounders the logistic regression analysis revealed significant positive relationships between intakes of UPFs and waist circumference (WC) (T2: OR; 1.34, 95% CI; 1.13-1.60 – T3: OR; 1.41, 95% CI; 1.18-1.69, P <0.001), low-density lipoprotein cholesterol (LDL-C) (T2: OR; 1.20, 95% CI; 1.05-1.37 – T3: OR; 1.27, 95% CI; 1.11-1.45, P <0.001), non-high-density lipoprotein cholesterol (non-HDL) (T2: OR; 1.21, 95% CI; 1.07-1.37 – T3: OR; 1.24, 95% CI; 1.10-1.41, P <0.001) and LDL-C to HDL-C ratio (T2: OR; 1.15, 95% CI; 1.02-1.31 – T3: OR; 1.21, 95% CI; 1.07-1.38, P = 0.002).

Conclusion: The consumption of UPFs was positively associated with WC and atherogenic blood lipids. However, increased intakes of fiber and unsaturated fats were also found in those consuming more UPFs, which was not expected. These findings offer insights into an understudied population and warrant further research.

Key words: ultra-processed food, cardiovascular disease, risk factors, adult, Iran

Introduction

Foods can be prepared in myriad ways, ranging from using minimal processing techniques, such as freezing, pasteurization, and fermentation, through to ultra-processing techniques involving chemical modification, extrusion, or the use of multiple treatments employed in tandem [1]. Many of these products are often highly palatable, convenient, and typically designed to maximize industry profitability [2]. Examples of ultra-processed foods (UPFs) include soft drinks, ice-cream, and pre-prepared items such as pizzas and pies and can also consist of food products sometimes regarded as healthy, including flavored yoghurts and breakfast cereals [2]. Given the heterogeneity of UPFs the NOVA classification system has been developed to enable food items to be categorized into four groups based upon the level of processing they have undergone [3]. According to the NOVA classification, UPFs are defined as formulations which contain little to no intact foods, as well as fats, salt, sugar, stabilizers, colorings, preservatives and emulsifiers added by manufacturers [2]. Furthermore, foods which contain at least one item associated with an UPF group would be regarded as an UPF [2]. However, despite the development and widespread usage of the system few studies have utilized the NOVA classification to investigate the consumption and health impact of UPFs in ethnically diverse populations.

This is concerning when considering that findings from the National Health and Nutrition Examination Survey (NHANES) and the Spanish Seguimiento Universidad de Navarra (SUN) cohort study have both demonstrated that UPF consumption is associated with an increased risk of all-cause mortality [4, 5]. Furthermore, a recent dose-response meta-analysis which attempted to quantify the magnitude of response to UPFs revealed that for every 10% increase in UPF consumption, there is a 15% increase in all-cause mortality risk and a positive linear association with CVD-cause mortality [6]. These links with UPFs and increased risks of CVD have also been shown in several other large-scale cohort studies. Examples being the NutriNet-Santé cohort study, which found that the consumption of UPFs is significantly associated with increased cardiovascular, cerebrovascular, and coronary heart diseases, even after adjustment for known risk factors [7]. Similarly, the Framingham Offspring Study showed that each additional serving of UPFs consumed per day increased the likelihood of hard CVD (i.e. sudden and non-sudden coronary death, myocardial infarction, and fatal/nonfatal stroke), hard coronary heart disease and overall CVD and CVD mortality by 7%, 9% and 5% respectively [8]. The Italian Moli-Sani study also revealed that consuming UPFs is associated with an increased risk of CVD and all-cause mortality in individuals with a history of CVD, and for the first time highlighted the public health implications of UPFs specifically regarding secondary CVD prevention [9].

Due to these relationships, several biological mechanisms have been proposed. These include dyslipidemia and insulin resistance resulting from the excess energy, fat, sugar, and refined carbohydrates which are abundant in UPFs [1]. High levels of sodium and additives may also promote hypertension and oxidative stress respectively and changes to the matrix of UPFs may render them more readily absorbed, negatively impacting upon glycemic responses and the gut microbiota, contributing to increased CVD risk [1]. Furthermore, indirect effects resulting from inadequate fruit, vegetable, and fiber intake in those who consume UPFs may be another contributing factor [1]. Consequently, organizations such as the American Heart Association have recommended individuals choose minimally processed foods as opposed to UPFs and in Latin America the avoidance of UPFs has been promoted as a 'Golden Rule' for dietary guidelines [2, 10].

Despite this progress little research regarding the impact of UPFs upon health has been conducted in the Middle East. This is particularly concerning since a global assessment of UPF consumption has shown increasing rates in the region [11] and a prospective cohort study of 21 countries highlighted that the Middle East had the second highest consumption of refined sweetened foods [12]. Also, a systematic review and meta-analysis of Iranian children showed high levels of sugar and fat consumption [13]. In terms of disease, a study of 139 healthy Iranian adolescents revealed increased DNA damage (as determined by 8-hydroxy-2 0-deoxyguanosine concentration) with increased UPF intake [14]. The relationship between UPFs and adiposity is unclear. For example, despite Iranians consuming a fifth of energy from UPF it appears that the relationship may be sex specific, with a positive association between UPF intake and overweight only existing in males [15]. However, this is not in agreement with data from a multi-national European cohort study, with similar positive associations between UPF consumption and weight gain being observed regardless of sex [16]. Paradoxical findings such as these suggest further work is required in ethnically diverse populations to account for cultural differences and unique dietary intakes. More broadly, the dearth of research investigating the impact of UPFs upon CVD in the Middle East warrants urgent attention.

Method

Study Design, Study Population & Covariates

The cross-sectional Prospective Epidemiological Research Studies in Iran (PERSIAN) [17], Kharameh cohort is a subgroup of PERSIAN conducted between 2014 and 2017 on a total of 10663 subjects aged 40–70 years [18]. After we excluded based on disease history, missing data, and reporting of under- and over-nutrition, 6611 participants were included in our final analysis. Eligible individuals were included in the study by census method. As part of the PERSIAN cohort study, demographic information, physical activity, smoking status, and medical history were collected. In addition, weight, height, waist circumference (WC), hip circumference (HC), systolic blood pressure, and diastolic blood pressure, biochemical assessments including fasting blood glucose (FBS), total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C) and diet were measured.

Among the participants of the Kharameh cohort, those who had one or more types of cardiovascular diseases (CVDs) [19], hypertension, diabetes, other diseases, and an energy intake of less than 800 kcal or more than 4200 kcal were excluded (Figure 1). The study was approved by the ethics committee of Shiraz University of Medical Sciences, Fars, Iran (code: IR.SUMS.REC.1399.1115).

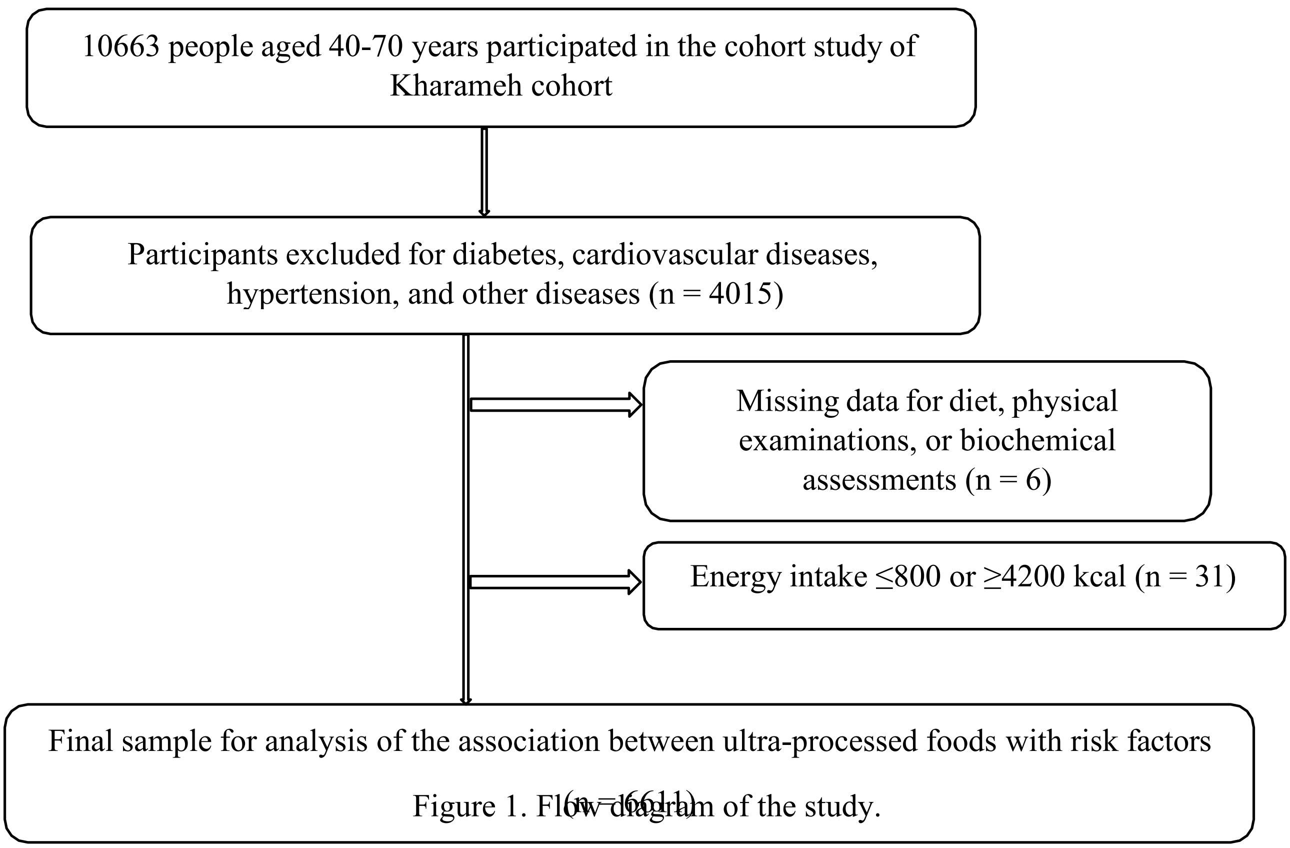

Figure 1. Flow diagram of the study.

Dietary Intake Assessment

Food intake was collected using a semi-quantitative 130-question food frequency questionnaire (FFQ), that was validated based upon the food habits and culture of the Iranian population [20]. Based on home scales, the recorded values of each food item in the FFQ were converted to grams. Nutritionist IV software for Iranians (version 7.0; N-Squared Computing, Salem, OR, USA) was used to calculate energy, macro- and micronutrients [21]. Finally, to calculate the ultra-processed foods index we selected food items which were defined as UPFs by the NOVA classification system. Then the total daily consumption of each UPF item was calculated based on their energy contribution (UPF items included: processed meats, confectionary, biscuits, cakes, pastries and sweets, buns, packaged breads, ice cream, sweetened milk-based beverages, industrial fruits drinks, salty snacks, margarine, fries, soft drinks, sauces and dressings etc.).These were divided into 8 subgroups (non-dairy beverages, cakes and cookies, dairy beverages, fast food and processed meats, oil and sauce, sweets, breads, and others). To understand the contribution of each food group to the total intake of highly processed foods the average daily energy intake of each of the 8 subgroups of UPFs was divided by the total daily energy intake of UPFs and multiplied by 100 [2, 22, 23]. As an exposure, we used a ratio based on the percentage of total calories from UPFs divided by total caloric intake. Also, to demonstrate the effect of UPFs and their poor nutritional quality, a healthy diet index was calculated based on 9 items (fruits and vegetables, pulses, nuts and seeds, protein, carbohydrate, fiber, saturated fatty acids (SFA), monounsaturated fatty acids (MUFA), polyunsaturated fatty acids (PUFA) and cholesterol intake) and we adjusted our results based upon this index (i.e. if the diet aligned with any of the 9 recommended components a score of 1 was given, otherwise, a score of 0 was applied) [24].

Anthropometric and Biochemical Assessments

The height, weight, WC, HC, and blood pressure of the participants were measured by trained experts. Weight was measured while wearing light clothing and height was measured without shoes. The accuracy of weight, HC and WC measurements were all within 0.1 cm accuracy. Body mass index (BMI) was calculated by dividing weight by the square of height (m). Blood pressure was measured after 10 minutes of rest in a sitting position using a calibrated German standard Reiser model sphygmomanometer. For laboratory evaluations, after 10-14 hours fasting, a 20 ml blood sample was taken from each participant and stored at -80°C prior to further analysis.

Glucose, TG, and TC were measured using a Mindray device (Japan) and Pars test kits. HDL-C, TG and TC levels were determined using enzymatic methods. The Friedwald formula was used to calculate LDL-C levels [25]. We dichotomized CVD risk factors based on: WC ≥ 88 cm for women and 102 for men, FBS ≥ 126 mg/dL, TG ≥ 150 mg/dL, TC ≥ 200 mg/dL L, LDL-C ≥ 130 mg/dL, HDL-C < 40 mg/dL for men and 50 mg/dL for women, and non-HDL-C ratio ≥ 130 were classed as abnormalities [21, 26-29].

Statistical Analysis

Demographic characteristics including age, gender, and education level of the participants were collected using a questionnaire. The educational level of the participants was determined by asking for the number of years spent in education. Physical activity was evaluated by using a questionnaire which included the time spent on various activities such as exercise, work, sleep, and eating during the day [19]. The metabolic equivalent of task (MET) was calculated for each activity. Finally, the total amount of metabolic equivalent of task (hours/day) was calculated for each participant [19].

All data were analyzed using SPSS software (version 20.0) and a P-value less than 0.05 was considered significant. The normality distribution of the variables was determined using the Kolmogorov-Smirnov test. First, we obtained energy-adjusted intakes of all food items using residual methods [30]. To compare the baseline characteristics of the participants one-way ANOVA or Chi-square tests were used for continuous and categorical variables respectively. Kruskal–Wallis tests were used to compare the intake of nutrients and food groups across tertiles of UPF intake. Three different multivariate logistic regression models were used to evaluate the relationship between the ultra-processed foods index and the odds of CVD risk factors. We chose to use three different models because some outcomes were dependent on BMI or gender. We used gender, age, physical activity, education, BMI status, and healthy diet index as confounding factors for the regression models.

Results

Baseline characteristics of the study population are shown in Table 1. There were significant differences in terms of gender (P <0.001), age (P <0.001), weight (P <0.001), BMI (P = 0.001), WC (P = 0.001), HC (P <0.001), education (P <0.001), systolic blood pressure (P = 0.043), TG

(P = 0.023), LDL-C (P = 0.004), HDL-C (P <0.001), non-HDL-C (P = 0.001) and LDL-C to HDL-C ratio (P <0.001) between tertiles of UPFs.

Higher consumption of UPFs were associated with higher intakes of energy, fat, fiber, cholesterol, MUFA, PUFA, non-dairy beverages, cookies and cakes, processed meat and fast food, margarine, and sauces and sweets, but lower intakes of protein, carbohydrate, and dairy products (P <0.001 for all) (Table 2).

Multivariable-adjusted odds ratio (OR) and 95% confidence intervals [31] for outcomes through UPFs tertiles are displayed in Table 3. In the crude model, the population in the second and last tertiles of UPFs were more likely to have higher odds of WC (T2: OR; 1.25, 95% CI; 1.11-1.40 – T3: OR; 1.23, 95% CI; 1.09-1.39, P <0.001), TG (T3: OR; 1.18, 95% CI; 1.03-1.36, P = 0.014), LDL-C (T2: OR; 1.23, 95% CI; 1.08-1.40, P = 0.001), HDL-C (T2: OR; 1.16, 95% CI; 1.10-1.40 – T3: OR; 1.25, 95% CI; 1.11-1.41, P <0.001), non-HDL-C (T2: OR; 1.25, 95% CI; 1.10-1.40 – T3: OR; 1.24, 95% CI; 1.10-1.41, P <0.001) and LDL-C to HDL-C ratio (T2: OR; 1.22, 95% CI; 1.08-1.37 – T3: OR; 1.29, 95% CI; 1.15-1.46, P <0.001) abnormalities compared to those in the first tertile. Moreover, after adjustment for potential confounders in the full adjusted model, positive relationships among intakes of UPFs and WC (T_2: OR; 1.34, 95% CI; 1.13-1.60 – T_3: OR; 1.41, 95% CI; 1.18-1.69, P <0.001), LDL-C (T_2: OR; 1.20, 95% CI; 1.05-1.37 – T_3: OR; 1.27, 95% CI; 1.11-1.45, P <0.001), non-HDL-C (T_2: OR; 1.21, 95% CI; 1.07-1.37 – T_3: OR; 1.24, 95% CI; 1.10-1.41, P <0.001) and LDL-C to HDL-C ratio (T_2: OR; 1.15, 95% CI; 1.02-1.31 – T_3: OR; 1.21, 95% CI; 1.07-1.38, P = 0.002) abnormalities remained significant.

Discussion

Our study aimed to address the dearth of literature concerning the impact of UPF consumption upon markers of CVD in a Middle Eastern population. We showed that an increased intake of UPFs was positively associated with WC and increased odds of a poorer overall blood lipid profile. These are findings which, although being described by others [32], have not been widely reported in a Middle Eastern population. We also found several dietary abnormalities, but no evidence to support a relationship between UPF consumption and glycemic control.

The positive relationship between UPF consumption and WC partially agrees with the literature. For example, several studies have failed to show an association between UPFs and numerous measures of adiposity, including ectopic fat, subcutaneous adipose tissue, total fat [33] and BMI, even after adjusting for physical activity [34]. Furthermore, a recent study conducted in Iranian children also revealed no associations between UPFs and measures of overweight and obesity [35]. These findings contrast with ours and the work of others, with one recent meta-analysis showing that the consumption of UPFs is associated with a 39% increased risk of overweight/obesity and greater waist circumference [36] and another showing an increased risk of overweight, obesity, and abdominal obesity [37]. A cross-sectional analysis of baseline data from the PREDIMED-PLUS trial also revealed direct associations between UPF consumption and weight using four different UPF classification systems and BMI when using the NOVA system [38]. Despite these contrary findings, it is important to note that most available evidence is observational. Currently only one randomized controlled trial (RCT) has been conducted (which took place in a metabolic ward setting) and found that energy intake and weight gain were both greater when consuming a diet of UPFs compared to a diet rich in whole foods [39]. Consequently, the authors recommended that the intake of UPFs should be limited in the context of obesity prevention and treatment [39].

With respect to other risk factors, our findings showed that the consumption of UPFs increased the odds of higher LDL-C, non-HDL-C and LDL-C to HDL-C ratio abnormalities. The potential for increased levels of LDL-C and other apolipoprotein B-containing lipoprotein particles is concerning, especially given their clear role in cardiovascular disease [40]. In this context, our findings agree with previous studies. For example, a cohort study of Brazilian children showed that after 3-4 years of follow-up, UPF intake was a predictor of LDL-C and total cholesterol levels [41]. A more recent extension of this work also highlighted other changes to blood lipids and showed that after 3 years of follow-up, children in the highest tertile of UPF consumption had higher concentrations of blood TG; a finding reflected in our own data [42]. These longitudinal trends are suggestive of the ability of UPFs to modulate blood lipids after exposure and is a cause for concern given that dietary patterns adopted earlier in life can persist into adulthood [43].

Similarly, evidence shows UPFs are negatively associated with HDL-C [36]. This was found in our study with those in the third tertile having the lowest concentrations. This occurred despite significantly higher proportions of MUFA and PUFA in tertile 3 compared to the first tertile, although there is the possibility that some of these unsaturated fatty acids may be trans fats which are still present in the Iranian diet despite government interventions [44]. This suggests that the impact of food processing may eclipse that of fat composition and may perhaps explain our findings. Despite this, our logistic regression analysis did not show a significant positive relationship between UPF consumption and HDL-C after adjustment for confounding factors.

The results from our logistic regression analysis also showed no significant associations between UPF consumption and FBS; a finding which is not concordant with the literature. Several large-scale European studies have demonstrated a significant positive relationship between UPF intake and Type 2 diabetes [31, 45, 46]. Potential mechanisms have also been proposed, which include the production of and exposure to endocrine disruptors which have been associated with diabetes and increased intakes of fructose contributing to the promotion of hepatic and whole-body insulin resistance [31, 47, 48]. The reason for this lack of agreement with the wider literature is unknown; however, we speculate that although those in the third tertile consumed higher levels of all UPF items apart from dairy products, many of which are likely to be high in sugar and fat, significantly higher levels of fiber were being consumed too. This finding was unexpected but given the ability of dietary fiber to regulate blood glucose and other markers of glycemic control provides a plausible rationale for the lack of association [49, 50]. Furthermore, this may be a finding unique to Iran due to the regional dietary pattern, elements of which are known to be rich in fiber [51].

Limitations and Strengths

Our study has several strengths, including the large sample size and the adjustments which were made for a variety of potentially limiting confounding factors. We recognized that UPF consumption and diet quality are inversely associated and so we adjusted our logistic regression analysis to account for a healthy diet index [52]. This allows us to theoretically infer that the associations found between UPF consumption and CVD risk markers are independent of the nutritional quality of UPFs and that the effects may result from non-nutritional mechanisms. This has also been postulated by others who have found that associations between UPFs and increased mortality may be explained by the high level of food processing rather than their poor nutrient quality [53]. Despite these aspects there are several limitations which should be mentioned. These include that the study was a cross-sectional, observational design and therefore does not offer any insights into the temporal effects of consuming UPFs. Furthermore, the study only recruited participants from Kharameh County and may not be nationally representative [54]. Similarly, although several confounding variables were accounted for there may be others that were not acknowledged which may have influenced the findings. Furthermore, although diet was assessed using a FFQ these instruments have been known to suffer from recall bias and have not been designed specifically for dietary data collection for subsequent NOVA classification, thus some UPF items may not have been properly listed. Similarly, there are known issues with the NOVA classification system regarding the misclassification of food items by evaluators which may also have affected the findings; however, the classification is widely used and allows comparison with previous studies [55, 56].

Conclusions

In summary, our findings show that the consumption of UPFs is associated with several physiological and dietary abnormalities which are in turn associated with CVD. More specifically, these include positive associations with waist circumference and atherogenic blood lipids. However, several unexpected findings were revealed, including a positive relationship between UPF consumption and increased consumption of unsaturated fats and fiber in those consuming higher levels of UPFs, which is perhaps an artefact of a unique regional dietary pattern. These findings offer insights into an understudied population and highlight a need for further evidence, particularly of a longitudinal nature, to determine the impact of UPFs on markers of CVD.

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Disclosure statement

All authors declare that they have no conflict of interest.

Availability of data and materials

Data is available on request from the authors.

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Authors' contributions: M.N, I.D, R.W, and M.M; Contributed to writing the first draft. M.N, M.M, and M.G.J; Contributed to all data and statistical analysis, and interpretation of data. S.F. and A.R; Contributed to the research concept, supervised the work and revised the manuscript. All authors read and approved the final manuscript.

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Table 1. Baseline characteristics of study participants.

	Ultra-processed Foods			
Variables	**T_1 (n=2295)**	**T_2 (n=2206)**	**T_3 (n=2110)**	**P-value**
Gender, male (%)	45.1	49.9	52.3	**<0.001**
Age (year)	51.16 ± 7.97	49.86 ± 7.60	49.08 ± 7.52	**<0.001**
Weight [40]	67.40 ± 12.30	68.86 ± 12.04	69.11 ± 12.07	**<0.001**
BMI (kg/m^2)	25.27 ± 4.40	25.74 ± 4.41	25.64 ± 4.42	**0.001**
WC (cm)	92.89 ± 11.89	94.10 ± 11.93	94.08 ± 12.05	**0.001**
HC (cm)	99.85 ± 8.27	100.79 ± 8.26	100.65 ± 8.15	**<0.001**
Education (year)	4.21 ± 4.33	5.23 ± 4.61	5.49 ± 4.57	**<0.001**
Physical Activity (met/day)	39.15 ± 6.34	38.77 ± 6.07	39.17 ± 6.61	0.062
Systolic Blood Pressure (mmHg)	111.15 ± 15.28	111.06 ± 15.06	110.11 ± 14.71	**0.043**
Diastolic Blood Pressure (mmHg)	70.42 ± 9.39	70.58 ± 9.46	70.18 ± 9.16	0.359
FBS (mg/dL)	91.43 ± 16.84	91.33 ± 15.61	90.68 ± 17.07	0.266
TG (mg/dL)	121.88 ± 80.54	122.97 ± 69.21	127.99 ± 83.59	**0.023**
TC (mg/dL)	186.54 ± 40.32	188.81 ± 39.60	189.00 ± 41.06	0.078
LDL-C (mg/dL)	113.52 ± 33.49	116.48 ± 33.37	116.39 ± 34.67	**0.004**
HDL-C (mg/dL)	48.80 ± 12.99	47.89 ± 12.58	47.24 ± 12.39	**<0.001**
Non-HDL-C	137.71 ± 38.71	140.94 ± 38.04	141.79 ± 39.63	**0.001**
LDL-C to HDL-C ratio	2.46 ± 0.91	2.56 ± 0.91	2.59 ± 0.91	**<0.001**
UPF intake (% energy)	5.60 ± 2.20	11.06 ± 1.61	20.50 ± 5.91	**<0.001**
UPF intake (kcal/day energy)	135.13 ± 71.25	272.27 ± 85.96	525.31 ± 212.70	**<0.001**

BMI, body mass index; WC, waist circumference; HC, hip circumference; FBS, fasting blood sugar; TG, triglyceride; TC, total cholesterol; LDL-C, low density lipoprotein-cholesterol; HDL-C, high density lipoprotein-cholesterol.
Values are mean ± SD for continuous and percentage for categorical variables.
P-values derived using one-way ANOVA for continuous and Chi-square tests for categorical variables.
Bold values show significant variables.

Table 2. Nutrients and food intakes between tertiles of UPFs.

	Ultra-processed Foods			
Variables	**T_1 (n=2295)**	**T_2 (n=2206)**	**T_3 (n=2110)**	**P-value**
Nutrients	**Median (25th-75th)**	**Median (25th-75th)**	**Median (25th-75th)**	
Energy (kcal/d)	2331.28 (1870.4-2858.2)	2395.79 (1944.1-2886.1)	2507.79 (2053.7-2998.1)	**<0.001**
Protein (%Energy)	12.86 (10.35-16.11)	12.57 (10.10-15.51)	11.87 (9.56-14.46)	**<0.001**
Carbohydrate (%Energy)	67.76 (55.45-84.61)	65.87 (53.95-80.15)	62.39 (50.73-75.83)	**<0.001**
Fat (%Energy)	9.99 (7.59-12.81)	10.12 (7.98-12.83)	10.33 (8.39-12.55)	**<0.001**
Fiber (g/day)	22.69 (19.68-26.69)	24.21 (20.98-28.18)	24.60 (21.10-28.69)	**<0.001**
Cholesterol (g/day)	216.29 (166.60-276.23)	237.26 (179.20-288.87)	242.19 (192.88-305.54)	**<0.001**
SFA (%Energy)	8.03 (5.89-10.65)	8.07 (6.11-10.35)	8.10 (6.33-10.28)	0.587
MUFA (%Energy)	6.19 (4.40-8.32)	6.62 (4.97-8.49)	6.96 (5.46-8.66)	**<0.001**
PUFA (%Energy)	3.28 (2.16-4.54)	3.65 (2.61-4.87)	4.04 (3.07-5.18)	**<0.001**
Food Items				
Non-dairy Beverage (%Energy)	4.70 (1.34-11.67)	7.01 (2.26-15.64)	8.36 (3.12-18.16)	**<0.001**
Cookies and cakes (%Energy)	14.55 (6.50-26.21)	20.48 (11.80-32.41)	28.72 (16.95-42.19)	**<0.001**
Dairy products (%Energy)	47.75 (30.72-63.66)	35.28 (24.40-46.30)	23.52 (15.26-33.71)	**<0.001**
Processed meat and fast food (%)	0.00 (0.00-3.17)	0.97 (0.00-4.71)	2.37 (0.00-8.52)	**<0.001**
Margarine and sauces (%Energy)	6.33 (2.11-13.80)	8.40 (3.51-16.67)	8.36 (3.53-16.35)	**<0.001**
Sweets (%Energy)	4.22 (1.15-9.02)	5.92 (2.57-10.95)	5.28 (2.59-9.56)	**<0.001**
Bread (%Energy)	0.33 (0.00-2.37)	0.82 (0.00-2.77)	0.80 (0.00-3.07)	**<0.001**
Others (%Energy)	1.61 (0.23-4.94)	1.92 (0.46-4.95)	1.65 (0.40-4.27)	**0.007**

UPFs, ultra-processed foods; SFA, saturated fatty acid; PUFA, polyunsaturated fatty acid; MUFA, monounsaturated fatty acid.

P-values derived from Kruskal–Wallis tests.

Values reported median (percentile 25th-75th).

Bold values show significant variables.

Table 3. Crude and multivariable-adjusted odds ratios and 95% CIs across tertile of UPFs.

	Ultra-processed Foods			
Variables	**T_1 (n=2295)**	**T_2 (n=2206)**	**T_3 (n=2110)**	**P_{trend}**
WC (cm)				
Crude Model	Ref.	**1.25 (1.11, 1.40)**	**1.23 (1.09, 1.39)**	**<0.001**
Adjusted Model[a]	Ref.	**1.26 (1.12, 1.43)**	**1.27 (1.12, 1.44)**	**<0.001**
Adjusted Model[b]	Ref.	**1.34 (1.13, 1.60)**	**1.41 (1.18, 1.69)**	**<0.001**
FBS (mg/dL)				
Crude Model	Ref.	0.81 (0.49, 1.32)	0.82 (0.50, 1.34)	0.415
Adjusted Model[c]	Ref.	0.83 (0.51, 1.37)	0.87 (0.53, 1.45)	0.596
TG (mg/dL)				
Crude Model	Ref.	1.11 (0.97, 1.27)	**1.18 (1.03, 1.36)**	**0.014**
Adjusted Model[c]	Ref.	1.03 (0.89, 1.19)	1.10 (0.96, 1.28)	0.160
LDL-C (mg/dL)				
Crude Model	Ref.	**1.20 (1.05, 1.37)**	**1.23 (1.08, 1.40)**	**0.001**
Adjusted Model[c]	Ref.	**1.20 (1.05, 1.37)**	**1.27 (1.11, 1.45)**	**<0.001**
HDL-C (mg/dL)				
Crude Model	Ref.	**1.16 (1.03, 1.31)**	**1.25 (1.11, 1.41)**	**<0.001**
Adjusted Model[b]	Ref.	1.05 (0.93, 1.19)	1.12 (0.99, 1.27)	0.065
Non-HDL-C				
Crude Model	Ref.	**1.25 (1.10, 1.40)**	**1.24 (1.10, 1.40)**	**<0.001**
Adjusted Model[c]	Ref.	**1.21 (1.07, 1.37)**	**1.24 (1.10, 1.41)**	**<0.001**
LDL-C to HDL-C Ratio				
Crude Model	Ref.	**1.22 (1.08, 1.37)**	**1.29 (1.15, 1.46)**	**<0.001**
Adjusted Model[c]	Ref.	**1.15 (1.02, 1.31)**	**1.21 (1.07, 1.38)**	**0.002**

UPFs, ultra-processed foods; WC, waist circumference; FBS, fasting blood sugar; TG, triglyceride; LDL-C, low density lipoprotein-cholesterol; HDL-C, high density lipoprotein-cholesterol.

Dichotomized CVD risk factors based on: WC ≥ 88 cm for women and 102 for men, FBS ≥ 126 mg/dL, TG ≥ 150 mg/dL, TC ≥ 200 mg/dL L, LDL-C ≥ 130 mg/dL, HDL-C < 40 mg/dL for men and 50 mg/dL for women, and non-HDL ratio ≥ 130.

Adjusted Model[a]: adjusted for age, physical activity, education and healthy diet index.

Adjusted Model[b]: adjusted for age, physical activity, education, BMI and healthy diet index.

Adjusted Model[c]: adjusted for gender, age, physical activity, education, and healthy diet index.

Values are odd ratio (95% CIs).

Ptrend obtained from logistic regression.

Bold values show significant variables.

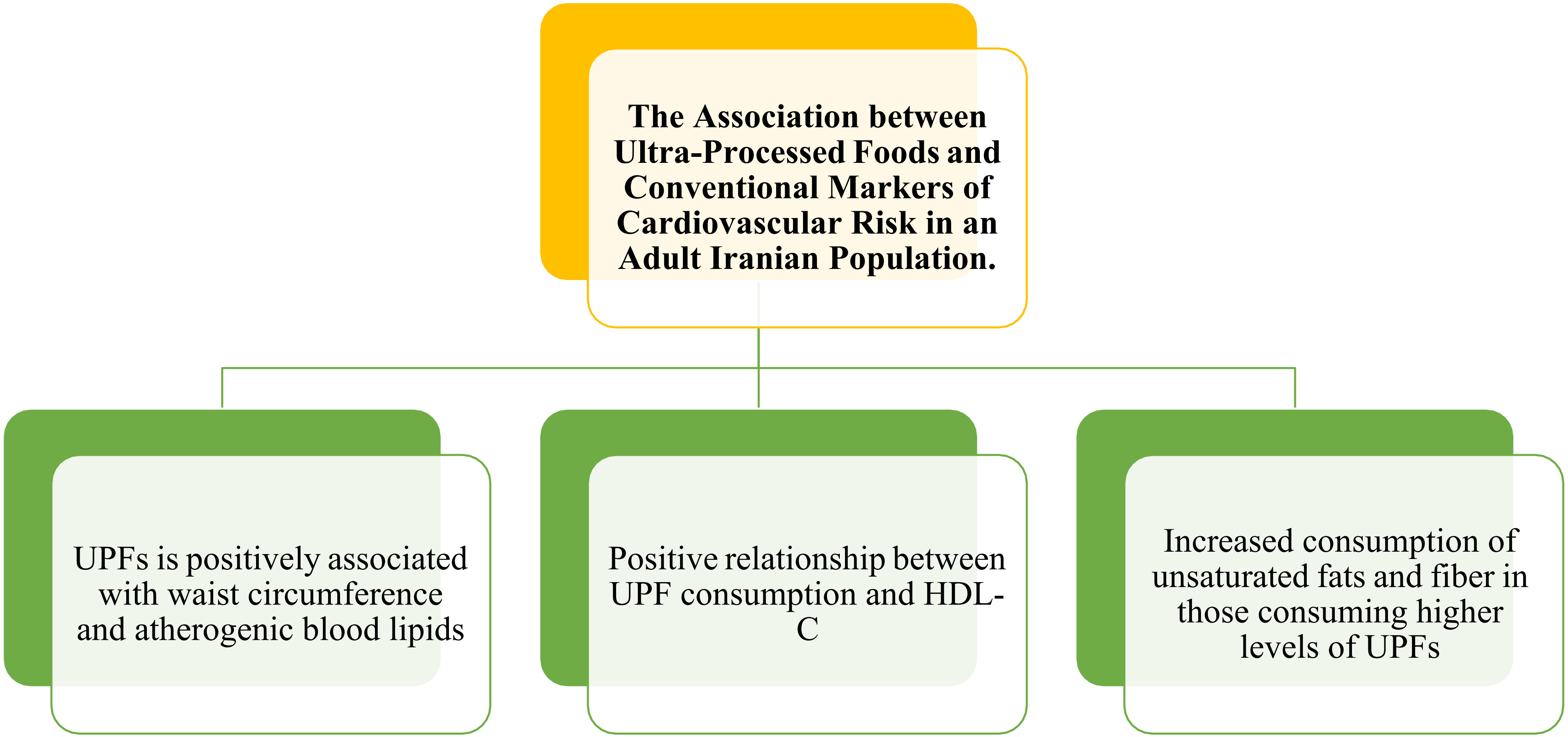
Highlight

1- Ultra-processed foods (UPFs) that prepared in myriad ways, ranging from minimum processing techniques, can be effect on cardiovascular diseases (CVD) risk factors

2- Our findings show that the consumption of UPFs is associated with several physiological and dietary abnormalities which are in turn associated with CVD.

3- A positive associations with waist circumference and atherogenic blood lipids.

4- Increased consumption of unsaturated fats and fiber in those consuming higher levels of UPFs, which is perhaps an artefact of a unique regional dietary pattern.


The Association between Ultra-Processed Foods and Conventional Markers of Cardiovascular Risk in an Adult Iranian Population.
UPFs is positively associated with waist circumference and atherogenic blood lipids
Positive relationship between UPF consumption and HDL-C
Increased consumption of unsaturated fats and fiber in those consuming higher levels of UPFs