Atherosclerosis 377 (2023) 12–23

Contents lists available at ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

Increased ultra-processed food consumption is associated with worsening of cardiometabolic risk factors in adults with metabolic syndrome: Longitudinal analysis from a randomized trial

Sandra González-Palacios [a,b], Alejandro Oncina-Cánovas [a,b], Manuela García-de-la-Hera [a,b], Miguel Ángel Martínez-González [c,d,e], Jordi Salas-Salvadó [c,g,h], Dolores Corella [c,f], Helmut Schröder [b,i], J. Alfredo Martínez [c,j,k], Ángel M. Alonso-Gómez [c,l], Julia Wärnberg [c,m], Dora Romaguera [c,n], José López-Miranda [c,o], Ramon Estruch [c,p], Francisco J. Tinahones [c,q], José Lapetra [c,r], J. Luís Serra-Majem [c,s], Naomi Cano-Ibañez [b,t,u], Josep A. Tur [c,v], Vicente Martín-Sánchez [b,w], Xavier Pintó [c,x], Miguel Delgado-Rodríguez [y], Pilar Matía-Martín [z], Josep Vidal [aa,ab], Clotilde Vázquez [c,ac], Lidia Daimiel [c,ad,ae], Emili Ros [c,af], Maira Bes-Rastrollo [c,d], Alessandro Atzeni [c,g,h], Jose V. Sorli [c,f], M. Dolors Zomeño [i,ah], Patricia J. Peña-Orihuela [c,o], Laura M. Compañ-Gabucio [a,b], Francisco J. Barón-López [c,m], María Ángeles Zulet [c,j], Jadwiga Konieczna [c,n], Rosa M. Casas [c,p], Eva M. Garrido-Garrido [ai], Lucas Tojal-Sierra [c,l], Ana M. Gomez-Perez [c,q], Miguel Ruiz-Canela [c,d], Antoni Palau [g,h,aj], Carmen Saiz [c,f], Karla A. Pérez-Vega [i], Antonio Garcia-Rios [c,o], Laura Torres-Collado [a,b], Javier Basterra-Gortari [c,d,ag], Tany E. Garcidueñas-Fimbres [c,g,h], Mireia Malcampo [i], Jesús Vioque [a,b,*], the PREDIMED-PLUS Trial investigators

[a] Unidad de Epidemiología de la Nutrición, Instituto de Investigación Sanitaria y Biomédica de Alicante. Universidad Miguel Hernández, (ISABIAL-UMH), Alicante, Spain
[b] CIBER de Epidemiología y Salud Pública (CIBERESP), Instituto de Salud Carlos III (ISCIII), 28029, Madrid, Spain
[c] Centro de Investigación Biomédica en Red Fisiopatología de la Obesidad y la Nutrición (CIBEROBN), Institute of Health Carlos III, Madrid, Spain
[d] University of Navarra, Department of Preventive Medicine and Public Health, IDISNA, Pamplona, Spain
[e] Department of Nutrition, Harvard T.H. Chan School of Public Health, Boston, MA, USA
[f] Department of Preventive Medicine, University of Valencia, Valencia, Spain
[g] Universitat Rovira i Virgili, Departament de Bioquímica i Biotecnologia, Unitat de Nutrició, Reus, Spain
[h] Institut d'Investigació Sanitària Pere Virgili (IISPV), Reus, Spain
[i] Unit of Cardiovascular Risk and Nutrition, Institut Hospital del Mar de Investigaciones Médicas Municipal d'Investigació Médica (IMIM), Barcelona, Spain
[j] Department of Nutrition, Food Sciences, and Physiology, Center for Nutrition Research, University of Navarra, Pamplona, Spain
[k] Precision Nutrition and Cardiometabolic Health Program. IMDEA Food, CEI UAM + CSIC, Madrid, Spain
[l] Bioaraba Health Research Institute, Cardiovascular, Respiratory and Metabolic Area; Osakidetza Basque Health Service, Araba University Hospital; University of the Basque Country UPV/EHU, Vitoria-Gasteiz, Spain
[m] EpiPHAAN research Group, School of Health Sciences, University of Málaga-Instituto de Investigación Biomédica en Málaga (IBIMA), Málaga, Spain
[n] Research Group on Nutritional Epidemiology & Cardiovascular Physiopathology (NUTRECOR), Health Research Institute of the Balearic Islands (IdISBa), University Hospital Son Espases (HUSE), Palma de Mallorca, Spain
[o] Department of Internal Medicine, Maimonides Biomedical Research Institute of Cordoba (IMIBIC), Reina Sofia University Hospital, University of Cordoba, Cordoba, Spain
[p] Department of Internal Medicine, Hospital Clinic, Institut d'Investigacions Biomèdiques August Pi Sunyer (IDIBAPS), Institut de Recerca en Nutrició i Seguretata Alimentaria (INSA-UB). University of Barcelona, Barcelona, Spain
[q] Virgen de la Victoria Hospital, Department of Endocrinology, Instituto de Investigación Biomédica de Málaga (IBIMA). University of Málaga, Málaga, Spain
[r] Department of Family Medicine, Research Unit, Distrito Sanitario Atención Primaria Sevilla, Sevilla, Spain
[s] Research Institute of Biomedical and Health Sciences (IUIBS), University of Las Palmas de Gran Canaria & Centro Hospitalario Universitario Insular Materno Infantil (CHUIMI), Canarian Health Service, Las Palmas de Gran Canaria, Spain
[t] Department of Preventive Medicine and Public Health, University of Granada, Granada, Spain
[u] Instituto de Investigación Biosanitaria de Granada (ibs.GRANADA), Granada, Spain

* Corresponding author. Dpto. Salud Pública, H[a] de la Ciencia y Ginecología. Facultad de Medicina. Avda. Ramón y Cajal s/n, 03550, Sant Joan d'Alacant, Alicante, Spain.
E-mail address: vioque@umh.es (J. Vioque).

https://doi.org/10.1016/j.atherosclerosis.2023.05.022
Received 21 February 2023; Received in revised form 31 May 2023; Accepted 31 May 2023
Available online 7 June 2023

[v] Research Group on Community Nutrition & Oxidative Stress, University of Balearic Islands, Palma de Mallorca, Spain
[w] Institute of Biomedicine (IBIOMED), University of León, León, Spain
[x] Lipids and Vascular Risk Unit, Internal Medicine, Hospital Universitario de Bellvitge-IDIBELL, Hospitalet de Llobregat, Barcelona, Spain
[y] Division of Preventive Medicine, Faculty of Medicine, University of Jaén, Jaén, Spain
[z] Department of Endocrinology and Nutrition, Instituto de Investigación Sanitaria Hospital Clínico San Carlos (IdISSC), Madrid, Spain
[aa] CIBER Diabetes y Enfermedades Metabólicas (CIBERDEM), Instituto de Salud Carlos III (ISCIII), Madrid, Spain
[ab] Department of Endocrinology, Institut d' Investigacions Biomédiques August Pi Sunyer (IDIBAPS), Hospital Clinic, University of Barcelona, Barcelona, Spain
[ac] Department of Endocrinology and Nutrition, Hospital Fundación Jimenez Díaz. Instituto de Investigaciones Biomédicas IISFJD. University Autonoma, Madrid, Spain
[ad] Nutritional Control of the Epigenome Group, Precision Nutrition and Obesity Program. IMDEA Food, CEI UAM + CSIC, Madrid, Spain
[ae] Departamento de Ciencias Farmacéuticas y de la Salud, Faculty de Farmacia, Universidad San Pablo-CEU, CEU Universities, 28660, Boadilla del Monte, Spain
[af] Lipid Clinic, Department of Endocrinology and Nutrition, Institut d'Investigacions Biomèdiques August Pi Sunyer (IDIBAPS), Hospital Clínic, Barcelona, Spain
[ag] Servicio de Endocrinología, Hospital Universitario de Navarra, Servicio Navarro de Salud-Osasunbidea, Pamplona, Spain
[ah] Blanquerna-Ramon Llull University, Barcelona, Spain
[ai] Primary Care Center Zaidín-Center, Servicio Andaluz de Salud, Granada, Spain
[aj] Centre d'Assistència Primària Marià Fortuny, ABS Reus V. Salut Sant Joan de Reus, Reus, Spain

ARTICLE INFO

Keywords:
Ultra-processed foods
Cardiometabolic risk factors
Metabolic syndrome
Body mass index
Blood pressure
Fasting blood glucose

ABSTRACT

Background and aims: The association between changes in ultra-processed food (UPF) consumption and cardiometabolic risk (CMR) factors remains understudied. We evaluated the association between changes in UPF consumption over 12 months of follow-up and changes in CMR factors in adults diagnosed with metabolic syndrome.

Methods: We analysed data from 5373 adults (aged 55–75 years) participating in the PREDIMED-Plus trial. Diet was evaluated at baseline, 6- and 12-month visits using a validated food frequency questionnaire, and UPF consumption (in grams/day and percentage of total daily dietary intake in grams) was categorized based on NOVA classification. We used mixed-effects linear models with repeated measurements at baseline, 6 and 12 months of follow-up to assess the associations between changes in UPF consumption and changes in CMR factors adjusting for sociodemographic and lifestyles variables.

Results: In multivariable-adjusted models, when comparing the highest *versus* the lowest quartile of UPF consumption, positive associations were found for several CMR factors: weight (kg, $\beta = 1.09$; 95% confidence interval 0.91 to 1.26); BMI (kg/m^2, $\beta = 0.39$; 0.33 to 0.46); waist circumference (cm, $\beta = 1.03$; 0.81 to 1.26); diastolic blood pressure (mm Hg, $\beta = 0.67$; 0.29 to 1.06); fasting blood glucose (mg/dl, $\beta = 1.66$; 0.61 to 2.70); HbA1c (%, $\beta = 0.04$; 0.01 to 0.07); triglycerides (mg/dl, $\beta = 6.79$; 3.66 to 9.91) and triglycerides and glucose index ($\beta = 0.06$; 0.04 to 0.08).

Conclusions: Higher UPF consumption was associated with adverse evolution in objectively measured CMR factors after 12 months of follow-up in adults with metabolic syndrome. Further research is needed to explore whether these changes persist for longer periods.

1. Introduction

Cardiovascular diseases have nearly doubled their prevalence in the last three decades and remain the major cause of premature mortality and morbidity worldwide [1]. In parallel, the number of people with cardiometabolic risk (CMR) factors such as hypertension, high fasting plasma glucose, high LDL cholesterol, and obesity has also increased [1].

Diet is a modifiable factor that could play a preventable or risk role in the development of cardiovascular disease. Different foods, specifically those with high density energy but low nutritional value, have been associated with an increase in CMR factors [2]. Mounting evidence relates cardiovascular diseases and CMR factors to the consumption of ultra-processed foods (UPF) [3–6]. According to the NOVA food classification system [7–9], the foods and beverages considered as UPF are mostly characterized by a high level of industrial processing with the objective to make them more palatable, accessible and ready to eat [7–9]. The consumption of UPF has dramatically increased in the last decades [6,8,10], and it is associated with lower diet quality [11] and a high consumption of free sugars, total and saturated fats and lower consumption of fibre, proteins, and several minerals and vitamins [12,13].

Emerging evidence from longitudinal and cross-sectional studies supports a positive association between UPF consumption and several CMR factors [14–21]. In a French prospective study examining the association between UPF consumption and the risk of cardiovascular disease and diabetes, a high UPF consumption was associated with a 12% higher risk of total cardiovascular disease [14] and a 15% higher risk of diabetes after 5–6 years of follow-up [15]. In the prospective follow-up study of Navarra University (SUN), the highest UPF consumption was also associated with a 21% higher risk of hypertension after a 9 year follow-up [16]. Other studies have also found an association between UPF consumption and higher risk of overweight, obesity, abdominal obesity [17–21] and visceral and overall adiposity accumulation [22]. However, the evidence is still limited, particularly regarding how changes in UPF consumption may influence changes in CMR factors.

Thus, we aimed to prospectively evaluate the association between changes in UPF consumption and simultaneous changes of several CMR factors such as weight, body mass index (BMI), waist circumference, blood pressure, fasting blood glucose, glycated haemoglobin (HbA1c), triglycerides, triglycerides and glucose index (TyG index) and cholesterol (total, HDL and LDL), using three repeated measurements during 12-month follow-up in an adult population with diagnosed metabolic syndrome.

2. Patients and methods

2.1. Study design

We performed a prospective analysis of data collected during the first 12 months of follow-up of the PREDIMED-Plus study (PREvención con DIeta MEDiterránea Plus, http://www.predimedplus.com). The PREDIMED-Plus is an ongoing multicentre, 6-year, randomized clinical trial whose main aim is to evaluate the effect on cardiovascular disease prevention of an intensive weight loss intervention based on an energy-restricted traditional Mediterranean diet, physical activity promotion and behavioural support. The control group received an unrestricted-energy Mediterranean diet supplemented with extra virgin olive oil. Meanwhile, the intervention group received an intensive intervention

based on an energy-restricted Mediterranean diet supplemented with extra virgin olive oil, behavioural support and physical activity goals to achieve weight loss. The primary endpoints of the trial are cardiovascular disease death, nonfatal myocardial infarction, nonfatal stroke, and long-term weight loss maintenance. Recruitment of participants began in September 2013 and ended in December 2016 in 23 centres throughout the Spanish territory. Participants were randomized (ratio 1:1) into two groups stratifying by sex, age (<65, 65–70, >70 years) and recruiting centre. The 309 couples (618 participants) enrolled in the study were randomly assigned as a unit to the same intervention group. More details of the study design have been previously described [23] and are available at http://predimedplus.com/.

The PREDIMED-Plus study followed ethical principles for medical research involving human subjects according to the Declaration of Helsinki. The Research Ethic Committees of each recruiting centre approved the study protocol, and all participants signed an informed consent. This trial was registered at http://www.isrctn.com/ISRCTN89898870 as ISRCT 89898870.

2.2. Study population

The participants were males (aged 55–75 years) and females (aged 60–75 years) without baseline history of cardiovascular diseases. In addition, all participants had excess of weight (BMI between 27 and 40 kg/m^2) and at least three of the following five risk factors of metabolic syndrome according to the updated criteria of the International Diabetes Federation and the American Heart Association and National Heart, Lung and Blood Institute [24]: hypertension, plasma triglycerides ≥150 mg/dL, plasma HDL cholesterol <40 mg/dL in males or < 50 mg/dL in females, fasting blood glucose >100 mg/dL and central obesity (≥102 cm in males or ≥88 cm in females).

Of the 9677 people assessed for eligibility, 6874 met the inclusion criteria and were randomized. Among those, we excluded 1316 participants without dietary information in one or more of the three visits carried out during the first 12 months of follow-up. We also excluded 185 participants with implausible reported energy intake according to the following established cut-off points [25]: <800 or >4000 kcal/day for males or <500 or >3500 kcal/day for females. Finally, 5373 participants were included in these analyses (Fig. 1).

2.3. Dietary assessment and ultra-processed foods consumption

Information on the participant's dietary intake was collected by trained interviewers using the same validated semi-quantitative food frequency questionnaire (FFQ) at baseline, 6 and 12 months of follow-up [26]. The FFQ included 143 different foods and had 9 possible frequency intake responses ranging from "never or hardly ever" to ">6 times a day". The usual daily nutrient intakes for each participant were calculated multiplying the reported frequency for each food by their nutrient content according to the portion size specified in the FFQ. Portion sizes were those standardized for adults and the nutrient values were obtained from Spanish food composition tables [27].

A specialized working group within the PREDIMED-Plus study composed by experts on nutritional epidemiology and dietitians classified all the items in the FFQ according to the four NOVA classification groups [8,9,28]. The first group, *Unprocessed or minimally processed foods,* includes edible parts of natural or unprocessed foods from plants, animals, fungi, algae and water. In addition, it comprises foods altered by processes to preserve or to make them safe and edible (e.g. drying, boiling, pasteurization, or similar.). For instance, this first group includes fruits, vegetables, fish, eggs, milk and water among others. The second group, *Processed culinary ingredients* includes food elements which are not usually eaten alone but are used for food preparation, seasoning and cooking, some examples are oils, butter, sugars and salt. The third group, *Processed foods*, includes foods from the first group that have been modified using non-alcoholic fermentations or processing in

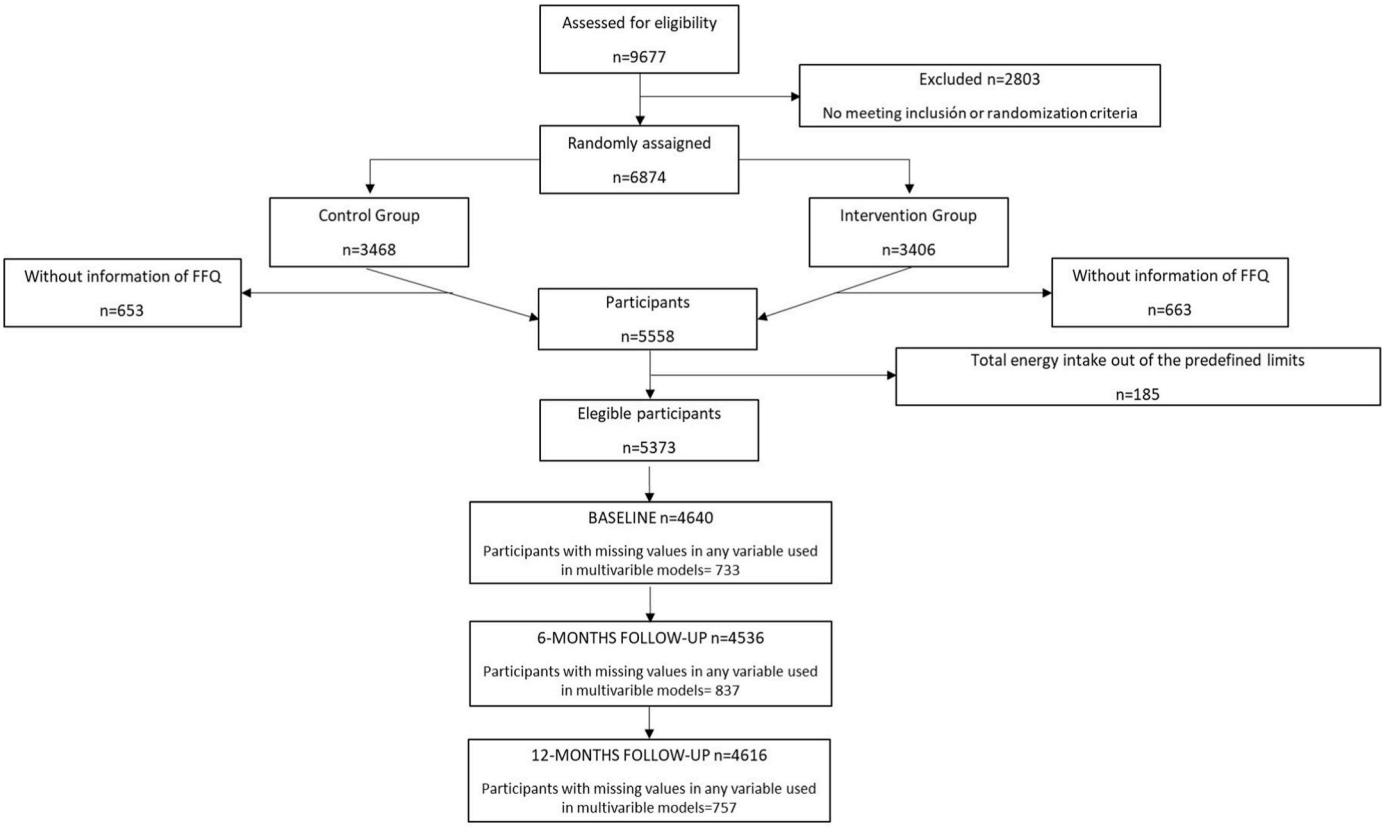

Fig. 1. Flow chart demonstrating selection of study participants on the PREDIMED-Plus study.

order to preserve them and/or to modify their sensory qualities. These foods are edible by themselves or in combination with other foods and usually include two or three ingredients. Examples include canned vegetables or fish, bread or cheese among others. This group also includes alcoholic beverages produced by fermentation: beer, cider and wine. Finally, the *UPF* group, are foods made of substances derived from other foods and additives using a series of processes and containing minimal whole foods. These foods usually include oils, fats, salt or sugars, in addition to other substances such as lactose or gluten as well as preservatives, antioxidants and stabilizers. Examples include soft drinks, packaged snacks, pre-prepared frozen dishes and ready-to-eat foods [8,9,28]. This group also includes alcoholic beverages produced by distillation such as whisky, gin, rum and vodka. Supplementary Table 1 shows detailed information about the classification of the 143 FFQ items into the four NOVA groups. The UPF consumption per person was estimated using the sum of the 36 items classified in the UPF group. In addition, the UPF group was subdivided into 6 subgroups: dairy products, processed meats, sweets, fast-foods, beverages and alcoholic beverages. Detailed information about food included in each subgroup is shown in Supplementary Table 2.

2.4. Cardiometabolic risk factors and assessments

The CMR factors considered were weight, BMI, waist circumference, blood pressure, fasting blood glucose, HbA1c, triglycerides, TyG index and cholesterol (total, HDL and LDL). Trained staff obtained anthropometric measures following standardized protocols at baseline, 6 and 12 months of follow-up visits. Weight was measured without shoes and with light clothing using calibrated scales (precision ±100 g). Height was measured with stadiometers without shoes or objects on the head, in compliance with the Frankfort plan (precision ±1 mm). We calculated BMI as weight in kilograms divided by height in meters squared (kg/m^2). Waist circumference was measured at the midpoint between the last rib and the upper part of the iliac crest with inextensible tapes situated horizontally to the ground (precision ±1 mm). Blood pressure was measured when seated after 5 min of resting, using a validated semi-automatic oscillometer (Omron HEM-705CP). Weight, height and waist circumference were measured in duplicate and blood pressure in triplicate. We calculated the average of all these measures for the analyses. In addition, trained nurses collected blood samples after 8 h of fasting to obtain levels of fasting blood glucose, HbA1c, triglycerides and cholesterol (total, HDL and LDL) at baseline, 6 and 12 months of follow-up, using standardized laboratory procedures. The TyG index was calculated using the following formula [Ln(triglycerides x fasting plasma glucose/2)].

2.5. Covariates

Additional information on sociodemographic and lifestyle behaviours was collected at baseline: age (in years), sex (males, females), marital status (married, others), educational level (primary or less, secondary, college or university), employment situation (current worker, retired, other status), smoking status (never, former, current), self-reported type 2 diabetes (no, yes), physical activity (METS in hours/week), screen time (hours/day) and ≥7 h/day of sedentary time (yes, no) and alcohol consumption (in grams/day, g/d). Finally, the adherence to the Mediterranean diet was also assessed using a validated 17-point scale [29], where a higher score means higher adherence to energy-restricted Mediterranean diet.

2.6. Statistical analyses

All the statistical analyses were performed using STATA software (version 16.1, StataCorp, Unites Estates of America, http://www.stata.com). *p*-values <0.05 were considered statistically significant.

Consumption of UPF was calculated for each participant and was divided into quartiles. Main characteristics of participants were described according to baseline quartiles of UPF consumption, and reported as the mean and standard deviation (SD) or percentages (%) in case of categorical variables. ANOVA tests were used for continuous variables and Chi-square tests for categorical variables. In addition, we described the total UPF consumption in g/d for each follow-up visit in both continuous (mean and SD) and the % of UPF within total daily dietary intake ([intake of UPF in grams/total dietary intake in grams]* 100). The consumption of each subgroup of UPF was also calculated in continuous (mean and SD) and in the % of each food group within total UPF consumption ([intake of each food group in grams/total UPF consumption in grams)*100]. Paired T-Student tests were performed to evaluate differences between UPF consumption among the different follow-up visits.

Mixed-effects linear models with random intercepts at cluster family and patient level were used to assess the association between the changes in CMR factors and simultaneous changes in UPF consumption at baseline, 6- and 12 months of follow-up. Mixed-effects linear models are an extension of simple linear models, and they are used for regression analyses involving dependent data when multiple observations are made on each participant. In this study, we evaluated concurrent changes in CMR factors by changes in the UPF consumption (in quartiles and per 100 g increments) over three measurements performed during the first year of follow-up (baseline, 6- and 12 months of follow-up). In addition, the association between CMR factors and UPF consumption was evaluated twice, with the UPF consumption expressed in g/d (in quartiles and per 100 g/d of increments) and in % of UPF within total daily dietary intake (in quartiles and per 10% of increments), with the first quartile set as the reference category. Adjustments were made for baseline covariates. The minimally adjusted model included age, sex, intervention group and follow-up time. Multivariable adjusted model included age, sex, intervention group, follow-up time, educational level, smoking status, physical activity and sedentary time.

We detected missing values in some variables of the multivariable adjusted model: educational level (n = 44), smoking status (n = 22), sedentary time (n = 38), systolic and diastolic blood pressure (n = 31), fasting blood glucose (n = 74), HbA1c (n = 478), triglycerides (n = 23), total cholesterol (n = 18), HDL cholesterol (n = 32) and LDL cholesterol (n = 106). Taking into account that the missing values represented 2% or less of the sample, multiple imputation was not considered, except for missing values in HbA1c (8,9%). Sensitivity analyses were performed for the association between imputed HbA1c and UPF consumption using mixed-effects linear models.

3. Results

Baseline characteristics for all samples and according to baseline quartile of UPF consumption are shown in Table 1. A total of 2782 (51.8%) males and 2591 (48.2%) females, whose mean (SD) age was 65.1 (4.9) years, were finally included in the present study. Participants in the highest quartile of UPF consumption were significantly younger, less physically active and had less adherence to energy-restricted Mediterranean diet. Moreover, they were more likely to be male, to have higher educational level, to be current smokers, to spend more screen time and to be sedentary. Among CMR factors, participants in the higher quartile of UPF consumption at baseline showed higher weight, BMI, waist circumference and levels of triglycerides, in addition to lower levels of HDL cholesterol ($p < 0.05$ for all the comparisons).

3.1. Consumption of ultra-processed foods

Consumption of UPF at baseline, 6 and 12 months of follow-up and changes in consumption between visits are shown in Table 2. The mean (SD) of total UPF consumption was 159.4 (155.1) g/d at baseline, 104.1 (116.9) g/d at 6 months and 100.7 (114.6) g/d after 12 months of follow-up. Participants significantly reduced their UPF consumption

Table 1
Baseline characteristics of all participants and according to baseline quartiles of ultra-processed food consumption consistent with NOVA classification[a].

	All sample	Q1 Low	Q2 Medium low	Q3 Medium high	Q4 High	*p*-value[b]
Range (g)		<67.6	67.6–113.4	113.5–195.7	>195.7	
n (frequency)	5373	1344	1343	1343	1343	
Intervention group						0.923
Control	2713 (50.5)	689 (51.3)	678 (50.5)	672 (50.0)	674 (50.2)	
Intervention	2660 (49.5)	655 (48.7)	665 (49.5)	671 (50.0)	669 (49.8)	
Age (years)	65.1 (4.9)	66.3 (4.6)	65.3 (4.8)	64.7 (4.8)	64.2 (5.1)	<0.001
Sex						<0.001
Males	2782 (51.8)	572 (42.6)	669 (49.8)	723 (53.8)	818 (60.9)	
Females	2591 (48.2)	772 (57.4)	674 (50.2)	620 (46.2)	525 (39.1)	
Marital status						0.060
Married	4131 (76.9)	989 (73.6)	1055 (78.6)	1048 (78.0)	1039 (77.4)	
Other situation	1223 (22.8)	349 (26.0)	285 (21.2)	290 (21.6)	299 (22.3)	
Educational level						<0.001
Primary or less	2660 (49.5)	731 (54.4)	679 (50.6)	650 (48.4)	600 (44.7)	
Secondary	1534 (28.6)	357 (26.6)	376 (28.0)	372 (27.7)	429 (31.9)	
College/university	1135 (21.1)	242 (18.0)	271 (20.2)	313 (23.3)	309 (23.0)	
Employment situation						<0.001
Current worker	1035 (19.3)	169 (12.6)	239 (17.8)	287 (21.4)	340 (25.3)	
Retired	3101 (57.7)	862 (64.1)	783 (58.3)	742 (55.3)	714 (53.2)	
Other status	1216 (22.6)	307 (22.8)	317 (23.6)	308 (22.9)	284 (21.2)	
Smoking status						<0.001
Never	2401 (44.7)	675 (50.2)	592 (44.1)	576 (42.9)	558 (41.6)	
Former	2301 (42.8)	535 (39.8)	587 (43.7)	588 (43.8)	591 (44.0)	
Current	649 (12.1)	130 (9.7)	157 (11.7)	173 (12.9)	189 (14.1)	
Self-reported type 2 diabetes						0.075
No	3.737 (69.6)	913 (67.9)	969 (72.2)	918 (68.4)	937 (69.8)	
Yes	1636 (30.4)	431 (32.1)	374 (27.9)	425 (31.7)	406 (30.2)	
Physical activity (METs-h/week)	41.8 (38.5)	43.3 (39.4)	43.3 (39.4)	40.1 (38.3)	40.5 (36.8)	0.035
Screen time (hours/day)	3.9 (1.9)	3.7 (1.8)	3.8 (1.8)	4.0 (1.9)	4.1 (1.9)	<0.001
Sedentary time (≥7 h/day)						<0.001
No	2954 (55.0)	826 (61.5)	754 (56.1)	699 (52.1)	675 (50.3)	
Yes	2381 (44.3)	512 (38.1)	578 (43.0)	634 (47.2)	657 (27.6)	
Alcohol consumption (g/day) mean (SD)	11.1 (15.1)	9.4 (14.1)	10.6 (14.5)	11.7 (15.0)	12.8 (16.3)	<0.001
E-R MedDiet (17-points)	8.5 (2.7)	9.6 (2.6)	8.7 (2.6)	8.2 (2.5)	7.6 (2.7)	<0.001
Weight (kg)	86.3 (12.9)	83.8 (12.1)	85.4 (12.5)	87.0 (13.2)	88.8 (13.3)	<0.001
BMI (kg/m^2)	32.5 (3.4)	32.2 (3.4)	32.3 (3.4)	32.6 (3.4)	32.7 (3.5)	0.003
Waist circumference (cm)	107.4 (9.6)	105.9 (9.1)	106.6 (9.3)	107.9 (9.6)	109.1 (9.9)	<0.001
Systolic BP (mmHg)	139.8 (16.8)	140.1 (17.3)	140.3 (16.5)	139.8 (16.8)	139.1 (16.6)	0.286
Diastolic BP(mmHg)	80.7 (9.9)	80.2 (9.6)	80.7 (9.7)	81.0 (10.0)	80.9 (10.1)	0.183
Fasting blood glucose (mg/dL)	113.3 (29.0)	113.8 (28.9)	112.8 (28.3)	113.4 (28.9)	113.2 (30.1)	0.831
HbA1c (%)	6.1 (0.9)	6.1 (0.8)	6.1 (0.9)	6.1 (0.8)	6.1 (0.9)	0.814
Triglycerides (mg/dL)	151.2 (76.5)	144.2 (69.6)	151.8 (77.1)	152.1 (74.3)	156.6 (84.0)	<0.001
TyG index	8.9 (0.5)	8.9 (0.5)	8.9 (0.5)	8.9 (0.5)	9.0 (0.5)	0.015
Total cholesterol (mg/dL)	197.3 (37.8)	197.2 (37.7)	197.6 (36.8)	198.7 (38.1)	195.8 (38.5)	0.238
HDL cholesterol (mg/dL)	48.1 (11.9)	49.1 (12.0)	48.6 (11.6)	47.9 (12.0)	46.9 (11.7)	<0.001
LDL cholesterol (mg/dL)	120.1 (34.5)	120.0 (33.2)	119.5 (32.2)	121.4 (33.1)	119.3 (38.9)	0.391

BP, blood pressure; BMI, body mass index; HbA1c, glycated hemoglobin; E-R MedDiet, energy-restricted Mediterranean diet adherence; MET, metabolic equivalent; SD, standard deviation; TyG index, triglyceride and glucose index.

[b] *p*-values were calculated by ANOVA test for continuous variables and $\chi 2$ test for categorical variables.

1 mmHg = 133.333 Pa. 1 mg/dL = 0.0556 mmol/L.

[a] Values are means (SD) or numbers of participants (percentages). Figures for some variables may differ from the total sample (n=5373) due to missing values.

[b] p-values were calculated by ANOVA test for continuous variables and X2 test for categorical variables.

Table 2
Consumption of ultra-processed food at baseline, 6- and 12-months of follow-up and their changes between visits in participants of PREDIMED Plus study (n = 5373).

	Baseline	6 months	12 months	6 months-Baseline		12 months-Baseline		12 months–6 months	
	mean (SD)	mean (SD)	mean (SD)	mean (SD)	*p*-value[a]	mean (SD)	p-value[a]	mean (SD)	*p*-value[a]
Total UPF consumption									
Grams/day	159.4 (155.1)	104.1 (116.9)	100.7 (114.6)	−55.3 (138.2)	<0.001	−58.6 (141.3)	<0.001	−3.4 (107.4)	0.011
% of UPF in total daily dietary intake[b]	7.7 (6.5)	5.1 (5.2)	4.9 (5.0)	−2.5 (5.9)	<0.001	−2.8 (5.9)	<0.001	−0.2 (4.5)	<0.001
Food groups within UPF									
Dairy products									
Grams/day	16.1 (29.3)	9.5 (21.0)	10.1 (20.4)	−6.5 (29.7)	<0.001	−6.0 (30.1)	<0.001	0.5 (23.1)	0.952
% within total UPF[c]	10.7 (14.0)	9.6 (15.0)	10.3 (15.5)	−1.2 (17.4)	<0.001	−0.5 (17.2)	0.049	0.7 (17.7)	0.003
Processed meats									
Grams/day	22.9 (17.7)	17.2 (13.6)	16.9 (12.8)	−5.6 (17.9)	<0.001	−6.0 (18.4)	<0.001	−0.4 (14.1)	0.044
% within total UPF[c]	21.8 (18.6)	28.0 (24.2)	28.0 (24.0)	6.2 (24.1)	<0.001	6.3 (24.2)	<0.001	0.1 (24.3)	0.669
Sweets									
Grams/day	35.9 (33.5)	22.0 (25.9)	21.0 (24.1)	−13.8 (33.8)	<0.001	−14.8 (33.4)	<0.001	−1.0 (24.9)	0.003
% within total UPF[c]	28.1 (22.1)	26.1 (23.4)	25.6 (22.8)	−2.0 (24.9)	<0.001	−2.5 (25.0)	<0.001	−0.5 (23.8)	0.113
Fast foods									
Grams/day	14.1 (15.8)	9.3 (11.6)	9.0 (11.1)	−4.9 (14.3)	<0.001	−5.1 (14.8)	<0.001	−0.3 (10.8)	0.068
% within total UPF[c]	11.6 (11.8)	12.0 (14.3)	12.0 (14.4)	0.4 (14.7)	0.050	0.4 (15.4)	0.035	0.04 (15.8)	0.849
Beverages									
Grams/day	67.1 (132.8)	43.5 (101.4)	41.5 (98.1)	−23.6 (120.4)	<0.001	−25.7 (121.5)	<0.001	−2.1 (95.4)	0.114
% within total UPF[c]	25.4 (27.7)	21.9 (28.7)	21.5 (28.4)	−3.6 (29.7)	<0.001	−3.9 (29.3)	<0.001	−0.35 (27.8)	0.364
Alcoholic beverages									
Grams/day	3.4 (10.5)	2.5 (8.9)	2.4 (9.6)	−0.8 (9.2)	<0.001	−1.0 (10.7)	<0.001	−0.2 (9.7)	0.250
% within total UPF[c]	2.4 (6.5)	2.5 (7.7)	2.5 (8.0)	0.2 (7.1)	0.123	0.11 (7.5)	0.290	−0.03 (7.8)	0.771

SD, standard deviation; UPF, Ultra-processed food.
[a] *p*-value from paired T-Student test.
Dairy products include flavored milk drinks, petit-suisse, cheese portions or cream cheese; custard, pudding or similar and ice cream. Processed meats include ham, processed meats such as dried sausage, chorizo or similar; patés and foie gras; burgers and meatballs. Sweets include biscuits; croissants, pastries or similar; doughnuts; muffins; Spanish churros or similar; pies; chocolates and chocolate; cocoa powder; Spanish nougat; marzipan or similar. Fast foods include crisps; pizza, croquettes; packet or canned soups; margarine; commercial mayonnaise; mustard; ketchup; packed fried tomato sauce and savory packed snacks. Beverages include soft drinks (sugar- and artificially-sweetened) and commercial fruit juices. Alcoholic beverages includes liquors and spirits (whisky vodka, gin and cognac).
[b] The consumption of ultra-processed foods was expressed as a percentage of total daily dietary intake (intake of UPF (g/d)/total dietary intake (g/d)*100).
[c] The consumption of each food subgroup was expressed as a percentage of total UPF consumption (consumption of each food subgroup (g/d)/total UPF consumption (g/d)*100).

Table 3
Association between concurrent changes in ultra-processed food consumption (g/d) and cardiovascular risk factors from baseline to 6- and 12 months of follow-up visits[a].

	Quartiles of UPF consumption					Continuous	
	Q1 Low	Q2 Medium low	Q3 Medium high	Q4 High		Per 100 g increments in UPF consumption	
	β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)	*p* for trend	β (95% CI)	*p*-value
Weight, kg							
Minimally-adjusted	reference	0.70 (0.56; 0.85)	1.21 (1.05-1.36)	1.66 (1.49; 1.83)	<0.0001	0.35 (0.30; 0.40)	<0.0001
Multivariable-adjusted	reference	0.50 (0.36; 0.63)	0.83 (0.67; 0.98)	1.09 (0.91; 1.26)	<0.0001	0.21 (0.17; 0.26)	<0.0001
Body mass index, kg/m^2							
Minimally-adjusted	reference	0.25 (0.20; 0.31)	0.44 (0.38; 0.50)	0.61 (0.54; 0.67)	<0.0001	0.13 (0.11; 0.14)	<0.0001
Multivariable-adjusted	reference	0.18 (0.12; 0.23)	0.30 (0 .24; 0.36)	0.39 (0.33; 0.46)	<0.0001	0.08 (0.06; 0.09)	<0.0001
Waist circumference, cm							
Minimally-adjusted	reference	0.61 (0.43; 0.80)	1.19 (0.99; 1.39)	1.64 (1.42; 1.86)	<0.0001	0.33 (0.27; 0.40)	<0.0001
Multivariable-adjusted	reference	0.41 (0.22; 0.59)	0.78 (0.58; 0.99)	1.03 (0.81; 1.26)	<0.0001	0.18 (0.11; 0.24)	<0.0001
Systolic BP, mmHg							
Minimally-adjusted	reference	0.59 (0.02; 1.17)	0.57 (-0.05; 1.19)	0.72 (0.06; 1.39)	0.194	-0.11 (-0.30; 0.08)	0.243
Multivariable-adjusted	reference	0.61 (0.02; 1.20)	0.41 (-0.22; 1.05)	0.45 (-0.25; 1.14)	0.736	-0.18 (-0.37; 0.01)	0.069
Diastolic BP, mmHg							
Minimally-adjusted	reference	0.45 (0.13; 0.77)	0.39 (0.05; 0.73)	0.75 (0.38; 1.12)	0.003	0.03 (-0.07; 0.14)	0.520
Multivariable-adjusted	reference	0.47 (0.15; 0.80)	0.37 (0.02; 0.72)	0.67 (0.29; 1.06)	0.022	0.02 (-0.09; 0.12)	0.754
Fasting blood glucose, mg/dL							
Minimally-adjusted	reference	0.98 (0.12; 1.83)	1.81 (0.89; 2.74)	2.42 (1.40; 3.43)	0.001	0.67 (0.38; 0.95)	<0.0001
Multivariable-adjusted	reference	0.73 (-0.13; 1.60)	1.35 (0.41; 2.30)	1.66 (0.61; 2.70)	0.050	0.44 (0.15; 0.73)	0.003
HbA1c, %							
Minimally-adjusted	reference	0.02 (0.001; 0.05)	0.04 (0.02; 0.06)	0.07 (0.04; 0.09)	<0.0001	0.02 (0.02; 0.03)	<0.0001
Multivariable-adjusted	reference	0.01 (-0.01; 0.04)	0.02 (-0.002; 0.05)	0.04 (0.01; 0.07)	0.039	0.02 (0.01; 0.03)	<0.0001
Tryglicerides, mg/dL							
Minimally-adjusted	reference	4.07 (1.47; 6.67)	7.36 (4.59; 10.14)	10.40 (7.39; 13.41)	<0.0001	2.01 (1.18; 2.85)	<0.0001
Multivariable-adjusted	reference	3.01 (0.37; 5.64)	5.01 (2.17; 7.86)	6.79 (3.66; 9.91)	<0.0001	1.09 (0.23; 1.94)	0.013
TyG index[b]							
Minimally-adjusted	reference	0.04 (0.02; 0.06)	0.07 (0.05; 0.08)	0.09 (0.07; 0.11)	<0.0001	0.02 (0.01; 0.02)	<0.0001
Multivariable-adjusted	reference	0.03 (0.01; 0.05)	0.05 (0.03; 0.06)	0.06 (0.04; 0.08)	<0.0001	0.01 (0.00; 0.01)	0.003
Total cholesterol, mg/dL							
Minimally-adjusted	reference	0.43 (-0.81; 1.67)	0.99 (-0.34; 2.32)	1.12 (-0.32; 2.56)	0.122	0.23 (-0.17; 0.63)	0.269
Multivariable-adjusted	reference	0.12 (-1.14; 1.38)	0.40 (-0.97; 1.76)	0.28 (-1.23; 1.78)	0.606	0.03 (-0.38; 0.45)	0.874
HDL cholesterol, mg/dL							
Minimally-adjusted	reference	-0.13 (-0.44; 0.19)	-0.43 (-0.76; -0.09)	-0.46 (-0.83; -0.09)	0.038	-0.06 (-0.17; 0.04)	0.237
Multivariable-adjusted	reference	-0.08 (-0.40; 0.23)	-0.33 (-0.68; 0.02)	-0.34 (-0.72; 0.05)	0.163	-0.02 (-0.13; 0.08)	0.686
LDL cholesterol, mg/dL							
Minimally-adjusted	reference	-0.11 (-1.26; 1.05)	0.12 (-1.12; 1.36)	0.03 (-1.31; 1.37)	0.666	0.03 (-0.34; 0.40)	0.876
Multivariable-adjusted	reference	-0.26 (-1.44; 0.91)	-0.16 (-1.43; 1.11)	-0.29 (-1.68; 1.11)	0.924	-0.04 (-0.42; 0.35)	0.843

BP, blood pressure; HbA1c, glycated hemoglobin; TyG index, triglycerides and glucose index; UPF, ultra-processed food.
Minimally adjusted model: baseline age, sex, intervention group and follow-up time.
Multivariable adjusted model: baseline age, sex, intervention group, follow-up time, educational level, smoking status, physical activity, energy-restricted Mediterranean diet adherence and sedentary time.
1 mmHg = 133.333 Pa. 1 mg/dL = 0.0556 mmol/L.

[a] Analyses were performed using mixed-effects linear models with random intercepts at cluster family and patient level. Beta represents changes in cardiometabolic risk factors in quartiles of UPF consumption (g/d), compared to quartile 1, the reference category.

[b] TyG index = [Ln(tryglicerides x fasting plasma glucose/2)].

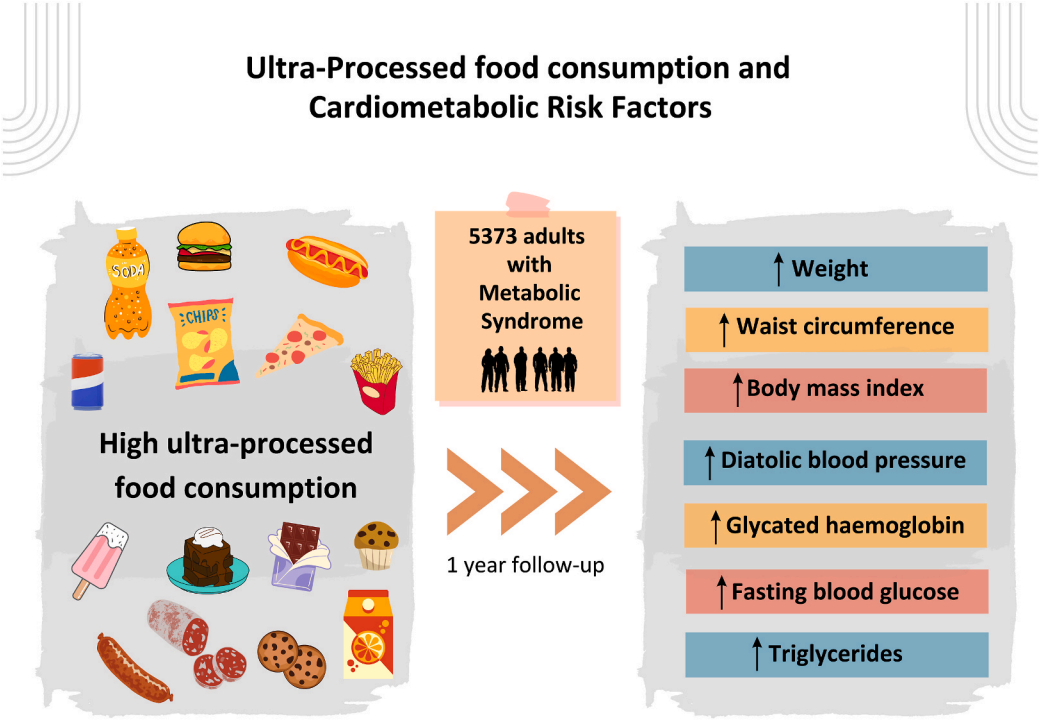

Fig. 2. Graphical abstract of main results obtained for the associations between concurrent changes in ultra-processed food consumption and in cardiometabolic risk factors from baseline to 6 and 12 months of follow-up in participants from the PREDIMED-Plus study.

during the first 12 months of follow-up (−58.6 [141.3] g/d; $p < 0.001$), especially during the first 6 months (−55.3 [138.2] g/d; $p < 0.001$). This reduction was also reflected on the proportion of UPF within total daily dietary intake, that changed from 7.7 (6.5) % to 4.9 (5.0) % ($p < 0.001$) from baseline to 12 months of follow-up.

In the same line, the consumption of specific food groups was also reduced during the follow-up, especially in the first 6 months. Only dairy products showed a non-significant increase of 0.5(23.1) g/d ($p = 0.952$) between 6-months and 12 months of follow-up. After the 12 months of follow-up, the proportion of the consumption of dairy products (−0.5 [17.2] %; $p = 0.049$), sweets (−2.5 [25.0] %; $p < 0.001$) and beverages (−3.9 [29.3] %; $p < 0.001$) was reduced. On the other hand, the proportion of processed meats (6.3 [24.2] %; $p < 0.001$) and fast foods (0.4 [15.4] %; $p = 0.035$) increased significantly.

3.2. Cardiometabolic risk factors

The CMR risk factors at baseline, 6 and 12 months of follow-up and their changes between visits are shown in Supplementary Table 3. All CMR factors decreased significantly between baseline and both 6- and 12-month visits, except for HDL cholesterol that showed a non-significant increase. Differences between 6- and 12-month visits were lower but still significant for weight, BMI, waist circumference, systolic and diastolic blood pressure, total and LDL cholesterol.

3.3. Cardiometabolic risk factors and ultra-processed food consumption associations

Table 3 shows the associations between concurrent changes in UPF consumption (by quartiles in g/d) and in CMR factors from baseline to 6 and 12 months of follow-up. Compared with the lower quartile, the highest quartile of UPF consumption was positively associated with weight (kg, β = 1.09; 95%CI = 0.91, 1.26), BMI (kg/m^2, β = 0.0.39; 95% CI = 0.33, 0.46), waist circumference (cm, β = 1.03; 95%CI = 0.81, 1.26), diastolic blood pressure (mm Hg,β = 0.67; 95%CI = 0.29,1.06), fasting blood glucose (mg/dl, β = 1.66; 95%CI = 0.61, 2.70), HbA1c (%, β = 0.04; 95%CI = 0.01, 0.07), plasma triglycerides (mg/dl, β = 6.79; 95%CI = 3.66, 9.91) and TyG index (β = 0.06; 95%CI = 0.04, 0.08) in the multivariable analyses. All the associations showed significant dose-response relationship (p-trend <0.05). No statistically significant associations were found between the highest UPF consumption and systolic blood pressure and all types of cholesterol (total, HDL and LDL cholesterol). Those results are graphically summarized in Fig. 2. Similar results were found per 100 g daily increments in UPF consumption and all CMR factors, except for diastolic blood pressure.

None of these associations changed substantially when the UPF consumption was expressed in % of UPF out of total daily intake (Supplementary Table 4). The exception was for diastolic blood pressure where the association with the highest quartile of UPF consumption became non-significant (β = 0.38; 95%CI = −0.01, 0.77) in the multivariable adjusted models.

Sensitivity analyses for the association between imputed HbA1c and UPF consumption showed similar results to non-imputed analyses and dose-response relationships (Supplementary Table 5).

4. Discussion

In this study, we analysed prospectively the concurrent changes in UPF consumption and cardiometabolic risk factors from baseline to 6 and 12 months of follow-up in an adult population with metabolic syndrome. Compared with the lowest quartile, the highest quartile of UPF consumption was associated positively with weight, BMI, waist circumference, diastolic blood pressure, fasting blood glucose, HbA1c, triglycerides and TyG index after adjustment by several sociodemographic and life-style characteristics.

Our results showed that UPF consumption decreased during the 12 months of follow-up in all-participants, perhaps because all participants were taught how to follow a Mediterranean diet as part of the study intervention. However, apparently, the baseline consumption was not influenced by the intervention and can be compared with the consumption reported in other studies [30–33]. For example, in line with our results about UPF consumption (nearly to 160 g/d), an Italian study

with 22475 participants (mean age 55 years) reported an UPF consumption of 181.5 g/d [30]. However, in a Spanish population-based cohort of 11989 individuals (mean age 46.9 years), UPF consumption was 384.7 g/d (SD 4.30), more than double the UPF consumption that we have found in our study [31], probably because they included younger populations than ours. In addition, we found in our sample that UPF represented 7.7% of the total amount of food consumed by weight (g/d). Nevertheless, other studies reported a higher proportion of UPF as part of total daily dietary intake. In a cohort with 44551 participants aged 56.7 years, UPF represented 14.4% of the total amount of food consumed by weight [32]. In another study, the daily % of UPF was 22.1 in 21730 participants whose mean age was 55.8 years [33]. Those differences could be explained by the mean age of our sample, which was higher (mean 65.1 years). In addition, our participants had metabolic syndrome and excess of weight at baseline so they may have changed their dietary intake as part of their usual health care.

Regarding the association between UPF consumption and CMR, few studies have evaluated these relationships previously, so the comparison between our findings and other studies is limited. Despite this, our results are in line with current evidence [18–20,34–36]. For example, in multivariable-adjusted analyses, we found that the highest UPF consumption was associated significantly with higher weight, BMI and greater waist circumference when compared with the lowest UPF consumption. Moreover, these associations showed a significant dose-response relationship. Our results are consistent with those from other longitudinal [19,34] and cross-sectional studies [18,20,35,36] in adults. However, direct comparison is difficult since these studies have evaluated UPF consumption as % of UPF in total calorie intake, whereas we have assessed UPF consumption in g/d and % of UPF out of total daily intake in grams. We did not evaluate the % of energy from UPF in total daily energy intake because some UPF are low-calorie or non-caloric (e.g. artificially-sweetened beverages) and they could be under-represented.

Little is known about the association between blood pressure and UPF consumption. Mendonça et al. evaluated 14790 Spanish adults who were free of hypertension at baseline. After 9.1 years of follow-up, the participants with the highest UPF consumption had a higher risk of developing hypertension (HR = 1.21; 95% CI = 1.06, 1.37; p for trend = 0.004) than those with the lowest consumption in adjusted models [16]. We found that the highest quartile of UPF consumption was positively associated with diastolic blood pressure in multivariable-adjusted models. However, when we evaluated per 100 g/d increments of UPF consumption, the association between diastolic blood pressure and UPF consumption lost statistical significance. We did not find any statistical significance with systolic blood pressure.

In addition, our study shows that as UPF consumption increases, the levels of fasting blood glucose and HbA1c also increase. In the same line, three large cohorts [15,33,37] found that compared with the group of lowest UPF consumption, adults with the highest consumption of UPF had more risk of developing type 2 diabetes mellitus in adjusted models [15,33,37]. Moreover, a study conducted in 6686 participants found that the more processed the foods were, the higher the glycaemic impact on an adult population aged ≥65 years [38].

Finally, we also identified that UPF consumption was associated with unfavourable levels of plasma triglycerides and TyG index, but not with total, HDL and LDL cholesterol. Little is known about the association between lipids profile and UPF consumption in adults. However, in a recent study that evaluated cross-sectionally four different classification systems of UPF, the authors found no significant association between LDL cholesterol and any of the classification systems of UPF. Nevertheless, the authors found positive associations between total cholesterol and a 5% increment in UPF consumption (% of g/d), which was calculated according to the classifications of the International Agency for Research on Cancer, the International Food Information Council and the University of North Carolina, but not with NOVA classification [39]. In addition, a recent systematic review performed in children and adolescents found that nine out of fourteen of the studies selected showed a significant association between UPF consumption and unfavourable levels of triglycerides, total, HDL, and LDL cholesterol [40].

Several hypotheses could clarify our findings. First, UPF are created to be highly palatable, accessible and ready to eat, which could explain why their consumption has been increasing in the last decades in high- and middle-income countries [8]. In fact, several studies have reported the % of UPF of total energy to be 17.0% in Spain [21], 24.6% in Brazil [34], 48.6% in United Kingdom [20], 45.0% in Canada [41] and 56.1% in the United States [18]. As well as to their high and widespread consumption, UPF have other characteristics that could be related with CMR factors. Fardet and colleagues [38] evaluated the relationship between the degree of food processing and satiety potential, and they found that the more processed the food, the lower its satiety potential [38], which could lead to a higher daily intake. In addition, UPF consumption has been related to poor nutrient intake. As the consumption of UPF increases, the dietary content of total energy, carbohydrates, free sugars, total fats and saturated fats also increase, while the dietary content of protein, fibre, several vitamins and minerals decrease [12,13]. In this sense, a recent review which evaluated the evidence on the biological mechanisms that support the associations between UPF and cardiovascular diseases reported increased energy intake, alterations in the gut–brain satiety signalling, hormonal effects, and changes to the gut microbiome as possible biological pathways [3]. In fact, in a subset of PREDIMED-Plus participants, we recently reported that UPF consumption is specifically related to a gut microbiota profile and we observed a positive association with specific taxa (Alloprevotella, Negativibacillus, Prevotella and Sutterella) related to inflammatory gastro-intestinal diseases [42].

This study has some limitations. Our study sample is not representative of the general population because participants were aged between 55 and 75 years, had excess of weight and metabolic syndrome at baseline. However, the proportion of people with CMR factors is constantly growing and they could represent a significant part of high-income countries populations [1]. A further limitation of this study could be the dietary assessment performed, which could have contained some measurement errors and underestimation may have occurred. However, dietary information was collected though face-to-face interviews by trained dietitians using a validated FFQ [26,43,44]. Moreover, the FFQ included a large variety of the most consumed foods in Spain (143 items) and UPF consumption was well represented by 36 different items. Finally, NOVA classification is not a perfect system to classify UPF, thus some misclassification may have occurred. Nevertheless, in the present study, a specialized working group composed by experts on nutritional epidemiology and dietitians were in charge of classifying all the FFQ foods according to the four NOVA food groups in order to minimize misclassification bias.

This study also has several strengths. Our analyses were based on a large sample recruited in 23 different centres throughout the Spanish territory. In addition, all the main characteristics of the study were performed under a standardized protocol for all centres, including recruitment, dietary assessment, anthropometric measurements and collection of blood samples. The same information was collected three times during the first year of study (at baseline, 6 and 12 months of follow-up) and anthropometric measurements and blood pressure were also collected using standardized repeated measurements.

To conclude, our results showed that compared with the lowest UPF consumption, the highest consumption was associated prospectively with unfavourable weight, body mass index, waist circumference, fasting blood glucose, glycated haemoglobin, triglycerides and triglycerides and glucose index in adults with metabolic syndrome after 12 months of follow-up. These results reinforce previous evidence on the negative impact of UPF consumption on cardiometabolic risk factors and emphasize the need to focus on reducing their consumption. However, the evidence about those associations is still limited and additional longitudinal studies are required to confirm these findings.

Clinical trial registration number

This trial was registered at http://www.isrctn.com/ISRCTN89898870 as ISRCT 89898870.

Financial support

This work was supported by the official Spanish Institutions for funding scientific biomedical research, CIBER Fisiopatología de la Obesidad y Nutrición (CIBEROBN) and Instituto de Salud Carlos III (ISCIII), through the Fondo de Investigación para la Salud (FIS), which is co-funded by the European Regional Development Fund (six coordinated FIS projects leaded by JS-S and JVi, including the following projects: PI13/00673, PI13/00492, PI13/00272, PI13/01123, PI13/00462, PI13/00233, PI13/02184, PI13/00728, PI13/01090, PI13/01056, PI14/01722, PI14/00636, PI14/00618, PI14/00696, PI14/01206, PI14/01919, PI14/00853, PI14/01374, PI14/00972, PI14/00728, PI14/01471, PI16/00473, PI16/00662, PI16/01873, PI16/01094, PI16/00501, PI16/00533, PI16/00381, PI16/00366, PI16/01522, PI16/01120, PI17/00764, PI17/01183, PI17/00855, PI17/01347, PI17/00525, PI17/01827, PI17/00532, PI17/00215, PI17/01441, PI17/00508, PI17/01732, PI17/00926, PI19/00957, PI19/00386, PI19/00309, PI19/01032, PI19/00576, PI19/00017, PI19/01226, PI19/00781, PI19/01560, PI19/01332, PI20/01802, PI20/00138, PI20/01532, PI20/00456, PI20/00339, PI20/00557, PI20/00886, PI20/01158); the Especial Action Project entitled: Implementación y evaluación de una intervención intensiva sobre la actividad física Cohorte PREDIMED-Plus grant to JS-S; the European Research Council (Advanced Research Grant 2014–2019; agreement #340918) granted to MÁM-G.; the Recercaixa (number 2013ACUP00194) grant to JS-S; grants from the Consejería de Salud de la Junta de Andalucía (PI0458/2013, PS0358/2016, PI0137/2018); the PROMETEO/2017/017 grant from the Generalitat Valenciana; the AICO/2021/347 grant from the Generalitat Valenciana, the SEMERGEN grant, funds provided by Ministerio de Ciencia e Investigación through grants from PROYECTOS DE I + D + I « RETOS INVESTIGACIÓN» (RTI2018-095569-B-I00 and RTI2018-098113-B-I00) and «PROGRAMACIÓN CONJUNTA INTERNACIONAL» (PCI2018-093009) granted to LD. Juan de la Cierva-Incorporación research grant (IJC2019-042420-I) of the Spanish Ministryof Economy, Industry and Competitiveness and European Social-Funds to JK; PROMETEO 21/2021 from the Generalitat Valenciana.to DC. None of the funding sources took part in the design, collection, analysis, interpretation of the data, or writing the report, or in the decision to submit the manuscript for publication.

Data statement

Data described in the manuscript, codebook, and analytic code will be made available upon request to the PREDIMED-Plus trial Steering Committee chair at: jordi.salas@urv.cat. The request will then be passed to members of the PREDIMED-Plus Steering Committee for deliberation. The data sets generated and analysed in the current study are not expected to be made available outside the core research group, as neither the participants' consent forms nor ethics approval included permission for open access.

Declaration of interest

Jordi Salas-salvadó reported receiving research support from the Instituto de Salud Carlos III, Ministerio de Educación y Ciencia, Departament de Salut Pública de la Generalitat de Catalunya, the European Commission, the USA National Institutes of Health; receiving consulting fees or travel expenses from Eroski Foundation, Instituto Danone, Mundipharma, receiving non-financial support from Hojiblanca, Patrimonio Comunal Olivarero, the Almond Board of California, Pistachio Growers and Borges S.A.; serving on the board of and receiving grant support through his institution from the International Nut and Dried Foundation and the Eroski Foundation; and personal fees from Instituto Danone; Serving in the Scientific Board of Danone Institute International. Ramón Estruch reports grants from Fundación Dieta Mediterránea, Spain and Cerveza y Salud, Spain. Also, personal fees for given lectures from Brewers of Europe, Belgium, Fundación Cerveza y Salud, Spain, Instituto Cervantes, Alburquerque, USA; Instituto Cervantes, Milan, Italy, Lilly Laboratories, Spain, and Wine and Culinary International Forum, Spain, and non-financial support to organize a National Congress on Nutrition. Also feeding trials with product from Grand Fountain and Uriach Laboratories, Spain. Emili Ros reports grants, personal fees, non-financial support, and other from California Walnut Commission, during the conduct of the study; grants, personal fees, nonfinancial support, and other from Alexion; personal fees and other from Amarin, outside the submitted work.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript; or in the decision to publish the results.

CRediT authorship contribution statement

Sandra González-Palacios: Formal analysis, Writing – original draft. **Alejandro Oncina-Cánovas:** Writing – review & editing. **Manuela García-de-la-Hera:** Writing – review & editing. **Miguel Ángel Martínez-González:** Conceptualization, Funding acquisition, Writing – review & editing. **Jordi Salas-Salvadó:** Conceptualization, Funding acquisition, Writing – review & editing. **Dolores Corella:** Conceptualization, Funding acquisition, Writing – review & editing. **Helmut Schröder:** Conceptualization, Funding acquisition, Writing – review & editing. **J. Alfredo Martínez:** Conceptualization, Funding acquisition, Writing – review & editing. **Ángel M. Alonso-Gómez:** Conceptualization, Funding acquisition, Writing – review & editing. **Julia Wärnberg:** Conceptualization, Funding acquisition, Writing – review & editing. **Dora Romaguera:** Conceptualization, Funding acquisition, Writing – review & editing. **José López-Miranda:** Conceptualization, Funding acquisition, Writing – review & editing. **Ramon Estruch:** Conceptualization, Funding acquisition, Writing – review & editing. **Francisco J. Tinahones:** Conceptualization, Funding acquisition, Writing – review & editing. **José Lapetra:** Conceptualization, Funding acquisition, Writing – review & editing. **J. Luís Serra-Majem:** Conceptualization, Funding acquisition, Writing – review & editing. **Naomi Cano-Ibañez:** Writing – review & editing. **Josep A. Tur:** Conceptualization, Funding acquisition, Writing – review & editing. **Vicente Martín-Sánchez:** Conceptualization, Funding acquisition, Writing – review & editing. **Xavier Pintó:** Conceptualization, Funding acquisition, Writing – review & editing. **Miguel Delgado-Rodríguez:** Conceptualization, Funding acquisition, Writing – review & editing. **Pilar Matía-Martín:** Conceptualization, Funding acquisition, Writing – review & editing. **Josep Vidal:** Conceptualization, Funding acquisition, Writing – review & editing. **Clotilde Vázquez:** Conceptualization, Funding acquisition, Writing – review & editing. **Lidia Daimiel:** Conceptualization, Funding acquisition, Writing – review & editing. **Emili Ros:** Conceptualization, Funding acquisition, Writing – review & editing. **Maira Bes-Rastrollo:** Writing – review & editing. **Alessandro Atzeni:** Writing – review & editing. **Jose V. Sorli:** Writing – review & editing. **M. Dolors Zomeño:** Writing – review & editing. **Patricia J. Peña-Orihuela:** Writing – review & editing. **Laura M. Compañ-Gabucio:** Writing – review & editing. **Francisco J. Barón-López:** Writing – review & editing. **María Ángeles Zulet:** Writing – review & editing. **Jadwiga Konieczna:** Writing – review & editing. **Rosa M. Casas:** Writing – review & editing. **Eva M. Garrido-Garrido:** Writing – review & editing. **Lucas Tojal-Sierra:** Writing – review & editing. **Ana M. Gomez-Perez:** Writing – review & editing. **Miguel Ruiz-Canela:** Writing – review & editing. **Antoni Palau:**

Writing – review & editing. **Carmen Saiz:** Writing – review & editing. **Karla A. Pérez-Vega:** Writing – review & editing. **Antonio Garcia-Rios:** Writing – review & editing. **Laura Torres-Collado:** Writing – review & editing. **Javier Basterra-Gortari:** Writing – review & editing. **Tany E. Garcidueñas-Fimbres:** Writing – review & editing. **Mireia Malcampo:** Writing – review & editing. **Jesús Vioque:** Conceptualization, Funding acquisition, Supervision, Writing – review & editing.

Acknowledgments

The authors especially thank the PREDIMED-Plus participants for the enthusiastic collaboration, the PREDIMED-Plus personnel for outstanding support, and the personnel of all associated primary care centres for the exceptional effort. CIBEROBN, CIBERESP, and CIBERDEM are initiatives of Instituto de Salud Carlos III (ISCIII), Madrid, Spain. The authors also thank the PREDIMED-Plus Biobank Network as a part of the National Biobank Platform of the ISCIII for storing and managing the PREDIMED-Plus biological samples. We also thank Jessica Gorlin for the English revision.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.atherosclerosis.2023.05.022.

References

[1] G.A. Roth, G.A. Mensah, C.O. Johnson, G. Addolorato, E. Ammirati, L.M. Baddour, et al., Global burden of cardiovascular diseases and risk factors, 1990-2019: update from the GBD 2019 study, J. Am. Coll. Cardiol. 76 (25) (2020 Dec 22) 2982–3021.
[2] W.C. Willett, M.J. Stampfer, Current evidence on healthy eating, Annu. Rev. Publ. Health 34 (1) (2013) 77–95.
[3] F. Juul, G. Vaidean, N. Parekh, Ultra-processed foods and cardiovascular diseases: potential mechanisms of action, Adv Nutr Bethesda Md 12 (5) (2021 Oct 1) 1673–1680.
[4] S.S. Anand, C. Hawkes, R.J. de Souza, A. Mente, M. Dehghan, R. Nugent, et al., Food consumption and its impact on cardiovascular disease: importance of solutions focused on the globalized food system: a report from the workshop convened by the world Heart federation, J. Am. Coll. Cardiol. 66 (14) (2015 Oct 6) 1590–1614.
[5] G. Pagliai, M. Dinu, M.P. Madarena, M. Bonaccio, L. Iacoviello, F. Sofi, Consumption of ultra-processed foods and health status: a systematic review and meta-analysis, Br. J. Nutr. 125 (3) (2021 Feb 14) 308–318.
[6] Y. Zhang, E.L. Giovannucci, Ultra-processed foods and health: a comprehensive review, Crit. Rev. Food Sci. Nutr. (2022 Jun 6) 1–13.
[7] C.A. Monteiro, R.B. Levy, R.M. Claro, IRR de Castro, G. Cannon, A new classification of foods based on the extent and purpose of their processing, Cad. Saúde Pública 26 (11) (2010 Nov) 2039–2049.
[8] C.A. Monteiro, J.C. Moubarac, G. Cannon, S.W. Ng, B. Popkin, Ultra-processed products are becoming dominant in the global food system, Obes Rev Off J Int Assoc Study Obes 14 (Suppl 2) (2013 Nov) 21–28.
[9] C.A. Monteiro, G. Cannon, J.C. Moubarac, R.B. Levy, M.L.C. Louzada, P.C. Jaime, The UN Decade of Nutrition, the NOVA food classification and the trouble with ultra-processing, Publ. Health Nutr. 21 (1) (2018 Jan) 5–17.
[10] P. Latasa, M.L.D.C. Louzada, E. Martinez Steele, C.A. Monteiro, Added sugars and ultra-processed foods in Spanish households (1990-2010), Eur. J. Clin. Nutr. 72 (10) (2018 Oct) 1404–1412.
[11] F. Lauria, M. Dello Russo, A. Formisano, S. De Henauw, A. Hebestreit, M. Hunsberger, et al., Ultra-processed foods consumption and diet quality of European children, adolescents and adults: results from the I.Family study, Nutr Metab Cardiovasc Dis NMCD 31 (11) (2021 Oct 28) 3031–3043.
[12] D. Martini, J. Godos, M. Bonaccio, P. Vitaglione, G. Grosso, Ultra-processed foods and nutritional dietary profile: a meta-analysis of nationally representative samples, Nutrients 13 (10) (2021 Sep 27) 3390.
[13] R. Costa de Miranda, F. Rauber, M.M. de Moraes, C. Afonso, C. Santos, S. Rodrigues, et al., Consumption of ultra-processed foods and non-communicable disease-related nutrient profile in Portuguese adults and elderly (2015-2016): the UPPER project, Br. J. Nutr. (2020 Sep 3) 1–11.
[14] B. Srour, L.K. Fezeu, E. Kesse-Guyot, B. Allès, C. Méjean, R.M. Andrianasolo, et al., Ultra-processed food intake and risk of cardiovascular disease: prospective cohort study (NutriNet-Santé), BMJ 365 (2019 29) l1451.
[15] B. Srour, L.K. Fezeu, E. Kesse-Guyot, B. Allès, C. Debras, N. Druesne-Pecollo, et al., Ultraprocessed food consumption and risk of type 2 diabetes among participants of the NutriNet-santé prospective cohort, JAMA Intern. Med. 180 (2) (2020 Feb 1) 283–291.
[16] R. de D. Mendonça, A.C.S. Lopes, A.M. Pimenta, A. Gea, M.A. Martinez-Gonzalez, M. Bes-Rastrollo, Ultra-processed food consumption and the incidence of hypertension in a Mediterranean cohort: the seguimiento universidad de Navarra project, Am. J. Hypertens. 30 (4) (2017 Apr 1) 358–366.
[17] R. de D. Mendonça, A.M. Pimenta, A. Gea, C. de la Fuente-Arrillaga, M.A. Martinez-Gonzalez, A.C.S. Lopes, et al., Ultraprocessed food consumption and risk of overweight and obesity: the University of Navarra Follow-Up (SUN) cohort study, Am. J. Clin. Nutr. 104 (5) (2016) 1433–1440.
[18] F. Juul, E. Martinez-Steele, N. Parekh, C.A. Monteiro, V.W. Chang, Ultra-processed food consumption and excess weight among US adults, Br. J. Nutr. 120 (1) (2018 Jul) 90–100.
[19] M. Beslay, B. Srour, C. Méjean, B. Allès, T. Fiolet, C. Debras, et al., Ultra-processed food intake in association with BMI change and risk of overweight and obesity: a prospective analysis of the French NutriNet-Santé cohort, PLoS Med. 17 (8) (2020 Aug), e1003256.
[20] F. Rauber, K. Chang, E.P. Vamos, M.L. da Costa Louzada, C.A. Monteiro, C. Millett, et al., Ultra-processed food consumption and risk of obesity: a prospective cohort study of UK Biobank, Eur. J. Nutr. (2020 Oct 18) 60(4):2169-2180.
[21] H. Sandoval-Insausti, M. Jiménez-Onsurbe, C. Donat-Vargas, J. Rey-García, J. R. Banegas, F. Rodríguez-Artalejo, et al., Ultra-processed food consumption is associated with abdominal obesity: a prospective cohort study in older adults, Nutrients 12 (8) (2020 Aug 7).
[22] J. Konieczna, M. Morey, I. Abete, M. Bes-Rastrollo, M. Ruiz-Canela, J. Vioque, et al., Contribution of ultra-processed foods in visceral fat deposition and other adiposity indicators: prospective analysis nested in the PREDIMED-Plus trial, Clin Nutr Edinb Scotl 40 (6) (2021 Jun) 4290–4300.
[23] M.A. Martínez-González, P. Buil-Cosiales, D. Corella, M. Bulló, M. Fitó, J. Vioque, et al., Cohort Profile: design and methods of the PREDIMED-Plus randomized trial, Int. J. Epidemiol. 48 (2) (2019 Apr 1) 387–388o.
[24] K.G.M.M. Alberti, R.H. Eckel, S.M. Grundy, P.Z. Zimmet, J.I. Cleeman, K. A. Donato, et al., Harmonizing the metabolic syndrome: a joint interim statement of the international diabetes federation task force on epidemiology and prevention; national Heart, Lung, and blood Institute; American Heart association; world Heart federation; international atherosclerosis society; and international association for the study of obesity, Circulation 120 (16) (2009 Oct 20) 1640–1645.
[25] W. Willett, Nutritional Epidemiology, 3 edition, Oxford University Press, Oxford ; New York, 2012, p. 552.
[26] J.D. Fernández-Ballart, J.L. Piñol, I. Zazpe, D. Corella, P. Carrasco, E. Toledo, et al., Relative validity of a semi-quantitative food-frequency questionnaire in an elderly Mediterranean population of Spain, Br. J. Nutr. 103 (12) (2010 Jun) 1808–1816.
[27] O. Moreiras, Á. Carbajal, L. Cabrera, C. Cuadrado, Tablas de composición de alimentos: Guía de prácticas, 2018, p. 496.
[28] C.A. Monteiro, G. Cannon, R.B. Levy, J.C. Moubarac, M.L. Louzada, F. Rauber, et al., Ultra-processed foods: what they are and how to identify them, Publ. Health Nutr. 22 (5) (2019 Apr) 936–941.
[29] H. Schröder, M.D. Zomeño, M.A. Martínez-González, J. Salas-Salvadó, D. Corella, J. Vioque, et al., Validity of the energy-restricted Mediterranean diet adherence screener, Clin Nutr Edinb Scotl 40 (8) (2021 Aug) 4971–4979.
[30] M. Bonaccio, A. Di Castelnuovo, S. Costanzo, A. De Curtis, M. Persichillo, F. Sofi, et al., Ultra-processed food consumption is associated with increased risk of all-cause and cardiovascular mortality in the Moli-sani Study, Am. J. Clin. Nutr. (2020 Dec 18) 113(2):446-455.
[31] R. Blanco-Rojo, H. Sandoval-Insausti, E. López-Garcia, A. Graciani, J.M. Ordovás, J.R. Banegas, et al., Consumption of ultra-processed foods and mortality: a national prospective cohort in Spain, Mayo Clin. Proc. 94 (11) (2019 Nov) 2178–2188.
[32] L. Schnabel, E. Kesse-Guyot, B. Allès, M. Touvier, B. Srour, S. Hercberg, et al., Association between ultraprocessed food consumption and risk of mortality among middle-aged adults in France, JAMA Intern. Med. 179 (4) (2019 Apr 1) 490–498.
[33] R.B. Levy, F. Rauber, K. Chang, ML. da C. Louzada, C.A. Monteiro, C. Millett, et al., Ultra-processed food consumption and type 2 diabetes incidence: a prospective cohort study, Clin Nutr Edinb Scotl (2020 Dec 28) 40(5):3608-3614.
[34] S.L. Canhada, V.C. Luft, L. Giatti, B.B. Duncan, D. Chor, M de JM da Fonseca, et al., Ultra-processed foods, incident overweight and obesity, and longitudinal changes in weight and waist circumference: the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil), Publ. Health Nutr. 23 (6) (2020 Apr) 1076–1086.
[35] F.M. Silva, L. Giatti, R.C. de Figueiredo, M.D.C.B. Molina, L. de Oliveira Cardoso, B. B. Duncan, et al., Consumption of ultra-processed food and obesity: cross sectional results from the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil) cohort (2008-2010), Publ. Health Nutr. 21 (12) (2018 Aug) 2271–2279.
[36] P. Pereira, E.M. Steele, R.B. Levy, M.L. da Costa Louzada, A. Rangan, J. Woods, et al., Ultra-processed food consumption and obesity in the Australian adult population, Nutr. Diabetes 10 (1) (2020 Dec 5) 39.
[37] M. Llavero-Valero, J. Escalada-San Martín, M.A. Martínez-González, F.J. Basterra-Gortari, C. de la Fuente-Arrillaga, M. Bes-Rastrollo, Ultra-processed foods and type-2 diabetes risk in the SUN project: a prospective cohort study, Clin Nutr Edinb Scotl 40 (5) (2021 May) 2817–2824.
[38] A. Fardet, C. Méjean, H. Labouré, V.A. Andreeva, G. Feron, The degree of processing of foods which are most widely consumed by the French elderly population is associated with satiety and glycemic potentials and nutrient profiles, Food Funct. 8 (2) (2017 Feb 22) 651–658.
[39] C. Martinez-Perez, R. San-Cristobal, P. Guallar-Castillon, M.Á. Martínez-González, J. Salas-Salvadó, D. Corella, et al., Use of different food classification systems to assess the association between ultra-processed food consumption and cardiometabolic health in an elderly population with metabolic syndrome (PREDIMED-Plus cohort), Nutrients 13 (7) (2021 Jul 20) 2471.
[40] J.B. Beserra, NI daS. Soares, C.S. Marreiros, CMRG de Carvalho, M. do C. de CE. Martins, B de JES de A. Freitas, et al., [Do children and adolescents who consume

ultra-processed foods have a worse lipid profile? A systematic review], Ciência Saúde Coletiva 25 (12) (2020 Dec) 4979–4989.

[41] M. Nardocci, B.S. Leclerc, M.L. Louzada, C.A. Monteiro, M. Batal, J.C. Moubarac, Consumption of ultra-processed foods and obesity in Canada, Can J Public Health Rev Can Sante Publique 110 (1) (2019 Feb) 4–14.

[42] A. Atzeni, M.Á. Martínez, N. Babio, P. Konstanti, F.J. Tinahones, J. Vioque, et al., Association between ultra-processed food consumption and gut microbiota in senior subjects with overweight/obesity and metabolic syndrome [Internet], Front. Nutr. 9 (2022). Available from: https://www.frontiersin.org/articles/10.3389/fnut.2022.976547. (Accessed 29 November 2022).

[43] J.M. Martin-Moreno, P. Boyle, L. Gorgojo, P. Maisonneuve, J.C. Fernandez-Rodriguez, S. Salvini, et al., Development and validation of a food frequency questionnaire in Spain, Int. J. Epidemiol. 22 (3) (1993 Jun) 512–519.

[44] C. de la Fuente-Arrillaga, Z.V. Ruiz, M. Bes-Rastrollo, L. Sampson, M.A. Martinez-González, Reproducibility of an FFQ validated in Spain, Publ. Health Nutr. 13 (9) (2010 Sep) 1364–1372.