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High Consumption of Ultra-Processed Food is Associated with Incident Dyslipidemia: A Prospective Study of Older Adults

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ABSTRACT

Background: Ultra-processed food (UPF) consumption has been associated with higher cardiovascular disease (CVD) and mortality risks.

Objectives: The aim of this study was to assess the relationship between UPF consumption and incident dyslipidemia in older adults, where evidence is limited.

Methods: We studied a prospective cohort of 1082 community-dwelling adults in Spain, older than 60 (mean age, 68 ± 6 years old). Participants (52% were women) were recruited between 2008–10 and followed up to 2015. At baseline, food intake data were collected using a validated computerized face-to-face dietary history. UPFs were identified according to the nature and extent of their industrial processing (NOVA classification). Triglycerides, HDL cholesterol, and LDL cholesterol were measured in fasting plasma samples collected at baseline and at follow-up. Statistical analyses were performed with logistic regression adjusted for the main potential confounders.

Results: Among those free of corresponding dyslipidemia at baseline, and after a follow-up of between 5 to 7 years, 60 (out of 895) developed incident hypertriglyceridemia (≥150 mg/dL), 112 (out of 878) had low HDL cholesterol (<40 in men/<50 mg/dL in women), and 54 (out of 472) had high LDL cholesterol (>129 mg/dL). The mean percentage of UPF consumption was 19% ± 11% of total energy intake. Those in the highest versus the lowest tertile of energy intake from UPFs had more than twice the odds of incident hypertriglyceridemia (OR, 2.66; 95% CI: 1.20–5.90; *P*-trend, 0.011) or low HDL cholesterol (OR, 2.23; 95% CI: 1.22–4.05; *P*-trend, 0.012). UPF consumption was not associated with high LDL cholesterol plasma concentrations.

Conclusions: Although UPF consumption in Spain was low among older adults, high consumption of UPFs was clearly associated with incident dyslipidemia. The increase in CVD risk recently found to be associated with UPF consumption might be mediated by these atherogenic lipid abnormalities. *J Nutr* 2021;151:2390–2398.

Keywords: ultra-processed food, nutritional epidemiology, atherogenic lipid abnormalities, dyslipidemia prevention, prospective cohort study

Introduction

The consumption of ultra-processed foods (UPFs), including beverages, has recently increased, encouraged by attractive packaging and intensive marketing (1). Currently, the consumption of UPFs in Spain is low to moderate (2) when compared to other developed countries, although it is increasing rapidly. In 1990, UPF consumption in Spain represented 11% of daily energy intake, but since then it has almost tripled (3). When consumption of UPFs was compared among various European countries in 2000 (using the same methodology), the mean contribution of UPFs to total energy intake in Spain and Italy was 35%, while it went up to 60% in the Netherlands, Sweden, Norway, Denmark, and the United Kingdom (4).

UPFs are formulated mostly or entirely with substances derived from food, with little, if any, of the original food remaining through processing and the addition of additives. Processing ensures greater durability, enhances flavors, and reduces preparation time. Likewise, because of its affordable

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cost compared to other unprocessed foods, such as fresh fruit, vegetables, meat, and fish, UPFs have become the more cost-conscious option for many families. UPFs are usually poor in nutritional value and have high energy density, with low fiber and vitamin content. UPFs have high amounts of added sugars, SFAs, *trans* fatty acids (TFAs), and sodium (5, 6), as well as additives and potentially neo-formed compounds created during thermal processing of food. Moreover, the packaging used with UPFs may contain toxic substances that could, for example, contaminate the food with endocrine disruptors, including phthalates and bisphenols (7), that are released from bottles and cans (8).

As a result, the scientific community has become more interested in evaluating the health risks associated with high consumption of UPFs on the general population (9). Consumption of UPFs has already been associated with increased mortality (2, 10, 11), cardiovascular disease (CVD) (12), and subclinical atherosclerosis (13), as well as several cardiometabolic risk conditions (14), such as hypertension (15), abdominal obesity (16), BMI (17), metabolic syndrome (18), or type 2 diabetes (19).

Dyslipidemia is also a well-established risk factor for the development of CVD (20); however, very little is known about the direct impact of UPFs on plasma lipid concentrations. To our knowledge, only 2 cross-sectional studies in adults have been published. In Canadian adults, the highest consumption of UPFs was associated with low HDL cholesterol (<1.03 mmol/L in men /<1.29 mmol/L in women), but not with high plasma concentrations of triglycerides (>1.7 mmol/L) (21). In Lebanese adults, the highest consumption of UPFs was not linked to the prevalence of metabolic syndrome, nor to any of its components (22).

Given the current limited data on the potential link between UPFs and dyslipidemia, along with the lack of prospective studies addressing this question in the adult population, our study aimed to prospectively evaluate the association between UPF consumption and triglyceride, HDL cholesterol, and LDL cholesterol plasma concentrations in older adults.

Methods

Study design and participants

Data were taken from the Seniors-Study on Nutrition and Cardiovascular Risk in Spain (ENRICA) cohort, whose methods have been previously reported (23, 24). In brief, this cohort was established between 2008 and 2010 with noninstitutionalized individuals aged ≥ 60 years old. Participants were followed up until 2015, when a subsequent data collection was carried out. After a response rate of 72%, the cohort was comprised of 1821 participants.

All participants gave informed consent prior to inclusion in the study. This investigation conformed to all principles outlined in the Declaration of Helsinki. The Clinical Research Ethics Committee of La Paz University Hospital in Madrid (Spain) approved both the baseline and the follow-up studies.

Baseline data collection

Trained and certified personnel collected information in 3 sequential stages: *1*) a telephone interview to obtain data on sociodemographic factors, health behaviors, self-rated health, and morbidity; *2*) a first home visit to collect blood and urine samples; and *3*) a second home visit to perform a physical examination and to obtain habitual diet data using a computerized dietary history questionnaire (24).

Self-reported information was obtained on sex, age, educational level (no formal education or primary, secondary, or university), marital status (single, married, widowed/divorced), and smoking status (current, former, and never smoker). Weight and height were measured at home under standardized conditions, and BMI was calculated as weight divided by the square of the body height (in kg/m^2). BMI was classified in 3 categories (<25, ≥25 to 29.9, and ≥ 30). Physical activity was assessed using the European Prospective Investigation into Cancer and Nutrition questionnaire, and a physical activity index was calculated based on a cross-tabulation of occupational, household, and recreational activities, categorizing individuals into 4 levels of activity: inactive, moderately inactive, moderately active, and active (25). Alcohol consumption (nondrinker, ex-drinker, moderate drinker, and heavy drinker who had an alcohol consumption of ≥40 g/d in men and ≥24 g/d in women), fiber intake, and total energy intake were derived from national food composition tables (26). The number of medications used were checked against drug packaging by a nurse. Finally, participants reported chronic conditions diagnosed by a physician (chronic respiratory disease, coronary heart disease, stroke, heart failure, osteoarthritis, cancer at any site, and depression requiring treatment).

Dietary assessment and UPF consumption

To ascertain the participant's habitual food consumption, we used a validated computer-based dietary history (DH-ENRICA). This dietary history consists of a structured questionnaire administered by a trained interviewer concerning the food consumed at each mealtime, from breakfast to bedtime. Participants were requested to indicate all the food usually consumed in the previous year, during the weeks and on the weekends. All the information refers to a typical week, in which conversion factors were used considering the weekly frequency of the consumption of a food, as well as the number of weeks/months in which that food was consumed during the year. A food was considered to be "usually consumed" when it was eaten at least once every 15 days. The DH-ENRICA questionnaire has standardized information on 880 foods and uses 184 recipes for dishes commonly eaten in Spain. A set of 129 photographs with different portion sizes helps to quantify the amount of food consumed (26). Spanish standard food composition tables allowed for the calculation of the amount of energy and nutrients consumed (27, 28).

All recorded foods were classified according to the NOVA classification (29), which organizes food into 4 groups based on the scope and purpose of their industrial processing. The first group includes unprocessed or minimally processed food, which is fresh or modified by filtering, freezing, drying, or pasteurization, with no addition of salt, sugar, oils, or fats. The second group contains processed culinary ingredients (i.e., salt, sugar, honey, vegetable oils, butter, lard, and vinegar). These are substances derived from nature, but have undergone processes such as pressing, refining, or milling, and might contain additives to preserve the original properties. The third group comprises processed food that has undergone preservation or preparation methods (e.g., smoking, curing, or fermentation) in order to last longer or to enhance sensory qualities. Examples include canned or bottled vegetables and legumes, fruit in syrup, canned fish, cheese, bread (freshly

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Abbreviations used: CVD, cardiovascular disease; RCT, randomized controlled trial; TC, total cholesterol; TFA, *trans* fatty acids; UPF, ultra-processed food.

made), and salted/sugared nuts and seeds. The fourth group comprises UPFs and beverages that are made predominantly or entirely from industrial substances that contain little or none of the food in its original form. Under this classification, we can find products such as hamburgers; frozen pizza and pasta dishes; French fries; breads; cakes; industrially manufactured biscuits (cookies); jams and confectionery; margarine; cereal bars; soft drinks and other sugary beverages, such as sugared milk and fruit drinks; fruit yogurts; instant packaged soups and noodles; and sweet or sweetened sodas like coke. The classification of the food items in the present study according to NOVA is described in detail elsewhere (2).

Outcome assessment

Laboratory determination was performed in 12-h fasting plasma samples collected at baseline (2008–10) and at the end of follow-up (2015). Blood was collected during home visits and plasma was immediately obtained using portable centrifuges. Then, the plasma was transported, maintaining cold chain storage. The laboratory analyses were carried out centrally at the Biological Diagnosis Centre of the "Hospital Clínic" in Barcelona. Triglycerides were measured by a colorimetric enzymatic method with lipase and glycerol kinase (30). HDL cholesterol was measured using a direct method (eliminating other particles) by reaction with cholesterol esterase and colorimetric lecture (31). Total cholesterol (TC) was measured by a colorimetric enzymatic method with cholesterol-oxidase, esterase, and peroxidase (32). LDL cholesterol was calculated with the Friedewald formula [TC − (triglycerides/5) − HDL cholesterol] (33). All techniques were employed using the Atellica Solution (Siemens Healthineers). The threshold for hypertriglyceridemia was ≥150 mg/dL, the threshold for low HDL cholesterol was <40 in men or <50 mg/dL in women, and the threshold for high LDL cholesterol was >129 mg/dL (34).

Statistical analysis

From the 1821 individuals who were followed up, we had complete lipid data on 1436. We excluded 348 participants with active lipid-lowering treatment and 6 with total energy intakes outside predefined limits (<800 or >5000 kcal/d in men; <500 or >4000 kcal/d in women). Thus, the main analyses were conducted with 1082 individuals (523 men and 559 women; **Supplemental Figure 1**).

For each participant, the energy percentage of UPFs in the total diet was calculated and thereafter classified into sex-specific tertiles. We measured the associations between the energy percentages of UPFs in the diet (for an absolute increment of 10%, coded as a continuous variable and as sex-specific tertiles). Multivariable-adjusted ORs and their 95% CIs of incident hypertriglyceridemia, low HDL cholesterol, and high LDL cholesterol according to the percentage of energy from UPF consumption were obtained using logistic regression. Participants with hypertriglyceridemia, low HDL cholesterol, or high LDL cholesterol at baseline were excluded, as appropriate. Furthermore, the association between percentage energy from UPF consumption and changes in lipid concentrations between baseline and at the end of follow-up were estimated by multiple linear regression, displaying beta coefficients (β) and their 95% CIs.

We also investigated the associations between the percentages of energy consumed from specific groups of UPFs (milk and milkshakes, snacks, alcohol, cheeses and creams, soft drinks and juices, dairy desserts, yogurts and fermented milk, precooked dishes and dressings, sugars and sweets, breakfast cereals and breads, meat and meat products, cookies and pastries) and the incidences of hypertriglyceridemia and low HDL cholesterol.

Three consecutive models were built. Model 1 was adjusted for sex and age, and Model 2 was further adjusted for total energy intake, educational level, marital status, smoking status, BMI, physical activity, alcohol consumption, fiber intake, number of medications, and number of chronic diseases. The adjustment for fiber intake was performed considering this variable as a proxy for the general quality of the diet. However, we further presented a Model 3, additionally adjusted for unprocessed or minimally processed food (NOVA group 1) consumption (percentage of energy). Supplementary adjustments for the poorer nutritional quality of UPFs were tested in different models: for free sugars (g/d), SFA intake (g/d), and TFA intake (g/d). The *P* value for a linear trend across tertiles was tested by calculating the median in each tertile and was modeled as a continuous variable.

We used stochastic regression for the imputation of missing values (<1%) in some covariates. This method adds a random error term that is more appropriate to reproducing the correlation between X and Y. All results were checked against models that were built after selecting participants with complete information for all covariates. Statistical significance was set at a 2-sided P value < 0.05. The analyses were performed with Stata/SE, version 16 (StataCorp).

Results

Among the 1082 participants, the mean age was 68 years old (± 6 years), and 52% were women. The mean percentage of energy from UPFs was 18.7% ± 11.2%. The UPF groups that contributed most to the quantity of UPFs consumed were the following: cookies and pastries (31.2%), processed meat and meat products (15.7%), breakfast cereals and breads (11.1%), and sweets (10.9%), among others (**Figure 1**).

The baseline mean concentrations of triglycerides, HDL cholesterol, and LDL cholesterol were 91.4 mg/dL ± 26.5 mg/dL, 58.7 mg/dL ± 12.1 mg/dL, and 109 mg/dL ± 16.3 mg/dL, respectively. As expected, important differences were observed between participants in the extreme tertiles of UPF consumption for unprocessed or minimally processed food (NOVA group 1) consumption and free sugar, SFA, and TFA intakes. Likewise, those participants with higher UPF consumptions reported higher total energy intakes and were more frequently smokers but also more frequently nondrinkers or moderate drinkers than those with the lowest UPF consumption. No other important differences in baseline characteristics were observed between participants in extreme tertiles of UPF consumption (**Table 1**).

After a follow-up of between 5–7 years, the mean concentrations of triglycerides, HDL cholesterol, and LDL cholesterol were 95.2 mg/dL ± 36.9 mg/dL, 56.8 mg/dL ± 13.1 mg/dL and 102 mg/dL ± 23.9 mg/dL, respectively. Concerning the incidences of dyslipidemia during follow-up, 60 participants (out of 895) developed hypertriglyceridemia (≥150 mg/dL), 112 (out of 878) had low HDL cholesterol (<40 in men or <50 mg/dL in women), and 54 (out of 472) had high LDL cholesterol (>129 mg/dL). After the greatest adjustment for potential confounders (Model 3), those in the highest versus the lowest tertile of percentage of energy from UPFs had more than twice the odds of developing hypertriglyceridemia (OR, 2.66; 95% CI: 1.20–5.90; *P*-trend, 0.011), or low HDL cholesterol (OR, 2.23; 95% CI: 1.22–4.05; *P*-trend, 0.012; **Table 2**). The corresponding ORs of developing hypertriglyceridemia and low HDL cholesterol for each 10% increase in energy intake from UPFs were 1.25 (95% CI: 0.94–1.66) and 1.20 (95% CI: 0.97–1.49), respectively (Table 2). These associations remained similar after adjustments for free sugar, SFA, and TFA intakes (**Supplemental Table 1**). UPF consumption was not associated with high LDL cholesterol plasma concentrations (Table 2).

When assessing changes in lipid concentrations between baseline and at the end of follow-up, no significant associations between UPF consumption and changes in HDL cholesterol or LDL cholesterol concentrations during follow-up were obtained. However, the difference between extreme tertiles

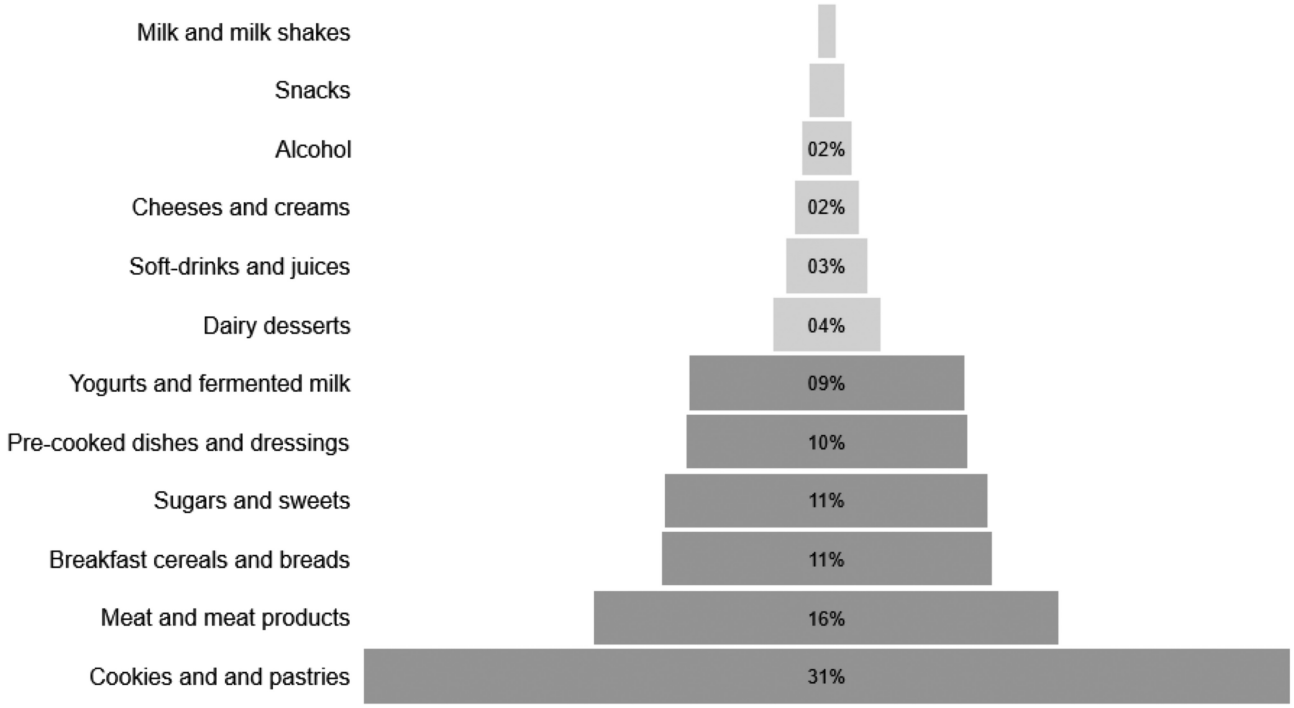

FIGURE 1 The contribution of different ultra-processed food groups to total energy intake from ultra-processed food in older adults from the Study on Nutrition and Cardiovascular Risk in Spain (ENRICA) 2008–2010 ($n = 1082$).

of UPFs for triglyceride was 6.87 mg/dL (95% CI: 1.48–12.27; *P*-trend, 0.010). Also, per each 10% increase of energy from UPFs, the triglyceride concentrations from baseline to follow-up increased by 1.48 mg/dL (95% CI: −0.60 to 3.55; Table 3).

When individual UPF groups were analyzed, there was no evidence for a positive association of any particular UPF group with hypertriglyceridemia, nor with low HDL cholesterol (Figure 2).

Discussion

In this population-based sample of participants aged 60 years old or over, high consumption of UPFs was associated with hypertriglyceridemia and low HDL cholesterol. These lipid abnormalities, along with increased blood concentrations of dense LDL particles, are components of atherogenic dyslipidemia, and part of the metabolic syndrome that has a direct association with CVD events (35, 36). These findings suggest that dyslipidemia could, at least partially, explain the already described association of UPFs with metabolic syndrome (18), atherosclerosis (13), CVD (12), and mortality (2, 10). UPF consumption was not linked to high LDL cholesterol.

To date, 2 other cross-sectional studies on UPFs and atherogenic lipids have been conducted among young adults. The first was conducted with 811 Canadian adults (mean age 36 years old). This study found that the higher the contribution of UPFs to total energy intake, the higher the prevalence of low HDL cholesterol (<1.03 mmol/L in men/<1.29 mmol/L in women). The ORs for the fourth (64.9%) and the fifth (83.0%) quintiles of the contribution of UPFs to energy intake compared with the first quintile (21.1%) were 1.72 (95% CI: 0.72–1.92) and 2.05 (95% CI: 1.25–3.38; *P*-trend, 0.020), respectively. However, that study did not observe associations with a higher prevalence of hypertriglyceridemia (>1.7 mmol/L) (21). It is worth mentioning that the consumption of UPFs in this Canadian study was very high. By contrast, in the second cross-sectional study, conducted among 302 Lebanese adults (mean age 39 years old), a medium to high consumption of UPFs (compared with low consumption) was not associated with a higher prevalence of low HDL cholesterol (<40 mg/dL in men or < 50 mg/dL in women). However, high adherence to a dietary pattern based on unprocessed or minimally processed foods (compared with low adherence) was associated with a higher prevalence of high HDL cholesterol (OR, 0.12; 95% CI: 0.03–0.47). Neither UPFs nor unprocessed or minimally processed foods were associated with a higher prevalence of hypertriglyceridemia (≥150 mg/dL) (22). These studies were conducted on young individuals, and their findings are limited by their cross-sectional designs and their small sample sizes, particularly for the last-mentioned study.

The combination of these 3 major elements of UPFs—poor nutritional composition (free sugars, TFA, SFA), additives largely added to UPFs and toxic packaging materials, together with the modification of the natural matrix of food as a result of processing—could potentially explain the observed associations. Moreover, UPF consumption replaces the consumption of other unprocessed or minimally processed foods rich in fiber and vitamins, as well as antioxidants with beneficial effects on atherogenic lipids (37).

Sugars occur naturally in unprocessed foods, such as fruit and vegetables, which are associated with a lower risk of CVD (38). These sugars occur in low amounts and are consumed with dietary fiber and other healthy nutrients. Thus, these types of sugars are not a major concern because they are within the food matrix and not free. However, concerns arise with refined and free sugars present in large quantities in UPFs, which are rapidly metabolized in the digestive tract. Sugar-containing UPFs may account for more than 60% of all UPFs. A systematic review

TABLE 1 Baseline characteristics according to tertiles of the percentage energy from ultra-processed food consumption in older adults from the Study on Nutrition and Cardiovascular Risk in Spain (ENRICA) 2008–2010 ($n = 1082$)

	Tertiles of ultra-processed food consumption (% of energy)			
Baseline characteristics	Tertile 1	Tertile 2	Tertile 3	*P*-trend
N	362	360	360	
Ultra-processed food, % energy	7.60 ± 3.6	17.2 ± 3.4	31.4 ± 8	<0.001
Women, *n* (%)	51.7	51.7	51.7	0.998
Age, years	67.6 ± 5.7	67.7 ± 5.7	67.5 ± 6.1	0.597
Total energy intake, kcal/d	1970 ± 541	2062 ± 563	2184 ± 580	<0.001
Educational level, *n* (%)				0.697
No formal education or primary	49.7	47.2	45.3	
Secondary	24.9	27.5	30.8	
University	25.4	25.3	23.9	
Marital status, *n* (%)				0.178
Single	9.39	7.78	8.06	
Married	73.5	75.3	70.3	
Widowed/divorced	17.1	16.9	21.7	
Smoking status, *n* (%)				0.068
Current smoker	61.3	61.7	55.0	
Former smoker	29.0	27.2	30.8	
Never smoker	9.70	11.1	14.2	
BMI, *n* (%)				0.334
<25 kg/m^2	23.5	20.6	20.0	
≥25 to 29.9 kg/m^2	48.6	48.9	50.6	
≥30 kg/m^2	27.9	30.6	29.4	
Physical activity index, *n* (%)				0.934
Inactive	43.1	38.1	43.6	
Moderately inactive	33.1	35.8	31.9	
Moderately active	17.7	20.8	18.6	
Active	6.08	5.28	5.83	
Alcohol consumption, *n* (%)				0.016
Nondrinker	38.1	45.3	44.7	
Ex-drinker	8.56	5.00	10.0	
Moderate drinker	43.1	39.7	38.1	
Heavy drinker	10.22	10.0	7.22	
Fiber intake, g/d	24.7 ± 8.4	25.3 ± 8.2	24.1 ± 7.9	0.505
Unprocessed or minimally processed food (NOVA group 1) consumption, % of energy	43.5 ± 12.2	39.1 ± 10.1	31.8 ± 8.9	<0.001
Free sugars intake, g/d	25.2 ± 17.9	37.8 ± 22.6	59.3 ± 31.8	<0.001
Saturated fatty acids intake, g/d	22.6 ± 10.9	24.4 ± 10.5	29.1 ± 11.6	<0.001
Trans fatty acids intake, g/d	1.54 ± 1.43	1.66 ± 1.25	2.17 ± 1.53	<0.001
Number of medications, *n* (%)				0.304
0	38.4	38.9	42.5	
1 to 3	49.2	50.3	46.9	
>3	12.4	10.8	10.6	
Number of chronic conditions,[1] *n* (%)				0.130
0	45.6	41.9	41.9	
1	40.1	41.9	39.4	
≥2	14.33	16.14	18.63	
Plasma lipids,[2] mg/dL				
Triglycerides	91.0 ± 27.3	91.3 ± 26.1	92.0 ± 26.2	0.577
HDL cholesterol	59.2 ± 12.3	58.9 ± 13.1	58.1 ± 10.8	0.442
LDL cholesterol	108 ± 15.3	108 ± 18.0	110 ± 15.3	0.128

Continuous variables are presented as means ± SDs and categorical variables as n (%).
[1] Includes chronic respiratory disease, coronary heart disease, stroke, heart failure, osteoarthritis, cancer, and diagnosed depression.
[2] Excluding those with hypertriglyceridemia ($n = 187$), low HDL cholesterol ($n = 204$), and high LDL cholesterol ($n = 610$) at baseline.

and meta-analysis of randomized controlled trials concluded that dietary free sugars significantly raised triglycerides and LDL cholesterol (39). As regards to animal studies, free sucrose intake, but not fat intake, led to a dose-response increase in atheroma plaques in rats (40). And also, adding liquid fructose to a Western-type diet in mice has been shown to increase the lipid burden and atherosclerosis, despite an identical calorie intake (41).

TFAs could also contribute to the harmful effects of UPFs. These partially hydrogenated oils are consumed in margarine,

TABLE 2 ORs (95% CI) for tertiles of percentage energy of ultra-processed food consumption and incidences of dyslipidemias

	Ultra-processed food consumption (% of energy)				
	Tertile 1	Tertile 2	Tertile 3	*P*-trend	Per 10% increase
Hypertriglyceridemia ($n = 895$)[1]					
Cases/total, *n/n*	15/289	18/283	27/263		
Model 1, OR (95% CI)	1 (ref.)	1.23 (0.61–2.50)	2.00 (1.04–3.85)	0.029	1.16 (0.92–1.46)
Model 2, OR (95% CI)	1 (ref.)	1.19 (0.57–2.49)	2.21 (1.09–4.49)	0.019	1.20 (0.94–1.55)
Model 3, OR (95% CI)	1 (ref.)	1.28 (0.60–2.74)	2.66 (1.20–5.90)	0.011	1.25 (0.94–1.66)
Low HDL cholesterol ($n = 878$)[2]					
Cases/total, *n/n*	26/281	41/245	45/240		
Model 1, OR (95% CI)	1 (ref.)	1.82 (1.08–3.06)	2.04 (1.22–3.41)	0.010	1.20 (1.00–1.43)
Model 2, OR (95% CI)	1 (ref.)	1.77 (1.04–3.03)	2.04 (1.18–3.53)	0.015	1.18 (0.97–1.43)
Model 3, OR (95% CI)	1 (ref.)	1.84 (1.06–3.17)	2.23 (1.22–4.05)	0.012	1.20 (0.97–1.49)
High LDL cholesterol ($n = 472$)[3]					
Cases/total, *n/n*	17/156	21/163	16/153		
Model 1, OR (95% CI)	1 (ref.)	1.19 (0.60–2.36)	0.95 (0.46–1.97)	0.850	1.02 (0.79–1.31)
Model 2, OR (95% CI)	1 (ref.)	1.32 (0.64–2.70)	1.13 (0.52–2.46)	0.803	1.08 (0.82–1.41)
Model 3, OR (95% CI)	1 (ref.)	1.26 (0.60–2.64)	1.03 (0.43–2.47)	0.996	1.05 (0.77–1.43)

$N = 1082$ participants were followed from baseline in 2008–2010 until 2015. Model 1 estimates were adjusted for sex and age (continuous). Model 2 estimates were additionally adjusted for total energy intake (continuous), educational level (no formal education or primary, secondary, or university), marital status (single, married, widowed/divorced), smoking status (current, former, and never smoker), BMI (<25, ≥25 to 29.9, and ≥ 30), physical activity (inactive, moderately inactive, moderately active, and active), alcohol consumption (nondrinker, ex-drinker, moderate drinker, and heavy drinker who had an alcohol consumption of ≥40 g/d in men and ≥24 g/d in women), fiber intake (continuous), number of medications (0, 1 to 3, >3), and number of chronic conditions (0, 1, ≥2). Model 3 estimates were additionally adjusted for unprocessed or minimally processed food (NOVA group 1) consumption (% of energy).

[1] Participants with hypertriglyceridemia at baseline were excluded ($n = 287$). The threshold for hypertriglyceridemia was ≥150 mg/dL.

[2] Participants with low HDL cholesterol at baseline were excluded ($n = 204$). The threshold for low HDL cholesterol was <40 mg/dL in men or <50 mg/dL in women.

[3] Participants with high LDL cholesterol at baseline were excluded ($n = 610$). The threshold for high LDL cholesterol was >129 mg/dL.

fast food, and other UPFs, such as cakes, chocolates, and potato chips. Controlled trials have shown that TFAs have adverse effects on blood lipids (42), for instance decreasing HDL cholesterol (43).

UPFs are also a source of SFAs. Food sources of SFAs also seem to be decisive for their beneficial or detrimental effects on health (44). While a high intake of SFAs from processed meat has been shown to increase the risks of CVD and mortality, a

TABLE 3 Mean difference in the change of plasma lipid concentrations between baseline (2008–2010) and follow-up (2015) by tertiles of percentage energy from ultra-processed food consumption in older adults from the Study on Nutrition and Cardiovascular Risk in Spain (ENRICA) ($n = 1082$)

	Ultra-processed food consumption (% of energy)				
	Tertile 1	Tertile 2	Tertile 3	*P*-trend	Per 10% increase
Δ Triglycerides (mg/dL) ($n = 895$)[1]					
Participants, *n*	304	301	290		
Δ Triglyceride change, mean ± SD	0.84 ± 28.8	1.62 ± 28.5	7.11 ± 32.2		
Model 1 MD (95% CI)	1 (ref.)	0.68 (−4.08 to 5.44)	6.11 (1.30 to 10.91)	0.010	1.23 (−0.57 to 3.03)
Model 2 MD (95% CI)	1 (ref.)	0.21 (−4.59 to 5.01)	6.23 (1.26 to 11.21)	0.011	1.40 (−0.49 to 3.29)
Model 3 MD (95% CI)	1 (ref.)	0.47 (−4.41 to 5.35)	6.87 (1.48 to 12.27)	0.010	1.48 (−0.60 to 3.55)
Δ HDL cholesterol (mg/dL) ($n = 878$)[2]					
Participants, *n*	307	286	285		
Δ HDL cholesterol, mean ± SD	−1.90 ± 8.72	−1.66 ± 9.24	−1.86 ± 8.14		
Model 1 MD (95% CI)	1 (ref.)	0.23 (−1.18 to 1.64)	0.03 (−1.38 to 1.44)	0.985	− 0.05 (−0.58 to 0.49)
Model 2 MD (95% CI)	1 (ref.)	0.24 (−1.18 to 1.65)	0.02 (−1.45 to 1.49)	0.995	− 0.07 (−0.64 to 0.49)
Model 3 MD (95% CI)	1 (ref.)	0.28 (−1.16 to 1.72)	0.13 (−1.46 to 1.71)	0.887	− 0.04 (−0.66 to 0.58)
Δ LDL cholesterol (mg/dL) ($n = 472$)[3]					
Participants, *n*	155	163	153		
Δ LDL cholesterol, mean ± SD	−5.12 ± 21.7	−5.10 ± 22.9	−9.52 ± 21.4		
Model 1 MD (95% CI)	1 (ref.)	− 0.23 (−5.04 to 4.57)	− 4.52 (−9.40 to 0.36)	0.058	− 1.40 (−3.17 to 0.37)
Model 2 MD (95% CI)	1 (ref.)	0.58 (−4.37 to 5.53)	− 3.43 (−8.60 to 1.74)	0.160	− 0.97 (−2.84 to 0.91)
Model 3 MD (95% CI)	1 (ref.)	1.23 (−3.87 to 6.33)	− 2.03 (−7.86 to 3.80)	0.431	− 0.35 (−2.49 to 1.78)

Model 1 estimates were adjusted for sex and age (continuous). Model 2 estimates were additionally adjusted for total energy intake (continuous), educational level (no formal education or primary, secondary, or university), marital status (single, married, widowed/divorced), smoking status (current, former, and never smoker), BMI (<25, ≥25 to 29.9, and ≥30), physical activity (inactive, moderately inactive, moderately active, and active), alcohol consumption (nondrinker, ex-drinker, moderate drinker, and heavy drinker who had an alcohol consumption of ≥40 g/d in men and ≥24 g/d in women), fiber intake (continuous), number of medications (0, 1 to 3, >3), and number of chronic conditions (0, 1, ≥2). Model 3 estimates were additionally adjusted for unprocessed or minimally processed food (NOVA group 1) consumption (% of energy). Abbreviation: MD, mean difference (β).

[1] Participants with hypertriglyceridemia at baseline were excluded ($n = 187$).

[2] Participants with low HDL cholesterol at baseline were excluded ($n = 204$).

[3] Participants with high LDL cholesterol at baseline were excluded ($n = 610$).

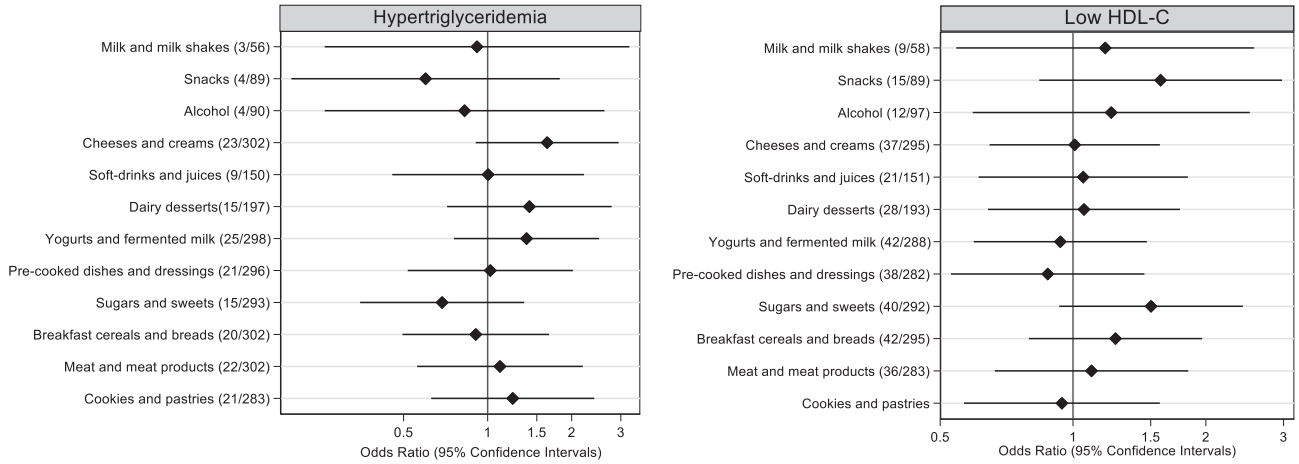

FIGURE 2 Multivariable associations between the percentage of energy intake from ultra-processed food groups and the incidences of hypertriglyceridemia and low HDL cholesterol. There were 1082 participants who were followed-up from baseline in 2008–2010 to 2015. The highest versus the lowest tertile was represented (n cases/n third tertile). Participants with hypertriglyceridemia at baseline were excluded ($n = 287$). The threshold for hypertriglyceridemia was ≥150 mg/dL. Participants with low HDL cholesterol at baseline were excluded ($n = 204$). The threshold for low HDL cholesterol was <40 mg/dL in men or <50 mg/dL in women. Estimates were adjusted for sex, age (continuous), total energy intake (continuous), educational level (no formal education or primary, secondary, or university), marital status (single, married, widowed/divorced), smoking status (current, former, and never smoker), BMI (<25, ≥25 to 29.9, and ≥30), physical activity (inactive, moderately inactive, moderately active, and active), alcohol consumption (nondrinker, ex-drinker, moderate drinker, and heavy drinker who had an alcohol consumption of ≥40 g/d in men and ≥24 g/d in women), fiber intake (continuous), number of medications (0, 1 to 3, >3), number of chronic conditions (0,1, ≥2), and unprocessed or minimally processed food (NOVA group 1) consumption (% of energy).

high intake of SFAs from dairy did not increase risks (44), but did decrease the CVD risk (45). Likewise, a high intake of SFAs from pastries (that are always UPFs) is associated with a higher risk of CVD, while SFAs from unprocessed food are not (46). Moreover, the effect of SFA intake on the lipid metabolism may be modulated by the content and/or availability of PUFAs (47, 48). This is interesting since UPFs are high in SFAs but low in PUFAs.

It is important to notice that our results remained similar after individual adjustments for free sugar, SFA, and TFA intakes, which is in agreement with most of the previous epidemiological studies adressing UPF consumption (10, 12, 17–19). Therefore, the poor nutritional quality of UPFs does not appear to be entirely responsible for the observed association. Therefore, other characteristics of UPFs beyond nutritional composition may also contribute to an explanation of the association. Dietary guidelines should shift focus to not only making recommendations to reduce refined sugars or SFA from UPFs, but also to reduce use of UPFs themselves in favor of fresh or minimally processed food.

Indeed, how intact foods are or in what ways and extents they are cooked, prepared, or processed determine the food structure and, consequently, its overall impact on health (49). Changes in the food structure influence the bioavailability of nutrients and other bioactive food components, and produce changes in the gut microbiota. Likewise, UPFs are characterized by a high content of food additives (50). In animals, some food additives have shown to deteriorate the lipid profile (51, 52) and to induce low-grade inflammation and obesity/metabolic syndrome (53). Also, noncaloric artificial sweeteners were shown to accelerate atherosclerosis in cellular models (54).

In addition, UPFs might be contaminated by the migration from packaging of contact materials, such as bisphenols and phthalates (7, 55). Bisphenol A has been related to CVD (56) and the development of dyslipidemia, affecting triglycerides, HDL cholesterol, and LDL cholesterol (57, 58). Also, urinary phthalate metabolites have been positively associated with disruptions in the metabolism of triglycerides, HDL cholesterol, and LDL cholesterol (59, 60).

There are some limitations in this study. Although the computer-based dietary history provides an adequate assessment of an individual's habitual diet, some inaccuracy in the exposure assessment cannot be ruled out because of its self-reported nature and the potential for recall bias (61). Also, the dietary history, although containing information on more than 880 foods, was not designed specifically to collect data on UPFs, and this could lead to some misclassification. Moreover, our analyses assumed that baseline habits remained stable throughout the 5–7-year follow-up period, yet there might have been some changes, which could probably lead to a nondifferential misclassification that biased the results to the null. However, we think that this bias is small because the participants are older adults, generally with more stable habits and lifestyles. Consequently, a 5–7-year follow-up period is rather prudent, and the majority of participants probably remain relatively stable within tertiles. The NOVA classification has not been free from criticism (mainly as a result of exposure misclassification), but it is useful and can easily be incorporated into health promotion messages and provide benefits for public health (62).

In comparison, from an etiological point of view, the necessary length of the induction period to observe the effects of high UPF consumption on lipid concentrations in healthy adults remains uncertain. However, similar follow-up periods have previously been used in the literature to assess dietary habits and subsequent changes in lipid concentrations. The Seniors-ENRICA cohort (mean age 68 years old) is a restricted sample comprised of older participants (60 and over) from the ENRICA cohort that was initially representative of the Spanish population (21, 22). Thus, while the mean percentage of energy consumption from UPFs in this study was around 18%, it was 24% in the whole ENRICA cohort (mean age 47 years old) (2).

Furthermore, it has been observed in previous studies that the association between UPFs and metabolic diseases is especially greater in young adults and decreases with age (18). In contrast, cutoff points for tertiles of UPF consumption are specific to this sample distribution; however, to facilitate comparisons we also reported the odds of dyslipidemia associated with an increase in 10% of energy consumed from UPFs. Lastly, the LDL cholesterol analyses might be underpowered because of the smaller sample size.

This study has several strengths, including the prospective design and an extended follow-up. Also, a validated habitual dietary assessment was performed that includes a larger number of foods than that seen in a typical FFQ. All blood samples at the beginning and at the end of follow-up were handled following the same protocols. Moreover, we accounted for several confounding factors in the analysis, which strengthens the internal validity of the study.

In this prospective study of Spanish older adults with low UPF consumption, high consumption of UPFs was linked to hypertriglyceridemia and low HDL cholesterol. This suggests that the risks of atherosclerosis and CVD recently associated with UPF consumption in the literature might be linked to changes in atherogenic lipids.

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