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Original article

Associations between ultra-processed food consumption and kidney function in an older adult population with metabolic syndrome

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S U M M A R Y

Background & aims: Ultra-processed food (UPF) consumption has increased dramatically over the last decades worldwide. Although it has been linked to some cardiometabolic comorbidities, there is limited evidence regarding kidney function. This study aimed to cross-sectionally and longitudinally assess the association between UPF consumption and estimated-glomerular filtration rate (eGFR) based on Cystatin C (CysC).
Methods: Older adults (mean age 65 ± 5.0 years, 46% women) with overweight/obesity and metabolic syndrome (MetS) who had available data of CysC at baseline (n = 1909), at one-year and at 3-years of follow-up (n = 1700) were analyzed. Food consumption was assessed using a validated 143-item semi-quantitative food frequency questionnaire and UPF consumption (% of g/d) at baseline and changes after one-year of follow-up were estimated according to NOVA classification system. Multivariable-adjusted linear and logistic regression models were performed to evaluate the cross-sectional associations between UPF consumption with eGFR levels and decreased kidney function (eGFR <60 ml/min/1.73 m2) at baseline. Multivariable-adjusted mixed-effects linear regression models were fitted to investigate the associations between one-year changes in UPF and eGFR over 3-years of follow-up.
Results: Individuals with the highest baseline UPF consumption showed lower eGFR (β: −3.39 ml/min/1.73 m^2; 95% CI: −5.59 to −1.20) and higher odds of decreased kidney function (OR: 1.64; 95% CI: 1.21 to

Abbreviations: BMI, Body Mass Index; CKD, Chronic Kidney Disease; CysC, Cystatin C; CI, Confidence Interval; E, Energy; FFQ, Food Frequency Questionnaire; eGFR, estimated-Glomerular Filtration Rate; MedDiet, Mediterranean Diet; MetS, Metabolic Syndrome; METS, Metabolic Equivalent Task; PREDIMED, Prevención con Dieta Mediterránea; OR, Odds Ratios; T2D, type 2 diabetes; UPF, Ultra-Processed Food.

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2.22) at baseline, compared to individuals in the lowest tertile. Participants in the highest tertile of one-year changes in UPF consumption presented a significant decrease in eGFR after one-year of follow-up (β: −1.45 ml/min/1.73 m^2; 95% CI: −2.90 to −0.01) as well as after 3-years of follow-up (β: −2.18 ml/min/1.73 m^2; 95% CI: −3.71 to −0.65) compared to those in the reference category.
Conclusions: In a Mediterranean population of older adults with overweight/obesity and MetS, higher UPF consumption at baseline and one-year changes towards higher consumption of UPF were associated with worse kidney function at baseline and over 3-years of follow-up, respectively.
Clinical Trial Registry number: ISRCTN89898870.

1. Introduction

The progressive loss of kidney function is one of the major health concerns in the ageing population, which could result in the onset of Chronic Kidney Disease (CKD) [1]. Recent evidence shows that CKD affects around 10% of the general population worldwide and it is expected to be the 5th non-communicable cause of death in 2040 [2]. Apart from the fact that this global public health challenge is associated with lower quality of life and several cardiometabolic comorbidities [1,3–5], it also involves an economic burden on healthcare systems [2,4]. Consequently, it requires the urgent identification of those risk factors associated with kidney dysfunction and CKD to implement suitable preventive measures.

Lifestyle changes towards healthier habits such as being physically active, non-smoking or following traditional, home-cooked and healthy dietary patterns could be considered the main modifiable lifestyle behaviours that contribute to preserve kidney function and prevent the development of CKD [6] as well as related cardio-metabolic risk factors [7]. Considering dietary patterns, a recent meta-analysis of observational studies suggested that adhering to diets rich in unprocessed or minimally processed food such as fruits, vegetables, legumes or nuts and poor in red or processed meat and sugar-sweetened beverages, could be involved in the prevention of kidney function impairment and the delay of CKD progression [8]. Unfortunately, adherence to the Western diet, which implies a higher consumption of ultra-processed food (UPF), has been dramatically raising over the last decades around the world [9,10]. In general, UPF are industrial formulations generally characterized for having a scarce nutritional quality, high energy density and several added ingredients such as simple sugars, salt, fats, artificial colors, flavors, emulsifiers and stabilizers between other additives, which make them convenient products, readily available, affordable, with a long shelf-life and hyperpalatable. In addition, most of them are products with low dietary components beneficial to health such as fiber, and certain vitamins or minerals [11,12].

A significant body of scientific evidence has been reported about the relationship between UPF consumption and several chronic diseases such as cardiovascular disease (CVD), hypertension, diabetes, obesity, even cancer and all-cause mortality [13,14]. However, only one cross-sectional study [15] and four prospective studies [16–19] have evaluated the potential relationship between UPF consumption and kidney function or CKD. Their findings suggested that higher consumption of UPF is inversely associated with reduced estimated glomerular filtration rate (eGFR) [15,17], higher risk of kidney function decline [16,17] or CKD incidence [17,18]. Furthermore, in renal transplant recipients adults, it has been suggested that UPF consumption is associated with higher risk of all-cause mortality and renal function decline [20]. In addition, in a recent review, it has been discussed the potential relationship between UPF, kidney health and CKD, claiming for the inclusion of UPF in dietary guidelines for CKD prevention and managing [21]. All studies have been conducted on adults or middle-aged individuals who were healthy or had CKD or renal transplant, and have assessed kidney outcomes through eGFR based on serum creatinine, a common biomarker of kidney function widely used in epidemiologic studies. However, long-term studies using optimal markers such as Cystatin C (CysC), which is not affected by sex, age, protein intake and muscle mass are absent [22,23]. In addition, it is still unclear whether the consumption of UPF is potentially associated with kidney health in elderly individuals who had underlying comorbid conditions such as obesity/overweight and metabolic syndrome (MetS). Hence, the main aims of this current study were to cross-sectionally and longitudinally assess the associations between UPF consumption and kidney function, through estimated-glomerular filtration rate (eGFR) based on Cystatin C (CysC), in a large cohort of Mediterranean older adults with overweight/obesity and MetS.

2. Material & methods

2.1. Study design and population

The present study is part of the PREvención con DIeta MEDiterránea (PREDIMED)-Plus trial, which is an ongoing, multicenter, 8-year parallel-group and controlled intervention trial conducted in 23 Spanish centers, aiming to evaluate the effect of an intensive lifestyle weight loss intervention on CVD morbi-mortality compared to usual care advice. From 2013 to 2016, primary health care clinics, hospitals, universities and research institutes contributed to the enrollment of 6789 men (aged 55–75 years) and women (aged 60–75 years) free of CVD at baseline, with overweight or obesity (BMI 27–40 kg/m^2) and who met at least 3 components of the MetS [24]. Full details of the protocol and the study design can be accessed at https://www.predimedplus.com, and the inclusion/exclusion criteria have been extensively described elsewhere [25,26]. The PREDIMED-Plus was registered at the International Standard Randomized Controlled Trial registry in July 2014 (https://www.isrctn.com/ISRCTN89898870).

In the current analysis, data from the LIKIDI sub-project conducted in the framework of the PREDIMED-plus trial was analyzed as an observational cross-sectional and prospective cohort study. In 5 out of the 23 PREDIMED-Plus recruiting centers, CysC levels were determined at baseline (n = 1909), at one-year (n = 1688) and at 3-years of follow-up (n = 1482). Participants who did not complete the food frequency questionnaire (FFQ) and who reported implausible total energy intakes according to predefined limits (men <800 and >4000 kcal/day and women <500 and >3500 kcal/day) [27] were excluded from the analyses.

After the final study protocol and procedures were approved by the Institutional Review Boards of each participating center in agreement with the ethical principles on human research established in the Declaration of Helsinki, written informed consent was provided by all participants.

2.2. Dietary assessment and ultra-processed food

At baseline and after one-year of follow-up, participants completed a 143-item semi-quantitative Food Frequency Questionnaire (FFQ) in a face-to-face interview held by trained dietitians. This FFQ, which is based on a previous validated one in the Spanish population [28], collected the frequency of consumption of each food item, with nine possible answers ranging from never or almost never to more than 6 times per day, during the preceding year. The responses for each item were subsequently transformed to grams per day. Two Spanish food composition tables were used to calculate total daily intake of energy, nutrients intake and food groups [29,30].

For the assessment of UPF consumption, NOVA classification system [31] was referred and food items were classified into one of the following four groups: unprocessed or minimally processed foods (NOVA 1), processed culinary ingredients (NOVA 2), processed foods (NOVA 3) and UPF (NOVA 4) [12]. Two independent dietitians performed the classification of the food items into one of the four groups and subsequently, different specialists in nutritional epidemiology from various recruiting centers participating in the study independently revised this procedure. Investigators discussed when discrepancies in classification of certain foods items raised and a decision was taken by consensus. Further details of the methods and the food items included in each group of de NOVA system in the PREDIMED-Plus have been described previously [32].

Therefore, the main exposure in this study was exclusively UPF. For each participant, the proportion of UPF in the total diet (% of grams of UPF/total grams of food intake per day) was calculated. Subsequently, one-year changes in UPF consumption were performed by subtracting the proportion of UPF in the total diet at one year minus the proportion at baseline.

2.3. Outcome ascertainment

Fasting blood samples were extracted at baseline, one-year and 3-years of follow-up. CysC concentrations were determined by Siemens Atellica NEPH 630 (Siemens Healthineers, Marburg, Germany) nephelometer using the Atellica CH CYSC_2 (Siemens Healthcare GmbH) assay with a limit of quantitation of 0.25 mg/L and an intra- and interassay coefficient of variation <10%. The eGFR was indirectly estimated from CysC using the Chronic Kidney Disease Epidemiology Collaboration equation [33]. Secondarily, baseline eGFR and decreased kidney function at baseline defined as eGFR lower than 60 ml/min/1.73 m^2, were assessed in the cross-sectional analysis.

2.4. Measurement of other covariates

Participants provided sociodemographic and lifestyle information through several questionnaires administered by trained staff. Physical activity was ascertained using the validated REGICOR (Registre Gironí del Cor) Short Physical Activity Questionnaire for adult population [34]. A validated 17-item energy-reduced Mediterranean Diet (erMedDiet) questionnaire [35] was used to assess the adherence to an MedDiet. Each item of this erMedDiet questionnaire was scored with 1 or 0 points, meaning compliance or not with a pre-established criterion. Therefore, the overall score ranged from 0 to 17 points, reflecting no-adherence or highest adherence to an erMedDiet, respectively. One-year changes in erMedDiet adherence were also calculated. Total daily energy, total carbohydrate, alcohol, sodium, phosphate, iron and fiber intakes, fruits and vegetables consumption and glycemic index were estimated according to data from the FFQ. One-year changes in the aforementioned dietary variables were also calculated (values at one-year minus values at baseline).

Following the study protocol, anthropometric variables such as weight, height or waist circumference were measured in duplicate, and body mass index (BMI) was calculated by dividing the weight in kilograms by the square of height in meters. Changes in body weight were calculated by subtracting weight at one-year minus weight at baseline. At baseline, urinary creatinine and albumin concentrations were determined using routine laboratory methods from spot morning urine samples and urine albumin creatinine ratio (UACR) was calculated by dividing these measures (mg/g). Resting blood pressure was measured in triplicate using a validated semiautomatic oscillometer (Omron HEM-705CP, Netherlands).

2.5. Statistical analysis

The data analyzed for this study was obtained from the latest available PREDIMED-plus database in December 2020. Participants were categorized into tertiles of proportions of UPF consumption at baseline and tertiles of changes of proportions of UPF consumption after one-year of follow-up. First tertile was used as the reference category. In addition, UPF consumption at baseline was also analyzed as a continuous variable (per 10% increment of UPF consumption). Baseline characteristics of the study population were reported as mean values and standard deviation (SD) for continuous variables or numbers and percentages (%) for categorical variables. One-way ANOVA and chi-square tests were used to compare the quantitative or general categorical characteristics of the studied population.

Based on the outcome of interest, we performed cross-sectional and longitudinal analyses. First, multivariate linear and logistic regression models were fitted to estimate the cross-sectional associations between tertiles of UPF at baseline and eGFR (ml/min/1.73 m^2) or decreased kidney function (eGFR <60 ml/min/1.73 m^2) at baseline, respectively. Results were expressed as β-coefficients or odd ratios (OR) and their 95% confidence intervals (CI), as appropriate. Robust variance estimators were used in this analysis to correct for possible intra-cluster correlation, considering the participants who shared the same household as intra-cluster. Moreover, tests for linear trend were conducted by assigning the median value to each tertile of UPF consumption at baseline and modelling it as a continuous variable. Second, linear mixed-effects linear regression models with random intercepts at recruitment center, cluster family and participant level were performed to examine the longitudinal associations between tertiles of changes in UPF consumption after one-year of follow-up and eGFR (ml/min/1.73 m^2) over 3-years of follow-up. The results were presented as β-coefficients and their 95% CI.

Based on previously reported risk factors for kidney function, in the cross-sectional analysis, four models with additional adjustment were fitted: Model 1 was adjusted by age (years) and sex (women/men); Model 2 was additionally adjusted by recruitment center (quartiles by number of participants), intervention group (intervention/control), BMI (kg/m^2), smoking status (current/former/never), education level (primary/secondary education/graduate), civil status (single/married/widowed/divorced), physical activity (MET-min/week), alcohol intake (tertiles), type 2 diabetes (T2D) prevalence (yes/no), hypercholesterolemia prevalence (yes/no), hypertension prevalence (yes/no), angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers drugs use (yes/no) and energy intake (kcal/d); Model 3: was additionally adjusted by erMedDiet adherence (tertiles). Model 4: was adjusted for the same variables that in the model 2 and for intake of sodium (mg/d), phosphate (U/l), iron (mg/d), fiber (g/d) and total carbohydrate (g/d), fruit and vegetables consumption (g/d) and glycemic index (continuous). In the longitudinal analysis, only a multivariable-adjusted model was shown, which included all the aforementioned covariates as a fixed effect and was further adjusted by follow-up time (0, 1 or 3 years), the tertiles of changes in UPF consumption by follow-up time interaction, baseline UPF consumption (% of g/day), one-year changes in body weight (kg), one-year changes in intake of sodium (mg/d), phosphate (U/l), iron (mg/d), fiber (g/d) and total carbohydrate (g/d), one-year changes in fruit and vegetables consumption (g/d) and one-year changes in glycemic index (continuous) instead of the variable at baseline. Moreover, an additional analysis adjusting this model for one-year changes in energy intake (kcal/d), in physical activity (MET-min/week) and in alcohol intake (g, tertiles) was performed.

As a sensitivity analysis, the association between tertiles of one-year changes in UPF consumption with eGFR over 3-years of follow-up by excluding individuals with T2D, eGFR <60 ml/min/1.73 m^2 and UACR ≥300 mg/g at baseline were conducted to test the robustness of the longitudinal results. In addition, stratified analysis by sex (men/women) and intervention group (intervention/control) were performed to assess potential modifications in the longitudinal associations. Interactions between tertiles of changes in UPF consumption and sex or intervention group were also explored by means of likelihood ratio tests, comparing the most adjusted linear mixed model with and without cross-product terms (all interactions, $p > 0.05$).

All statistical analyses were performed using Stata/SE software, version 17.0 (StataCorp LP, College Station, TX, USA) and two-tailed p value < 0.05 was deemed as statistically significant.

3. Results

Among the 1909 PREDIMED-Plus participants with available data for CysC levels, 58 and 209 individuals were excluded due to missing data in the FFQ and reporting extreme total energy intake at baseline and after one-year of follow-up, respectively. Therefore, a total of 1851 participants were included in the current cross-sectional analysis and 1700 participants in the longitudinal analysis (Fig. 1). Baseline characteristics according to included or excluded participants from the cross-sectional analysis are depicted in Supplementary Table 1. The mean (±SD) age of these individuals was 65 ± 5 years and 45.5% were women. The mean (±SD) of eGFR at baseline was 72.7 ± 18.4 ml/min/1.73 m^2. At baseline, participants presented a mean (±SD) proportion of UPF consumption of 7.6 ± 6.3%, for processed foods was 20.8 ± 10.5%, for processed culinary ingredients was 2.8 ± 1.2% and for UMPF was 68.8 ± 11.8%, all of which were reported in g/day. The general characteristics of the studied population according to UPF consumption tertiles at baseline are summarized in Table 1. Compared to participants in the lowest category of UPF consumption, those in the highest category were more likely to be men, younger, to have higher BMI, higher educational level and were less likely to be physically active. In terms of dietary assessment, participants with higher consumption of UPF presented a higher energy intake, a lower adherence to an erMedDiet and lower consumption of UMPF and processed foods at baseline, compared to those with a lower UPF consumption. Furthermore, individuals in the top tertile of UPF consumption presented higher CysC levels than those in the lowest tertile.

Table 2 shows cross-sectional associations between UPF consumption and kidney function. In the full-adjusted model, UPF consumption showed a statistically significant inverse association with eGFR (β: −2.72 ml/min/1.73 m^2; 95% CI: −4.89 to −0.54) and was positively associated with decreased kidney function showing an OR of 1.57 (95% CI: 1.16 to 2.12) at baseline. Similar results were observed when UPF was analyzed per 10% increment of UPF consumption across the different models. In the fully adjusted model, every 10% increase in the amount of UPF consumed in the diet was associated with a decrease in eGFR (β: −1.35 ml/min/1.73 m^2; 95% CI: −2.74 to −1.00) and higher odds of decreased kidney function at baseline (OR: 1.27; 95% CI: 1.06 to 1.52). Findings were in the same

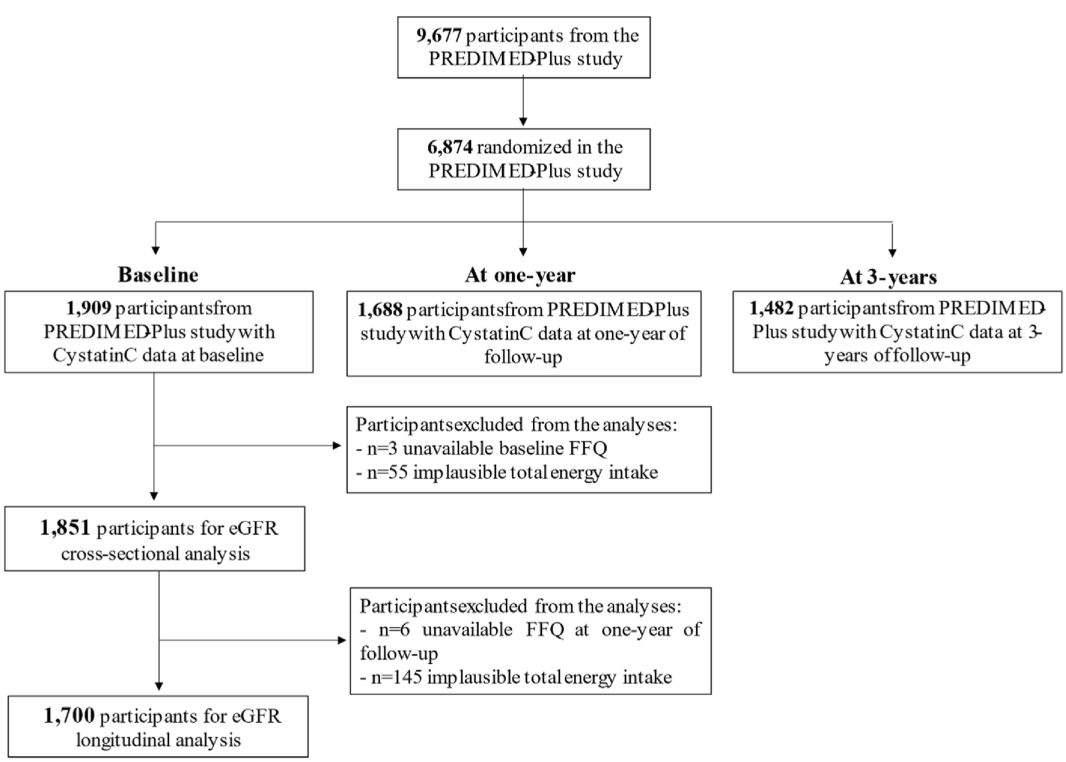

Fig. 1. Flow diagram for study participants. *Abbreviations* eGFR, glomerular filtration rate; FFQ, food frequency questionnaire.

line in the longitudinal associations of changes in UPF consumption after one-year of follow-up with eGFR over 3-years of follow-up (Table 3). Participants in the highest tertile of changes in UPF consumption after one-year of follow-up presented a statistically significant decrease in eGFR after one-year of follow-up (β: −1.43 ml/min/1.73 m^2; 95% CI: −2.85 to −0.01) as well as after 3-years of follow-up (β: −2.12 ml/min/1.73 m^2; 95% CI: −3.62 to −0.62) compared to those in the lowest tertile. These findings remained unchanged after adjusting for energy intake changes, physical activity changes and alcohol intake changes after one-year of follow-up (data not shown).

Results were essentially the same when we restricted the main longitudinal analysis to individuals without T2D, with eGFR > 60 ml/min/1.73 m^2 and UACR ≤300 mg/g at baseline (Supplementary Table 2). No statistically significant interactions between UPF consumption and sex (p = 0.195) and intervention group assignment (p = 0.220) were found. However, the associations between one-year changes in UPF consumption and eGFR over 3-years of follow-up were statistically significant only in men and the control group (Supplementary Table 3).

4. Discussion

As far as we know, this is the first time that the association between UPF consumption and kidney function has been assessed through eGFR based on the novel and accurate CysC biomarker in older individuals with overweight/obesity and MetS. The results showed that higher consumption of UPF was associated with a lower eGFR and higher odd of decreased kidney function at baseline. Moreover, one-year changes towards a higher consumption of UPF were related to a decrease in eGFR over 3-years of follow-up. These results may provide new insights for the design of future evidence-based strategies to prevent kidney dysfunction or even help in clinical practice targeting older populations with cardiovascular risk.

So far, the evidence regarding the relationship between UPF consumption and kidney function is scarce. Nonetheless, our findings were consistent with the preceding studies. Mirroring our results from the cross-sectional analysis, the HEXA (Health Examinees) study which included 134,544 healthy Korean middle-aged individuals showed that higher consumption of UPF was

Table 1
Baseline characteristics of the study participants according to tertiles of ultra-processed food consumption in the PREDIMED-Plus (n = 1851).

	Proportions of UPF consumption in the diet at baseline (% of g/day)			
	T1	T2	T3	p-value
	n = 617	n = 617	n = 617	
Age, years	65.9 ± 4.8	65.1 ± 4.9	64.1 ± 5.2	<0.001
Women, n (%)	313 (50.7)	292 (47.3)	237 (38.4)	<0.001
Intervention group, n (%)	312 (50.6)	314 (51.0)	292 (47.3)	0.383
BMI, kg/m^2	32.2 ± 3.3	32.6 ± 3.3	32.6 ± 3.5	0.024
Physical activity, METS/min/week	2846 ± 2449	2532 ± 2232	2325 ± 2248	<0.001
Smoking status, n (%)				0.126
Never smoked	278 (45.1)	249 (40.4)	237 (38.4)	
Former smoker	266 (43.1)	294 (47.7)	291 (47.2)	
Current smoker	73 (11.8)	74 (12.0)	89 (14.4)	
Education level, n (%)				<0.001
Primary education	344 (55.8)	328 (53.2)	268 (43.4)	
Secondary education	178 (28.9)	174 (28.2)	216 (35.0)	
Academic or graduate	95 (15.4)	115 (18.6)	133 (21.6)	
NOVA 4: UPF consumption, % of g/day	2.7 ± 1.0	5.9 ± 1.1	14.2 ± 7.0	<0.001
NOVA 3: Processed foods consumption, % of g/day	21.6 ± 12.0	20.6 ± 10.0	20.2 ± 9.3	0.064
NOVA 2: Processed culinary ingredients consumption, % of g/day	2.8 ± 1.2	2.9 ± 1.2	2.8 ± 1.1	0.023
NOVA 1: Unprocessed and minimally processed foods consumption, % of g/day	72.9 ± 12.1	70.6 ± 10.2	62.9 ± 10.6	<0.001
erMedDiet score, 17-points	9.5 ± 2.6	8.4 ± 2.4	7.5 ± 2.5	<0.001
Fruits and vegetables consumption (g/d)	784.3 ± 283.0	729.2 ± 242.7	666.4 ± 239.8	<0.001
Energy intake, kcal/d	2311 ± 530	2415 ± 505	2577 ± 548	<0.001
Total carbohydrate intake (g/d)	233.8 ± 70.9	246.5 ± 69.0	264.3 ± 75.0	<0.001
Sugar intake, g/day	8.6 ± 13.7	15.7 ± 22.1	52.3 ± 93.1	<0.001
Fiber intake, g/day	27.4 ± 9.4	26.5 ± 8.4	25.1 ± 7.8	<0.001
Sodium intake (mg/d)	2316.5 ± 805.0	2452.1 ± 745.3	2674.3 ± 814.7	<0.001
Phosphorus intake (mg/d)	1740.7 ± 428.5	1741.2 ± 414.8	1781.7 ± 407.1	0.140
Iron intake (mg/d)	16.4 ± 4.0	16.6 ± 3.8	17.0 ± 3.8	0.022
Glycemic index	55.6 ± 5.0	55.1 ± 4.8	54.5 ± 5.7	0.001
Cystatin C, mg/dl	1.04 (0.2)	1.04 (0.2)	1.08 (0.3)	0.003
eGFR, ml/min/1.73 m^2 at baseline	73.4 ± 18.4	73.27 ± 18.0	71.6 ± 18.9	0.149
Type 2 diabetes, n (%)	188 (30.5)	165 (26.8)	183 (29.7)	0.316
Hypertension, n (%)	512 (83.0)	532 (86.2)	527 (85.4)	0.255
Hypercholesterolemia, n (%)	413 (67.0)	395 (64.0)	410 (66.5)	0.512
Medication use, n (%)				
Lipid-lowering drugs	323 (52.4)	297 (48.1)	311 (50.4)	0.334
Oral blood glucose-lowering drugs	161 (26.1)	134 (21.7)	148 (24.0)	0.197
Insulin treatment	32 (5.2)	24 (3.9)	32 (5.2)	0.466
Antihypertensive drugs	489 (79.3)	505 (81.9)	500 (81.0)	0.498
ARBs	195 (31.6)	203 (32.9)	210 (34.0)	0.661
ACEis	200 (32.4)	213 (34.5)	222 (36.0)	0.415

Abbreviations: *ACEis*, Angiotensin-Converting Enzyme Inhibitors; *ARBs*, Angiotensin II receptor blockers; *eGFR*, Estimated Glomerular Filtration Rate; *erMedDiet*, energy-restricted Mediterranean diet, *METS,* Metabolic Equivalent of Task; *T*, tertile; *BMI*, Body Mass Index; *UPF*, Ultra-processed food. Decreased Kidney Function was defined as eGFR <60 ml/min/1.73 m^2. Values are reported as means ± standard deviations for continuous variables and number (%) for categorical variables. P-value was calculated by one-way analysis of variance test or chi-square for continuous and categorical variables, respectively.

Table 2
Cross-sectional associations between ultra-processed food consumption and kidney function in the PREDIMED-Plus study (n = 1851).

	Proportions of UPF consumption in the diet at baseline (% of g/day)				Per 10% increment of UPF consumption at baseline
	T1 (n = 617)	T2 (n = 617)	T3 (n = 617)	p-trend	(n = 1851)
UPF consumption at baseline, % of g/day	2.7 ± 1.0	5.9 ± 1.1	14.2 ± 7.0		7.6 ± 6.3
eGFR (ml/min/1.73 m²)[a]	73.93(72.49–75.37)	73.44 (72.12–74.75)	70.82 (69.41–72.23)		
Model 1[b]	0 (Ref.)	−1.01 (−2.95 to 0.94)	−4.16 (−6.15 to −2.17)	<0.001	−2.46 (−3.79 to −1.14)
Model 2[b]	0 (Ref.)	−0.72 (−2.64 to 1.19)	−3.51 (−5.54 to −1.47)	0.001	−1.86 (−3.18 to −0.55)
Model 3[b]	0 (Ref.)	−0.49 (−2.44 to 1.46)	−3.11 (−5.19 to −1.02)	0.003	−1.60 (−2.93 to −0.28)
Model 4[d]	0 (Ref.)	−0.30 (−2.26 to 1.66)	−2.72 (−4.89 to −0.54)	0.015	−1.35 (−2.74 to −1.00)
Decreased Kidney Function, n (%)[c]	144 (23.3)	153 (24.8)	184 (29.8)		481 (26.0)
Model 1[d]	1 (Ref.)	1.18 (0.90 to1.55)	1.76 (1.35 to 2.29)	<0.001	1.41 (1.20 to 1.66)
Model 2[d]	1 (Ref.)	1.15 (0.87 to 1.52)	1.66 (1.25 to 2.20)	<0.001	1.33 (1.13 to 1.57)
Model 3[d]	1 (Ref.)	1.16 (0.88 to 1.53)	1.66 (1.25 to 2.22)	<0.001	1.32 (1.11 to 1.57)
Model 4[d]	1 (Ref.)	1.10 (0.83 to 1.46)	1.57 (1.16 to 2.12)	0.004	1.27 (1.06 to 1.52)

Abbreviations: eGFR, estimated Glomerular Filtration Rate; UPF, Ultra-processed food; T, Tertiles; *Ref*, Reference.
Model 1 was adjusted for age (years) and sex (women/men). Model 2 was additionally adjusted for center (quartiles by number of participants), intervention group (intervention/control), body mass index (kg/m²), smoking status (current/former/never), education level (primary/secondary education/graduate), civil status (single/married/widowed/divorced), physical activity (MET-min/week), alcohol intake (g, tertiles), diabetes prevalence (yes/no), hypercholesterolemia prevalence (yes/no), hypertension prevalence (yes/no), angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers drugs (yes/no) and energy intake (kcal/d). Model 3 was additionally adjusted for Mediterranean Diet adherence (points, tertiles). Model 4 was adjusted for the same variables that in model 2 and for intake of sodium (mg/d), phosphorus (mg/d), iron (mg/d), fiber (g/d) and total carbohydrate (g/d), fruits and vegetables consumption (g/d) and glycemic index (continuous).
[a] Multivariable adjusted means of eGFR (ml/min/1.73 m²) at baseline. (Model 3).
[b] Multivariable adjusted β-coefficients and 95% CI for baseline eGFR (ml/min/1.73 m²) according to baseline tertiles of proportions of UPF consumption in the diet as well as per 10% increment of the UPF consumption at baseline.
[c] Decreased Kidney Function was defined as eGFR <60 ml/min/1.73 m².
[d] Multivariable adjusted Odd Ratios and 95% CI for baseline eGFR <60 ml/min/1.73 m² according to baseline tertiles of proportions of UPF consumption in the diet as well as per 10% increment of the UPF consumption at baseline.

Table 3
Longitudinal associations between ultra-processed food consumption and kidney function in the PREDIMED-Plus study (n = 1700).

	Changes in proportions of UPF consumption in the diet after one-year of follow-up (% of g/day)						
	T1 (n = 567)	T2 (n = 567)	T3 (n = 566)	T2 vs. T1 difference	p-value	T3 vs. T1 difference	p-value
Change in UPF consumption after one-year of follow-up, % of g/day	−7.9 ± 5.3	−2.0 ± 0.8	1.8 ± 3.1				
eGFR (ml/min/1.73 m²) over 3-years							
Multivariable adjusted model							
Baseline	72.09 (69.65 to 74.54)	71.55 (69.24 to 73.86)	71.92 (69.53 to 74.31)				
1-year	70.91 (68.45 to 73.36)	69.55 (67.22 to 71.87)	69.31 (66.91 to 71.70)				
1-year change	−1.19 (−2.19 to −0.18)	−2.01 (−3.01 to −1.00)	−2.61 (−3.62 to −1.61)	−0.81 (−2.24 to 0.60)	0.259	−1.43 (−2.85 to −0.01)	0.049
3-years	67.56 (65.07 to 70.05)	66.50 (64.14 to 68.86)	65.27 (62.83 to 67.71)				
3-years change	−4.54 (−5.59 to −3.48)	−5.05 (−6.10 to −3.99)	−6.65 (−7.72 to −5.58)	−0.51 (−2.00 to 0.98)	0.501	−2.12 (−3.62 to −0.62)	0.006

Abbreviations: eGFR, estimated Glomerular Filtration Rate; UPF, Ultra-processed food; T, Tertiles.
Model was adjusted for age (years), sex (women/men), follow-up time (years), the tertiles of changes in UPF consumption by follow-up time interaction, baseline UPF consumption (% of g/day, continuous), intervention group (intervention/control), body mass index (kg/m²), smoking status (current, former, never), education level (primary, secondary education, graduate), civil status (single, married, widowed, divorced), physical activity (MET-min/week), alcohol intake (g, tertiles), diabetes prevalence (yes/no), hypercholesterolemia prevalence (yes/no), hypertension prevalence (yes/no), angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers drugs (yes/no), energy intake (kcal/d), one-year changes in body weight (kg), one-year changes in intake of sodium (mg/d), phosphorus (mg/d), iron (mg/d), fiber (g/d) and total carbohydrate (g/d), one-year changes in fruits and vegetables consumption (g/d) and one-year changes in glycemic index (continuous).

associated with higher prevalence of CKD and lower values of eGFR at baseline [15]. Our prospective analysis supports the results from the four previously published cohort studies [16–19]. In the Seniors-ENRICA (Estudio sobre Nutrición y RIesgo CArdiovascular en España) cohort, Spanish older individuals with higher consumption of UPF presented higher risk of renal function decline after 6-years of follow-up [16]. Similarly, in The Lifelines cohort, UPF consumption was positively associated with incident CKD after approximately 4-years of follow-up among Dutch adults [17]. Moreover, results from the ARIC (Atherosclerosis Risk in Communities) study showed a positive association between UPF consumption and risk of incident CKD during a median follow-up of 24-years in a population of 14,679 middle-aged US adults [18]. Additionally, in two large-scale adult populations from China (TCLSIH, Tianjin Chronic Low-grade Systemic Inflammation and Health) and the United Kingdom (UK Biobank), higher UPF consumption was also statistically significant associated with a higher risk of incident CKD [19]. The fact that the present study used for the first time CysC to estimate eGFR when evaluating its association with UPF consumption strengthens the evidence concerning the relationship between UPF consumption and kidney function since this biomarker is reported to be independent of several factors in contrast to creatinine [23].

In contrast to the limited research focus on UPF and kidney function, it is worth mentioning that there is more evidence on the association between dietary patterns aligned with lower consumption of UPF, such as the Mediterranean diet, and kidney function or CKD [36]. To date, the most recent systematic review and meta-analysis performed by Hansrivijit et al., suggested that adhering to a Mediterranean diet is associated with a lower risk of CKD [37].

Several factors linked to UPF could partially explain the observed associations. It is well-known that UPF have a poor nutritional profile due to their low fiber content [38,39], as well as their high simple sugars [40–42] and sodium content [43,44], which might play a harmful role in kidney health. In fact, we observed that those participants in the highest tertile of UPF consumption at baseline presented significantly lower fruit and vegetables consumption, fiber intake and higher sugar consumption. In addition, the integration of additives to UPF composition makes them an inorganic phosphate source which has been associated with eGFR decline and CKD by previous research [45–47]. Furthermore, recent evidence suggests that certain plastic packaging compounds such as phthalates or bisphenols are related to CKD [48]. All these compounds and others not mentioned before, as non-caloric artificial sweeteners or neo-formed contaminants, may also have an indirect effect on kidney function by being implicated in inflammation procedures [39], gut barrier permeability [49,50], and the onset or even the progression of comorbidities including obesity [51,52], hypertension [45,53], diabetes [54,55], and cardiovascular disease [46,56].

Some limitations deserve to be mentioned. First, as participants included in our analysis were older Mediterranean individuals with overweight/obesity and MetS, findings cannot be extrapolated to the general population. Second, causality cannot be established due to the observational study design. Third, individuals included in the current study are under a lifestyle intervention program which may influence our results. Nevertheless, our analyses were adjusted by intervention group and body weight changes, obtaining similar findings. Furthermore, subgroup analyses stratifying by intervention group assignment were in the same line with those for the entire cohort. Fourth, the FFQ used in this study was not specifically developed to assess UPF consumption and the estimation through NOVA classification system has been subject of discussion in the last year, existing disagreement between authors regarding some concerns such as the definition of UPF, bias for misclassification or whether the concept of UPF inform dietary guidelines beyond information already available in conventional classification systems [57–59]. However, the NOVA system has been widely used in epidemiological studies as a suitable food processing classification method and could be a good tool to give simple advice messages to the general population. Finally, although the FFQ is an appropriate and common tool used in nutritional studies, recall bias and potential measurement errors cannot entirely be ruled out. Nevertheless, this validated FFQ was carefully administered by trained dietitians, and individuals reporting implausible energy intake were excluded in attempt to avoid this bias. The current study also has several strengths that should be highlighted such as the novel estimation of eGFR based on CysC, a more optimal and accurate biomarker of kidney function [22,23]. Other strengths include the relatively large sample size, the consistent results using repeated measures for outcomes over 3-years of follow-up, the control for an extended range of confounders and the robust results from our subgroup and sensitivity analysis.

5. Conclusion

In conclusion, in a Mediterranean population of older adults with overweight/obesity and MetS, higher UPF consumption at baseline and one-year changes towards higher consumption of UPF were associated with worse kidney function at baseline and over 3-years of follow-up, respectively. Although this study supports existing evidence regarding the potentially harmful association between UPF and health and specifically kidney function, further long-term studies are needed, especially those applying suitable methods such as CysC based-eGFR, and conducted in different populations, which explore the underlying mechanism for these associations.

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Authors' contributions

CV-H, AD-L, NB-T, ET, IC-P, IA, AS, MB-R, JAM, FJT, JAT, TEG-F, FP-P, AG, NG-R, JS-S, and NB designed and conducted the research. CV-H and NB analysed the data. CV-H, NB, AD-L and NB-T wrote the article. All authors revised the manuscript for important intellectual content and read and approved the final manuscript. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. CV-H and NB are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Ethical standards

All participants provided written informed consent. The study protocol and procedures were approved according to the ethical standards of the Declaration of Helsinki by the Institutional Review Boards (IRBs) of all the participating institutions.

Data availability

There are restrictions on the availability of data for the PREDIMED-Plus trial, due to the signed consent agreements around data sharing, which only allow access to external researchers for studies following the project purposes. Requestors wishing to access the PREDIMED-Plus trial data used in this study can make a request to the PREDIMED-Plus trial Steering Committee chair: predimed_plus_scommitte@googlegroups.com. The request will then be passed to members of the PREDIMED-Plus Steering Committee for deliberation.

Conflict of interest

JS-S reported receiving research support from the California Walnut Commission, Patrimonio Comunal Olivarero, La Morella Nuts, and Borges S.A; receiving consulting fees or travel expenses from Instituto Danone, Abbott Laboratories and Mundifarma, receiving nonfinancial support from Hojiblanca, Patrimonio Comunal Olivarero, and Almond Board of California; serving on the board of and receiving grant support through his institution from the International Nut and Dried Foundation and the Eroski Foundation. All other authors declare no competing interests.

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Appendix A. Supplementary data

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