DIETARY FACTORS AND KIDNEY FUNCTION: INSIGHTS FROM A POPULATION OF OLDER MEDITERRANEAN ADULTS WITH OVERWEIGHT OR OBESITY AND METABOLIC SYNDROME

Cristina Valle Hita

UNIVERSITAT ROVIRA i VIRGILI

Dietary factors and kidney function: insights from a population of older Mediterranean adults with overweight or obesity and metabolic syndrome

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DOCTORAL THESIS
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DOCTORAL THESIS

Thesis supervised by Dr. Nancy Babio, Dr. Nerea Becerra-Tomás, and Dr. Andrés Díaz-López

UNIVERSITAT ROVIRA i VIRGILI

Human Nutrition Unit
Department of Biochemistry and Biotechnology
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I STATE:
That the present study, entitled "**Dietary factors and kidney function: insights from a population of older Mediterranean adults with overweight or obesity and metabolic syndrome**", presented by Cristina Valle Hita for the award of the degree of Doctor, has been carried out under my supervision at the Department of Biochemistry and Biotechnology of this university and it is currently up for an international distinction.

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A mis pilares fundamentales,

quienes me enseñaron a volar,

mi madre y mi padre

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ABBREVIATIONS

A

ACEIs, Angiotensin-converting enzyme inhibitors

ARBs, Angiotensin receptor blockers

B

BMI, Body mass index

C

CIs, Confidence intervals

CKD, Chronic kidney disease

CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration

CVD, Cardiovascular disease

CysC, Cystatin C

D

DASH, Dietary Approaches to Stop Hypertension

E

eGFR, Estimated glomerular filtration rate

erMedDiet, Energy-reduced Mediterranean diet

F

FFQ, Food frequency questionnaire

G

g/d, grams per day

GFR, Glomerular filtration rate

H

HDL-C, High-density lipoprotein-cholesterol

HRs, Hazard Ratios

K

KDIGO, Kidney Disease: Improving Global Outcomes

kg, kilograms

L

LDL-C, Low-density lipoprotein-cholesterol

M

m, meters

MDRD, Modification of Diet in Renal Disease

MedDiet, Mediterranean Diet

MET, Metabolic equivalent of task

MetS, Metabolic syndrome

N

NEAP, Net endogenous acid production

O

ORs, Odd Ratios

P

PREDIMED-Plus, PREvención con Dieta MEDiterránea Plus study

PRAL, Potential renal acid load

R

RAAS, Renin-angiotensin-aldosterone system

S

SCr, Serum creatinine

T

T2D, Type 2 diabetes

U

UARC, Urinary albumin/creatinine ratio

UPF, Ultra-processed food

W

WHO, World Health Organization

ABSTRACT

English

The gradual deterioration of kidney function can eventually lead to chronic kidney disease (CKD), an emerging public health concern affecting approximately 9-13% of the worldwide population. The significant morbidity and mortality associated with CKD, closely related to cardiovascular disease, as well as the high socioeconomic and healthcare burden emphasize its importance as a critical global health problem. Several lifestyle behaviors have been suggested as modifiable risk factors for CKD, especially dietary habits, that appear to play an important role in kidney function. In fact, healthy dietary patterns have been associated with better levels of kidney function, as determined by the estimated glomerular filtration rate (eGFR). However, there has been a recent global shift towards a greater consumption of a Western diet, characterized by a high consumption of ultra-processed foods (UPF), which may contribute to an increase in the dietary acid load. This change in diet has been related to the worldwide progressive increase in non-communicable diseases, including CKD. Unfortunately, scientific evidence specifically focused on the impact of diet on populations at high risk of developing CKD, such as people of older age with underlying comorbid conditions, is relatively limited.

The principal objective of this thesis was to assess the association between certain modifiable dietary factors - dietary patterns, dietary acid load, and UPF - and kidney function in an older adult population with overweight or obesity and metabolic syndrome (MetS). The current dissertation was conducted within the frame of the PREvención con DIeta MEDiterránea-Plus (PREDIMED-Plus) study, an ongoing parallel-group, multi-center, randomized controlled clinical trial conducted in Spain for the primary prevention of cardiovascular disease. The different statistical analyses were performed using data from this study as if it was an observational prospective cohort study.

The results of the current doctoral research showed a statistically significant association between changes towards a greater adherence to the 17-item energy-reduced Mediterranean Diet (erMedDiet) score and higher eGFR after one-year of follow-up, together with lower odds of eGFR decline. However, the Dietary Approach to Stop Hypertension (DASH) score was not significantly associated with eGFR, and the Protein Diet Score was negatively associated. In addition, dietary acid load was associated with the two primary markers of kidney function. After one-year of follow-up, higher potential renal acid load (PRAL) index was associated with lower eGFR levels as well as higher odds of eGFR decline, and urinary

albumin/creatinine ratio increase, whereas net endogenous acid production (NEAP) index was only associated with eGFR. Finally, there was also a statistically significant inverse association between UPF consumption and eGFR at baseline and over 3-years of follow-up.

In conclusion, the findings of this thesis support the potential benefits of a Mediterranean diet on kidney function in older adults with overweight or obesity and MetS. In addition, the results suggest that higher dietary acid load and consumption of UPF might contribute to the deterioration of kidney function. Further long-term and interventional studies are warranted to confirm our findings before they can be incorporated into future dietary guidelines for the prevention of CKD.

Castellano

El deterioro progresivo de la función renal puede conducir con el tiempo a la enfermedad renal crónica (ERC), un problema de salud pública emergente que afecta alrededor del 9-13% de la población mundial. Su gran morbilidad y mortalidad, estrechamente relacionada a la enfermedad cardiovascular, así como su alta carga socio-económica y sanitaria, resalta su importancia como un problema de salud global crítico. Varios hábitos de vida han sido sugeridos como factores de riesgo modificables para la ERC, especialmente hábitos dietéticos, que parecen desempeñar un papel esencial en la función renal. De hecho, algunos patrones dietéticos saludables se han asociado con mejoras en la función renal, determinada a través de tasa de filtración glomerular estimada (TFGe). No obstante, recientemente se ha producido un cambio mundial hacia un mayor consumo de una dieta tipo occidental, rica en alimentos ultra-procesados (AUP), que podrían contribuir al incremento de la carga ácida de la dieta. Este cambio en la dieta se ha relacionado con el aumento progresivo a nivel mundial de las enfermedades no transmisibles, entre las cuales se incluye la ERC. Desafortunadamente, la evidencia científica centrada específicamente en el impacto de la dieta en poblaciones con alto riesgo de desarrollar ERC, como las personas mayores con comorbilidades asociadas, es relativamente limitada.

El objetivo principal de esta tesis fue evaluar las asociaciones entre ciertos factores dietéticos modificables (patrones dietéticos, la carga ácida de la dieta y los AUP) y la función renal en una población de adultos mayores con sobrepeso u obesidad y síndrome metabólico (SM). La presente tesis se llevó a cabo en el contexto del estudio *PREvención con DIeta MEDiterránea-Plus* (PREDIMED-Plus), un ensayo clínico paralelo, controlado, aleatorizado y multicéntrico llevado a cabo en España para la prevención primaria de las enfermedades cardiovasculares. Se realizaron múltiples análisis estadísticos utilizando los datos de este estudio como si se tratara de un estudio de cohortes prospectivo observacional.

Los resultados de la presente investigación doctoral mostraron una asociación estadísticamente significativa entre los cambios hacia una mayor adherencia a la dieta Mediterránea (17-item erMedDiet) y una mayor TFGe después de un año de seguimiento, así como también, una menor probabilidad de declive en la TFGe. Sin embargo, la dieta DASH (*Dietary Approach to Stop Hypertension*) no se asoció significativamente con la TFGe y la puntuación de dieta proteica (*Protein Diet Score*) se asoció negativamente. Además, la carga ácida de la dieta se asoció con los dos marcadores principales de la función renal. Después de un año de seguimiento, un índice más alto de PRAL (*potential renal acid load*) se asoció con

niveles más bajos de la TFGe, así como con mayores probabilidades de declive en la TFGe y de incremento del cociente de albúmina creatinina en orina. En cambio, el índice NEAP (*net endogenous acid production*) solo se asoció con los resultados relacionados con la TFGe. Finalmente, también se observó una asociación estadísticamente significativa e inversa entre el consumo de AUP y la TFGe al inicio del estudio y durante los 3 primeros años de seguimiento.

En conclusión, los hallazgos de esta tesis apoyan los posibles beneficios de la dieta Mediterránea sobre la función renal en adultos mayores con sobrepeso u obesidad y SM. Asimismo, los resultados apuntan a que una mayor carga ácida de la dieta y el consumo de AUP podrían contribuir al deterioro de la función de los riñones. Sin embargo, se necesitan más estudios de seguimiento a largo plazo y estudios de intervención para confirmar estos hallazgos, previo a que puedan ser incorporados en las guías dietéticas para la prevención de la ERC.

Català

El deteriorament progressiu de la funció renal pot conduir amb el temps a la malaltia renal crònica (MRC), un problema de salut pública emergent que afecta al voltant del 9-13% de la població mundial. La seva gran morbiditat i mortalitat, estretament relacionada a la malaltia cardiovascular, així com la seva alta càrrega socioeconòmica i sanitària, ressalta la seva importància com un problema de salut global crític. Diversos hàbits de vida han estat suggerits com a factors de risc modificables per a la MRC, especialment hàbits dietètics, que semblen exercir un paper essencial en la funció renal. De fet, alguns patrons dietètics saludables s'associen amb millores en la funció renal, determinats a través de la taxa de filtració glomerular estimada (TFGe). No obstant això, recentment hi ha hagut un canvi mundial cap a un major consum d'una dieta tipus occidental, rica en aliments ultra-processats (AUP), que podrien contribuir a un increment de la càrrega àcida de la dieta. Aquest canvi en la dieta s'ha relacionat amb l'augment progressiu a nivell mundial de les malalties no transmissibles, entre les quals s'inclou la MRC. Malauradament, l'evidència científica centrada específicament en l'impacte de la dieta en poblacions amb alt risc de desenvolupar MRC, com les persones majors amb comorbiditats associades, és relativament limitada.

L'objectiu principal d'aquesta tesi va ser avaluar les associacions entre certs factors dietètics modificables (patrons dietètics, la càrrega àcida de la dieta i els AUP) i la funció renal en una població d'adults majors amb sobrepès o obesitat i síndrome metabòlica (SM). La present tesi es va dur a terme en el context de l'estudi *PREvención con DIeta MEDiterránea-Plus* (PREDIMED-Plus), un assaig clínic paral·lel, controlat, aleatoritzat i multicèntric dut a terme a Espanya per a la prevenció primària de les malalties cardiovasculars. Es van realitzar múltiples anàlisis estadístiques utilitzant les dades d'aquest estudi com si es tractés d'un estudi de cohorts prospectiu observacional.

Els resultats de la present tesi doctoral van mostrar una associació estadísticament significativa entre els canvis cap a una major adherència a la dieta Mediterrània (17-item erMedDiet) i una major TFGe al cap d'un any de seguiment, així com també, amb una menor probabilitat de declivi en la TFGe. No obstant això, la dieta DASH (*Dietary Approach to Stop Hypertension*) no es va associar significativament amb la TFGe i la puntuació de la dieta proteica (*Protein Diet Score*) es va associar negativament. A més, la càrrega àcida de la dieta es va associar amb els dos marcadors principals de la funció renal. Al cap d'un any de seguiment, un índex més alt de PRAL (*potential renal acid load*) es va associar amb nivells més baixos de la TFGe, així com amb majors probabilitats de declivi en la TFGe i d'increment del quocient

d'albúmina creatinina en orina. En canvi, l'índex NEAP (*net endogenous acid production*) només es va associar amb els resultats relacionats amb la TFGe. Finalment, també es va observar una associació estadísticament significativa i inversa entre el consum de AUP i la TFGe a l'inici de l'estudi i durant els 3 primers anys de seguiment.

En conclusió, els resultats d'aquesta tesi donen suport als possibles beneficis de la dieta Mediterrània sobre la funció renal en adults majors amb sobrepès o obesitat i SM. Així mateix, els resultats apunten al fet que una major càrrega àcida de la dieta i el consum d'AUP podrien contribuir al deteriorament de la funció dels ronyons. No obstant això, es necessiten més estudis de seguiment a llarg termini i estudis d'intervenció per a confirmar aquests resultats, previ al fet que puguin ser incorporats en les guies dietètiques per a la prevenció de la MRC.

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I. Introduction

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I. INTRODUCTION

The human body is endowed with a pair of kidneys, which are integral components of the renal system, along with the two ureters, the bladder, and the urethra. The kidneys are crucial organs with primary functions (see **Figure 1**) that include maintaining the transport balance of electrolytes and water, preserving essential nutrients, expelling by products of metabolism, and regulating the acid-base balance of the body[1,2]. Furthermore, kidneys are actively involved in the regulation of blood pressure, the production of erythropoietin, and bone-mineral metabolism[3]. The impairment of kidney function may give rise to an unstable environment for normal physiological procedures.

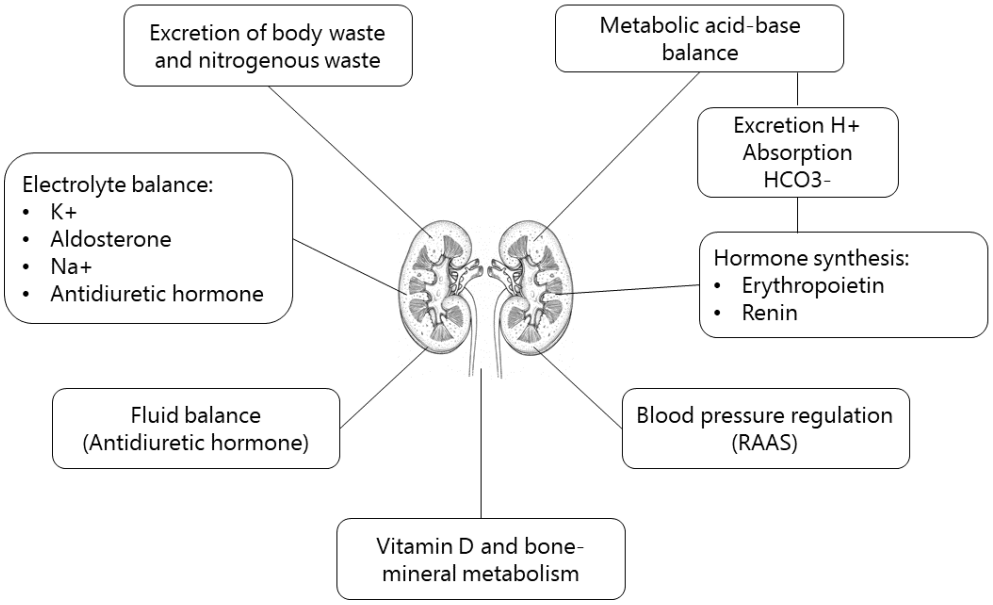

Figure 1. The function of the kidneys. Adapted from: Naber T, Purohit S. Chronic Kidney Disease: Role of Diet for a Reduction in the Severity of the Disease. Nutrients. 2021;13(9):3277. doi:10.3390/nu13093277

1. Chronic kidney disease

1.1. Definition and diagnosis of chronic kidney disease

Chronic kidney disease (CKD) is defined as "abnormalities of kidney structure or function, present for a minimum of three months, with implications for health", according to the latest update of the Clinical Practice Guidelines for Evaluation and Management of Chronic Kidney Disease by the Kidney Disease: Improving Global Outcomes (KDIGO)[4]. The established criteria for CKD diagnosis (see **Table 1**) include a decreased glomerular filtration rate (GFR) or evidence of one or more markers of kidney damage[4].

Table 1. Criteria for CKD diagnosis (either of the following present for a minimum of 3 months)

Criteria	Description
Decreased GFR	GFR lower than 60 ml/min/1.73m^2
Markers of kidney damage (one or more)	Albuminuria (defined as UARC greater than or equal to 30 mg/g or 3 mg/mmol) Persistent hematuria Urine sediment abnormalities Electrolyte and other abnormalities due to tubular disorders Abnormalities detected by histology Structural abnormalities detected by imaging History of kidney transplantation

Adapted from KDIGO guidelines.
GFR, Glomerular Filtration Rate; UARC, urinary albumin/creatinine ratio.

1.1.1. Glomerular filtration rate

The GFR corresponds to the plasma filtration per unit of time, predominantly executed by nephrons - the functional units of the kidneys[2]. Therefore, the sum of the GFR of each nephron corresponds to the total GFR[5]. Despite the inability to directly measure GFR in clinical practice, this index of kidney function can be easily estimated through equations based on serum levels of endogenous filtration biomarkers, with serum creatinine (SCr) or cystatin C (CysC) being the most frequently used[6–8]. Both compounds are considered small molecular weight proteins which, under normal kidney function conditions, are generally filtered, reabsorbed, and metabolized by the glomerulus membrane and the tubule - integral structures within the kidneys. Consequently, SCr and CysC have been considered appropriate biomarkers of GFR[9]. However, the estimated GFR equations described later in this section are proposed to be more reliable than using solely the biomarker concentration for kidney function assessment. Hence the estimated GFR method is recommended for assessing kidney function in clinical practice and research settings[4].

SCr is an amino acid metabolite derived from the breakdown of protein in muscles, as well as from the digestion of dietary proteins. This metabolite circulates throughout total body water, undergoes filtration by the glomerulus, experiences secretion by the tubule, is excreted in the urine, and can also be degraded by gut bacteria[6].

CysC is a glycosylated low molecular mass protein generated by all nucleated cells of the human body. By contrast, this protein circulates within the extracellular fluid, but it is also filtered by the glomerulus and degraded by the tubule and is minimally excreted in the urine and through other extra-renal pathways[6,9]. In contrast with SCr, CysC is less affected by

certain factors such as muscle mass, diet, age, and sex. However, glucocorticoids, smoking, thyroid dysfunction, inflammation, and adiposity have been suggested as factors influencing CysC concentrations[6,9].

During the last decades, several formulas have been developed for estimating GFR utilizing SCr and/or CysC concentrations. For GFR based on SCr estimation, MDRD (*Modification of Diet in Renal Disease*) Study and CKD-EPI (*Chronic Kidney Disease Epidemiology Collaboration*) equations are the ones that have currently gathered the most evidence and validation. The MDRD Study equation was initially developed in 1999 and it was improved in 2006. A few years later, in 2009, CKD-EPI SCr equation was created to address the limitations of the MDRD formula. Despite, both equations accounting for SCr concentration, age, sex and ethnicity, the CKD-EPI SCr equation has been demonstrated to be more accurate and presents with less bias than the MDRD Study equation[6,8,10]. Accordingly, the CKD-EPI SCr equation has been stated as the primary SCr-equation choice, especially in populations from Europe, North America, and Australia[8]. Considering CysC, the CKD- EPI CysC and SCr–CysC equations were developed for the first time in 2012[6]. These equations are based on each corresponding biomarker, age, and sex. Furthermore, ethnicity is also considered in the CKD-EPI SCr–CysC formula. Previous evidence comparing the capacity of all CKD-EPI equations suggests that the CKD-EPI CysC equation is the one which entails less bias and the CKD-EPI SCr–CysC equation is the most accurate in comparison with the single-biomarkers formulas[6–8]. Moreover, the CysC-based CKD-EPI equations[9] have shown to be particularly meaningful in the older adults since this population eventually presents with lower muscle mass and SCr levels[11]. Nonetheless, in the KDIGO guidelines, it is suggested to use the CKD-EPI SCr equation for the initial estimation of GFR. These guidelines also recommend performing the CKD-EPI SCr–CysC formula when the GFR estimation based on SCr is less accurate (i.e., conditions or diseases contributing to muscle loss) and GFR affects making clinical decisions[4].

Regarding the levels of GFR, according to the latest report by KDIGO, a threshold of less than 60 ml/min/1.72m^2 for more than three months has generally been agreed as indicative of decreased kidney function and CKD. KDIGO has classified GFR levels into six groups (see **Table 2**), ranging from normal kidney function to kidney failure[4].

Table 2. Chronic kidney disease prognosis according to categories of GFR and albuminuria

	Albuminuria (mg/g or mg/mmol)		
GFR categories (ml/min/ 1.73m²)	A1: **Normal to mildly increased** (<30 or <3)	A2: **Moderately increased** (30 to 300 or 3 to 30)	A3: **Severely increased** (>300 or >30)
G1: **Normal or high** (≥ 90)	Low risk	Moderately increased risk	High risk
G2: **Mildly decreased** (60-89)	Low risk	Moderately increased risk	High risk
G3a: **Mildly to moderately decreased** (45-59)	Moderately increased risk	High risk	Very high risk
G3b: **Moderately to severely decreased** (30-44)	High risk	Very high risk	Very high risk
G4: **Severely decreased** (15 -29)	Very high risk	Very high risk	Very high risk
G5: **Kidney failure** (<15)	Very high risk	Very high risk	Very high risk

Adapted from Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney Int. 2024 Apr;105(4S):S117-S314. doi: 10.1016/j.kint.2023.10.018. PMID: 38490803.

1.1.2. Urinary albumin/creatinine ratio

Albuminuria is considered an indicator of the severity and progression of kidney damage, reflecting the capacity of the glomerular capillary wall to be permeable to certain macromolecules[5]. Furthermore, albuminuria has been closely linked to cardiovascular disease risk and early diabetic nephropathy[12]. Although the measurement of total urinary protein or proteinuria has traditionally been used to assess kidney damage, the significance of albuminuria has increased in recent years, given that albumin is the predominant protein present in urine and its accumulation in the tubules may indicate damage in these structures and even glomerulosclerosis[5,12] – the scarring of the tiny blood vessels in the kidneys, known as glomeruli[2]. The changeable configuration of the albumin molecule has made it challenging to establish an appropriate approach to evaluate albuminuria. However, urinary albumin/creatinine ratio (UACR) measured in an early morning urine sample has currently become the most recommended method[5,12].

Microalbuminuria and *macroalbuminuria* terms have typically been defined as albuminuria between 30-300 mg/dL and greater than 300 mg/dL, respectively[13]. Nevertheless, KDIGO

guidelines discourage the continued use of this terminology in their 2012 report[14]. Instead, they have proposed a novel albuminuria classification (see **Table 2**) comprising of three groups: a) normal to mildly, b) moderately, and c) severely increased albuminuria[4].

Based on both markers, GFR and albuminuria, a well-established classification of the prognosis of CKD (see **Table 2**) was first introduced in the 2012 KDIGO guidelines report[14]. Since then, it has been the subject of various reviews and studies[5,15–18]. In fact, this classification has been maintained in the recent updated KDIGO report of 2024[4]. The level of risk of CKD is thereby determined by the six GFR categories and the three albuminuria categories. Furthermore, whether the cause of the disease is a primary kidney disease or a systemic disease should also be considered for this prognosis classification[4,14].

1.2. Epidemiology of chronic kidney disease

CKD represents a substantial global health concern. It has been suggested that, over the last decade, the number of individuals affected by this disease ranges from approximately 9 to 13% of people worldwide. This implies that globally around 700 million to one billion individuals have CKD[19–22]. When examining CKD stages, categories G1 and G2 combined with A2 or A3 are the most prevalent, accounting for approximately 5%, followed by stages G3a and G3b, which present a prevalence of approximately 4%[21]. In 2017, it was also reported that CKD appeared to be more prevalent in women than in men[21]. Nevertheless, this sex difference was not observed in a recent study focused on estimating CKD across 11 countries around the world[20]. Additionally, in this study, the average age for individuals with this chronic disease was estimated to be between 74 and 75 years[20].

Estimates of mortality attributable to CKD stand at around 7.6%[20,21]. In the global list of causes of death, CKD has climbed from being the 36th leading cause in 1990[19] to the 11th in 2017[4]. Subsequently, it has been estimated that this disease will occupy the 5th place on the mortality risk list by 2040[19,21,23]. It is worth mentioning that this epidemiological information should be taken with caution, as the definition of CKD may vary among studies. However, regardless of the precision with which CKD prevalence is understood, it still poses a significant burden on healthcare systems, particularly when CKD progresses to an advanced stage, needing expensive and complex treatments such as dialysis or kidney transplantation[20].

This becomes particularly significant since, during the early years of CKD, individuals often do not experience any symptoms, and treatments or preventive measures are lacking. In fact,

it has been estimated that only 10% of individuals with CKD are aware of their condition[4,24]. Therefore, by the time symptoms begin to appear, the disease is so advanced that it requires kidney replacement therapy[3,4].

In the Spanish context, the prevalence of CKD has been estimated to be approximately 15%, which corresponds to one in seven adults[25], surpassing the global estimate. According to the 2020 survey conducted by the *Instituto Nacional de Estadística* (INE, the National Statistical Institute), CKD affects 279.9 thousand people in Spain, with women being more affected than men. The regions with the highest prevalence were observed to be Catalunya, Andalusia, and the Valencian Community (see **Figure 2**)[26].

Figure 2. Prevalence of CKD in Spain by region. Source: *Instituto Nacional de Estadística* (INE, National Statistical Institute of Spain). *Encuesta de discapacidad, autonomía personal y situaciones de dependencia* (Survey on disability, personal autonomy and situations of dependency). 2020

The 2023 INE report on mortality by cause of death estimated that kidney impairment contributed to 8,117 deaths in 2020[27]. Additionally, CKD is expected to represent the second major cause of mortality in Spain within the next 60-70 years[28]. Furthermore, it has been reported that Spain is one of the European countries with the highest hospital healthcare costs for CKD[20].

1.3. Physiopathology of chronic kidney disease

In brief, CKD physiopathology could be summarized as progressive decline in kidney function due to a disruption of the self-regulation mechanisms targeted at protecting the kidneys. For a better understanding of these mechanisms, which have been extensively described in previous scientific literature[3,29], it would be crucial to consider the structure and anatomy of the kidney and nephron (see **Figure 3**).

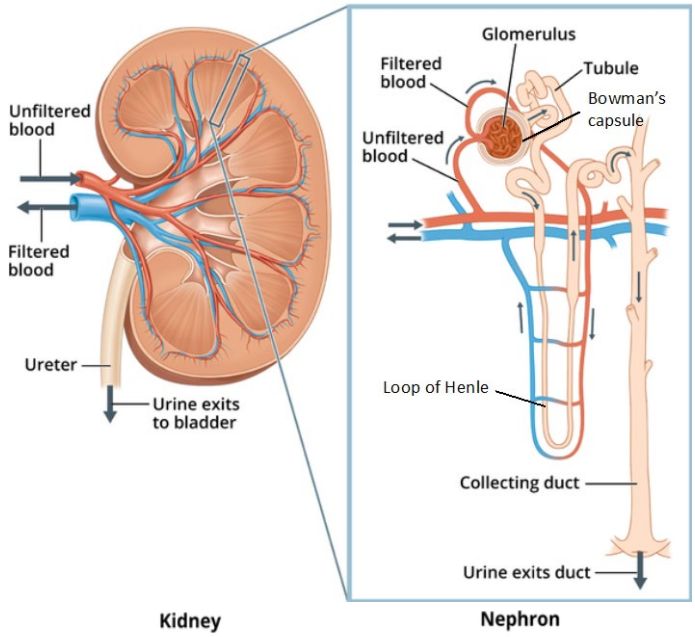

Figure 3. Anatomy of the kidney and nephron. Adapted from: NIH: National Institute of Diabetes and Digestive and Kidney Diseases

The damage of the kidney's structures can be initiated by sustained inflammatory or immune reactions, exogenous toxic substances, and endogenous compounds including glucose and certain proteins, as well as specific kidney conditions such as genetic defects[3,29,30]. Consequently, the injured nephrons are unable to perform their usual function, and the remaining `survivor´ nephrons will take over, leading to their hypertrophy and a status of hyperfiltration. An increase in the arterial pressure within the nephrons will follow, causing damage to the glomerular structure and podocytes[30–32] – the specialized epithelial cells that constitute the glomerular basement membrane, and play an essential role in the glomerular filtration barrier[33]. Finally, the compromised filtration system, deposition of the extracellular matrix, nephron sclerosis, and loss of kidney function become evident[30–32].

Therefore, the progression of kidney disease is marked by kidney inflammation, reduced capillary vascularization, tubular atrophy, and, most significantly, glomerulosclerosis and tubulointerstitial fibrosis. These histopathological changes ultimately lead to end-stage kidney disease[3].

Glomerulosclerosis, characterized as the scarring of the glomerulus, has been linked to the injury and loss of function of endothelial cells, which, along with the glomerular basement membrane, form the glomerular filtration barrier. Moreover, podocyte damage, alterations in their actin cytoskeleton, and their detachment or apoptosis are also considered contributors to glomerulosclerosis. Matrix production and accumulation by mesangial cells -

stromal contractile cells within the glomerulus of the kidneys[34], are further suggested to be factors in this process[3].

Tubulointerstitial fibrosis can be defined as the excessive accumulation of extracellular matrix in the interstitial space of the kidney's tubule. This process involves the release of chemotactic factors, infiltration of inflammatory cells, activation of fibroblasts and pericytes, generation and activation of myofibroblasts, excessive production of extracellular matrix, defects in its degradation and over-deposition in the interstitium, tubular apoptosis and atrophy, microvascular rarefaction, culminating in kidney dysfunction[3].

Some of the signaling cascades and molecules that have been detected as taking part in the physiopathology of CKD, include the Renin-Angiotensin-Aldosterone System (RAAS), oxidative stress, TGF-β, Wnt–β-catenin pathway, mTOR signaling, microRNAs and hypoxia-induced factor[3]. The RAAS may deserve special attention as angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) are nowadays commonly prescribed for kidney disease[35,36]. Aldosterone and angiotensin II appear to be related to pro-inflammatory and pro-oxidant processes, generation of extracellular matrix, and dysfunction of the endothelium. In addition, angiotensin II is a known vasoconstrictor which can contribute to glomerular hypertension. Hence, RAAS is intricately linked to tubulointerstitial fibrosis, kidney dysfunction, and CKD[3,29,32].

1.4. CKD as a risk factor for Cardiovascular Disease, Anemia, and Mineral and Bone Disorder

According to the WHO, cardiovascular disease (CVD) is considered the primary cause of mortality worldwide and encompasses a group of disorders affecting the blood circulatory system, involving the heart and blood vessels[37]. It has been widely recognized that CKD is a relevant risk factor for CVD; thus, low levels of GFR and albuminuria have been suggested to be strong and independent CVD indicators[10,14,28]. In the latest KDIGO guidelines, it was stated that all individuals suffering from CKD should be considered at a high risk for CVD[4]. The burden of CVD due to CKD has been estimated to be around 7%. Additionally, the global age-standardized rate of disability-adjusted life-years resulting from CVD attributable to impaired kidney function in 2017 was approximately 318.3 disability-adjusted life-years per 100,000 population[21]. In addition, sudden cardiac death accounts for 59 deaths per 1000 person-years, representing 26% of total mortality in people with CKD. In contrast, these figures are notably lower in the general population, with one death per 1000 person-years,

accounting for 6 to 13% of total mortality[38]. It has been indicated that the risk of experiencing a CVD event, including CVD-related death, is much higher than the progression from impaired kidney function to end-stage kidney disease[14,38]. Left ventricular hypertrophy is the most common myocardial disease associated with CKD[3], along with cardiac failure and myocardial fibrosis. Moreover, arteriosclerosis and atherosclerosis are the main remarkable arterial vascular pathologies in CKD[3,14,38,39].

Several risk factors for CVD in people with CKD have been identified and are typically classified into traditional and non-traditional risk factors. Hypertension, diabetes and smoking habits are considered the major traditional risk factors. In addition, modifications in blood lipids have been observed in CKD, characterized by an atherogenic profile with an increase in blood triglycerides and a decrease in high-density lipoprotein-cholesterol (HDL-C)[38,39]. Therefore, dyslipidemia has also been considered a traditional risk factor. Regarding non-traditional factors, vascular calcification, anemia, calcium-phosphorus metabolism alterations[3,10,39], oxidative stress, low-grade inflammation, and proteinuria[3,39], as well as elevated activity of the RAAS system and sympathetic nerve, along with vitamin D deficiency, have been suggested[38].

Anemia and CKD-mineral and bone disorder are usual complications as kidney function declines, along with metabolic acidosis[14]. According to the WHO, an anemia condition is defined by a lower number of red blood cells or hemoglobin concentration than normal[40]. The peritubular interstitial cells of the kidneys are involved in erythropoietin production. Consequently, diminished erythropoiesis has usually been reported in populations experiencing GFR declining conditions[14,31]. The mineral and bone disorder in CKD is a systemic complication affecting the bones, heart, and blood vessels, which typically develops in individuals at advanced stages of kidney disease. This disorder results from alterations in serum levels of calcium, phosphate, and other related hormones, such as the parathyroid hormone, the fibroblast growth factor 23, and calcitriol - the active hormonal form of vitamin D[14,41–43]. High concentrations of phosphate in serum and vitamin D deficiency are common among individuals with CKD[14,38]. The combination of these complications ultimately contributes to a higher risk of bone fractures, cardiovascular events, poorer quality of life, and mortality when kidney function becomes impaired[14,41–43]. Regarding metabolic acidosis, maintaining the acid-base balance is one of the principal functions of the kidney. Therefore, the continuous decrease in GFR may be accompanied by low concentrations of

serum bicarbonate, which ultimately could exacerbate not only the progression of CKD but also inflammation, and cardiovascular, and bone problems[14,44].

Several interventions have been recommended to prevent complications of CKD, particularly the onset of CVD. These interventions align with general population recommendations and include smoking cessation, regular physical activity[3,13,14,28,38], adopting a healthy diet while monitoring dietary sodium and protein intake[38], addressing anemia, and managing blood pressure, blood glucose, and lipid levels, inflammation, as well as disorders of calcium and phosphorus metabolism[3,13,14,28,38].

2. Risk factors for chronic kidney disease

Several factors have been postulated as predisposing individuals to kidney dysfunction and CKD, which can be classified as non-modifiable and modifiable. The latter, often related to lifestyle and environmental factors, requires special attention, as it is essential to identify and incorporate them into preventive measures to maintain proper kidney health and avoid the onset or progression of CKD. An overview of the multifactorial etiology of CKD, in which various non-modifiable and modifiable risk factors are potentially coexisting and synergistically acting, is described in detail below.

2.1. Non-modifiable risk factors

2.1.1. Genetic factors and family history

Previous evidence suggests a heritable component in the development of CKD[45]. Genetic variations in genes such as APOL1 and MYH9 have been related to a higher risk of CKD[45], particularly in populations of African ancestry[46–48]. The APOL1 risk variant has been associated with up to a 10 to 17-fold higher risk of end-stage kidney disease in individuals with hypertension or glomerulosclerosis, respectively[49,50].

Other variants in genes which have been associated with CKD are GPX1, GSTO1, GSTO2, UMOD, and MGP, as reported by *Corredor et al.* in their study where 38 single nucleotide polymorphisms from 31 candidate genes were genotyped in Spanish individuals. Moreover, they also identified genes related to biomarkers of kidney function such as GPX1, GSTO1, KL, ICAM-1, and MGP for GFR, as well as genes associated with other risk factors of CKD, such as hypertension, with variants in GPX4, CYP11B2, ERCC4 genes[51].

Furthermore, polymorphisms in genes of the renin–angiotensin system have been previously suggested, specifically ACE-A2350G and AGTR1-C573T[49,52]. In addition, mutations in the uromodulin gene, encoding the protein named Tamm-Horsfall, have been extensively associated as the main cause of one of the subtypes of autosomal dominant tubulointerstitial kidney diseases, establishing a connection to kidney function and CKD[49,53,54].

Therefore, a family history of CKD can be considered a risk factor for this disease, given the fact that gene variations may be inherited, and culture and lifestyle habits pass down through generations. Irrespective of the motive, previous studies examining the familial history of CKD in individuals undergoing dialysis treatment and/or with end-stage kidney disease have shown a relationship between CKD risk and having close family members with kidney disease[49,55,56].

2.1.2. Ethnicity

CKD appears to vary across ethnicities, as previously alluded to above. African American individuals have shown a greater decline in GFR worldwide[57–59]. Previous evidence has also indicated a higher risk of CKD or even end-stage kidney disease in African Americans compared to other ethnic groups, such as Caucasians[49,60,61].

However, despite the evidence found in relation to the APOL1 gene and African populations[50,60], it has been suggested that differences in certain risk factors such as socioeconomic status, unhealthy behaviors, or inadequate control of glycemia and blood pressure are primarily behind these disparities beyond ethnicity[58,61]. In fact, recent results from The REasons for Geographic And Racial Differences in Stroke (REGARDS) Study reported that the higher incidence of CKD and decreased GFR in Black individuals compared to White participants were attenuated after adjusting for other traditional risk factors such as blood pressure, body mass index (BMI), or history of diabetes[62]. Thus, it is worth mentioning that ethnicity and race in relation to CKD have been a matter of debate in recent years[63].

2.1.3. Age

The aging process substantially affects all organs and their function. As individuals age, structural changes occur in the kidneys, resulting in a decrease in the size and number of the nephrons, modifications in the interstitial tubule and membrane, and the development of glomerulosclerosis[64,65]. These alterations related to age are termed nephrosclerosis and may

contribute to a decline in the function of the kidneys, primarily manifesting as a lower GFR and increased albuminuria[14,64]. The classification of these changes in kidney function as either part of the 'normal aging' process or indicative of CKD is a subject of controversy[64–66]. However, there is supporting evidence suggesting that these changes go beyond the natural aging process; for example, whereas some older adults exhibit abnormal GFR and albuminuria levels, others maintain levels within the normal range[14,66]. Furthermore, it has been asserted that screening for CKD should be conducted in individuals with risk factors for this disease and those aged over 50 to 60 years[67–69].

The average GFR level has been estimated at approximately 78-80 ml/min/1.73m^2 in individuals aged 65 years[65,70]. Moreover, the decline in GFR appears to be around 0.7–0.9 ml/min/1.73m^2 per year in populations aged between 30 and 75 years and might be even faster beyond the age of 75 years[71]. One of the largest systematic reviews and meta-analyses estimating CKD prevalence in observational studies based on data from general populations, observed an age-related increase in CKD prevalence. Specifically, this study found a CKD prevalence of 27.6% and 34.3% in people aged 60 and 70 years, respectively[22]. Consistent with these findings, the prevalence of CKD was estimated in the Spanish population according to age, revealing a rate of 37.3% in those aged 65 years or older[25].

2.1.4. Sex

Awareness of the role of sex in different medical disciplines, along with the incorporation of gender perspective in medicine is currently on the rise. Although there has been some progress, there is still a long way to go, particularly in the field of kidney disease, where comparative prevalence studies and gender-based risk analysis are limited and needed for a more comprehensive understanding[72].

Some findings have pointed out that women seem to show lower GFR[17] and, as mentioned above, a higher prevalence of CKD[73] than men. By contrast, the progression from CKD to end-stage kidney disease has been observed to be faster in men than in women[72–76]. In addition, different potential predictors of kidney function according to sex have been identified; better kidney function seems to be related to waist circumference and total cholesterol/HDL-C ratio in men, whereas triglycerides appear to be related in women[77]. Several factors have been postulated to contribute to these sex-related disparities, including differences in kidney physiology and hemodynamics, sex hormones, psycho-socioeconomic

and cultural components, lifestyle and dietary habits as well as disparities in healthcare utilization[72–74,78].

However, it should be additionally mentioned that there is a lack of agreement between studies regarding the contribution of sex to kidney health since not all studies have not found significant differences in CKD risk among women and men[20,73,79].

2.1.5. Low birth weight

The *Barker hypothesis*, also known as the fetal programming hypothesis, argues that adverse conditions during intrauterine development, such as malnutrition, or preterm birth may lead to growth deficit of particular organs, with low birth weight as a major indicator. This condition has been related to the development of non-communicable chronic diseases later in life[80–83]. Consequently, birth weight has been potentially presented as another risk factor for CKD. Low birth weight has been linked to a lower number of nephrons, contributing to an increased vulnerability to kidney dysfunction and CKD[80,84]. Prior findings have indicated that there is an association between low birth weight, lower GFR levels[85,86], and higher risk of CKD[87–89]. Silverwood et al. estimated that GFR levels increase by approximately 2.13 ml/min/1.73 m^2 per kg increase in birth weight, in a British cohort[90].

2.2. Modifiable risk factors

2.2.1. Obesity

The WHO defines obesity as an abnormal or excessive accumulation of fat with health implications, often measured through BMI. Where obesity is commonly defined as a BMI greater than 30 kg/m^2 [91]. In this context, waist circumference and waist-to-hip ratio are additional valuable tools for evaluating fat distribution[92]. Obesity has been extensively discussed to have an important role in CKD as a risk factor[4,32,49,78,93–97]. In the meta-analysis of individual participant data by Chang et al., which included data from 40 countries, higher BMI, waist circumference, and waist-to-height ratio were found to be independent risk factors for GFR decline and death in people with normal or even decreased GFR[98]. There is also evidence supporting the fact that obesity being a contributor to the risk of end-stage kidney disease[49,99,100].

Obesity and adiposity have been related to hyperfiltration, hypertrophy, and, consequently, glomerulopathy[49,67,78,95,101], as well as increased RAAS activity and synthesis of hormones and other pro-inflammatory compounds, which contribute to oxidative stress, endothelial

dysfunction, vasoconstriction, and inflammation[32,95,101,102]. These mechanisms may underline the direct impact of obesity on kidney function. Furthermore, obesity may indirectly contribute to CKD development through its association with lipotoxicity, insulin resistance, adipokine dysregulation[89], diabetes, and hypertension[89,101]. In fact, both diabetes and hypertension will be discussed in detail below as they are the most common risk factors for the development and progression of CKD.

In the Obesity Atlas 2024, approximately 2.2 billion people worldwide, comprising over 42% of the population, were affected by overweight or obesity in 2020, with this figure projected to rise to 3.3 billion by 2035[103]. Concerning kidney disease, it has been estimated that obesity accounts for 20 to 25% of the global burden of CKD[101]. Obesity prevalence is rapidly increasing and poses a significant health concern, particularly due to its association with several diseases, including CKD. As such, interventions focused on weight loss and based on diet and physical activity are suggested as appropriate measures to improve kidney function[89,95,104]. Other proposed strategies include RAAS blockade, weight loss drugs, bariatric surgery, melatonin, prebiotic and symbiotic[89,95].

Given that some of the pathways linking obesity and kidney dysfunction are components of metabolic syndrome (MetS), the potential association between MetS and CKD is increasingly being explored[95,105,106]. MetS, which affects approximately 30% of the worldwide population[107], is a cluster of the following metabolic conditions: abdominal adiposity, high blood pressure, elevated triglycerides levels, reduced HDL-C concentrations, and high fasting glucose. Criterion has been established that indicates the presence of MetS when at least three of these five components mentioned above are present[108]. It has been reported that MetS appears to be related to a higher risk of CKD beyond any of its five components that had been individually associated with kidney function[105,106,109]. In fact, it has been estimated that individuals affected by MetS may face a 2.5-fold higher risk of CKD[105].

2.2.2. Diabetes mellitus

Type 2 diabetes (T2D), the most common type of diabetes mellitus, is a metabolic disorder characterized by chronic hyperglycemia – elevated levels of glucose in the blood, which often develops in individuals over the age of 40 years, primarily because of insulin resistance[110,111].

Currently, diabetes is considered the principal leading cause of CKD worldwide, as stated in numerous scientific articles[19,31,49,94,110]. In a large systematic review and meta-analysis of

observational studies by Shen et al., it was demonstrated that T2D was a strong risk factor for CKD, as well as for end-stage kidney disease[112]. The most widely accepted mechanisms by which hyperglycemia might lead to diabetic nephropathy involve hyperfiltration, hypertrophy of the kidney, thickening of the glomerular filtration barrier, and subsequent damage, along with tubulointerstitial changes and inflammation procedures[3,49,113].

The simultaneous existence of T2D and CKD, coupled with poorly controlled management of both diseases, can contribute to the onset of several complications, such as retinopathy, diabetic foot issues, end-stage kidney disease, and different cardiovascular outcomes (ischemia, arrhythmia, myocardial infarction, or heart failure)[114]. Maintaining glycosylated hemoglobin levels below approximately 7% has been recommended as a means of controlling levels of blood glucose in individuals with CKD[114,115].

According to the International Diabetes Federation (IDF), 537 million people worldwide had diabetes in 2021, and over 90% of them had T2D[116]. It has been estimated that among adults with T2D, 25% to 40% have CKD[94]. Moreover, other studies have indicated that nephropathy is expected to develop in up to 50% of the individuals having T2D, and kidney function decline is expected in 10%[49,113]. As both T2D and CKD are rapidly increasing[94], it would be crucial to identify and manage the common lifestyle and modifiable risk factors, which will be extensively discussed further below.

2.2.3. Hypertension

Hypertension, also referred to as high blood pressure, is widely recognized as one of the primary causes of kidney function decline and CKD[31,49,96,117]. Previous evidence has shown that hypertension is associated with the risk of CKD and end-stage kidney disease, with that risk being higher in men than in women[118]. In addition, hypertension and CKD are intricately interconnected since kidney dysfunction can lead to complications in the control of blood pressure[3,119]. Therefore, hypertension may be both a risk factor for CKD and an outcome in individuals with CKD.

The transmission of systemic hypertension to the intraglomerular capillaries is presented as a potential mechanism behind the impact of hypertension on CKD. It is supposed that initially, increased blood pressure causes a vasoconstrictor response in the afferent arterioles to maintain normal levels of kidney blood pressure. However, if this condition persists, the initial protective process becomes pathological, resulting in glomerulosclerosis[32,96],

endothelial complications, changes in the hormonal system[120], and ultimately, loss of kidney function[96].

Controlling blood pressure is suggested as a suitable intervention to help halt or slow the progression of CKD. According to the KDIGO guidelines, maintaining systolic blood pressure levels below 120 mm Hg is recommended for individuals with CKD[4,121]. Dietary modifications, such as reducing the intake of sodium or following the Dietary Approaches to Stop Hypertension (DASH) diet have been proposed to manage blood pressure[96]. Besides, considering the common elevation of angiotensin II levels in individuals with CKD and hypertension, ACEIs or ARBs are the preferred first-line pharmacotherapy for treating hypertension in CKD individuals, which should not be taken in combination[96,119,121]. Preceding studies have observed that reducing blood pressure may offer protection against CKD progression[122,123].

2.2.4. Smoking

Tobacco smoking has been widely recognized as a leading cause of preventable deaths worldwide, as well as a risk factor for non-communicable diseases[124,125]. In fact, smoking habits have been identified as a potentially detrimental factor to kidney function[14,49,78,126–128]. In the meta-analysis of prospective cohort studies conducted by Xia et al., a significant association was reported between cigarette smoking and an increased risk of CKD and end-stage kidney disease compared with non-smokers in the general population. Moreover, a decreased risk of CKD was observed upon cessation of smoking; even though this risk persisted for many years in the former smokers[126]. Other studies have estimated that smoking approximately 25 to 49 packs of cigarettes per year could increase the risk of CKD by up to 42%[78], and this risk appears to be accumulative with increased smoking[126,129,130]. Additionally, it has been suggested that not only active smoking, but also passive smoking (i.e., second-hand smoke) could be relevant[131].

The potential mechanisms by which tobacco smoking could damage kidney function may include endothelial dysfunction, vascular permeability, production of extracellular matrix, tubular atrophy, glomerulosclerosis as well as pro-inflammation, oxidative stress, and insulin resistance[126,132]. Considering the clear relationship between smoking and CKD, global guidelines, such as those from KDIGO, recommend quitting smoking along with other lifestyle modification advice to prevent CKD or even avoid its progression[4]. Some public health strategies have been proposed to assist people in smoking cessation, which include

social network and media campaigns for smoking cessation, in combination with tobacco advertising restrictions, warnings in the packets of cigarettes, increased cigarette taxes, and limitations on smoking in public areas and workplaces[94].

2.2.5. Physical activity

The beneficial impact of physical activity and exercise on health is well-known, as it has been extensively related to a reduced risk of various chronic diseases and complications[133]. These benefits have been specifically documented concerning obesity, diabetes, and hypertension, among others[134,135], which were discussed above as important risk factors for kidney function decline and CKD. Hence, physical inactivity could be considered a modifiable and relatively addressable risk factor of CKD[128,136,137]. A recent systematic review and meta-analysis of cohort studies has suggested that physical activity diminished the risk of CKD in the general population. In addition, physical activity has also been observed to be associated with better kidney function in individuals already suffering from CKD[138], and provides a more favorable prognosis in terms of mortality risk in populations with pre-dialysis CKD[139,140]. Implications on the modulation of insulin resistance, blood pressure, inflammation, oxidative stress procedures, endothelial function, adiposity, and adipocytokines production, such as adiponectin, are among the potential explanations for how performing physical activity could contribute to the protection of kidney function[141,142].

Although the ideal intensity and frequency of physical activity to prevent CKD has not been yet determined, the KDIGO guidelines have stated a recommendation for individuals with CKD to prevent its progression; thus, a minimum of 150 minutes of moderate-intensity physical activity per week, taking into consideration cardiovascular health and tolerance, has been indicated[4]. However, further, more specific, advice includes the following: engage in daily physical activity, if possible; incorporate balance, flexibility, and strength activities at least two days per week; moderate-intensity aerobic activities for 150 minutes per week, vigorous-intensity activities for 75 minutes per week, or a combination of both; and include standing or light physical activity to avoid prolonged periods of inactivity[143].

2.2.6. Dietary habits

There has been a global shift in dietary intake trends over the past few decades, resulting in lower consumption of fresh foods such as fruits, vegetables, and legumes, and conversely, a notable increase in the consumption of ultra-processed food (UPF)[144–146]. As a result, this

global change has entailed a diet rich in added sugars, salt, saturated and trans fatty acids, while simultaneously being low in fiber, vitamins, phytochemicals, antioxidants, and minerals[147,148]. This nutritional transition has been observed to coincide with the rising development of non-communicable diseases[144,145]. As a result, the potential impact of diet, along with the other lifestyle factors discussed in this dissertation, on people`s health is attracting scientific interest and is becoming increasingly evident. This is crucial for the implementation of appropriate preventive measures.

In the context of kidney function, there is growing evidence supporting the significant effect of the diet[149,150]. Indeed, nutritional therapy is currently a fundamental part of the treatment for the control and delay of the progression of CKD to end-stage kidney disease[151]. Nevertheless, dietary recommendations seem to vary slightly depending on the specific goal, whether it is to address the onset of CKD, its progression, or end-stage kidney disease[128]. Unfortunately, efforts directed towards preventive measures to avoid CKD are more limited, as most scientific research on kidney function is conducted in individuals with some degree of impaired kidney function or those having CKD[4,128,152]. Independently, the role of the diet as a risk factor for CKD appears to be clear. In fact, it has been estimated that dietary factors could account for more than 24% of the cases of CKD[153]. Previous studies have highlighted both positive and negative health effects of specific food groups in the general population. For instance, vegetables, fruits, legumes, nuts, whole grains, and low-fat dairy have been identified as beneficial, while sugar-sweetened beverages, and red and processed meat are considered detrimental[149,150]. Nevertheless, scientific literature is placing greater emphasis on investigating the diet as a whole (i.e., dietary patterns), as dietary choice involves the consumption of a wide variety of foods and nutrients that are not naturally consumed in isolation. Thus, this approach could properly capture the combined synergistic impact of all the components comprising the diet on kidney function[149]. Soltani et al. have suggested that adhering to a healthier dietary pattern is associated with approximately 30% lower risk of kidney disease in the general population[150]. In addition, certain plant-based diets, such as the Mediterranean diet (MedDiet)[154,155], the DASH diet[155,156], or the vegetarian diet[155], have been related to improved kidney function or a reduced risk of CKD. The latest 2020 KDOQI report on clinical practice guidelines for nutrition in CKD has recommended these dietary patterns, particularly the MedDiet, as a reno-protective measure in all stages of this disease, in contrast to the restrictive dietary practices that have prevailed in the past[157]. Recommending adherence to these types of diets could convey a simple message to the general population and be more easily feasible to follow, offering beneficial effects not only

for kidney disease prevention but also for overall health. Furthermore, this could be particularly relevant considering that, as noted above, the shift in global nutrition trends has resulted in a decrease in adherence to these types of healthy dietary patterns in favor of westernized diets[144,146]. These healthy diets are predominantly plant-based and, in contrast to those rich in animal-origin foods, present a low dietary acid load, which has been related to GFR and CKD[158]. In addition, the consumption of UPF, which is a hallmark of Western diets, can displace the consumption of healthy fresh foods and may contribute to an increase in dietary acid load, with several health consequences, including alterations in kidney function[147].

3. A focus on dietary components related to kidney function and CKD

In view of the current relevance of dietary patterns, dietary acid load, and UPF on kidney function and CKD, this section of the doctoral thesis will provide detailed scientific evidence on these specific dietary components.

3.1. Dietary patterns

Traditionally, nutrition recommendations have been based on individual nutrients or food groups. However, this approach has posed some challenges as the overall diet consists of a combination of various nutrients and food groups that may interact with each other, potentially having synergistic or antagonistic effects on health. Accordingly, there has been a shift towards studying dietary patterns, which is considered more appropriate as it takes into consideration not only the potential interactions between nutrients but also cultural and societal eating habits. Moreover, as following advice on specific nutrients can be difficult for individuals, dietary patterns could serve as a more useful guide for dietary recommendations[159].

A priori numerical indexes are commonly used in nutritional epidemiology to evaluate dietary patterns. These indexes are predefined based on previous evidence and may involve different scoring criteria depending on the population's food intake or specific cutoffs in line with recommended food intakes. Certain variations of the same *a priori* dietary pattern have been also described. Among all the *a priori* dietary patterns outlined in the scientific literature, the MedDiet and the DASH diet have accumulated the most evidence regarding kidney function[159].

The traditional MedDiet has its origins in the social behaviors and lifestyle of the Mediterranean Sea regions. This dietary pattern is characterized by a high intake of fresh, seasonal plant-based foods, including fruits, vegetables, legumes, nuts, and minimally refined cereals and seeds. Virgin or extra virgin olive oil is used as the primary source of fat, with a moderate intake of dairy products and eggs, and a low-to-moderate intake of fish and poultry. Red meat intake is limited, and red wine may be consumed in moderation during meals[160]. The DASH diet was developed almost 30 years ago as a potential treatment for lowering blood pressure[161]. This diet includes a high intake of fruits, vegetables, legumes, nuts, whole grains, low-fat dairy products, and fish; while limiting red and processed meat, sweets, added sugars, saturated fats, and sodium intake[162,163]. Therefore, both dietary patterns are mainly based on plant-origin foods, which are typically rich in unsaturated fats, fiber, plant protein, vitamins, and minerals with antioxidant and anti-inflammatory properties[160,163]. Numerous studies have suggested that both the Mediterranean and DASH diets may have potential benefits for various health outcomes, which include CVD, mortality, obesity or overweight, hypertension, MetS, T2D[160,164,165], CKD[166], and even cancer or cognitive function, among others[160].

Systematic reviews and meta-analyses have reported that healthy plant-based dietary patterns, such as the Mediterranean and DASH diets, are significantly associated with improved kidney function[167], reduced risk of CKD[168], lower incidence of CKD and albuminuria[169] and a lower risk of mortality among individuals with end-stage kidney disease[170]. In the updated meta-analysis of observational studies conducted by He et al., participants with a higher adherence to healthy dietary patterns had 20% lower odds of having CKD (Odd Ratio (OR)=0.69; 95 % confidence intervals (CIs) (0.57, 0.84); I^2=83%; n=17)[168].

It is worth mentioning that dietary recommendations have primarily been directed towards individuals with CKD rather than towards preventing kidney dysfunction. Conventionally, these recommendations have focused on controlling the intake of specific nutrients. Specifically, it has been recognized for many years that monitoring the amount of protein, organic and inorganic phosphorus, potassium, and sodium intake could be crucial for individuals with some degree of kidney impairment[151,153,171]. However, the foods constituting the Mediterranean and DASH diets, which have been linked to several kidney benefits, are significant sources of organic phosphorus and potassium[171]. In this context, both minerals are supplied by plant-based foods, and it is well-documented that the phytate content of these types of foods can inhibit the gastrointestinal absorption of organic phosphorus[171,172].

Moreover, plant-based food should not be excluded from a diet aimed at improving or maintaining kidney function, as it may help manage hyperkalemia; in fact, some previous studies have reported that the treatment of CKD-related metabolic acidosis with fruit and vegetable consumption could be better than the standard treatment based on sodium bicarbonate supplementation[173,174]. In addition, restriction of protein intake has generally been the focus of dietary practice and trials in people with CKD[153,171]. Although high protein intake has been suggested to increase intraglomerular hypertension and, thus, may contribute to hyperfiltration and glomerular damage[153,175], the source of protein has become more relevant to kidney function than the total quantity of this macronutrient[153]. This shift is mainly a consequence of the potentially beneficial relationship that has been reported between CKD and dietary patterns, such as the Mediterranean or DASH, which contain higher amounts of plant-derived protein in contrast to reduced animal protein[153,156]. Therefore, while restricting protein intake in the management of CKD progression is controversial, it should not be a concern from a preventive standpoint, as long as the source of this protein is plant-based.

3.2. Dietary acid load

Diet is one of the main components affecting the acid-base balance of the human body; since as a result of the metabolism procedure, dietary components can act as precursors of acids or alkalis[158,176,177]. After food ingestion, hydrogen ions are released by the stomach, while the digestive system releases alkalis. Subsequently, sulfur-containing amino acids and alkaline salts are absorbed in the gastrointestinal tract and oxidized in the liver and other metabolically active tissues. This process leads to the release of protons and alkalis, which are considered responsible for modifying the acid-base balance[158,176]. Acid-producing foods are those that contain phosphorus, sulfur, and cationic amino acids, such as cysteine, methionine, taurine lysine, or arginine. In contrast, alkaline-inducing foods are characterized by their potassium, magnesium, calcium, and bicarbonate content[176]. Therefore, this means that diets high in processed animal products and cereals, and low in fruit and vegetables may contribute to the acidification of the environment[176] (see **Figure 4**). The modern Western diet, as opposed to the Mediterranean or the DASH diet, represents a clear example of such an acid-producing diet, commonly characterized by a wide selection of UPF, which ultimately exacerbates this acidic effect[178].

Figure 4. Acid or base-producing potential of specific food. Source: Medium: How can nutrition balance the body's pH levels?

In addition, as previously mentioned, kidneys are the primary organs maintaining the acid-base balance, along with the lungs and the buffer system. The lungs remove carbon dioxide (CO_2), working in conjunction with the kidneys, which reabsorb bicarbonate ($HCO3^-$), and eliminate ammonium ($NH4^+$) through urine. When this mechanism functions properly, the arterial pH is maintained within optimal ranges, typically between 7.35 to 7.45. An alteration in this acid-base balance, characterized by a decrease in arterial pH lower than 7.35 or a reduction of $HCO3^-$ concentrations, is defined as metabolic acidosis[176,179]. This complication has been associated with some adverse effects, including impaired glucose tolerance, increased muscle wasting and sarcopenia, decreased bone mineralization and increased bone fractures, high blood pressure, and acceleration of the progression of CKD[176,180], many of which are recognized risk factors for CVD[176,179,180].

There are two main methods to assess dietary acid load, the net endogenous acid production (NEAP) and the potential renal acid load (PRAL)[158]. The NEAP corresponds to the total amount of acid that must be excreted in urine to maintain acid-base balance. Thus, NEAP can be measured directly in urine or estimated through dietary intake. Specifically, the equation for calculating this index involves the amount of protein and potassium intake[181].

$$\text{NEAP (mEq/d)} = \frac{54.5 \times \text{Protein (g/d)}}{\text{Potassium (mEq/d)}} - 10.2$$

This index interprets increased or diminished values as high or low dietary acid load, respectively.

PRAL could be described as the quantity of diet-derived acids and alkalis, which can be estimated for individual foods as well as for the whole diet. PRAL is computed using a

mathematical model that incorporates the content of protein, phosphorus, potassium, calcium, and magnesium in the diet[182].

$$\begin{aligned}\text{PRAL (mEq/d)} = {} & 0.4888 \times \text{Protein (g/d)} + 0.0366 \times \text{Phosphorus (mg/d)} \\ & - 0.0205 \times \text{Potassium (mg/d)} - 0.0125 \times \text{Calcium (mg/d)} \\ & - 0.0263 \times \text{Magnesium (mg/d)}\end{aligned}$$

Positive values of PRAL are indicative of acidic foods or a high acid load in the diet; conversely, a negative value indicates basic foods or a low acid load in the diet[176].

Previous evidence has indicated that dietary acid load appears to have a relevant impact on the risk, progression, and morbidity of CKD[158]. Mofrad et al. led a systematic review and meta-analysis of observational studies evaluating the association between dietary acid load, kidney function, and risk of CKD. These authors found that acid load in the diet was significantly associated with a higher risk of CKD (1.31; 95 % CIs (1.06 to 1.62); I^2=77%; n=8)[183]. However, there was a high between-study heterogeneity, which reduced the confidence in the effect estimates. Given that most of the research has been conducted on populations consisting of healthy young, middle-aged, or people with advanced CKD, and that there is limited evidence in high-risk populations, coupled with the fact that all these studies are observational, there is a considerable need for further research. This is especially important if recommendations based on a diet low in acid load are to be included in future guidelines for the prevention of CKD.

3.3. Ultra-processed food (UPF)

UPF was defined as 'formulations of ingredients, mostly of exclusive industrial use, that result from a series of industrial processes' in the 2018 report by Monteiro et al. for the Food and Agriculture Organization (FAO) of the United Nations[184]. Therefore, UPF is obtained through sophisticated industrial processing techniques, such as hydrogenation, hydrolysis, extrusion, molding, or pre-frying. In addition, this procedure typically involves the addition of various components such as simple sugars or non-caloric artificial sweeteners, oils and fats, salt, artificial colors, flavors, emulsifiers, stabilizers, and other additives. Consequently, this type of food has some notable characteristics, including high palatability, which could potentially lead to addictive eating behavior, long shelf-life, relative microbiological safety, and convenience as ready-to-consume, affordable, and accessible products[184].

Industrial food processing began almost two centuries before the definition of UPF, with the development of techniques such as pasteurization and canning, which aimed to produce more shelf-stable products. However, concerns have arisen in recent decades due to the high degree of processing that alters the food matrix, resulting in UPF with a high energy density and poor nutritional quality[178]. Hence, consuming this type of food generally results in a higher intake of total energy, total, saturated and trans-fats, free sugar, and salt. In contrast, it leads to a lower intake of dietary fiber, unsaturated fats, vitamins, minerals, and other beneficial phytochemicals[178,184]. Furthermore, there has been a significant shift in dietary habits over the last few decades. The westernization of diets has led to a problematic increase in the consumption of UPF and a decrease in the consumption of less-processed foods worldwide[147]. This fact has coincided with the increasing prevalence of non-communicable diseases, suggesting a potential role of UPF in their development. In particular, previous evidence has shown significant associations between UPF and various health conditions, including all-cause and cause-specific mortality, CVD, diabetes, cancer, cognitive impairment, gastrointestinal disorders, overweight, obesity, body composition, and fat deposition[147,178,185,186].

Several methods have been proposed to categorize foods based on their degree of industrial processing[147,184]. However, the NOVA classification system has been considered a more precise, clear, and practical tool than other classification systems, which may partially explain its widespread use in nutritional epidemiological research[184,186]. This system classifies food into four groups (see **Figure 5**):

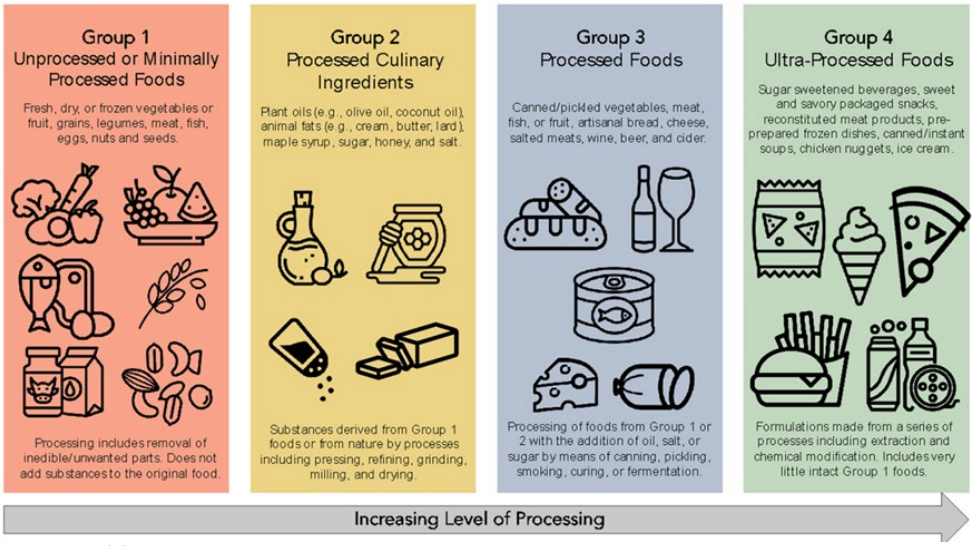

Figure 5. The NOVA classification system. Source: Crimarco A, Landry MJ, Gardner CD. Ultra-processed Foods, Weight Gain, and Co-morbidity Risk. Curr Obes Rep. 2022;11(3):80-92. doi:10.1007/s13679-021-00460-y

- NOVA Group 1 - Unprocessed and minimally processed foods: Unprocessed or natural foods are the parts of plants, animals, fungi, algae, and water, which have been sourced as is from nature. Minimally processed foods are natural foods slightly altered by removing inedible or unwanted parts, as well as through processes such as drying, crushing, fractioning, filtering, roasting, boiling, non-alcoholic fermentation, pasteurization, and vacuum packaging, among others[184,186].

- NOVA Group 2 - Processed culinary ingredients: Substances obtained directly from group 1 foods or from nature through industrial processes, such as pressing, refining, grinding, or drying[184,186].

- NOVA Group 3 - Processed foods: Products that have undergone preservation techniques, such as canning, bottling, and non-alcoholic fermentation, and to which salt, oil, sugar, or other substances from group 2 to group 1 food have been added[184,186].

- NOVA Group 4 - UPF: The definition of UPF was presented at the beginning of this section. This group includes foods such as baked goods (pastries, cookies, biscuits, cakes), dairy products (ice-cream, sugar or artificial sweetened yoghurts, ultra-processed cheese), reconstituted meat products (sausages, burgers, nuggets), sugary products (candies), sugar-sweetened beverages, industrial pizzas, noodles, instantaneous soups, dessert, etc.[184,186].

In the last few years, a special interest has emerged regarding the potential relationship between UPF consumption and kidney health. Although the evidence to date is limited, findings suggest that consuming UPF is associated with lower levels of GFR[187,188] and increased risk of decline in kidney function[188,189] and incidence of CKD[188,190–192]. However, similar to the uncertainty surrounding dietary acid load, it is unclear whether this relationship also applies to older adults at high risk, as most studies have been conducted in other populations and utilized an observational design. It would be particularly important to clarify the potential impact of UPF on kidney health, considering that recommendations to reduce the consumption of UPF could be a simple and understandable message to spread to the general population.

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II. Justification

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II. JUSTIFICATION

The gradual decline in kidney function can eventually lead to developing CKD. As previously stated, CKD has emerged as a major public health concern over the last few decades, affecting a growing and substantial number of people around the world. The mortality rate associated with CKD is also steadily increasing and is predicted to become one of the leading causes of death in the coming years. In addition, CKD is considered an important risk factor for CVD, which is currently the biggest cause of mortality globally. CKD has also been related to a reduced quality of life and life expectancy. Beyond its health impact, it is worth noting that CKD also represents a huge economic burden on healthcare, mainly because it is a clinically silent disease that goes undetected in the early stages, yet requires more invasive and costly treatments and even hospitalization when symptoms manifest. Therefore, it is imperative to promptly address this health issue by identifying potential modifiable risk factors for the decline in kidney function to be able to implement effective and appropriate evidence-based preventive strategies.

Scientific evidence has identified several lifestyle factors, such as diet, smoking, and physical activity, as modifiable risk factors affecting the development of CKD. These factors may directly or indirectly impact kidney function, since they are also linked to hypertension, T2D, obesity, and MetS, which are widely recognized as the main risk factors of CKD. Consequently, adopting healthier lifestyle behaviors could be the key to preventing not only the onset of CKD, but also the progression to more advanced stages and ultimately end-stage kidney disease.

Among these lifestyle risk factors, dietary habits appear to play a crucial role in the prevention and management of CKD. In the past, nutritional epidemiology research has focused mainly on individual nutrients or foods, overlooking the potential interactions between the different components of the overall diet. However, in recent years, there has been a shift towards evaluating dietary patterns as a more comprehensive approach to assessing diet and how it may contribute to a particular health condition or disease outcome. Few epidemiological studies have suggested that healthy dietary patterns, such as the Mediterranean or the DASH diets, are associated with better kidney function and lower risk of CKD. These dietary patterns are characterized by a low dietary acid load due to their food composition. Accumulating evidence has also reported a statistically significant association between dietary acid load and kidney function as well as CKD risk. Unfortunately, the nutrition transition has resulted in a change from more nutritious, locally-sourced, and traditional home-cooked

diets to Western diets with significant amounts of UPF, which in turn have a high dietary acid load. The consumption of UPF has been considered harmful for various non-communicable diseases, such as CVD, hypertension, diabetes, and cancer. However, only a few studies in the last two years have investigated the possible relationship between UPF and kidney function or CKD, suggesting that UPF may also contribute to damaging kidney function.

It is crucial to have solid scientific evidence before promoting specific dietary patterns or diets with a particular level of dietary acid load as well as recommending a reduction in UPF consumption with a view to benefit kidney function. Even though there is a growing body of epidemiological studies evaluating the associations between these dietary factors and kidney function decline or CKD, most of the studies have focused on healthy young or middle-aged adults, or people with established CKD. Furthermore, the findings of these studies have been inconclusive, with some showing significant results and others not. There is therefore a need for further in-depth research, especially in older adult populations who may have additional underlying comorbidities that increase their risk of developing kidney disease.

Global dietary guidelines for kidney health have traditionally been based on quantities of individual nutrients or foods, such as protein, phosphorus, potassium, or sodium, and have primarily been aimed at individuals with kidney dysfunction or diagnosed with CKD. However, primary prevention is fundamental not only to reduce the comorbidities and mortality related to CKD but also to diminish the huge social and healthcare economic costs (derived from the invasive and costly treatments). Besides, advice that focuses on a certain amount of specific nutrients may be more challenging for the general population to follow than the simple message of adhering to a healthy eating pattern or emphasizing the consumption of unprocessed or minimally processed foods.

Therefore, taking into consideration what has been discussed in this section, the current doctoral thesis sought to provide new insights into the potential role of certain modifiable dietary factors - including dietary patterns, dietary acid load, and UPF - on kidney function, using data from the PREDIMED-Plus trial, as an observational cohort study. This trial represents an excellent opportunity to thoroughly investigate these associations in older adults with overweight or obesity and MetS, who are also at increased risk of CKD.

III. Hypothesis and aims

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III. HYPOTHESIS AND AIMS

Hypothesis 1: High adherence to *a priori* healthy dietary patterns might be associated with better kidney function in a Mediterranean population of older adults with overweight or obesity and MetS.

- **Objective 1:** To evaluate the association between one-year changes in the adherence to three *a priori* dietary patterns (17-item energy-reduced Mediterranean Diet (erMedDiet) Score, Trichopoulou-MedDiet and DASH) and kidney function decline after one-year of follow- up.
- **Objective 2:** To assess the association between one-year changes in the Protein Diet Score and kidney function after one-year of follow- up.

Hypothesis 2: Higher dietary acid load might be associated with worse kidney function in a Mediterranean population of older adults with overweight or obesity and MetS.

- **Objective 1:** To investigate the association between baseline PRAL and NEAP and one-year changes in kidney function.

Hypothesis 3: Consumption of UPF might decrease kidney function in a Mediterranean population of older adults with overweight or obesity and MetS.

- **Objective 1:** To assess the association between UPF consumption and kidney function at baseline.
- **Objective 2:** To evaluate the association between one-year changes in UPF consumption and kidney function over 3-years of follow-up.

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IV. Material and methods

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IV. MATERIAL AND METHODS

The current doctoral thesis is a compendium of three original articles published in international peer-reviewed scientific journals in the field of nutritional epidemiology. All chapters within this thesis encompass a blend of cross-sectional and prospective observational studies conducted as part of the PREDIMED-Plus clinical trial.

1. The PREDIMED-Plus study

1.1. Main objective of the PREDIMED-Plus study

The PREDIMED-Plus (trial registration number: ISRCTN89898870) study is an ongoing 8-year parallel-group, multi-center and randomized controlled clinical trial conducted in 23 Spanish centers, aiming to assess the effect of an intensive lifestyle weight loss intervention, based on an energy-restricted MedDiet, physical activity promotion and motivational behavior changes, on CVD morbi-mortality in a population of older adults with overweight or obesity and MetS. This intervention group is compared to a control group with usual care advice, which involves a healthy energy non-restricted MedDiet. The project was approved by the Institutional Review Boards of each participating center in accordance with the ethical principles on human research established in the Declaration of Helsinki, and written informed consent was provided by all participants before starting the study.

The **primary outcomes** of the trial include to evaluate the incidence of CVD events (non-fatal myocardial infarction, non-fatal stroke, or cardiovascular death) and weight change, which includes both weight loss and long-term weight-loss maintenance. Other **secondary outcomes** involve assessing waist circumference and adiposity-related conditions, such as total mortality, myocardial infarction, stroke, heart failure, atrial fibrillation, peripheral artery disease, T2D, incidence of overall and some specific types of cancer (breast, colorectal, prostate, lung and stomach), osteoporotic fractures, cholelithiasis, cataracts, neurodegenerative disorders (dementia and Parkinson's disease), unipolar depression, and eating behavior disorders. In addition, **intermediate outcomes** including overall dietary patterns and nutrient intake, blood pressure, several biochemical indicators such as serum lipid concentrations, fasting plasma glucose, C-reactive protein, glycosylated hemoglobin, kidney function, uric acid, liver function, pharmacological treatment, quality of life, and psychopathological symptoms, are also evaluated in this trial.

1.2. **Study design**

The participants were recruited between October 2013 and December 2016 by different research institutes, universities, hospitals and primary health care centers located in Alicante, Barcelona, Córdoba, Granada, Jaén, Las Palmas de Gran Canaria, León, Madrid, Málaga, Navarra, Palma de Mallorca, Reus, Sevilla, Valencia, and Vitoria. The study included community-dwelling men (aged 55 to 75 years) and women (aged 60 to 75 years) who were free from CVD at enrollment, but at high CVD risk. The **inclusion criteria** were having overweight or obesity (BMI 27–40 kg/m^2) and meeting at least three components of the MetS criteria, in accordance with the guidelines from the American Heart Association, the National Heart, Lung and Blood Institute and the International Diabetes Federation[108].

Moreover, the following **exclusion criteria** were considered:

- Previous history of CVD (angina pectoris, myocardial infarction, stroke, symptomatic peripheral artery disease, ventricular arrhythmias, uncontrolled atrial fibrillation, congestive heart failure, hypertrophic cardiomyopathy and aortic aneurism).
- Cancer diagnosis, whether in the present or past, within the last 5 years (excluding non-melanoma skin cancer).
- Previous weight-loss surgery or plans to undergo bariatric surgery within the next 12 months.
- History of small or large bowel resection or inflammatory bowel disease.
- Obesity with a recognized endocrine origin, excluding treated hypothyroidism.
- Immunodeficiency or HIV-positive status.
- Cirrhosis or severe liver failure.
- Severe psychiatric disorders: schizophrenia, bipolar disease, eating disorders, or depression with hospitalization within the last 6 months.
- Co-morbidity condition with limited life expectancy less than one year.
- History of vital organ transplantation.
- Acute infection or inflammation (e.g., pneumonia) resolution within the last 3 months.
- Concurrent treatment with immunosuppressive drugs, cytotoxic agents, or corticosteroids.
- Present use of weight loss medication.

- Chronic alcoholism, problematic use of alcohol or total alcohol intake >50 g/d, or illegal drug abuse within the past 6 months.
- Illiteracy, inability or unwillingness to give written consent or communicate with the study staff.
- Impossibility to follow the recommended diet due to religious reasons, swallowing problems or food allergy with hypersensitivity to any of the components of the dietary intervention.
- Inability to attend the scheduled intervention visits.
- Limited likelihood of modifying dietary habits according to the Prochaska and DiClemente stages of change model.
- Enrollment in another weight loss program with >5kg weight loss within 6 months before the selection visit.
- Participation in another ongoing randomized clinical trial.
- Any additional condition that could interfere with compliance to the study protocol.

The design of the PREDIMED-Plus study is depicted in **Figure 6**. The **recruitment process** started by identifying potential participants from the clinical records through physicians at primary health care centers. After giving their consent, the names and telephone numbers of the candidates were sent to the PREDIMED-Plus investigators, who contacted them and briefly explained the study by a telephone call. If they were still interested in participating, a face-to-face interview was scheduled, where a more detailed description of the characteristics and objectives of the study was provided.

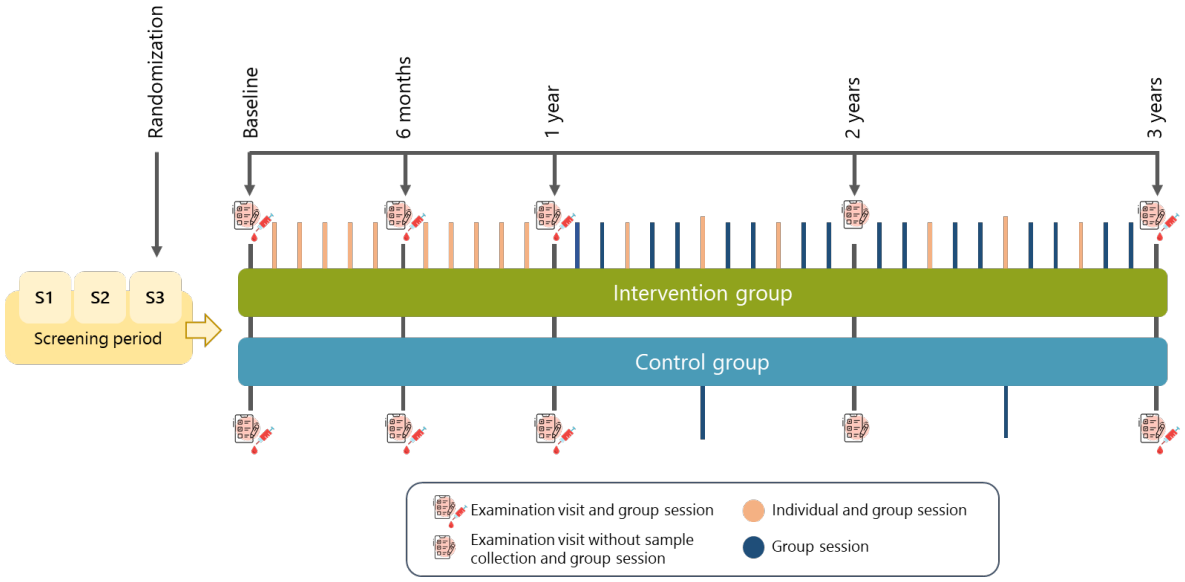

Figure 6. Design of the PREDIMED-Plus study

During this **first screening visit**, if the candidates finally agreed to participate, written informed consent was obtained, and blood pressure, anthropometric measurements (including height, weight, and waist circumference), lifestyle habits and medical history were collected. Additionally, trained staff were responsible for conducting a 3-day prospective food record on two working days and one non-working, questionnaires on physical activity, clinical-psychopathology and quality of life, and provided self-monitoring records on body weight, waist and hip circumference to be completed and returned at the last screening visit. Finally, if the eligibility criteria were met and candidates correctly fulfilled and returned the administered questionnaires and records in the **last screening visit**, an invitation to attend the baseline visit was scheduled.

A total of 6874 participants attended the **baseline visit** and were randomly and equally assigned in a 1:1 ratio to one of the two intervention groups, using a centrally controlled, computer-generated random number system. Stratification by center, sex, and age group (<65, 65-70, >70 years) was performed for the random assignment of participants, and couples both meeting the eligibility criteria and living in the same household were randomized together as clusters.

Briefly, the participants of the PREDIMED-Plus trial underwent:

- **Intervention group:** An energy-reduced MedDiet, with a 30% energy reduction (~600 kcal/day according to each participant's basal metabolic rate and physical activity level) to promote weight loss, in combination with physical activity promotion and behavioral support.
- **Control group:** An energy non-restricted traditional MedDiet advice.

Trained PREDIMED-Plus dieticians were mainly responsible for the dietary interventions and conducted periodical group sessions of informative talks regarding lifestyle-related topics and motivational aspects. Moreover, participants were provided, free of charge, extra virgin olive oil and raw nuts to reinforce their adherence and compliance to the intervention, regardless of the assignment group.

2. Study population for the analyses

2.1. Study design and participant selection

For the present dissertation, data from all randomized PREDIMED-plus participants was used as if it was an observational cross-sectional or prospective cohort study:

Sample for analyses considering dietary patterns as an exposure: A total of 5,675 participants were included. Participants without completed food frequency questionnaire (FFQ) information (n=777) and reporting implausible total energy intake (<800 and >4,000 kcal/day in men and <500 and >3,500 kcal/day in women) (n=160) at baseline and at a one-year of follow-up were excluded. Moreover, individuals with missing data on SCr (n=262) at baseline and at a one-year of follow-up to determine kidney function were additionally excluded.

Sample for analyses considering dietary acid load as an exposure: From all the participants randomized to the PREDIMED study, a total of 5,874 participants were included in the estimated-GFR (eGFR) analysis and 3,639 in the UACR analysis. Those individuals without completed FFQ information and reporting implausible total energy intake (n=254) at baseline were excluded. Moreover, participants with missing data on SCr (n=746) or urine albumin and creatinine (n=2,981) at baseline and at one-year of follow-up to estimate eGFR or UACR biomarkers of kidney function, respectively, were excluded.

Sample for analyses considering UPF as an exposure: A total of 1,851 participants were included in the cross-sectional analysis and 1,700 participants in the longitudinal analysis. Those participants who did not complete the FFQ and who also reported implausible total energy intakes according to the predefined limits applied in both previous analyses at baseline (n=58) and at one-year of follow-up (n=209) were excluded. We also excluded individuals with missing data on CysC at baseline (n=4,965) to determine kidney function.

2.2. Data collection

2.2.1. Dietary assessment

Dietary intake was assessed at baseline and yearly during the follow-up using a validated 143-item semi-quantitative FFQ[193] (see **Appendix 4**). During a face-to-face interview, trained dieticians asked the participants about their frequency of consumption of food items over the preceding year. The nine possible answers, ranging from never or almost never to more than six times per day, were recorded in standard portion sizes and subsequently converted to grams per day by multiplying serving sizes according to their frequency of consumption and dividing the findings by the assessed period. Total daily intake of energy, nutrients, and food groups were calculated using Spanish food composition tables[194,195].

A validated 17-item erMedDiet questionnaire[196] was used to assess the degree of adherence to an erMedDiet (see **Table 3**). Each item in this erMedDiet questionnaire was assigned a

score of 1 or 0 points, based on whether the criterion was met or not, respectively. Consequently, the overall score ranged from 0 to 17 points, indicating either no adherence or the highest adherence to an erMedDiet, respectively.

Table 3. 17-item questionnaire of adherence to an energy-reduced Mediterranean Diet

Foods and frequency of consumption	Criteria for 1 point
1. Do you use extra-virgin olive oil as the main culinary fat?	Yes
2. How many servings of vegetables do you consume per day? (Count garnish and side servings as ½ point; 1 serving=200g)	≥ 2
3. How many pieces of fruit or 100% natural fruit juice do you consume per day?	≥ 3
4. How many servings of red meat, hamburgers, or meat products (ham, sausages, etc.) do you consume per week? (1 serving=100-150g)	≤ 1
5. How many servings of butter, margarine, or cream do you consume per week? (1 serving=12g)	< 1
6. How many sugar-sweetened beverages (sodas, tonic waters, energy drinks, fruit juices with added sugar) do you consume per week?	< 1
7. How many servings of legumes do you consume per week? (1 serving=150g)	≥ 3
8. How many servings of fish/shellfish do you consume per week? (1 serving=100-150g, or 4 – 5 pieces of fish, or 200g of shellfish)	≥ 3
9. How many times per week do you consume pastries, such as cookies, sweets, or cakes?	< 3
10. How many times per week do you consume nuts? (1 serving=30g)	≥ 3
11. Do you preferentially consume chicken, turkey, or rabbit meat instead of beef, pork, hamburgers, or sausage?	Yes
12. How many times per week do you consume vegetables, pasta, rice, or other dishes seasoned with sofrito (sauce made with tomato and onion, leek or garlic and simmered with olive oil)	≥ 2
13. Do you add sugar to beverages (coffee, tea)?	No/use of artificial sweeteners
14. How many servings of white bread do you consume per day? (1 serving=75 g)	≤ 1
15. How many servings of whole grains (bread, rice, pasta) do you consume per week?	≥ 5
16. How many servings of refined bread, rice, and/or pasta do you consume per week?	< 3
17. Do you drink wine? How much do you consume per week? (One glass=100ml)	Men: 2-3 glasses/day Women:1-2 glasses/day

2.2.2. Ascertainment of the kidney function

Fasting blood samples were obtained at baseline and at years 1 and 3 by PREDIMED-Plus nursing staff. After collection, blood samples were immediately centrifuged, processed, and stored at -80ºC according to the study protocol. Urinary creatinine and albumin concentrations were determined using routine laboratory methods from spot morning urine samples collected at baseline and one-year following overnight fasting. SCr levels were determined by the enzymatic creatinine assay method (coefficient of variation < 4%). 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 SCr (chapter 1 and 2) or CysC (chapter 3) using the CKD-EPI equation[8,197] for Caucasian individuals (see **Table 4**).

Table 4. CKD-EPI equations[8,197] for estimating glomerular filtration rate according to serum creatinine or cystatin C biomarkers

CKD-EPI formula for SCr biomarker	
Women with SCr ≤0.7 mg/dL	$eGFR = 144 \times (SCr/0.7)^{-0.329} \times 0.993^{Age}$
Women with SCr ≥0.7 mg/dL	$eGFR = 144 \times (SCr/0.7)^{-1.209} \times 0.993^{Age}$
Men with SCr ≤0.9 mg/dL	$eGFR = 141 \times (SCr/0.9)^{-0.411} \times 0.993^{Age}$
Men with SCr ≥0.9 mg/dL	$eGFR = 141 \times (SCr/0.9)^{-1.209} \times 0.993^{Age}$
CKD-EPI formula for CysC biomarker	
Women with CysC ≤0.8 mg/dL	$eGFR = 133 \times (SCr/0.8)^{-0.499} \times 0.996^{Age} \times 0.932$
Women with CysC ≥0.8 mg/dL	$eGFR = 133 \times (SCr/0.8)^{-1.328} \times 0.996^{Age} \times 0.932$
Men with CysC ≤0.8 mg/dL	$eGFR = 133 \times (SCr/0.8)^{-0.499} \times 0.996^{Age}$
Men with CysC ≥0.8 mg/dL	$eGFR = 133 \times (SCr/0.8)^{-1.328} \times 0.996^{Age}$

eGFR, Glomerular Filtration Rate; CysC, Cystatin C; SCr, Serum Creatinine.

One-year changes in eGFR were performed by subtracting eGFR at one-year minus eGFR at baseline. Decreased kidney function was defined as eGFR lower than 60 ml/min/1.73m^2. Decline in eGFR (≥ 10%) was estimated using the following formula:

$$\frac{\text{Baseline eGFR - One-year eGFR}}{\text{Baseline eGFR}} \times 100$$

Urinary creatinine and albumin concentrations were determined using routine laboratory methods spot morning urine samples collected at baseline and at one-year, following the overnight fasting. UACR was calculated by dividing urine albumin (mg/l) by urine creatinine concentrations (mg/l). One-year changes in UACR were also calculated by subtracting values at one-year minus values at baseline. UACR increase (≥10%) was estimated by applying the formula:

$$\frac{\text{Baseline UACR- One-year UACR}}{\text{Baseline UACR}} \times 100$$

2.2.3. Assessment of other lifestyle and clinical variables

At baseline, 6 months, and yearly during the follow-up, PREDIMED Plus-trained staff collected personal and medical data including age, education level, socioeconomic status, occupation, family history of disease, history of illnesses, cardiovascular risk factors, smoking and alcohol use, medication use, new-onset cardiovascular events, and other medical

conditions through general and follow-up questionnaires as well as by reviewing medical records.

The validated REGICOR (Registre Gironí del Cor) Short Physical Activity Questionnaire for adult population[198] adapted from the Minnesota Leisure Time Physical Activity Questionnaire (MLTPAQ) was used to record not only the type of physical activity but also its frequency (number of days) and duration (minutes per day). The sum of frequency and duration was calculated, and the result was subsequently divided by 30 to obtain daily physical activity in minutes. The intensity of specific activities (in metabolic equivalent task, MET) was assigned based on the 2015 Compendium of Physical Activity. Finally, physical activity was further classified into three levels: light (< 4.0 MET), moderate (4 ± 5.5 MET), and vigorous (≥ 6.0 MET).

Anthropometric measurements and blood pressure were collected during the interviews by study dieticians using standardized techniques and calibrated scales. Weight (in kg) and height (in m) were measured with light clothing and without shoes or accessories, using calibrated scales and a wall-mounted stadiometer, respectively. Subsequently, BMI (in kg/m^2) was calculated by dividing the weight by the square of the height. Waist circumference (in cm) was also collected by identifying the midpoint between the lowest rib and the iliac crest using an anthropometric tape. A validated oscillometer (Omron HEM705CP, Hoofddorp, Netherlands) was used to measure blood pressure in triplicate, awaiting a 5 minutes interval between each measurement, and then, the mean of these values was recorded.

As previously mentioned, biological samples were collected after an overnight fast. In addition to the determinations of kidney function biomarkers, a complete blood count and routine biochemical measurements were performed. These included glucose, glycosylated hemoglobin, total cholesterol, HDL-C, LDL-C, triglycerides, calcium, sodium, potassium, uric acid, urea, albumin, C-reactive protein, erythrocyte sedimentation rate, and hepatic function biomarkers (bilirubin, alkaline phosphatase, and transaminases).

An overview of the PREDIMED-Plus data collection scheduled per visit, which was used for the current doctoral dissertation, is presented below (see **Table 5**).

Table 5. Data collection in the PREDIMED-plus Study visits

	Screening	Baseline	Year 1	Year 3
Eligibility questionnaire	X			
General questionnaire		X	X	X
Anthropometric measurements	X	X	X	X
143-item FFQ		X	X	X
17-items erMedDiet questionnaire		X	X	X
Physical activity questionnaire	X	X	X	X
Blood pressure measurement	X	X	X	X
Blood sample collection		X	X	X
Urine sample collection		X	X	X

Anthropometric measurements included weight, height, waist and hip circumference.
Abbreviations: FFQ, food frequency questionnaire; erMedDiet, energy-reduced Mediterranean Diet.

3. Statistical analyses

A comprehensive explanation of the statistical analyses performed in the current doctoral thesis has been described in the results section of each respective publication. All statistical analyses were conducted using STATA statistical software, versions 14.0 and 17.0 (StataCorp, Texas, USA). The level of significance for all statistical tests was $P < 0.05$ for bilateral contrast.

In brief, in all the papers,

- ANOVA and Pearson chi-square tests were used to compare the differences between continuous and categorical variables among the study participants, respectively.
- Multivariable linear (β-coefficients and 95% confidence intervals (CIs)) or logistic (ORs and 95% CIs) regression models adjusted for potential confounder factors were performed to assess the association between the main exposures (dietary patterns, dietary acid load, ultra-processed food) and kidney function.
- Linear mixed-effects linear (β-coefficients and 95% CIs) regression models with random intercepts at recruitment center, cluster family and participant level were conducted to assess the longitudinal associations between the specific exposure and kidney function over time.
- Tests for linear trend were conducted by assigning the median value to each category and modeling it as a continuous variable
- Statistical interactions between categories of exposure and covariates were explored by means of likelihood ratio tests, comparing the most adjusted model with and without cross-product terms (all interactions, $p > 0.05$).

-

V. Results

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DIETARY FACTORS AND KIDNEY FUNCTION: INSIGHTS FROM A POPULATION OF OLDER MEDITERRANEAN ADULTS WITH OVERWEIGHT OR OBESITY AND METABOLIC SYNDROME
Cristina Valle Hita

V. RESULTS

The three published original articles which are part of the results of this thesis are presented in **Table 6**.

Table 6. Reference, impact factor, category and journal rank of the publications presented in the current doctoral thesis

Reference	Impact factor	Category	Journal rank
Chapter 1			
Valle-Hita C, Díaz-López A, Becerra-Tomás N, et al. Prospective associations between a priori dietary patterns adherence and kidney function in an elderly Mediterranean population at high cardiovascular risk. Eur J Nutr. 2022;61(6):3095-3108. doi:10.1007/s00394-022-02838-7	5.0	Nutrition & dietetics	28/88 (Q2)
Chapter 2			
Valle-Hita C, Becerra-Tomás N, Díaz-López A, et al. Longitudinal association of dietary acid load with kidney function decline in an older adult population with metabolic syndrome. Front Nutr. 2022;9:986190. Published 2022 Sep 30. doi:10.3389/fnut.2022.986190	5.0	Nutrition & dietetics	28/88 (Q2)
Chapter 3			
Valle-Hita C, Díaz-López A, Becerra-Tomás N, et al. Associations between ultra-processed food consumption and kidney function in an older adult population with metabolic syndrome. Clin Nutr. 2023;42(12):2302-2310. doi:10.1016/j.clnu.2023.09.028	6.3	Nutrition & dietetics	14/88 (Q1)

Q, Quartile
Accessed date: February 28th, 2024 (Journal Citation Reports of the ISI web of Knowledge, Thompson Reuters).

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DIETARY FACTORS AND KIDNEY FUNCTION: INSIGHTS FROM A POPULATION OF OLDER MEDITERRANEAN ADULTS WITH OVERWEIGHT OR OBESITY AND METABOLIC SYNDROME
Cristina Valle Hita

Chapter 1. Prospective associations between a priori dietary patterns adherence and kidney function in an elderly Mediterranean population at high cardiovascular risk.

Cristina Valle-Hita, Andrés Díaz-López, Nerea Becerra-Tomás, Miguel A. Martínez-González, Verónica Ruiz García, Dolores Corella, Albert Goday, J. Alfredo Martínez, Ángel M. Alonso-Gómez, Julia Wärnberg, Jesús Vioque, Dora Romaguera, José López-Miranda, Ramon Estruch, Francisco J. Tinahones, José Lapetra, Luís Serra-Majem, Naomi Cano-Ibáñez, Josep A. Tur, María Rubín-García, Xavier Pintó, Miguel Delgado-Rodríguez, Pilar Matía-Martín, Josep Vidal, Sebastian Mas Fontao, Lidia Daimiel, Emilio Ros, Estefania Toledo, José V. Sorlí, C. Roca, Iztiar Abete, Anai Moreno-Rodriguez, Edelys Crespo-Oliva, Inmaculada Candela-García, Marga Morey, Antonio Garcia-Rios, Rosa Casas, Jose Carlos Fernandez-Garcia, José Manuel Santos-Lozano, Javier Diez-Espino, Carolina Ortega-Azorín, M. Comas, M. Angeles Zulet, Carolina Sorto-Sanchez, Miguel Ruiz-Canela, Montse Fitó, Jordi Salas-Salvadó and Nancy Babio.

Overview of the novelty and significance of this publication

What is already known?

- Healthy dietary patterns, mainly those based on food from plant sources, are inversely associated with the incidence of CKD or kidney function decline. However, inconsistent results are found in those studies focusing on the relationship between *a priori* dietary patterns (MedDiet or DASH) and kidney function.
- Most of these epidemiological studies have not been conducted in high-risk populations such as the elderly or individuals with cardiometabolic comorbidities.

What does this study add?

- For the first time, a prospective study examined the association between adherence to different *a priori* defined dietary patterns and kidney function in Mediterranean older adults at high cardiovascular risk and found that changes towards greater adherence in the 17-item erMedDiet score were positively associated with eGFR and with 38% lower odds of eGFR decline. In contrast, no associations were observed with the other dietary patterns evaluated.
- Vegetables, legumes, wine and the *sofrito* sauce were the individual components of the Mediterranean Score that were associated with better kidney function.

Conclusion:

- Our findings suggest that improvements in dietary habits, through adherence to a MedDiet, contribute to maintaining better kidney health. Additionally, this could be taken into consideration in future guidelines for CKD prevention.

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ORIGINAL CONTRIBUTION

Prospective associations between a priori dietary patterns adherence and kidney function in an elderly Mediterranean population at high cardiovascular risk

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Abstract

Purpose To assess the association between three different a priori dietary patterns adherence (17-item energy reduced-Mediterranean Diet (MedDiet), Trichopoulou-MedDiet and Dietary Approach to Stop Hypertension (DASH)), as well as the Protein Diet Score and kidney function decline after one year of follow-up in elderly individuals with overweight/obesity and metabolic syndrome (MetS).

Methods We prospectively analyzed 5675 participants (55–75 years) from the PREDIMED-Plus study. At baseline and at one year, we evaluated the creatinine-based estimated glomerular filtration rate (eGFR) and food-frequency questionnaires-derived dietary scores. Associations between four categories (decrease/maintenance and tertiles of increase) of each dietary pattern and changes in eGFR (ml/min/1.73m^2) or ≥ 10% eGFR decline were assessed by fitting multivariable linear or logistic regression models, as appropriate.

Results Participants in the highest tertile of increase in 17-item erMedDiet Score showed higher upward changes in eGFR (β: 1.87 ml/min/1.73m^2; 95% CI: 1.00–2.73) and had lower odds of ≥ 10% eGFR decline (OR: 0.62; 95% CI: 0.47–0.82) compared to individuals in the decrease/maintenance category, while Trichopoulou-MedDiet and DASH Scores were not associated with any renal outcomes. Those in the highest tertile of increase in Protein Diet Score had greater downward changes in eGFR (β: − 0.87 ml/min/1.73m^2; 95% CI: − 1.73 to − 0.01) and 32% higher odds of eGFR decline (OR: 1.32; 95% CI: 1.00–1.75).

Conclusions Among elderly individuals with overweight/obesity and MetS, only higher upward change in the 17-item erMedDiet score adherence was associated with better kidney function after one year. However, increasing Protein Diet Score appeared to have an adverse impact on kidney health. Trial Registration Number: ISRCTN89898870 (Data of registration: 2014).

Keywords Dietary patterns · Mediterranean diet · DASH diet · Protein diet score · Kidney function · Glomerular filtration rate

Cristina Valle-Hita and Andrés Díaz-López these authors contributed equally to this work.

Extended author information available on the last page of the article

Abbreviations

BMI	Body mass index
CKD	Chronic kidney disease
CI	Confidence interval

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DASH	Dietary approach to stop hypertension
E	Energy
FFQ	Food frequency questionnaire
GFR	Glomerular filtration rate
MedDiet	Mediterranean diet
MetS	Metabolic syndrome
METS	Metabolic equivalent task
PREDIMED	Prevención con dieta Mediterránea
SCr	Serum creatinine
CKD-EPI	Chronic kidney disease epidemiology collaboration equation for caucasian individuals
OR	Odds ratios

Introduction

Chronic Kidney Disease (CKD) is an increasing global public health problem, which affects about 9.1% of the worldwide population and 35% of those over 70 years [1]. CKD is characterized by abnormalities in kidney structure and a decline in its function [2], often accompanied by several comorbidities, decreased quality of life and premature mortality [1–3]. In fact, this heterogeneous condition is accelerated at older ages when comorbidities such as obesity, diabetes, hypertension and/or cardiovascular disease are present [1, 4]. As this disease involves a huge health and economic burden, preserving renal function, especially in old people, it is essential to ensure the well-being and reduce adverse health outcomes [1]. Accordingly, effective strategies to deal with the spread of CKD and its harmful consequences are urgently needed.

Among the lifestyle risk factors of CKD, diet may play an important role as potential modulator of kidney function decline and CKD progression [5]. However, most of the investigations have been predominantly focused on single nutrients [6, 7] or food groups [5, 8] instead of dietary patterns, hence it is likely to not exhibit the synergistic effect between its dietary components. Thus, considering that meals are composed by a combination of foods and nutrients, analysis of diet as a whole could be a more all-inclusive approach not only to assess dietary exposure but also to examine its relationship with kidney health [3, 9, 10].

In this regard, results of a recent meta-analysis of prospective studies reported that a healthy dietary pattern characterized by a high consumption of plant-based food was associated with reduced incidence of CKD or albuminuria, but not with glomerular filtration rate (GFR) decline [11]. When studies are focused on particular dietary patterns such as the Mediterranean diet (MedDiet) or the Dietary Approach to Stop Hypertension (DASH), which are the most commonly investigated a priori dietary scores in the context of CKD [3, 12], there are inconsistent results. Whereas some studies reported a decrease in GFR decline [13], microalbuminuria or lower CKD risk [14], others failed to demonstrate any relationship between these dietary patterns and kidney outcomes [15, 16]. It is noteworthy that most of these epidemiologic studies were conducted in healthy young or middle-aged individuals, instead of high-risk participants such as elders or people with cardiometabolic comorbidities.

Furthermore, MedDiet and DASH diet are characterized by a high plant protein content and, even though protein intake has been previously associated with kidney function deterioration [17], this potential harmful effect could depend on the protein source. Accordingly, it may be of interest to investigate the association between not only the quantity but also the quality of dietary protein and renal function using specific tools as the recently developed Protein Diet Score [18].

Consequently, in view of the above, further research is required to clarify whether specific healthy dietary patterns could preserve kidney function and even prevent its decline in elderly population with underlying comorbid conditions. Therefore, the main aim of the present study was to prospectively evaluate the association between changes towards an increase in the adherence to three a priori dietary patterns (17-item erMedDiet Score, Trichopoulou-MedDiet and DASH) and kidney function decline after 1 year of follow-up in a large Spanish cohort of middle-aged individuals with overweight/obesity and metabolic syndrome (MetS). Secondarily, we evaluated the association between changes in the Protein Diet Score and kidney function.

Material and methods

Study design and participants

In the present study, data was analyzed using an observational prospective design conducted within the framework of the Prevención con Dieta Mediterránea (PREDIMED)-Plus trial, which included 6874 older adults enrolled between 2013 and 2016 by 23 Spanish centers working in collaboration with primary care clinics. The study design and protocol have been described in detail elsewhere [19], and are available at http://www.predimedplus.com. In brief, the PREDIMED-Plus study is an ongoing, 8-year, parallel-group, randomized and controlled clinical trial which combines dietary and physical activity intervention with behavioral support for primary cardiovascular prevention. Eligible participants were men (55–75 years) and women (60–75 years) with overweight or obesity (BMI $\geq$ 27 kg/m^2 and $<$ 40 kg/m^2) and free from cardiovascular disease who satisfied at least 3 criteria for the MetS definition [20]. More specific details of inclusion/exclusion criteria have been previously reported [19]. All participants provided written informed consent and

the Institutional Review Boards of each participating center approved the final study protocol and procedures, which followed the standards of the Declaration of Helsinki. The trial was registered in 2014 at the International Standard Randomized Controlled Trial registry (https://www.isrctn.com/ISRCTN89898870).

For the current analysis, we excluded 777 participants who did not complete food frequency questionnaires (FFQ) at baseline and after a 1 year of follow-up; 160 participants with extreme total energy intake (women < 500 and > 3500 kcal/day, and men < 800 and > 4000 kcal/day) [21]; and 262 participants with missing creatinine data at baseline and after 1 year of follow-up. Consequently, the final sample for the present study was 5675 participants. Supplementary table S3 depicts the baseline characteristics by included and excluded participants.

Dietary assessment

Dietary intake was evaluated at baseline and yearly during the follow-up using a 143-item semi-quantitative FFQ [22]. Trained dieticians asked the participants about their frequency consumption of each specific item during the preceding year in a face-to-face interview. There were nine possible answers ranging from never or almost never to more than six times per day. Each item answer was collected in standard portion sizes and then transformed to g/day. Total daily intake of energy, nutrients and food groups were estimated using Spanish food composition tables [23, 24].

Moreover, in order to assess the degree of adherence to an energy reduced-MedDiet of each participant, a recently validated 17-item test (17-items erMedDiet Score) [25] was filled in every visit. This questionnaire specifically asked about the frequency consumption of extra virgin olive oil, other fats (butter, margarine, or cream), fruits and fruit juices, vegetables, meat, legumes, fish, nuts, pastries, "sofrito", non-caloric artificial sweeteners, refined grains, wholegrains, and wine. Each item of the questionnaire is scored with 1 or 0 points, when the criterion is met or not met respectively, ranging the overall score from 0 to 17 points, with 0 meaning no adherence and 17 meaning maximum adherence. Hence, this pre-defined questionnaire has the remarkable characteristic of being based on the scientific knowledge on what is a health level of intake and not on the study population distribution, unlike other indices that are calculated based on specific cut-off points (mean or quintiles) of the population included for each item of the score.

We also constructed the Trichopoulou-MedDiet Score and the DASH Score following previous detailed description in the scientific literature [26, 27]. Briefly, Trichopoulou-MedDiet Score, one of the most used MedDiet scores in nutritional epidemiological studies, is comprised of nine components and a sex-specific cutoff point, based on the median of each item consumption (g/day), is established. Components which consumption is highly recommended were 1 point scored when their consumption was equal to or greater than the median (vegetables, fruits and nuts, legumes, cereals and potatoes, fish and others, monounsaturated: saturated ratio) and zero otherwise. Non favourable components were scored with 0 when their intake was equal to or greater than the median (meat and meat products, dairy) and one otherwise. With regard to alcohol, it has been recommended a moderate consumption; therefore, the consumption of 10–50 g/day in men and 5–25 g/day in women was scored with 1 point. Alcohol consumption above or below these limits was assigned a score of 0. The total final score ranged from 0 to 9 points. For DASH Score, study population was classified into quintiles according to each score item (g/day). A progressive score from 1 to 5 was given to each quintile in case of highly recommended foods (fruits, vegetables, legumes and nuts, low-fat dairy, and whole grains). Nevertheless, an inverse score was assigned to components quintiles whose consumption is not recommended (sodium, red and processed meats, and sweetened-sugar beverages). Thus, the total score after summing up every single component ranged from 8 to 40 for DASH score.

We also included the pre-defined Protein Diet Score in our analyses [18]. The study population was divided in 11 strata according to total protein intake (E%) and in another 11 strata according to plant to animal protein ratio. Subjects in the highest stratum received 10 points and those in the lowest stratum received 0 points. Therefore, the overall score could range from 0 to 20 points, with 0 meaning the lowest total protein intake (E%) and lowest plant to animal protein ratio, and 20 meaning the highest total protein intake (E%) and the highest plant to animal protein ratio. Each component of the score was also considered separately.

Ascertainment of renal function

For the present study, we considered as main outcomes of interest, absolute changes in eGFR and ≥ 10% eGFR decline after 1 year of follow-up. For this purpose, eGFR was estimated indirectly from serum creatinine (SCr) at baseline and after a 1 year of follow-up using the Chronic Kidney Disease Epidemiology Collaboration equation for Caucasian individuals (CKD-EPI) [28]. Fasting blood samples were collected and SCr levels were determined by the enzymatic creatinine assay method (coefficient of variation < 4%). Decline in eGFR (≥ 10%) was estimated using the following formula: (one-year eGFR− baseline eGFR)/(baseline eGFR)*100. Participants were categorized in those with $a \geq 10\%$ eGFR decline and those with < 10% eGFR decline [29].

Assessment of other covariates

At baseline and after 1 year of follow-up, socio-demographic (age, sex, educational level) and lifestyle (physical activity, smoking habits) information, medication use and history of disease were collected by PREDIMED-Plus-trained staff through several questionnaires or reviewing medical records. Anthropometric measurements as weight, height or waist circumference were assessed following the study protocol. Body Mass Index (BMI) was calculated by dividing the weight (in kg) by the square of the height (in meters). For weight change after 1 year of follow-up, we constructed a new covariate by subtracting weight at 1 year minus weight at baseline. Resting blood pressure was measured in triplicate by an automated digital device (Omron-HEM297705C).

Statistical analyses

Data were analyzed using the available PREDIMED-Plus database updated to December 2020. Participants were categorized in four categories according to changes in dietary pattern scores after 1 year of follow-up: decrease or maintenance of changes and tertiles of increasing changes. Baseline characteristics of the study population were compared among categories of dietary patterns changes by using one-way ANOVA and Chi-square, as appropriate. Values were presented as percentages and numbers for categorical variables and means ± standard deviations for continuous variables.

Multivariable linear regression models were fitted to evaluate associations between categories of changes in dietary patterns and changes in eGFR (ml/min/1.73m^2); results were expressed as β-coefficients and their 95% confidence interval (CI). Besides, logistic regression models were used to assess the association between categories of changes in dietary patterns and eGFR decline (≥ 10%); results were expressed as odds ratios (OR) and their 95% CI. In both regression models, the first category (decrease or maintenance of changes) was used as reference. Changes in dietary pattern exposures were also modeled as continuous per 1-point increase. All regression models were adjusted for several potential confounders: Model 1 was adjusted for sex and age; model 2 was additionally adjusted for BMI (kg/m^2), smoking habits (never, current or former smoker), educational level (primary, secondary education or graduate), leisure time physical activity (METS/min/week), diabetes prevalence (yes/no), hypertension prevalence (yes/no), hypercholesterolemia prevalence (yes/no), center (categorized into quartiles by number of participants), intervention group and energy intake (kcal/day); and model 3, additionally adjusted for each baseline dietary pattern score and 1-year changes in body weight. All linear regression models were further adjusted for baseline eGFR (ml/min/1.73m^2).

We used the robust variance estimators to account for intra-cluster correlations in all regression models. The p for linear trend was calculated assigning the median value of each category and modelling it as a continuous variable.

We also evaluated whether the associations observed between categories of changes in dietary pattern scores and changes in eGFR could be modified by sex, age, diabetes, and intervention group. Interaction was tested with the likelihood ratio tests, which involved comparing models with and without cross-product terms.

An additional analysis was included to assess the importance of each individual item of the 17-item erMedDiet Score on changes in eGFR and ≥ 10% decline in eGFR. Following a previous described method [30], each item was consecutively removed one at a time from the total score. The exclusion of each item reduced the total score to 16 items. Therefore, to assure comparability with the original score, which could have a maximum punctuation of 17, we multiplied the estimated β-coefficients and the logarithm of the estimated odds ratios by 16/17. The latest was back-transformed to the original scale through exponentiation.

Statistical analyses were performed with Stata/SE software, version 14.0 (StataCorp, College Station, TX). All tests were considered significant at a 2-tailed p value < 0.05.

Results

Baseline characteristics of the study population according to 1-year changes categories (decrease/maintenance *vs.* tertile 3) of 17-item erMedDiet, Trichopoulou-MedDiet and DASH dietary pattern scores are presented in Table 1. Participants located in the highest tertile of increase in the 17-item erMedDiet score were less likely to be older, women and physically active, had less prevalence of diabetes, had more energy intake and consumed less proteins. Participants with higher increase in the Trichopoulou-MedDiet score adherence were more likely to exercise, had higher hypertension prevalence, less energy intake and consumed more proteins. Those individuals with higher increase in the DASH score were younger and mainly men. They had a higher energy intake and consumed less protein. Furthermore, differences in smoking status and education level were also observed. Regarding baseline scores of each dietary pattern, participants who most changed their adherence to the corresponding dietary pattern after one year of follow-up showed lower points at the beginning of the study. Baseline characteristics of the population under study according to the four categories of changes of each dietary pattern and Protein Diet Score are displayed in Supplementary Tables 1 and 2.

The mean eGFR of the study population at baseline was 84.2 mL/min/1.73 m^2. Over the first year of follow-up, the mean eGFR change was -0.94 mL/min/1.73 m^2.

Table 1 Baseline characteristics according to categories of changes in the Mediterranean diet (17-item erMedDiet score and Trichopoulou) and the Dietary Approaches to Stop Hypertension (DASH) scores after 1 year of follow-up in the PREDIMED-PLUS cohort

	Δ Mediterranean diet (17-item erMedDiet score)		*p* value	Δ Mediterranean diet (Trichopoulou)		*p* value	Δ Dietary approaches to stop hypertension (DASH)		*p* value
	Decr/maint	T3		Decr/maint	T3		Decr/maint	T3	
	n = 1124	*n* = 1423		*n* = 3408	*n* = 534		*n* = 2793	*n* = 852	
Baseline 17-item erMedDiet score, points	10.5 ± 2.5	6.5 ± 1.9	< 0.01	8.7 ± 2.7	7.7 ± 2.6	< 0.01	9 ± 2.7	7.4 ± 2.4	< 0.01
Baseline Trichopoulou MedDiet, points	4.6 ± 1.6	4.2 ± 1.6	< 0.01	5 ± 1.5	2.7 ± 1.3	< 0.01	4.7 ± 1.6	3.8 ± 1.6	< 0.01
Baseline DASH, points	25.3 ± 5.2	22.6 ± 4.9	< 0.01	24.7 ± 5.1	21.9 ± 5	< 0.01	26.2 ± 4.8	19.3 ± 3.8	< 0.01
Age, years	65.3 ± 5	64.6 ± 4.8	< 0.01	65.2 ± 4.9	64.8 ± 4.9	0.09	65.3 ± 4.9	64.7 ± 4.8	< 0.01
Women, % (*n*)	51.4 (578)	43.6 (621)	< 0.01	48.2 (1643)	47.6 (254)	0.91	51.2 (1431)	37.8 (322)	< 0.01
BMI, kg/m^2	32.5 ± 3.5	32.6 ± 3.5	0.19	32.5 ± 3.4	32.6 ± 3.5	0.45	32.5 ± 3.5	32.7 ± 3.5	0.35
PA, METS/min/week	2622.5 ± 2468.1	2375.8 ± 2321.4	0.01	2534.7 ± 2296.4	2745 ± 2615.5	0.04	2597.5 ± 2322.2	2413.6 ± 2202.9	0.16
Energy intake, kcal/d	2347.9 ± 549.5	2423 ± 544	< 0.01	2409.6 ± 542.8	2311.4 ± 551.8	< 0.01	2355.9 ± 533.7	2476.8 ± 559.8	< 0.01
Protein intake, % energy	17 ± 2.8	16.3 ± 2.7	< 0.01	16.6 ± 2.7	17.1 ± 2.9	< 0.01	16.9 ± 2.8	16.4 ± 2.8	< 0.01
Smoking status, % (*n*)			0.39			0.89			0.02
Never smoked	45.3 (509)	43 (612)		44.9 (1530)	42.7 (228)		45.9 (1283)	40.6 (346)	
Former smoker	40.9 (459)	44.6 (634)		42.9 (1463)	43.6 (233)		41.2 (1150)	47.3 (403)	
Current smoker	13.9 (156)	12.4 (177)		12.2 (415)	13.7 (73)		12.9 (360)	12.1 (103)	
Education level, % (*n*)			0.20			0.27			0.02
Primary education	51.4 (578)	48.6 (692)		49.4 (1684)	50.4 (269)		51.1 (1427)	49.4 (421)	
Secondary education	26 (292)	30.9 (439)		28.3 (965)	31.7 (169)		27 (754)	30.6 (261)	
Academic or graduate	22.6 (254)	20.5 (292)		22.3 (759)	18 (96)		21.9 (612)	20 (170)	
eGFR, mL/min/1.73m^2	83.4 ± 14.4	84.7 ± 13.5	0.12	84.1 ± 13.9	83.6 ± 14.3	0.72	84.4 ± 13.8	84.1 ± 14.2	0.46
CKD, % (*n*)	7.4 (83)	6.1 (87)	0.42	6.6 (224)	7.5 (40)	0.76	6.3 (176)	7 (60)	0.43
Type 2 diabetes, % (*n*)	31.2 (351)	27.1 (385)	0.01	30.7 (1047)	27.5 (147)	0.38	30.8 (859)	28.8 (245)	0.21
Hypertension, % (*n*)	83.9 (943)	85.2 (1212)	0.58	83.8 (2856)	86 (459)	0.02	83.2 (2324)	86 (733)	0.17
Hypercholesterolemia, % (*n*)	68.8 (773)	70.6 (1004)	0.50	69.6 (2372)	70.6 (377)	0.83	70.1 (1959)	69.1 (589)	0.55

Values are presented as percentages (*n*) for categorical variables and means ± standard deviations for continuous variables. *p* value for the comparison among all categories was calculated by chi-square or one-way analysis of variance test for categorical and continuous variables, respectively

Decr/Maint, Decrease/Maintenance; *T*, tertile; *MedDiet*, Mediterranean Diet; *BMI*, Body mass index; *PA*, Physical activity; *eGFR*, estimated Glomerular filtration rate; *CKD*, Cronic kidney disease (eGFR < 60 mL/min/1.73m^2)

Multivariable linear regression analyses for the associations between categories of changes in the adherence to the different dietary patterns and changes in eGFR at one year are depicted in Table 2. In the fully adjusted model, one year 17-item erMedDiet score changes were directly associated with eGFR changes (β: 0.78; 95% CI: 0.12–1.44 for T1 *vs*. decrease/maintenance; β: 1.06; 95% CI: 0.31–1.82 for T2 *vs*. decrease/maintenance; and β: 1.87; 95% CI: 1.00–2.73 for T3 *vs*. decrease/maintenance). Similar results were observed when we modeled this dietary pattern as continuous variable (β: 0.23; 95% CI: 0.13–0.32 for each 1-point increment). Changes in the Trichopoulou-MedDiet and DASH scores were not associated with eGFR changes neither when analyzed as categories nor in continuous manner, in any of the adjusted models.

Table 2 Multivariable adjusted β-coefficients and 95% CI for changes in eGFR (ml/min/1.73m^2) across categories of changes to the Mediterranean Diet (17-item erMedDiet score and Trichopoulou) and DASH Diet adherence after 1 year of follow-up in the PREDIMED-PLUS cohort

	Δ Mediterranean diet (17-item erMedDiet score)				
	Decr/Maint	T1	T2	T3	*p* for trend
	(*n* = 1124)	(*n* = 1917)	(*n* = 1211)	(*n* = 1423)	
Δ 17-item erMedDiet score	− 1.2 ± 1.4	2.1 ± 0.8	4.5 ± 0.5	7.5 ± 1.6	
Δ eGFR, ml/min/1.73m^{2a}	− 1.92 (− 2.49 to − 1.34)	− 1.10 (− 1.5 to − 0.71)	− 0.83 (− 1.29 to − 0.37)	− 0.03 (− 0.55–0.48)	
β (95% CI)					
Model 1	0 (Ref.)	0.41 (− 0.23–1.05)	0.54 (− 0.14–1.22)	1.02 (0.35–1.69)*	0.003
Model 2	0 (Ref.)	0.45 (− 0.19–1.08)	0.5 (− 0.20–1.19)	0.96 (0.25–1.68)*	0.010
Model 3	0 (Ref.)	0.78 (0.12–1.44)*	1.06 (0.31 to 1.82)*	1.87 (1.00–2.73)*	< 0.001
	Δ Mediterranean diet (Trichopoulou)				
	(*n* = 3408)	(*n* = 1055)	(*n* = 678)	(*n* = 534)	
Δ Trichopoulou-MedDiet	− 1.2 ± 1.2	1 ± 0	2 ± 0	3.5 ± 0.7	
Δ eGFR, ml/min/1.73m^{2a}	− 1.11 (− 1.41 to − 0.81)	− 0.56 (− 1.07 to − 0.05)	− 0.75 (− 1.42 to − 0.08)	− 0.81 (− 1.57 to − 0.05)	
β (95% CI)					
Model 1	0 (Ref.)	0.41 (− 0.17–1.00)	0.23 (− 0.49–0.95)	0.23 (− 0.52–0.98)	0.258
Model 2	0 (Ref.)	0.48 (− 0.1–1.07)	0.25 (− 0.47–0.97)	0.19 (− 0.57–0.95)	0.253
Model 3	0 (Ref.)	0.56 (− 0.05–1.16)	0.35 (− 0.41–1.11)	0.33 (− 0.52–1.18)	0.169
	Δ Dietary approaches to stop hypertension (DASH)				
	(*n* = 2793)	(*n* = 1131)	(*n* = 899)	(*n* = 852)	
Δ DASH	− 3.7 ± 3.3	2.0 ± 0.8	4.9 ± 0.8	9.6 ± 2.7	
Δ eGFR, ml/min/1.73m^{2a}	− 0.98 (− 1.33 to − 0.62)	− 0.74 (− 1.2 to − 0.28)	− 1.03 (− 1.62 to − 0.45)	− 0.98 (− 1.63 to − 0.33)	
β (95% CI)					
Model 1	0 (Ref.)	0.24 (− 0.32–0.80)	0.07 (− 0.58–0.73)	0.19 (− 0.47–0.86)	0.536
Model 2	0 (Ref.)	0.25 (− 0.31–0.81)	− 0.00 (− 0.67–0.66)	0.06 (− 0.62–0.75)	0.819
Model 3	0 (Ref.)	0.22 (− 0.37– 0.81)	− 0.06 (− 0.78–0.66)	− 0.04 (− 0.84–0.77)	0.957

Decr/Maint, Decrease/Maintenance; *T*, tertile; *eGFR*, Estimated glomerular filtration rate; *MedDiet*, Mediterranean Diet; *DASH*, Dietary approaches to stop hypertension

Linear regression models were used to assess changes in eGFR by categories of changes in dietary patterns score. Model 1 was adjusted for baseline eGFR, sex and age. Model 2 was additionally adjusted for BMI, smoking habits (never, current or former smoker), educational level (primary, secondary education, graduate), leisure time physical activity (METS/min/week), diabetes prevalence (yes/no), hypertension prevalence (yes/no), hypercholesterolemia prevalence (yes/no), center (categorized into quartiles by number of participants), intervention group and energy intake (kcal/day). Model 3 was additionally adjusted for each baseline dietary pattern score and 1-year changes in body weight

[a]Multivariable adjusted mean changes in eGFR (ml/min/1.73m^2) after 1 year of follow-up

*p value < 0.05

No statistically significant interactions were observed between sex, age, diabetes status or intervention group and the changes in the dietary patterns scores mentioned above in relation to changes in eGFR (data not shown).

Table 3 shows the association between changes in dietary patterns and ORs of ≥ 10% eGFR decline after 1 year of follow-up. Changes in the 17-item erMedDiet score showed a significant graded association with eGFR decline in the fully adjusted model (OR: 0.75; 95% CI: 0.61–0.92 for T1 of increase vs. decrease/maintenance; OR: 0.68; 95% CI: 0.53–0.87 for T2 of increase *vs*. decrease/maintenance; OR: 0.62; 95% CI: 0.47–0.82, for T3 of increase *vs*. decrease/maintenance). No significantly associations were observed between changes in the Trichopoulou-MedDiet neither in the DASH score and ≥ 10% eGFR decline after 1 year. When these dietary patterns were modeled as continuous variables,

Table 3 Multivariable adjusted odd ratios and 95% CI for eGFR decline (> 10%) across categories of changes to the Mediterranean Diet (17-item erMedDiet score and Trichopoulou) and DASH Diet after 1 year of follow-up

	Δ Mediterranean diet (17-item erMedDiet score)				
	Decr/Maint	T1	T2	T3	*p* for trend
	(*n* = 1124)	(*n* = 1917)	(*n* = 1211)	(*n* = 1423)	
Δ 17-item erMedDiet score	− 1.2 ± 1.4	2.1 ± 0.8	4.5 ± 0.5	7.5 ± 1.6	
eGFR decline, % (*n*)	18.33 (206)	15.86 (304)	15.03 (182)	15.11 (215)	
Model 1	1 (Ref.)	0.84 (0.69–1.02)	0.80 (0.64–0.99)*	0.80 (0.65 to 0.99)*	0.052
Model 2	1 (Ref.)	0.81 (0.66–0.99)*	0.77 (0.61–0.97)*	0.76 (0.60 to 0.96)*	0.029
Model 3	1 (Ref.)	0.75 (0.61–0.92)*	0.68 (0.53–0.87)*	0.62 (0.47 to 0.82)*	0.001
	Δ Mediterranean diet (Trichopoulou)				
	(*n* = 3408)	(*n* = 1055)	(*n* = 678)	(*n* = 534)	
Δ Trichopoulou-MedDiet	− 1.2 ± 1.2	1 ± 0	2 ± 0	3.5 ± 0.7	
eGFR decline, % (*n*)	16.08 (548)	16.30 (172)	14.90 (101)	16.10 (86)	
Model 1	1 (Ref.)	1.02 (0.85–1.24)	0.92 (0.73–1.16)	1.01 (0.79–1.29)	0.809
Model 2	1 (Ref.)	1.00 (0.83–1.21)	0.91 (0.72–1.15)	1.00 (0.77–1.29)	0.686
Model 3	1 (Ref.)	1.02 (0.84–1.25)	0.94 (0.73–1.20)	1.05 (0.79–1.39)	0.998
	Δ Dietary approaches to stop hypertension (DASH)				
	(*n* = 2793)	(*n* = 1131)	(*n* = 899)	(*n* = 852)	
Δ DASH	− 3.7 ± 3.3	2.0 ± 0.8	4.9 ± 0.8	9.6 ± 2.7	
eGFR decline, % (*n*)	16.36 (457)	14.41 (163)	17.02 (153)	15.73 (134)	
Model 1	1 (Ref.)	0.87 (0.72–1.05)	1.06 (0.87–1.30)	0.97 (0.78–1.20)	0.872
Model 2	1 (Ref.)	0.85 (0.70–1.04)	1.04 (0.84–1.28)	0.95 (0.76–1.18)	0.685
Model 3	1 (Ref.)	0.85 (0.70–1.05)	1.05 (0.83–1.32)	0.97 (0.74–1.26)	0.862

Logistic regression models were used to assess eGFR decline (> 10%) by categories of dietary patterns score changes. Model 1 was adjusted for sex and age. Model 2 was additionally adjusted for BMI, smoking habits (never, current or former smoker), educational level (primary, secondary education, graduate), leisure time physical activity (METS/min/week), diabetes prevalence (yes/no), hypertension prevalence (yes/no), hypercholesterolemia prevalence (yes/no), center (categorized into quartiles by number of participants), intervention group and energy intake (kcal/day). Model 3 was additionally adjusted for each baseline dietary pattern score and 1-year changes in body weight

Decr/Maint, Decrease/Maintenance; *T*, tertile; *eGFR*, Estimated glomerular filtration rate; *MedDiet*, Mediterranean Diet; *DASH*, Dietary approaches to stop hypertension

*p value < 0.05

similar associations were obtained, being only the 17-item erMedDiet score associated with lower odds of ≥ 10% eGFR decline (OR: 0.95; 95%: CI 0.92–0.98 for 1-point increment). Similar results were observed after excluding 378 participants with CKD at baseline from the main analysis, which are depicted in Supplementary Table 4.

Figure 1 displays the association between changes in Protein Diet score and eGFR changes and ≥ 10% eGFR decline after one year of follow-up. We observed a significant association between this score and both renal outcomes. Compared to participants without changes or with a decrease in the Protein Diet score, those in the highest tertile of increase had greater downward changes in eGFR (β: − 0.87; 95% CI: − 1.73 to − 0.01) and a 32% higher odds of eGFR decline (OR: 1.32; 95% CI: 1.00–1.75) in the fully adjusted model. When each component of this score was examined separately, only the change in total protein intake (E%) score presented a significant inverse association with eGFR changes (β: − 1.04; 95% CI: − 1.88 to − 0.21; for T3 *vs.* decrease/maintenance) in the multivariate adjusted model.

Table 4 shows the additional analysis after the alternatively removal of each individual component of the 17-item erMedDiet score modeled as continuous in the regression models. The results remained consistent with those from the main analyses for both eGFR changes and ≥ 10% eGFR decline. We observed that the greatest contributors to the association between changes in 17-item erMedDiet score and eGFR changes after 1 year of follow-up were the consumption of ≥ 2 units/day of vegetables, ≥ 3 servings/week of legumes (13% reduction in the association after removing these items from the total score); the use of sofrito ≥ 2 times/week (17% reduction) and moderate consumption of wine (22% reduction). Similar results were obtained when we

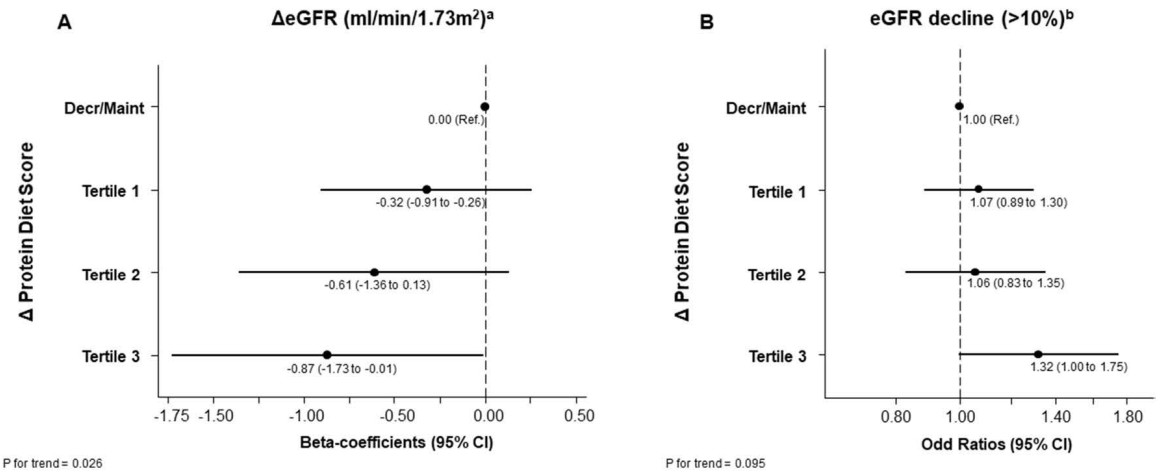

Fig. 1 Associations between changes in Protein Diet score and kidney function. **A** Multivariable adjusted β-coefficients and 95%CI for changes in eGFR (ml/min/1.73m^2) across categories of changes to the protein diet score adherence after 1 year of follow-up. **B** Multivariable adjusted odd ratios and 95%CI for eGFR decline (> 10%) across categories of changes to the protein diet score adherence after 1 year of follow-up. *Decr/Maint*, Decrease/Maintenance; *eGFR*, Estimated glomerular filtration rate; *Decr/Maint*, Decrease/Maintenance. [a]Mean changes in eGFR (ml/min/1.73m^2): Decr/Maint (− 0.71; − 1.02 to − 0.41), tertile 1 of changes (− 1.05; − 1.52 to − 0.57), tertile 2 of changes (− 1.31; − 1.96 to − 0.65), tertile 3 of changes (− 1.61; − 2.38 to − 0.84). [b]Percentage of participants with eGFR decline(> 10%): Decr/Maint (n = 507; % = 15.54), tertile 1 of changes (n = 196; % = 16.27), tertile 2 of changes (n = 106; % = 15.57), tertile 3 of changes (n = 98; % = 18.60). All models were adjusted for baseline eGFR (except for eGFR decline > 10%), sex, age, BMI, smoking habits (never, current or former smoker), educational level (primary, secondary education, graduate), leisure time physical activity (METS/min/week), diabetes prevalence (yes/no), hypertension prevalence (yes/no), hypercholesterolemia prevalence (yes/no), center (categorized into quartiles by number of participants), intervention group and energy intake (kcal/day) and 1-year changes in body weight

performed the same removing items procedures for ≥ 10% eGFR decline as an outcome variable.

Discussion

To the best of our knowledge, this is the first prospective study examining the association between different a priori defined dietary patterns adherence and kidney function in elderly individuals with overweight/obesity and MetS. We found that a higher upward change in the adherence to a 17-item erMedDiet score was associated with improvements in eGFR changes and with 38% lower odds of eGFR decline after controlling for potential confounders. However, changes in the adherence to the Trichopoulou-MedDiet and DASH Score were not associated with changes in eGFR, neither with a ≥ 10% eGFR decline. Regarding the Protein Diet Score, higher changes toward a greater adherence were associated with a worsening of eGFR.

Previous studies have reported that MedDiet adherence is inversely associated with eGFR decline [31], incidence of CKD [32, 33], and risk of end-stage of kidney disease (ESKD) [34] in populations of youth to middle-age with apparently preserved eGFR. Our results regarding the prespecified 17-item Med Diet score are in line with two prior randomized clinical trials, the PREDIMED in Spain [35] and the DIRECT [36] in Israel, in which MedDiet improved levels of eGFR in participants with overweight/obesity, whereas the data-driven by the Trichopoulou score not. In the Lifelines cohort study conducted on apparently healthy middle-aged adults of Netherlands, an inverse association between the MedDiet adherence according to Trichopoulou and eGFR decline was reported in men, but not in women [31]. Besides, in the Uppsala Longitudinal Study of Adult Men cohort (ULSAM), conducted in middle-age men, it was observed that a greater adherence to the MedDiet according Trichopoulou was significantly associated with lower odds of having CKD when it was estimated by cystatine C, but not by creatinine estimation [33]. In our study, the analysis was performed in the whole study population because we did not observe any interaction with sex. However, considering that previous evidence has reported significant associations in men but not in women, future studies stratifying by sex are needed to shed new light on whether the MedDiet could have a different role in kidney function in men than women. In the Northern Manhattan Study (NOMAS), a prospective multiethnic cohort conducted in 3298 middle-age participants with no previous history of stroke, no significant association were observed across their four categories of Trichopoulou-MedDiet adherence and eGFR decline, neither change in eGFR [15]. The apparent disagreement between 17-MedDiet and Trichopoulou-MedDiet Scores in our study reveals the disparities between both tools concerning the items included. The inclusion of more food groups

Table 4 Association between 1-point increment in the 17-item erMedDiet score and changes in eGFR (ml/min/1.73m^2) and eGFR decline (> 10%) after alternate subtraction of each of its dietary components

	β-coefficient (95%CI Δ eGFR	Reduction/ increase (%)	OR (95%CI) eGFR decline (> 10%)	Reduction/ increase (%)
17-item erMedDiet score overall	0.23 (0.13–0.32)	–	0.95 (0.92–0.98)	–
Minus item 1	0.21 (0.12–0.30)	− 8.70	0.96 (0.93–0.98)	− 20
Minus item 2	0.20 (0.11–0.30)	− 13.04	0.96 (0.93–0.99)	− 20
Minus item 3	0.22 (0.12–0.31)	− 4.35	0.96 (0.93–0.99)	− 20
Minus item 4	0.24 (0.14–0.33)	4.35	0.96 (0.92–0.99)	− 20
Minus item 5	0.22 (0.13–0.31)	− 4.35	0.95 (0.93–0.98)	0
Minus item 6	0.22 (0.12–0.31)	− 4.35	0.96 (0.93–0.98)	− 20
Minus item 7	0.20 (0.10–0.29)	− 13.04	0.96 (0.93–0.99)	− 20
Minus item 8	0.22 (0.13–0.31)	− 4.35	0.95 (0.92–0.98)	0
Minus item 9	0.24 (0.15–0.34)	4.35	0.95 (0.92–0.98)	0
Minus item 10	0.24 (0.15–0.34)	4.35	0.95 (0.92–0.98)	0
Minus item 11	0.21 (0.12–0.31)	− 8.70	0.95 (0.92–0.98)	0
Minus item 12	0.18 (0.09–0.28)	− 17.39	0.96 (0.93–0.99)	− 20
Minus item 13	0.24 (0.15–0.34)	4.35	0.95 (0.92–0.98)	0
Minus item 14	0.23 (0.13–0.33)	0	0.95 (0.92–0.98)	0
Minus item 15	0.22 (0.12–0.32)	− 4.35	0.95 (0.92–0.98)	0
Minus item 16	0.28 (0.18–0.38)	13.04	0.93 (0.90–0.96)	40
Minus item 17	0.20 (0.11–0.29)	− 21.73	0.96 (0.93–0.99)	− 20

Models were adjusted for baseline eGFR (only for β-coefficient), sex, age, BMI, smoking habits (never, current or former smoker), educational level (primary, secondary education, graduate), leisure time physical activity (METS/min/week), diabetes prevalence (yes/no), hypertension prevalence (yes/no), hypercholesterolemia prevalence (yes/no), center (categorized into quartiles by number of participants), intervention group and energy intake (kcal/day), 1-year changes in body weight, baseline dietary pattern score and changes in corresponding subtracted components

eGFR, Estimated glomerular filtration rate; *MedDiet*, Mediterranean diet; *Item 1*, use only extra virgin olive oil for cooking; *Item 2*, consume ≥ 2 of vegetables units/day; *Item 3*, consume ≥ 3 fruits units/day; *Item 4*, consume ≤ 1 serving/week of red meat and processed meats; *Item 5*, consume < 1 serving/week of butter, margarine or cream; *Item 6*, drink < 1 sugar-sweetened beverage or fruit juice/week; *Item 7*, consume ≥ 3 servings/week of legumes; *Item 8*, consume ≥ 3 servings/week of fish or shellfish; *Item 9*, consume < 3 times/week commercial sweets or pastries; *Item 10*, consume ≥ 3 servings/week of nuts; *Item 11*, consume preferentially lean meats; *Item 12*, consume ≥ 2 times/week dishes seasoned with sofrito (tomato, onion, leek or garlic sauce simmered in olive oil); *Item 13*, add preferentially noncaloric artificial sweeteners to beverages; *Item 14*, consume ≥ 1 servings/day of white bread; *Item 15*, consume ≥ 5 times/week whole grain cereals and pasta; *Item 16*, consume < 3 times/week refined pasta or white rice; *Item 17*, moderate consume of wine /day (2–3 glasses in men/1–2 in women)

into the 17-MedDiet Score screener tool maybe would imply a more representative assessment of diet to observe changes in eGFR. Additionally, scoring criteria are quite different; while the 17-item erMedDiet uses absolute values derived from a predefined questionnaire, the Trichopoulou-MedDiet score is assigned according to gender-specific medians of food group consumption of the study population [26]. The later may hinder comparability with other publications where particular cultural and dietary habits are present. Likewise, these issues may explain the controversial results observed between both MedDiet scoring methods in our sample. Of note, this is the first study so far analyzing the association between the adherence to the MedDiet, using the 17-MedDiet score screener tool, and renal function. Further studies, considering both scores (Trichopoulou-MedDiet and 17-item erMedDiet) are needed to clarify and strengthen our results.

Although the DASH diet has been formerly associated with better kidney function outcomes such as rapid eGFR decline [13] or CKD incidence [37], a recent meta-analysis did not confirm such associations [11], which is partly agreed with our findings. In fact, in the Healthy Aging in Neighborhoods of Diversity across the Life Span (HANDLS) study [16], the authors not only reported a lack of association between this dietary pattern and eGFR decline or incident CKD but also even greater risk of rapid kidney function decline among the group of middle-age individuals with hypertension after 5 years of follow-up. Whether a plant-based diet like the DASH, which is apparently similar to the MedDiet, is not associated with a better kidney

function, despite being protective against hypertension [38], which in turn is a well-known risk factor for kidney disease, needs to be further investigated.

The underlying biological mechanisms whereby changes toward a greater adherence to a plant-based diet as the MedDiet, but not the DASH diet, could preserve or improve kidney function are not entirely clear. When we analyzed individual components of the 17-item erMedDiet Score, vegetables, legumes, wine and the traditional Mediterranean tomato and olive oil sauce (*sofrito*) were associated with better renal function. These foods represent the main differences between the two dietary aforementioned patterns and are rich in some beneficial nutrients such as fiber, antioxidants and anti-inflammatory compounds that may play a protective role by reducing the levels of inflammatory biomarkers, improving endothelial function, plasma lipid profiles and insulin resistance, lowering high blood pressure, and preserving a low glycemic index and load [6, 39–45].

Both Mediterranean diet and DASH, which has been usually associated with better markers of kidney function, are rich in plant-protein. Despite some evidence has raised concerns about the detrimental effects of high-protein intake on kidney damage [46], it seems that besides the quantity, the source of protein intake might be considered when analyzing these associations. Likewise, its long-term effects in vulnerable elderly individuals are still unknown. Our results regarding the Protein Diet Score are not in line with those of a previous cross-sectional study based on three cohort [18], NQplus, Lifelines, and the Young Finns Study, where a positive association between the protein score and eGFR was repy, by assuming that participants with renal dysfunction have already changed their protein intake [18]. Besides, our results from each component of the Protein Diet Score suggest that increased protein total intake could be the major drive for the deleterious renal association observed. Further research with long duration is warranted using this score to clarify its potential implication in kidney function and damage.

Limitations of the current study must be considered when interpreting the results. Firstly, eGFR measurement was estimated using SCr, as in most of epidemiologic studies, but other more optimal biomarkers exist. However, the procedures of those biomarkers are expensive, time consuming and difficult to be used in large population studies. Secondly, although the FFQ is an appropriate tool to assess usual dietary intake when it is carefully administered by trained staff, recall bias could not be ruled out. Thirdly, this study was conducted in elderly Mediterranean individuals with overweight/obesity and MetS; consequently, our findings cannot be extrapolated to other study populations. Fourthly, PREDIMED-Plus study is a randomized controlled trial; therefore, the lifestyle advice in turn could affect our findings. Nevertheless, we adjusted our analyses by the intervention group. Finally, SCr has a well-known biological variability and as we only measured it at baseline and 1 year (at short term), some degree of misclassification could be present. The present study also has notable strengths, which deserve to be mentioned, such as its prospective design, the relatively large sample size and the inclusion of different dietary patterns in main analyses. Moreover, we adjusted our models for a substantial number of covariates which could affect renal function, to try to control for potential bias. Even so, as in any observational study, we cannot rule out the possibility of residual or unmeasured confounding.

Conclusion

In summary, changes towards a greater adherence in the 17-item erMedDiet score after 1 year of follow-up were associated with better eGFR and lower odds of ≥ 10% eGFR decline in an elderly population with MetS. Not significant results were observed with regards to the Trichopoulou-MedDiet and DASH Score. These discrepancies could be partially explained by their differences in the calculation of the score, which in contrast to the 17-item erMedDiet depends on cut-off points based on the study population distribution of each item. Future studies in the renal function field should consider including the 17-item erMedDiet score in their analyses to clarify and strengthen our findings. Besides, the Protein Diet Score was associated with changes towards a worse eGFR and higher odds of ≥ 10% eGFR decline. Our results provide further insights to the evidence concerning a priori dietary patterns associated with kidney function in populations at high cardiovascular risk and reinforce the role of a plant-protein-based healthy diet in preserving renal function, particularly among this vulnerable population group. Therefore, improving dietary habits following a MedDiet could lead to a better kidney function, and even it could be considered an appropriate and safe preventive strategy against the onset or progression of CKD. However, these findings should be confirmed by future long-term studies and randomized controlled trials before including this kind of diet in the prevention and management guidelines of CKD.

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Declarations

Conflict of interest JS-S reported receiving research support from the Instituto de Salud Carlos III (ISCIII), Ministerio de Educación y Ciencia, Departament de Salut Pública de la Generalitat de Catalunya, the European Commission, the California Walnut Commission, Patrimonio Comunal Olivarero, La Morella Nuts, and Borges S.A; receiving consulting fees or travel expenses from California Walnut Commission, Eroski Foundation, 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; and grants and personal fees from Instituto Danone. ER reported receiving grants, personal fees, and nonfinancial support from the California Walnut Commission during the conduct of the study and grants, personal fees, nonfinancial support from Alexion; personal fees from Amarin; and nonfinancial support from the International Nut Council outside the submitted work. RE reported receiving grants from Instituto de Salud Carlos III and olive oil for the trial from Fundacion Patrimonio Comunal Olivarero\during the conduct of the study and personal fees from Brewers of Europe, Fundación Cerveza y Salud, Interprofesional del Aceite de Oliva, Instituto Cervantes, Pernaud Richar, Fundación Dieta Mediterránea, Wine and Culinary International Forum; nonfinancial support from Sociedad Española de Nutrición and Fundación Bosch y Gimpera; and grants from Uriach Laboratories outside the submitted work. XP reported receiving grants from ISCIII during the conduct of the study; receiving consulting fees from Sanofi Aventis, Amgen, and Abbott laboratories; receiving lecture personal fees from Esteve, Lacer and Rubio laboratories. All other authors have no relevant financial or non-financial interests to disclose.

Ethical approval 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.

Consent to participate Written informed consent was obtained from all individual participants included in the study.

Consent for publication All authors have approved this manuscript for publication.

Availability of the data and materials 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.

Code availability Not applicable.

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Online supplementary material

Supplementary table 1. Baseline characteristics according to categories of changes in the Mediterranean diet (17-item erMedDiet score and Trichopoulou) adherence after 1 year of follow-up in the PREDIMED-PLUS cohort

	Δ Mediterranean Diet (17-item erMedDiet score)					Δ Mediterranean Diet (Trichopoulou)				
	Dec/Maint n=1124	**T1** n=1917	**T2** n=1211	**T3** n=1423	p-value	**Dec/Maint** n=3408	**T1** n=1055	**T2** n=678	**T3** n=534	p-value
Baseline 17-item erMedDiet score, points	10.5 ± 2.5	9.1 ± 2.4	8 ± 2.2	6.5 ± 1.9	<0.01	8.7 ± 2.7	8.3 ± 2.6	8.1 ± 2.6	7.7 ± 2.6	<0.01
Baseline Trichopoulou-MedDiet, points	4.6 ± 1.6	4.5 ± 1.6	4.3 ± 1.7	4.2 ± 1.6	<0.01	5 ± 1.5	3.9 ± 1.3	3.4 ± 1.3	2.7 ± 1.3	<0.01
Baseline DASH, points	25.3 ± 5.2	24.5 ± 5.2	23.7 ± 5.1	22.6 ± 4.9	<0.01	24.7 ± 5.1	23.4 ± 5.2	22.7 ± 5.2	21.9 ± 5	<0.01
Baseline Protein Diet, points	10.3 ± 3	10 ± 3	10 ± 3	9.7 ± 2.9	<0.01	10.3 ± 3	9.9 ± 3	9.6 ± 2.9	9.1 ± 2.9	<0.01
Age, years	65.3 ± 5	65.3 ± 4.8	64.9 ± 4.9	64.6 ± 4.8	<0.01	65.2 ± 4.9	64.8 ± 4.8	64.8 ± 4.9	64.8 ± 4.9	0.09
Women, % (n)	51.4 (578)	49.5 (949)	47.3 (573)	43.6 (621)	<0.01	48.2 (1643)	48.1 (507)	46.8 (317)	47.6 (254)	0.91
BMI, kg/m^2	32.5 ± 3.5	32.4 ± 3.4	32.5 ± 3.4	32.6 ± 3.5	0.19	32.5 ± 3.4	32.4 ± 3.3	32.7 ± 3.5	32.6 ± 3.5	0.45
PA, METS/min/week	2622.5 ± 2468.1	2618.7 ± 2280.7	2519.6 ± 2316.8	2375.8 ± 2321.4	0.01	2534.7 ± 2296.4	2553.8 ± 2456	2361.6 ± 2108.2	2745 ± 2615.5	0.04
Energy intake, kcal/d	2347.9 ± 549.5	2344.7 ± 542.8	2373.8 ± 563.3	2423 ± 544	<0.01	2409.6 ± 542.8	2311 ± 544.2	2318.9 ± 574.2	2311.4 ± 551.8	<0.01
Protein intake, % energy	17 ± 2.8	16.9 ± 2.9	16.8 ± 2.8	16.3 ± 2.7	<0.01	16.6 ± 2.7	16.9 ± 2.8	17 ± 3	17.1 ± 2.9	<0.01
Smoking status, % (n)					0.39					0.89
Never smoked	45.3 (509)	45.5 (872)	43.5 (527)	43 (612)		44.9 (1530)	43.6 (460)	44.5 (302)	42.7 (228)	
Former smoker	40.9 (459)	42.1 (807)	44.4 (538)	44.6 (634)		42.9 (1463)	43.1 (455)	42.3 (287)	43.6 (233)	
Current smoker	13.9 (156)	12.4 (238)	12.1 (146)	12.4 (177)		12.2 (415)	13.3 (140)	13.1 (89)	13.7 (73)	
Education level, % (n)					0.20					0.27
Primary education	51.4 (578)	49.5 (948)	49.5 (599)	48.6 (692)		49.4 (1684)	50.8 (536)	48.4 (328)	50.4 (269)	
Secondary education	26 (292)	28.6 (548)	29.9 (362)	30.9 (439)		28.3 (965)	29.1 (307)	29.5 (200)	31.7 (169)	
Academic or graduate	22.6 (254)	22 (421)	20.6 (250)	20.5 (292)		22.3 (759)	20.1 (212)	22.1 (150)	18 (96)	
eGFR, mL/min/1.73m^2	83.4 ± 14.4	84.1 ± 13.9	84.3 ± 14.2	84.7 ± 13.5	0.12	84.1 ± 13.9	84.4 ± 13.9	84.4 ± 14	83.6 ± 14.3	0.72
CKD, % (n)	7.4 (83)	6.3 (120)	7.3 (88)	6.1 (87)	0.42	6.6 (224)	6.9 (73)	6.1 (41)	7.5 (40)	0.76
Type 2 diabetes, % (n)	31.2 (351)	32.1 (616)	31.1 (376)	27.1 (385)	0.01	30.7 (1047)	31.6 (333)	29.7 (201)	27.5 (147)	0.38
Hypertension, % (n)	83.9 (943)	84.4 (1618)	83.2 (1008)	85.2 (1212)	0.58	83.8 (2856)	82.7 (872)	87.6 (594)	86 (459)	0.02
Hypercholesterolemia, % (n)	68.8 (773)	70.3 (1347)	68.3 (827)	70.6 (1004)	0.50	69.6 (2372)	70.1 (739)	68.3 (463)	70.6 (377)	0.83

Abbreviations: Decr/Maint, Decrease/Maintenance; MedDiet, Mediterranean Diet; BMI, Body Mass Index; PA, Physical activity; eGFR, estimated Glomerular Filtration Rate; CKD, Chronic Kidney Disease (eGFR<60 mL/min/1.73m^2).

Values are presented as percentages (n) for categorical variables and means ± standard deviations (SD) for continuous variables. P-value was calculated by chi-square or one-way analysis of variance test for categorical and continuous variables, respectively.

Online supplementary material

Supplementary table 2. Baseline characteristics according to categories of changes in the Dietary Approaches to Stop Hypertension (DASH) and the Protein Diet adherence after 1 year of follow-up in the PREDIMED-PLUS cohort

	Δ Dietary Approaches to Stop Hypertension (DASH)					**Δ Protein Diet score**				
	Decr/Maint n= 2793	**T1** n= 1131	**T2** n= 899	**T3** n= 852	p-value	**Decr/Maint**	**T1**	**T2**	**T3**	p-value
Baseline 17-item erMedDiet score, points	9 ± 2.7	8.4 ± 2.6	8.1 ± 2.5	7.4 ± 2.4	<0.01	8.7 ± 2.7	8.4 ± 2.7	8.2 ± 2.6	7.9 ± 2.5	<0.01
Baseline Trichopoulou-MedDiet, points	4.7 ± 1.6	4.3 ± 1.6	4.1 ± 1.6	3.8 ± 1.6	<0.01	4.6 ± 1.6	4.2 ± 1.6	4.1 ± 1.6	3.9 ± 1.6	<0.01
Baseline DASH, points	26.2 ± 4.8	23.5 ± 4.6	22.0 ± 4.4	19.3 ± 3.8	<0.01	24.6 ± 5.2	23.5 ± 5.2	22.9 ± 5.2	22.2 ± 4.9	<0.01
Baseline Protein Diet, points	10.5 ± 3	10 ± 2.9	9.5 ± 3	9 ± 2.8	<0.01	-2.3 ± 2.1	1.5 ± 0.5	3.5 ± 0.5	6.3 ± 1.7	<0.01
Age, years	65.3 ± 4.9	64.8 ± 4.8	64.8 ± 5	64.7 ± 4.8	<0.01	65.2 ± 4.9	65.1 ± 4.8	64.8 ± 4.9	64.7 ± 5	0.12
Women, % (n)	51.2 (1431)	47.9 (542)	47.4 (426)	37.8 (322)	<0.01	48 (1566)	49.1 (591)	46.8 (319)	46.5 (245)	0.71
BMI, kg/m^2	32.5 ± 3.5	32.5 ± 3.4	32.4 ± 3.3	32.7 ± 3.5	0.35	32.4 ± 3.4	32.6 ± 3.5	32.6 ± 3.5	32.6 ± 3.4	0.24
PA, METS/min/week	2597.5 ± 2322.2	2542 ± 2381.2	2461.8 ± 2452.5	2413.6 ± 2202.9	0.16	2583.4 ± 2349.9	2527.8 ± 2373.3	2455.4 ± 2270.3	2379.9 ± 2267.7	0.21
Energy intake, kcal/d	2355.9 ± 533.7	2317.8 ± 563.5	2385.9 ± 558.3	2476.8 ± 559.8	<0.01	2364.8 ± 552	2379.8 ± 542.1	2390.9 ± 534.5	2365.9 ± 571.8	0.64
Protein intake, % energy	16.9 ± 2.8	16.7 ± 2.8	16.6 ± 3	16.4 ± 2.8	<0.01	17 ± 2.8	16.5 ± 2.8	16.4 ± 2.7	15.9 ± 2.7	<0.01
Smoking status, % (n)					0.02					0.40
Never smoked	45.9 (1283)	44.5 (503)	43.2 (388)	40.6 (346)		44.0 (1436)	44.8 (540)	48.0 (327)	41.2 (217)	
Former smoker	41.2 (1150)	44.3 (501)	42.7 (384)	47.3 (403)		43.1 (1407)	42.8 (516)	40.4 (275)	45.5 (240)	
Current smoker	12.9 (360)	11.2 (127)	14.1 (127)	12.1 (103)		12.8 (419)	12.4 (540)	11.6 (327)	13.3 (70)	
Education level, % (n)					0.02					0.07
Primary education	51.1 (1427)	48.4 (547)	46.9 (422)	49.4 (421)		50.7 (1654)	49.1 (591)	48 (327)	46.5 (245)	
Secondary education	27 (754)	29.1 (329)	33.0 (297)	30.6 (261)		27.3 (889)	30.4 (366)	31.3 (213)	32.8 (173)	
Academic or graduate	21.9 (612)	22.6 (255)	20.0 (180)	20 (170)		22 (719)	20.6 (248)	20.7 (141)	20.7 (109)	
eGFR, mL/min/1.73m^2	84.4 ± 13.8	84.1 ± 13.8	83.6 ± 14.5	84.1 ± 14.2	0.46	84.5 ± 13.7	83.6 ± 13.9	83.8 ± 14.4	84.1 ± 14.9	0.29
CKD, % (n)	6.3 (176)	6.4 (72)	7.8 (70)	7 (60)	0.43	6.1 (197)	7.7 (93)	6.6 (45)	8.2 (43)	0.11
Type 2 diabetes, % (n)	30.8 (859)	32.4 (366)	28.7 (258)	28.8 (245)	0.21	30.8 (1003)	30.8 (371)	30.3 (206)	28.1 (148)	0.66
Hypertension, % (n)	83.2 (2324)	84.9 (960)	85 (764)	86 (733)	0.17	84.8 (2766)	83.7 (1009)	83.4 (568)	83.1 (438)	0.60
Hypercholesterolemia, % (n)	70.1 (1959)	70.2 (794)	67.7 (609)	69.1 (589)	0.55	69.6 (2271)	69.6 (839)	69.8 (475)	69.5 (366)	1.00

Abbreviations: Decr/Maint, Decrease/Maintenance; MedDiet, Mediterranean Diet; BMI, Body Mass Index; PA, Physical activity; eGFR, estimated Glomerular Filtration Rate; CKD, Cronic Kidney Disease (eGFR<60 mL/min/1.73m^2).

Values are presented as percentages (n) for categorical variables and means ± standard deviations (SD) for continuous variables. P-value was calculated by chi-square or one-way analysis of variance test for categorical and continuous variables, respectively.

Online supplementary material

Supplementary table 3. Baseline characteristics of excluded vs included individuals for analysis

	PREDIMED-Plus participants		
	Excluded n=4002	Included n=5675	p-value
Baseline 17-item erMedDiet score, points	8.5 ± 2.7	8.5 ± 2.7	0.535
Baseline Trichopoulou MedDiet, points	4.3 ± 1.6	4.4 ± 1.6	0.512
Baseline DASH, points	23.8 ± 5.2	24.0 ± 5.2	0.271
Age, years	65.5 ± 5.1	65.0 ± 4.9	<0.01
Women, % (n)	53.05 (2123)	47.95 (2721)	<0.01
BMI, kg/m^2	32.9 ± 3.5	32.5 ± 3.4	<0.01
PA, METS/min/week	2109.5 ± 2080.9	2537.3 ± 2338.3	<0.01
Energy intake, kcal/d	2636.2 ± 906.1	2371.2 ± 549.6	<0.01
Protein intake, % energy	16.7 ± 2.8	16.7 ± 2.8	0.849
Smoking status, % (n)			<0.01
Never smoked	48.6 (1945)	44.41 (2520)	
Former smoker	38.6 (1544)	42.9 (2438)	
Current smoker	12.8 (513)	12.6 (717)	
Education level, % (n)			<0.01
Primary education	45.2 (540)	49.6 (2817)	
Secondary education	28.9 (345)	28.9 (1641)	
Academic or graduate	25.9 (309)	21.4 (1217)	
eGFR, mL/min/1.73m^2	84.8 ± 14.3	84.2 ± 13.9	0.167
CKD, % (n)	5.7 (63)	6.7 (378)	0.229
Type 2 diabetes, % (n)	30.4 (365)	30.5 (1728)	0.996
Hypertension, % (n)	79.5 (3182)	84.3 (4781)	<0.01
Hypercholesterolemia, % (n)	69.8 (2795)	69.6 (3951)	0.817

Abbreviations: Decr/Maint, Decrease/Maintenance; T, tertile; MedDiet, Mediterranean Diet; BMI, Body M Index; PA, Physical activity; eGFR, estimated Glomerular Filtration Rate; CKD, Cronic Kidney Dise (eGFR<60 mL/min/1.73m^2).

Values are presented as percentages (n) for categorical variables and means ± standard deviations for continu variables. P-value was calculated by chi-square or one-way analysis of variance test for categorical and continu variables, respectively.

Online supplementary material

Supplementary table 4. Multivariable adjusted β-coefficients and 95% CI for changes in eGFR (ml/min/1.73m^2) and multivariable adjusted odd ratios and 95% CI for eGFR decline (>10%) across categories of changes to the Mediterranean Diet (17-item erMedDiet score and Trichopoulou) and DASH Diet adherence in participants without CKD (eGFR >60 ml/min/1.73m2) at baseline after 1 year of follow-up (n=5297)

	Δ Mediterranean Diet (17-item erMedDiet score)				
	Decr/Maint	**T1**	**T2**	**T3**	**p for trend**
	(n = 1041)	(n = 1797)	(n = 1123)	(n = 1336)	
Δ 17-item erMedDiet score	-1.2 ± 1.4	2.1 ± 0.8	4.5 ± 0.5	7.5 ± 1.5	
Δ eGFR, ml/min/1.73m^2[a]	-2.30 (-2.88 to -1.71)	-1.44 (-1.84 to -1.03)	-1.29 (-1.74 to -0.83)	-0.64 (-1.16 to -0.12)	
Multivariable model (β-coefficients and 95% CI)	0 (Ref.)	0.86 (0.19 to 1.53)	1.01 (0.24 to 1.78)	1.65 (0.77 to 2.54)	<0.001
eGFR decline >10%, % (n)	19.2 (200)	15.9 (286)	15.4 (173)	15.0 (200)	
Multivariable model (OR and 95% CI)	1 (Ref.)	0.72 (0.58 to 0.88)	0.67 (0.52 to 0.86)	0.59 (0.44 to 0.79)	0.001
	Δ Mediterranean Diet (Trichopoulou)				
	(n = 3184)	(n = 982)	(n = 637)	(n = 494)	
Δ Trichopoulou-MedDiet	-1.2 ± 1.2	1 ± 0	2 ± 0	3.5 ± 0.7	
Δ eGFR, ml/min/1.73m^2[a]	-1.49 (-1.80 to-1.19)	-1.03 (-1.54 to -0.52)	-1.42 (-2.11 to -0.73)	-1.22 (-2.00 to -0.44)	
Multivariable model (β-coefficients and 95% CI)	0 (Ref.)	0.46 (-0.14 to 1.07)	0.07 (-0.70 to 0.84)	0.27 (-0.60 to 1.15)	0.386
eGFR decline >10%, % (n)	16.1 (514)	16.7 (164)	15.5 (99)	16.6 (82)	
Model 3 (OR and 95% CI)	1 (Ref.)	1.06 (0.86 to 1.29)	0.99 (0.77 to 1.28)	1.10 (0.82 to 1.48)	0.605
	Δ Dietary Approaches to Stop Hypertension (DASH)				
	(n = 2617)	(n = 1059)	(n = 829)	(n = 792)	
Δ DASH	-3.7 ± 3.3	2.0 ± 0.8	4.9 ± 0.8	9.5 ± 2.6	
Δ eGFR, ml/min/1.73m^2[a]	-1.37 (-1.72 to -1.01)	-1.12 (-1.58 to -0.65)	-1.34 (-1.94 to -0.74)	-1.78 (-2.44 to -1.13)	
Multivariable model (β-coefficients and 95% CI)	0 (Ref.)	0.25 (-0.35 to 0.85)	0.03 (-0.70 to 0.76)	-0.42(-1.22 to 0.39)	0.520
eGFR decline >10%, % (n)	16.5 (432)	14.7 (156)	17.25 (143)	16.2 (128)	
Multivariable model (OR and 95% CI)	1 (Ref.)	0.89 (0.72 to 1.09)	1.10 (0.87 to 1.39)	1.04 (0.80 to 1.36)	0.702

Abbreviations: Decr/Maint, Decrease/Maintenance; T, tertile; eGFR, Estimated glomerular filtration rate; MedDiet, Mediterranean Diet; DASH, Dietary Approaches to Stop Hypertension.
[a]Multivariable adjusted mean changes in eGFR (ml/min/1.73m^2) after 1 year of follow-up.
Linear regression models were used to assess changes in eGFR by categories of changes in dietary patterns score. Logistic regression models were used to assess eGFR decline (>10%) by categories of dietary patterns score changes. Multivariable model was adjusted for baseline eGFR (except for logistic regression model), sex, age. BMI, smoking habits (never, current or former smoker), educational level (primary, secondary education, graduate), leisure time physical activity (METS/min/week), diabetes prevalence (yes/no), hypertension prevalence (yes/no), hypercholesterolemia prevalence (yes/no), center (categorized into quartiles by number of participants), intervention group, energy intake (kcal/day), each baseline dietary pattern score and 1-year changes in body weight.
*p-value < 0.05

Chapter 2. Longitudinal association of dietary acid load with kidney function decline in an older adult population with metabolic syndrome.

Cristina Valle-Hita, Nerea Becerra-Tomás, Andrés Díaz-López, Zenaida Vázquez-Ruiz, Isabel Megías, Dolores Corella, Albert Goday, J Alfredo Martínez, Ángel M Alonso-Gómez, Julia Wärnberg, Jesús Vioque, Dora Romaguera, José López-Miranda, Ramon Estruch, Francisco J Tinahones, José Lapetra, Lluís Serra-Majem, Aurora Bueno-Cavanillas, Josep A Tur, Vicente Martín-Sánchez, Xavier Pintó,José J Gaforio, Pilar Matía-Martín, Josep Vidal, Angela Amengual-Galbarte, Lidia Daimiel, Emilio Ros, Ana García-Arellano, Rocío Barragán, Montse Fitó, Patricia J Peña-Orihuela, Alberto Asencio-Aznar, Enrique Gómez-Gracia, Diego Martinez-Urbistondo, Marga Morey, Rosa Casas, Eva María Garrido-Garrido, Lucas Tojal-Sierra, Miguel Damas-Fuentes, Estibaliz Goñi, Carolina Ortega-Azorín, Olga Castañer, Antonio Garcia-Rios, Cristina Gisbert-Sellés, Carmen Sayón-Orea, Helmut Schröder, Jordi Salas-Salvadó and Nancy Babio.

Overview of the novelty and significance of this publication

What is already known?

- The relationship between dietary acid load and kidney function has been evaluated in several cross-sectional studies, but in few prospective studies. Given the disparities in findings between studies, it is difficult to confirm the apparently negative association that some of the investigations have pointed out.
- These analyses have barely been evaluated in Mediterranean populations at high cardiovascular risk.

What does this study add?

- This was the first prospective study assessing the association between dietary acid load and kidney function by concurrently using eGFR and UACR, the main complementary markers of kidney function.
- We found that higher dietary acid load was associated with changes toward worse eGFR and higher odds of eGFR decline and UACR increase.

Conclusion:

- This study provides further evidence to recommend a diet low in acid load to improve kidney function and, even prevent CKD onset and its progression among older individuals with underlying comorbid conditions.

UNIVERSITAT ROVIRA I VIRGILI
DIETARY FACTORS AND KIDNEY FUNCTION: INSIGHTS FROM A POPULATION OF OLDER MEDITERRANEAN ADULTS WITH OVERWEIGHT OR OBESITY AND METABOLIC SYNDROME
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Longitudinal association of dietary acid load with kidney function decline in an older adult population with metabolic syndrome

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Background: Diets high in acid load may contribute to kidney function impairment. This study aimed to investigate the association between dietary acid load and 1-year changes in glomerular filtration rate (eGFR) and urine albumin/creatinine ratio (UACR).

Methods: Older adults with overweight/obesity and metabolic syndrome (mean age 65 ± 5 years, 48% women) from the PREDIMED-Plus study who had available data on eGFR ($n = 5,874$) or UACR ($n = 3,639$) at baseline and after 1 year of follow-up were included in this prospective analysis. Dietary acid load was estimated as potential renal acid load (PRAL) and net endogenous acid production (NEAP) at baseline from a food frequency questionnaire. Linear and logistic regression models were fitted to evaluate the associations between baseline tertiles of dietary acid load and kidney function outcomes. One year-changes in eGFR and UACR were set as the primary outcomes. We secondarily assessed ≥ 10% eGFR decline or ≥10% UACR increase.

Results: After multiple adjustments, individuals in the highest tertile of PRAL or NEAP showed higher one-year changes in eGFR (PRAL, β: −0.64 ml/min/1.73 m^2; 95% CI: −1.21 to −0.08 and NEAP, β: −0.56 ml/min/1.73 m^2; 95% CI: −1.13 to 0.01) compared to those in the lowest category. No associations with changes in UACR were found. Participants with higher levels of PRAL and NEAP had significantly higher odds of developing ≥10% eGFR decline (PRAL, OR: 1.28; 95% CI: 1.07–1.54 and NEAP, OR: 1.24; 95% CI: 1.03–1.50) and ≥10 % UACR increase (PRAL, OR: 1.23; 95% CI: 1.04–1.46) compared to individuals with lower dietary acid load.

Conclusions: Higher PRAL and NEAP were associated with worse kidney function after 1 year of follow-up as measured by eGFR and UACR markers in an older Spanish population with overweight/obesity and metabolic syndrome.

KEYWORDS

kidney function, chronic kidney disease (CKD), glomerular filtration rate (GFR), net endogenous acid production (NEAP), potential renal acid load (PRAL), dietary acid load, albuminuria, renal nutrition

Introduction

Impaired renal function is a common condition in older individuals with comorbidities as diabetes, hypertension or obesity that usually predicts the onset of Chronic Kidney Disease (CKD) (1). In the last few years, there has been a growing concern about this disease since it has a huge impact worldwide affecting around 700 million people (2). In addition, CKD is linked to several complications, such as cardiovascular events, hospitalization and/or premature death (2, 3). Consequently, appropriate and affordable prevention measures are required to preserve renal function, especially in high-risk populations (1). Prevention measures could also reduce the severe impact of CKD on the wellbeing of individuals and health systems (3–5).

Dietary habits appear to be one of the major modifiable risk factors markedly influencing renal impartment and its progression to CKD (5, 6). Additionally, the role of diet in preserving the acid-base balance of the body has recently become more relevant, given the emerging evidence linking dietary acid load with the development of different chronic diseases (7, 8), including CKD (9). It has been previously documented that healthy dietary patterns provide an alkaline environment in the body (10, 11) since plant-based food such as vegetables, fruit and some nuts or legumes have the capacity of inducing a basic environment (12). However, red and processed meats as well as ultra-processed foods are acid-producing (9, 12). Thus, these foods might be implied in the onset of a low-grade metabolic acidosis state, thereby, resulting in faster progression of kidney disease (11, 13). Overall, potential renal acid load (PRAL) and net endogenous acid production (NEAP) are the most common and suitable indexes used to estimate the acid load of the diet (9, 11). Considering the aforementioned evidence, following a healthy diet characterized by a low acid load may be a useful preventive strategy against kidney dysfunction.

To date, results from epidemiological studies focused on dietary acid load and kidney function or CKD development are inconsistent (9) and this relationship needs to be further explored. In some studies, an association between higher levels of PRAL and/or NEAP indexes and an estimated-glomerular filtration rate (eGFR) decline or higher risk of incident CKD (14–18) has been reported, but others have observed no such associations (19, 20). Also, the quality of evidence is moderate as most of the studies were mainly cross-sectional (14–17, 21, 22), and only a few were longitudinal studies (18–20). Furthermore, since most research has been conducted in healthy young or middle-aged individuals or in patients with advanced CKD, little is known about the potentially harmful association between dietary acid load and kidney function of older populations with underlying comorbid conditions. In addition, analyses assessing dietary acid load on kidney function have rarely been conducted in Mediterranean populations at high cardiovascular risk. Hence, as more scientific evidence and longitudinal studies in this field are required, we prospectively investigated the association between PRAL and NEAP and 1-year changes in two markers of kidney function decline, eGFR and Urine Albumin/Creatinine Ratio (UACR), in a large Spanish cohort of older adults with overweight/obesity and metabolic syndrome (MetS).

Materials and methods

Study population and design

The present study is a prospective analysis of baseline and 1-year data within the framework of the PREvención con DIeta MEDiterránea (PREDIMED)-Plus trial. Briefly, the PREDIMED-Plus is an ongoing, parallel-group, randomized and controlled clinical trial aiming to assess the effect of an intensive weight loss intervention on cardiovascular disease (CVD) morbidity and mortality. An energy-restricted Mediterranean diet (MedDiet), physical activity promotion and behavioral support are compared to usual care advice in 6,874 older adults enrolled between 2013 and 2016 by 23 Spanish recruitment centers. Eligible participants were

Abbreviations: BMI, Body Mass Index; CKD, Chronic Kidney Disease; CI, Confidence Interval; E, Energy; FFQ, Food Frequency Questionnaire; GFR, Glomerular Filtration Rate; MedDiet, Mediterranean Diet; MetS, Metabolic Syndrome; METS, Metabolic Equivalent Task; NEAP, Net Endogenous Acid Production; PRAL, Potential Renal Acid Load; PREDIMED, Prevención con Dieta Mediterránea; SCr, Serum Creatinine; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration equation for Caucasian individuals; OR, Odds Ratios; UACR, Urine Albumin/Creatinine Ratio.

men aged 55–75 years and women aged 60–75 years with overweight or obesity [Body Mass Index (BMI) 27–40 kg/m^2], who satisfied at least 3 criteria for the MetS (23). Further details of the inclusion and exclusion criteria and the study design have been described elsewhere (24). A detailed explanation of the protocol is also available at https://www.predimedplus.com. This trial was registered on the International Standard Randomized Controlled Trial registry (https://www.isrctn.com/ISRCTN89898870) with number 89898870 in July of 2014. The final study protocol and procedures were approved following the standards of the Declaration of Helsinki by the Institutional Review Boards of participating centers and all participants provided written informed consent.

For the current study, participants without completed food frequency questionnaire (FFQ) information and reporting implausible total energy intake (men $<$ 800 and $>$4,000 kcal/day and women $<$ 500 and $>$3,500 kcal/day) at baseline were excluded (n = 227) from the analyses (25). We also excluded participants who died (n = 11) or were lost to follow-up (n = 16) during the first year. Moreover, participants with missing data on eGFR (n = 746) or UACR (n = 2,981) at baseline and/or at the 1-year assessment were excluded when eGFR or UACR were the outcomes, respectively. Therefore, a final sample of 5,874 participants for eGFR and 3,639 participants for UACR were analyzed (Supplementary Figure 1).

Assessment of dietary intake and dietary acid load

To evaluate dietary intake, trained dieticians administered a 143-item FFQ, based on a previously validated one for the Spanish population (26), in face-to-face interviews at baseline. Each participant was asked about their frequency of consumption during the preceding year of each specific item, which had nine possible answers ranging from never to more than 6 times per day. The typical portion size of each item was subsequently transformed into grams or milliliters per day, as appropriate. Two Spanish food composition databases were referenced to calculate total daily energy and nutrient intake (27, 28).

Dietary acid load was estimated at baseline using individual nutritional data obtained from the FFQ. Previously published methods proposed by Remer and Manz (29) and Frassetto et al. (8) were applied for the calculation of PRAL and NEAP scores, respectively. PRAL (mEq/day) = 0.4888 $\times$ protein intake (g/day) + 0.0366 $\times$ phosphorus (mg/day) − 0.0205 $\times$ potassium (mg/day) − 0.0125 $\times$ calcium (mg/day) − 0.0263 $\times$ magnesium (mg/day). NEAP (mEq/day) = 54.5 $\times$ protein (g/day)/potassium (mEq/day) − 10.2.

Ascertainment of the outcome

Serum creatinine (SCr) levels and urinary creatinine and albumin concentrations were determined using routine laboratory methods from blood and spot morning urine samples collected at baseline and 1-year following overnight fasting. For the current study, 1-year changes in eGFR and UACR were considered our primary outcomes. We indirectly determined eGFR from SCr using the Chronic Kidney Disease Epidemiology Collaboration equation for Caucasian individuals (CKD-EPI) (30) and the UACR was calculated by dividing urine albumin (mg/l) by urine creatinine concentrations (mg/l). UACR values were truncated at 500 mg/g to minimize the influence of outliers. There were 21 observations $>$ 500 mg/g at baseline and 24 at 1 year that were $>$500 mg/g and subsequently set to 500 mg/g. One-year changes in both eGFR and UACR were calculated by subtracting values at 1 year minus values at baseline. Secondary outcomes were $\geq$10% eGFR decline and $\geq$10% UACR increase following a 1-year follow-up. These were estimated by applying the formula: [(1-year eGFR or UACR − baseline eGFR or UACR)/baseline eGFR or UACR]*100. Participants were categorized as those with a $\geq$10% or $<$10% eGFR decline (31) or with a $\geq$10% or $<$10% increase in UACR.

Covariate assessment

At baseline, trained PREDIMED-Plus staff collected socio-demographic and lifestyle information including age, sex, educational level, physical activity, smoking status, as well as medication use and history of disease using several questionnaires or reviewing medical records. Moreover, adherence to the energy-reduced MedDiet was evaluated using a validated 17-item MedDiet questionnaire (32). Compliance with each item of the MedDiet questionnaire was scored with one point and non-compliance with 0. Thereafter, a cut-off point based on the median of the score was determined by dividing individuals into those with high adherence to a MedDiet ($\geq$9 points) or a low adherence ($<$9 points). Moreover, other cut-off points were tested arbitrarily and defined as the highest tertiles or quartiles (in both cases high adherence was observed to be $\geq$12 points). Total daily energy intake and sodium intake were estimated according to data from the FFQ. Anthropometric variables were measured in duplicate and resting blood pressure was measured in triplicate using an automated digital device (Omron-HEM297705C). BMI was calculated as weight in kilograms divided by the square of height in meters. In our analysis, white blood cell count was used to assess inflammation (leucocytes $>$ 10 $\times$ 10^9/L).

Statistical analyses

For the present report, we used the PREDIMED-Plus database generated in December 2020. Participants were categorized into tertiles of PRAL and NEAP. One-way ANOVA and chi-square tests were used to evaluate differences among tertiles of PRAL and NEAP for the baseline characteristics of the study population. Descriptive data were expressed as means ± SD for continuous variables and percentages (%) and numbers for categorical variables.

Multivariate linear regression models were performed to examine the associations between tertiles of PRAL and NEAP at baseline and 1-year changes in eGFR (ml/min/1.73 m^2) and UACR (mg/g). For these associations, PRAL and NEAP were also analyzed as continuous variables (both for each 1-SD increase). β-coefficients and 95% confidence intervals (CIs) were assessed using two different models: Model 1 was adjusted for sex and age; and Model 2 was further adjusted for study center (categorized into quartiles by number of participants), intervention group (treatment/control), BMI (kg/m^2), smoking status (never/current/former smoker), educational level (primary education/secondary education/graduate), leisure-time physical activity (METs/min/week, tertiles), diabetes prevalence (yes/no), hypertension prevalence (yes/no), hypercholesterolemia prevalence (yes/no), angiotensin-converting enzyme inhibitors (ACEis) (yes/no), angiotensin II receptor blockers (ARBs) (yes/no), MedDiet adherence (high/low adherence), energy intake (kcal/day, tertiles), sodium intake (mg/day, tertiles) and high leukocyte levels (yes/no). Moreover, odds ratios (OR) and their 95% CIs were calculated for the association between tertiles of NEAP and PRAL and ≥10% eGFR decline and ≥10% UACR increase at 1-year of follow-up adjusting for the same confounders as mentioned in model 2. The first tertile was used as a reference category in all regression models. Additionally, linear regression models were further adjusted for baseline eGFR (ml/min/1.73 m^2) or baseline UACR (mg/g) depending on the main outcome. Variance inflation factors (VIFs) were used to assess collinearity for the multivariable models and, as VIFs were <2.5, none of the covariates needed to be removed. All analyses were conducted with robust estimates of the variance to correct for possible intra-cluster correlation. Intra-cluster was defined as the participants who shared the same household. To assess the linear trend, the median value of each tertile of PRAL and NEAP were modeled as continuous variables.

We also conducted subgroup analyses for the 1-year changes in eGFR and UACR stratifying by baseline categories of eGFR (≥90; 60–90; <60 ml/min/1.73 m^2) and UACR (<30; ≥30 mg/g). Interaction between tertiles of PRAL and NEAP with categories of eGFR, UACR, and energy-reduced MedDiet adherence (high/low), as well as the intervention/control group were checked in the fullest multivariable model using likelihood ratio tests and non-significant results were observed. In a sensitivity analysis, we repeated our main analysis investigating the association between PRAL and NEAP with 1-year changes in eGFR and UACR after excluding individuals with eGFR < 60 ml/min/1.73 m^2 or with UACR > 300 mg/g at baseline. In addition, as a supplementary analysis, we evaluated the association between dietary acid load and ≥5% eGFR decline and ≥5% UACR increase following the same procedure mentioned previously. Statistical analyses were conducted using Stata/SE software, version 14.0 (StataCorp, College Station, TX) and significance level was set at a 2-tailed $p < 0.05$.

Results

Table 1 shows the baseline characteristics of the study population according to tertiles of PRAL and NEAP. In general, participants with higher values of PRAL and NEAP at baseline were more likely to be younger, men, have a higher BMI, smoke, have a higher educational level, and were less likely to exercise. Participants in the highest tertiles of PRAL and NEAP also had higher levels of creatinine and eGFR than those in the lowest tertile. In terms of mediations, participants in the highest tertiles of PRAL and NEAP were more likely to have used insulin, ACEis treatment, and took less antihypertensive and ARB drugs. Furthermore, individuals in the highest tertile of NEAP were more likely to have type 2 diabetes. However, no significant differences were observed between tertiles of PRAL nor NEAP regarding the UACR or CKD. Concerning dietary assessment, adherence to an energy-reduced MedDiet was lower in individuals with higher dietary acid load levels than those in the lowest tertile of PRAL and NEAP. Moreover, participants in the highest tertile of PRAL and NEAP had a lower intake of vegetable/animal protein ratio, carbohydrates and fiber while they had a higher energy, protein and fat consumption than those with low values of both dietary acid load indexes. Similar trends were observed when baseline consumption of food groups across tertiles of PRAL and NEAP were analyzed (Supplementary Table 1). Supplementary Table 2 presents further information regarding macronutrient and micronutrient intake, especially those related to dietary acid load, at 1-year of follow-up. Baseline characteristics according to included and excluded participants from the eGFR or UACR analyses are described in Supplementary Table 3.

The association (β-coefficient; 95% CI) between tertiles of PRAL and NEAP and 1-year changes in eGFR and UACR are displayed in Table 2. In the most adjusted model, PRAL showed a significant inverse association with 1-year changes in eGFR (β: −0.17 ml/min/1.73 m^2; 95% CI: −0.71 to 0.36 for T2 vs. T1, β: −0.64 ml/min/1.73 m^2; 95% CI: −1.21 to −0.08 for T3 vs. T1). We found similar results when PRAL and NEAP were analyzed as continuous variables (PRAL: β: −0.25 ml/min/1.73 m^2; 95% CI: −0.47 to −0.03 for each

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TABLE 1 Baseline characteristics of the study population with data on eGFR at 1-year follow-up by tertiles of PRAL and NEAP (n = 5,874).

		PRAL (mEq/d)				NEAP (mEq/d)			
	Total n = 5,874	T1 n = 1,958	T2 n = 1,958	T3 n = 1,958	p-value	T1 n = 1,958	T2 n = 1,958	T3 n = 1,958	p-value
PRAL, mEq/day	−5.4 ± 15.6	–	–	–	–	−21.4 ± 11.3	−5.0 ± 5.4	10.1 ± 8.7	<0.01
NEAP, mEq/day	36.9 ± 8.1	29.0 ± 3.8	36.4 ± 2.8	45.6 ± 6.0	<0.01	–	–	–	–
Age, years	65.0 ± 4.9	65.7 ± 4.7	65.1 ± 5.0	64.2 ± 4.9	<0.01	65.7 ± 4.7	65.3 ± 4.9	64.1 ± 4.9	<0.01
Women, % (n)	48.0 (2,818)	52.7 (1, 31)	49.1 (961)	42.2 (826)	<0.01	56.0 (1,097)	48.9 (957)	39.0 (764)	<0.01
Intervention group, % (n)	49.4 (2,901)	49.3 (966)	50.3 (984)	48.6 (951)	0.57	50.0 (978)	49.9 (976)	48.4 (947)	0.54
BMI, kg/m^2	32.5 ± 3.4	32.4 ± 3.4	32.4 ± 3.4	32.8 ± 3.5	<0.01	32.3 ± 3.4	32.5 ± 3.4	32.7 ± 3.5	<0.01
PA, METS/min/week	2,528.0 ± 2,350.4	2,740.2 ± 2,483.6	2,526.2 ± 2,342.2	2,317.7 ± 2,198.8	<0.01	2,681.7 ± 2,434.1	2,547.4 ± 2,373.8	2,355.1 ± 2,228.2	<0.01
Smoking status, % (n)					<0.01				<0.01
Never smoked	44.4 (2,605)	47.9 (939)	45.5 (891)	39.6 (775)		49.9 (976)	44.7 (875)	38.5 (754)	
Former smoker	43.0 (2,528)	40.3 (789)	42.3 (828)	46.5 (911)		38.6 (756)	43.0 (842)	47.5 (930)	
Current smoker	12.6 (741)	11.8 (230)	12.2 (239)	13.9 (272)		11.5 (226)	12.3 (241)	14.0 (274)	
Education level, % (n)					<0.01				<0.01
Primary education	49.22 (2,891)	54.9 (1,075)	49.2 (963)	43.6 (853)		54.0 (1,058)	50.0 (979)	44.6 (854)	
Secondary education	29.18 (1,714)	25.2 (494)	28.9 (565)	33.4 (655)		25.6 (501)	28.3 (555)	33.6 (658)	
College/university	21.60 (1,269)	19.9 (374)	22.0 (430)	23.0 (450)		20.4 (399)	21.7 (424)	22.8 (446)	
Creatinine	0.8 ± 0.2	0.8 ± 0.2	0.8 ± 0.2	0.9 ± 0.2	<0.01	0.8 ± 0.2	0.8 ± 0.2	0.9 ± 0.2	<0.01
eGFR, ml/min/1.73 m^2	84.2 ± 13.9	83.6 ± 13.6	84.7 ± 13.9	84.3 ± 14.4	0.04	83.5 ± 13.6	84.9 ± 13.7	84.1 ± 14.5	<0.01
UACR, mg/g	16.8 ± 48.9	16.2 ± 45.0	16.8 ± 50.0	17.5 ± 51.5	0.78	16.4 ± 46.4	15.9 ± 47.0	18.2 ± 53.1	0.42
CKD, % (n)	4.4 ± 3.7	6.5 (126)	6.5 (128)	6.8 (133)	0.79	6.6 (129)	5.8 (113)	7.6 (145)	0.10
Type 2 diabetes, % (n)	30.6 (1,797)	28.9 (567)	30.7 (601)	32.1 (629)	0.10	28.8 (564)	30.4 (595)	32.6 (638)	0.04
Hypertension, % (n)	84.1 (4,941)	85.1 (1,666)	84.5 (1,654)	82.8 (1,621)	0.13	85.1 (1,667)	84.4 (1,653)	82.8 (1,621)	0.12
Hypercholesterolemia, % (n)	69.7 (4,096)	69.4 (1,359)	69.2 (1,356)	70.5 (1,381)	0.63	70.2 (1,375)	69.3 (1,356)	69.7 (1,365)	0.80
Hypertriglyceridemia, % (n)[x]	39.7 (2,327)	40.7 (795)	39.1 (763)	42.5 (831)	0.10	40.8 (795)	39.2 (765)	42.4 (829)	0.13
Low HDL, % (n)[y]	40.8 (2,389)	38.5 (751)	39.4 (768)	41.3 (808)	0.18	39.1 (763)	39.0 (760)	41.1 (804)	0.30

(Continued)

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TABLE 1 (Continued)

		PRAL (mEq/d)				NEAP (mEq/d)			
	Total $n = 5,874$	T1 $n = 1,958$	T2 $n = 1,958$	T3 $n = 1,958$	*p*-value	T1 $n = 1,958$	T2 $n = 1,958$	T3 $n = 1,958$	*p*-value
Medication use, % (*n*)	51.8 (3, 42)	52.6 (1, 30)	51.7 (1, 13)	51.0 (999)	0.66	52.8 (1, 35)	51.9 (1, 17)	50.6 (990)	0.35
Lipid-lowering drugs									
Oral blood glucose-lowering drugs	26.0 (1,528)	25.2 (494)	26.3 (516)	26.5 (518)	0.62	25.3 (495)	25.7 (504)	27.0 (529)	0.44
Insulin treatment	4.1 (239)	3.5 (68)	3.7 (73)	5.0 (98)	0.03	3.2 (64)	4.1 (81)	4.8 (94)	0.05
Antihypertensive drugs	78.7 (4,625)	81.7 (1,599)	77.9 (1,525)	76.7 (1,501)	<0.01	81.0 (1,585)	79.1 (1,549)	76.2 (1,491)	<0.01
ARBs	36.3 (2,131)	39.6 (776)	34.9 (683)	34.3 (672)	<0.01	39.5 (774)	35.2 (689)	34.1 (668)	<0.01
ACEis	30.2 (1,775)	28.6 (559)	31.2 (611)	30.9 (605)	0.11	27.9 (546)	32.0 (624)	30.9 (605)	0.02
Dietary assessment	8.5 ± 2.7	9.2 ± 2.6	8.4 ± 2.7	7.9 ± 2.5	<0.01	9.3 ± 2.6	8.6 ± 2.6	7.7 ± 2.5	<0.01
erMedDiet score, 17-points									
Energy intake, kcal/d	2,370.5 ± 548.9	2,366.1 ± 537.9	2,303.1 ± 531.8	2,442.3 ± 567.8	<0.01	2,277.5 ± 531.2	2,278.6 ± 533.1	2,455.7 ± 562.5	<0.01
Protein intake, % energy	16.7 ± 2.8	16.1 ± 2.6	16.7 ± 2.7	17.4 ± 3.0	<0.01	16.1 ± 2.7	16.9 ± 2.7	17.3 ± 2.9	<0.01
Vegetal /animal protein ratio, g/d	0.5 ± 0.2	0.67 ± 0.27	0.56 ± 0.19	0.48 ± 0.17	<0.01	0.68 ± 0.28	0.56 ± 0.19	0.49 ± 0.17	<0.01
Fat intake, % energy	39.6 ± 6.5	38.4 ± 6.4	39.7 ± 6.4	40.8 ± 6.5	<0.01	38.5 ± 6.5	39.5 ± 6.3	40.9 ± 6.5	<0.01
Carbohydrate intake, % energy	40.5 ± 6.8	42.4 ± 6.6	40.4 ± 6.5	38.7 ± 6.8	<0.01	42.4 ± 6.8	40.5 ± 6.4	38.6 ± 6.8	<0.01
Fiber intake, g/day	26.1 ± 8.7	30.4 ± 9.1	25.2 ± 7.8	22.8 ± 7.5	<0.01	29.9 ± 9.5	26.4 ± 7.9	22.2 ± 7.0	<0.01
Potassium intake, mg/day	4,477.0 ± 1,079.6	5,108.6 ± 1,124.3	4,313.1 ± 898.2	4,009.2 ± 884.4	<0.01	4,953.4 ± 1,189.3	4,501.7 ± 924.5	3,975.8 ± 866.0	<0.01
Calcium intake, mg/day	1,034.0 ± 347.0	1,062.8 ± 353.6	999.2 ± 327.9	1,040.1 ± 355.9	<0.01	1,030.0 ± 350.5	1,049.6 ± 337.1	1,022.5 ± 352.7	0.04
Magnesium intake, mg/day	420.4 ± 108.2	457.7 ± 112.5	407.6 ± 102.2	396.0 ± 99.3	<0.01	446.2 ± 117.8	425.2 ± 102.5	389.8 ± 95.6	<0.01
Phosphorus intake, mg/day	1,759.1 ± 419.9	1,750.1 ± 429.1	1,703.8 ± 401.9	1,823.5 ± 419.7	<0.01	1,713.1 ± 438.3	1,783.5 ± 403.4	1,780.8 ± 413.6	<0.01
Sodium intake, mg/day	2,430.0 ± 774.8	2,272.5 ± 736.8	23,183.0 ± 679.8	2,699.4 ± 828.6	<0.01	2,187.8 ± 712.4	2,412.4 ± 689.3	2,689.6 ± 832.1	<0.01

ACEis, Angiotensin-Converting Enzyme Inhibitors; ARBs, Angiotensin II receptor blockers; eGFR, Estimated Glomerular Filtration Rate; erMedDiet, energy-restricted Mediterranean diet; HDL, High-Density Lipoprotein; NEAP, Net Endogenous Acid Production; MET, Metabolic Equivalent of Task T, tertile; BMI, Body Mass Index; PRAL, Potential Renal Acid Load; PA, Physical activity; eGFR, estimated Glomerular Filtration Rate; CKD, Chronic Kidney Disease (eGFR < 60 ml/min/1.73 m^2); UACR, Urine Albumin/Creatinine Ratio. Values are presented as percentages (n) for categorical variables and means ± standard deviations for continuous variables. P-value was calculated by chi-square or one-way analysis of variance test for categorical and continuous variables, respectively.

[z]Fasting triglyceride concentration ≥150 mg/dL or specific treatment for lipid abnormality.

[y]HDL concentration <40 mg/dL in men and <50 mg/dL in women or specific treatment for lipid abnormality.

1-SD increment. NEAP: β: −0.28 ml/min/1.73 m^2; 95% CI: −0.51 to −0.05 for each 1-SD increment). Results remained essentially the same after adding 1-year BMI change to the most adjusted model (data not shown). PRAL and NEAP were not significantly associated with UACR changes after 1-year of follow-up after modeling them as tertiles, nor as continuous variables. In the sensitivity analyses, excluding individuals with <60 ml/min/1.73 m^2 of eGFR or with >300 mg/g of UACR did not modify the main findings for both outcomes (data not shown). When we repeated the principal analyses, stratifying by baseline categories of eGFR (≥90; 60–90; <60 ml/min/1.73 m^2) and UACR (<30; ≥30 mg/g), the results presented a similar tendency (Supplementary Table 4). In participants with eGFR ≥ 90 ml/min/1.73 m^2, significant associations were observed with eGFR changes when both dietary acid load indexes were modeled as continuous variables (PRAL: β: −0.28 ml/min/1.73 m^2; 95% CI: −0.56 to −0.01 for each 1-SD increment. NEAP: β: −0.31 ml/min/1.73 m^2; 95% CI: −0.58 to −0.03 for each 1-SD increment). The main analysis was repeated using other cut-offs points for the MedDiet score confounding factor (i.e., ≥12 points for high adherence) and similar results were found (Supplementary Table 5). We also explored the interactions between tertiles of PRAL and NEAP and the adherence to energy-reduced MedDiet, categories of eGFR and UACR, as well as intervention/control group, and no statistically significant findings were observed (all interactions, $p > 0.05$).

Figure 1 depicts the OR and 95% CI for ≥10% eGFR decline and ≥10% UACR increase according to tertiles of PRAL and NEAP. After multiple adjustments, participants in the highest tertile of PRAL and NEAP were significantly more likely to have a ≥10% eGFR decline after 1 year of follow up compared to those in the lowest tertile, with ORs of 1.28 (95% CI: 1.07–1.54) for PRAL and 1.24 (95% CI: 1.03–1.0) for NEAP. When PRAL and NEAP were modeled as continuous variables (per each 1-SD increment) higher ORs were also observed. Compared to participants with low PRAL values at baseline, participants with the highest levels had a 23% (95% CI: 1.04–1.46) higher odds of ≥10% UACR increase after 1 year of follow-up after adjusting for potential confounders. No significant associations were found between NEAP and the odds of ≥10% UACR increase or for 1-SD increment of PRAL and NEAP. When a ≥5% eGFR decline and a ≥5% UACR increase were assessed, the same results were found (Supplementary Table 6).

Discussion

The results of this prospective study conducted in older Spanish adults at high cardiovascular disease risk suggest that PRAL and NEAP are inversely associated with 1-year changes in eGFR, but not with 1-year UACR changes. Furthermore, participants with higher levels of both estimates of dietary acid load had higher odds of a ≥10% eGFR decline, and those in the highest tertile of PRAL had 23% higher odds of a ≥10% UACR increase. GFR and albuminuria are the main complementary biomarkers used in epidemiological studies to assess kidney function (3). As far as we know, this is the first study to prospectively evaluate the association between dietary acid load and kidney function concurrently assessing eGFR and UACR in a population of older adults with underlying comorbidities.

A large body of evidence has linked dietary acid load with kidney outcomes in several studies (9). However, to the best of our knowledge, there are only four cross-sectional studies and one longitudinal study investigating the potential relationship of dietary acid load with renal function defined by eGFR and/or CKD in older adults without CKD. These cross-sectional studies conducted in different cohorts of adults reported that higher dietary acid load was associated with higher odds of CKD and/or impaired kidney function as indicated by low eGFR after adjusting for multiple confounders (14, 16, 17, 33). Our observations are in accordance with these cross-sectional studies since we observed a greater eGFR decline at 1 year with higher PRAL and NEAP scores, even after adjusting for baseline eGFR and other essential confounding factors. Interestingly, our supplementary stratified analyses according to categories of eGFR, which have seldom been performed in previous studies, revealed a similar non-significant tendency to worsen kidney function with increased dietary acid load. Consistent with our findings, the prospective analysis from the cohort of the Atherosclerosis Risk in Communities (ARIC) study of 15,055 apparently healthy middle-aged participants with preserved kidney function showed that higher levels of PRAL were associated with a 13% higher risk of CKD incidence over 21 years of follow-up (18).

Regarding albuminuria, which is considered a reliable marker of kidney damage (3), preceding studies have assessed its cross-sectional association with dietary acid load obtaining inconclusive findings. In The Jackson Heart Study, there was no association between estimated Net Acid Excretion (NAE_{es}) and albuminuria (16). In contrast, the NHANES study reported a positive association between dietary acid load and albuminuria in 12,293 healthy American adults (17). Additionally, the researchers from The Uonuma CKD Cohort Study also found that higher NEAP was associated with a higher UACR and risk of albuminuria among 6,684 middle-aged Japanese adults (21). To date, no large prospective cohort study has focused on the relationship between dietary acid load and albuminuria in vulnerable older adults. In the current study, we report no association between PRAL and NEAP scores and 1-year changes in UACR. This could suggest that high dietary acid load may promote tubule-interstitial injury rather than glomerular damage. Nevertheless, we were not able to check this tubular damage hypothesis since spot/24 h total proteinuria data were not available in our dataset (34). However, it is worthwhile to mention that when UACR was also assessed as an increase ≥ 10%

TABLE 2 Multivariable-adjusted β-coefficients and 95% CI of 1-year changes in eGFR (ml/min/1.73 m^2) or in UACR (mg/g) across tertiles and per 1-SD increment of baseline PRAL and NEAP.

	PRAL (mEq/d)				
	T1	T2	T3	*p* for trend	Continuous (1 SD**)
	n = 1,958	*n* = 1,958	*n* = 1,958		*n* = 5,874
Δ in eGFR, ml/min/1.73 m^2	−0.69 (−1.07 to −0.31)	−0.86 (−1.24 to −0.49)	−1.34 (−1.72 to −0.95)		
Model 1	0 (Ref.)	−0.16 (−0.70 to 0.37)	−0.52 (−1.06 to 0.03)	0.062	−0.21 (−0.42 to 0.01)
Model 2	0 (Ref.)	−0.17 (−0.71 to 0.36)	−0.64 (−1.21 to −0.08)*	0.026	−0.25 (−0.47 to −0.03)*
	n = 1,213	*n* = 1,213	*n* = 1,213		*n* = 3,639
Δ in UACR, mg/g	4.37 (1.96 to 6.78)	2.74 (0.60 to 4.88)	1.39 (−0.62 to 3.39)		
Model 1	0 (Ref.)	−1.20 (−4.32 to 1.93)	−2.31 (−5.28 to 0.66)	0.128	−0.88 (−2.00 to 0.25)
Model 2	0 (Ref.)	−1.63 (−4.84 to 1.58)	−2.99 (−6.34 to 0.37)	0.082	−1.22 (−2.51 to 0.08)
	NEAP (mEq/d)				
	n = 1,958	*n* = 1,958	*n* = 1,958		*n* = 5,874
Δ in eGFR, ml/min/1.73 m^2	−0.68 (−1.06 to −0.30)	−0.97 (−1.35 to −0.60)	−1.24 (−1.63 to −0.84)		
Model 1	0 (Ref.)	−0.28 (−0.81 to 0.25)	−0.44 (−0.99 to 0.11)	0.116	−0.22 (−0.44 to −0.01)*
Model 2	0 (Ref.)	−0.30 (−0.83 to 0.24)	−0.56 (−1.13 to 0.01)	0.056	−0.28 (−0.51 to −0.05)*
	n = 1,213	*n* = 1,213	*n* = 1,213		*n* = 3,639
Δ in UACR, mg/g	3.92 (1.49 to 6.34)	3.09 (1.14 to 5.03)	1.49 (−0.54 to 3.53)		
Model 1	0 (Ref.)	−0.81 (−3.82 to 2.20)	−1.96 (−5.07 to 1.15)	0.214	−0.93 (−2.13 to 0.28)
Model 2	0 (Ref.)	−0.83 (−3.87 to 2.21)	−2.42 (−5.79 to 0.95)	0.154	−1.26 (−2.63 to 0.10)

eGFR, Estimated glomerular filtration rate; *NEAP*, Net Endogenous Acid Production; *T*, tertile; *PRAL*, Potential Renal Acid Load; *UACR*, Urine albumin/creatinine ratio. Model 1: adjusted for age (years), sex and baseline eGFR or baseline UACR (in continuous, depending on the main outcome). Model 2: additionally adjusted for participating center (categorized into quartiles by number of participants), intervention group (treatment/control), body mass index (kg/m^2), smoking habits (never, current or former smoker), educational level (primary, secondary education or graduate), leisure-time physical activity (METS/min/week in tertiles), diabetes prevalence (yes/no), hypertension prevalence (yes/no) and hypercholesterolemia prevalence (yes/no), ARBs (yes/no), ACEis (yes/no), Mediterranean diet adherence (high/low adherence), energy intake (kcal/day in tertiles), sodium intake (mg/g in tertiles) and high leukocytes levels (yes/no).

*p-value < 0.05.

**One SD = 15.6 mEq/d in PRAL and 8.1 mEq/d in NEAP.

after 1 year of follow-up, which is a more clinical approach, we found a significant association with PRAL. Consequently, future longitudinal studies and clinical trials would be helpful to clarify these observations related to albuminuria and dietary acid load.

Overall, our findings in conjunction with the evidence available to date, suggests that following a diet with a low acid load could be an appropriate measure to improve renal function and, accordingly, decrease the risk of CKD development and progression among older individuals from middle-aged to elderly with underlying comorbid conditions.

The potential mechanisms by which high dietary acid load may induce kidney dysfunction are unclear, though possible mechanisms have been proposed for consideration. Acid retention has been proposed to activate the intracellular renin-angiotensin system, through the previous stimulation of aldosterone production, which might be implicated in the onset or progression of kidney damage (35, 36). Moreover, metabolic acidosis appears to contribute to endothelin-1 production, which in turn could be related to tubulointerstitial injury (37–39). Besides, high dietary acid load would also induce tubular toxicity activating the complement pathway and increasing renal medullary ammonia concentrations (40–42). There is also a high probability that acid retention increases the production of oxygen-free radicals and oxidative stress (43, 44). Consequently, it is crucial for kidney health to maintain appropriate levels of acid load, and diet may play an important role in this respect (11). It should be noted that in our study individuals with high levels of dietary acid load reported higher intakes of some food groups which have been directly or indirectly implicated in kidney function damage, such as total and animal protein intake (33, 45) or sugar and sweetened products (46). By contrast, as dietary acid load increased there was a lower consumption of fiber-rich foods, including fruits, vegetables, whole-grain cereals, and nuts. Thus, the potential beneficial effects of fiber on the kidney (47) could be lacking in those individuals with high dietary acid load.

This study has some limitations that deserve to be mentioned. First, the population consisted of older Spanish individuals at high cardiovascular risk, meaning the findings may not be generalizable to other populations. Furthermore, the Mediterranean lifestyle could imply healthier habits which, at the same time, may result in different macro- and

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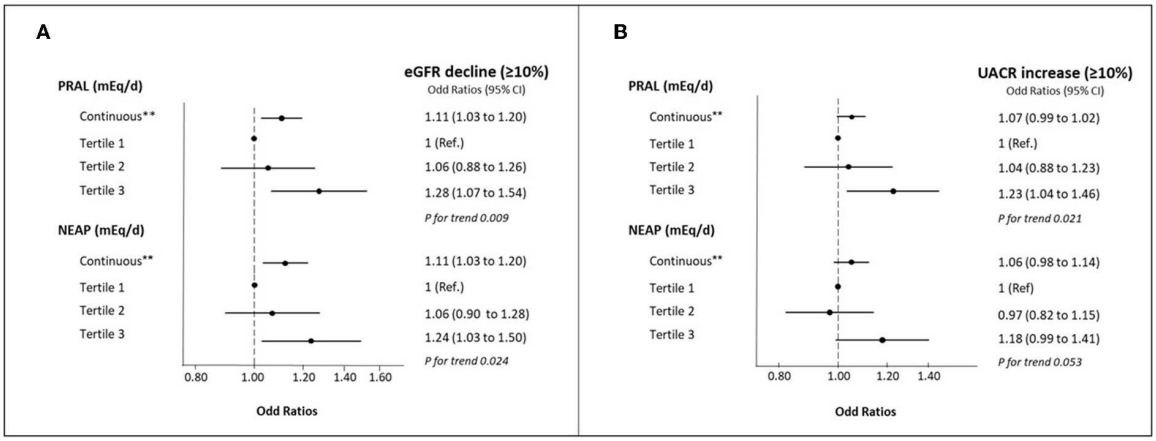

FIGURE 1
(A) Multivariable-adjusted OR (95% CIs) for ≥10% eGFR decline by tertiles of baseline PRAL and NEAP and per 1-SD increment. **(B)** Multivariable-adjusted OR (95% CIs) for ≥10% UACR increase by tertiles of baseline PRAL and NEAP and per 1-SD increment. eGFR, Estimated glomerular filtration rate; NEAP, Net Endogenous Acid Production; T, tertile; PRAL, Potential Renal Acid Load; UACR, Urine albumin/creatinine ratio. Percentage of participants with eGFR decline (>10%): tertile 1 of PRAL ($n = 296$; % = 15.1), tertile 2 of PRAL ($n = 304$; % = 15.5), tertile 3 of PRAL ($n = 346$; % = 17.7); tertile 1 of NEAP ($n = 297$; % = 15.2), tertile 2 of NEAP ($n = 312$; % = 15.9). tertile 3 of NEAP ($n = 337$; % = 17.2). Percentage of participants with UACR increase (>10%): tertile 1 of PRAL ($n = 539$; % = 44.4), tertile 2 of PRAL ($n = 547$; % = 45.1), tertile 3 of PRAL ($n = 597$; % = 49.2); tertile 1 of NEAP ($n = 550$; % = 45.3), tertile 2 of NEAP ($n = 539$; % = 44.4), tertile 3 of NEAP ($n = 594$; % = 49.0). All models were adjusted for age (years), sex, participating center (categorized into quartiles by number of participants), intervention group (treatment/control), body mass index (kg/m^2), smoking habits (never, current or former smoker), educational level (primary, secondary education or graduate), leisure-time physical activity (METS/min/week in tertiles), diabetes prevalence (yes/no), hypertension prevalence (yes/no) and hypercholesterolemia prevalence (yes/no), ARBs (yes/no), ACEis (yes/no), Mediterranean diet adherence (high/low adherence), energy intake (kcal/day in tertiles), sodium intake (mg/g in tertiles), and high leukocytes levels (yes/no). **one SD = 15.6 mEq/d in PRAL and 8.1 mEq/d in NEAP.

micronutrients intake related to kidney function, such as potassium-rich or low-sodium dietary intakes. Second, as PREDIMED-Plus is a randomized controlled trial, though, all the analyses were adjusted for the intervention group, the lifestyle advice that participants received could be affecting our findings. Third, dietary acid load was calculated using PRAL and NEAP from dietary nutrient intake information obtained from FFQ data. Although this questionnaire was validated and carefully administered by trained dietitians, potential measurement errors and reporting bias could be present. Fourth, while SCr-based eGFR was used as a biomarker of kidney function, as is common in most epidemiologic studies, there are other more optimal markers such as inulin, iothalamate or 24-h urinary creatinine clearance. Nevertheless, these procedures are expensive, time-consuming, and difficult measure in large populations. Finally, as in any observational study, although a substantial number of confounding factors were considered, confounding bias could not be completely ruled out and direct causality cannot be inferred. However, our study also has several strengths. Analyses were conducted using data from a large cohort, which has a wide selection of different variables to adjust the models for kidney function related-potential confounders. Moreover, it is important to highlight the prospective design that we performed and the joint assessment of two commonly used biomarkers of renal function. Another novel aspect of this study is the sensitivity and supplementary analyses conducted which gave robustness to the main results.

Conclusion

In conclusion, the current study conducted in a population of older Spanish adults with overweight/obesity and MetS shows that higher dietary acid load is associated with changes toward a worse eGFR and higher odds of ≥10% eGFR decline and ≥10% UACR increase. Nevertheless, further longitudinal and interventional studies are needed to clarify and confirm the consistency of these associations before considering a reduction in dietary acid load as part of strategies for preventing kidney function decline.

Data availability statement

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.

Ethics statement

The studies involving human participants were reviewed and approved by the ethical standards of the Declaration of Helsinki by the Institutional Review Boards (IRBs). The patients/participants provided their written informed consent to participate in this study.

Author contributions

CV-H, NB-T, AD-L, ZV-R, IM, DC, AG, JM, ÁA-Gó, JW, JVio, DR, JL-M, RE, FT, JL, LS-M, AB-C, JT, VM-S, XP, JG, PM-M, JVid, AA-Ga, LD, ER, AG-A, RB, MF, PP-O, AA-A, EG-G, DM-U, MM, RC, EMG-G, LT-S, MD-F, EG, CO-A, OC, AG-R, CG-S, CS-O, HS, JS-S, and NB designed and conducted the research. CV-H and AD-L analyzed the data. CV-H, NB-T, AD-L, and NB wrote the article. CV-H and AD-L are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors revised the manuscript for important intellectual content and read and approved the final manuscript.

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Conflict of interest

Author JS-S reported receiving research support from the Instituto de Salud Carlos III (ISCIII), Ministerio de Educación y Ciencia, Departament de Salut Pública de la Generalitat de Catalunya, the European Commission, the California Walnut Commission, Patrimonio Comunal Olivarero, La Morella Nuts, and Borges S.A; receiving consulting fees or travel expenses from California Walnut Commission, Eroski Foundation, Instituto Danone, Abbott Laboratories and Mundifarma, receiving non-financial 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

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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.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2022.986190/full#supplementary-material

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UNIVERSITAT ROVIRA I VIRGILI
DIETARY FACTORS AND KIDNEY FUNCTION: INSIGHTS FROM A POPULATION OF OLDER MEDITERRANEAN ADULTS WITH OVERWEIGHT OR OBESITY AND METABOLIC SYNDROME
Cristina Valle Hita

Online supplementary material

Supplementary Table 1. Consumption of food groups across tertiles of PRAL and NEAP at baseline of the study population with data on eGFR at 1-year of follow-up (n= 5874).

	PRAL (mEq/d)				NEAP (mEq/d)			
	T1 n= 1958	**T2** n= 1958	**T3** n= 1958	p-value	**T1** n= 1958	**T2** n= 1958	**T3** n= 1958	p-value
Food groups								
Fruits, g/day	495.9 ± 233.9	333.3 ± 153.9	254.4 ± 140.0	<0.01	480.4 ± 237.7	355.2 ± 161.9	248.0 ± 136.2	<0.01
Vegetables, g/day	406.0 ± 152.4	313.2 ± 112.7	263.3 ± 101.8	<0.01	395.1 ± 154.5	326.1 ± 117.5	261.3 ± 100.8	<0.01
Cereals, g/day	134.6 ± 67.6	147.1 ± 75.4	170.6 ± 86.5	<0.01	128.0 ± 65.1	151.9 ± 75.9	172.4 ± 86.2	<0.01
Whole grains, g/day	88.5 ± 118.8	87.3 ± 129.8	81.2 ± 133.2	0.157	98.1 ± 124.3	93.7 ± 135.7	65.2 ± 119.3	<0.01
Refined grains, g/day	117.4 ± 83.7	132.7 ± 91.2	165.5 ± 108.2	<0.01	104.9 ± 77.6	135.8 ± 92.6	174.8 ± 105.7	<0.01
Legumes, g/day	23.1 ± 13.1	20.0 ± 9.7	18.8 ± 9.7	<0.01	22.3 ± 12.9	20.7 ± 10.1	18.9 ± 9.8	<0.01
Meat, fish and eggs, g/day	248.6 ± 75.7	264.7 ± 74.1	308.0 ± 85.7	<0.01	235.9 ± 73.2	274.9 ± 71.5	310.5 ± 84.9	<0.01
Milk and dairy products, g/day	349.0 ± 210.9	342.9 ± 196.0	344.5 ± 194.2	0.61	344.4 ± 210.0	362.4 ± 201.2	329.7 ± 188.5	<0.01
Nuts, g/day	17.3 ± 18.6	14.5 ± 16.3	13.1 ± 15.4	<0.01	17.1 ± 18.9	15.0 ± 16.1	12.7 ± 15.1	<0.01
Olive oil, g/day	40.2 ± 17.2	39.8 ± 16.8	40.8 ± 16.5	0.14	39.2 ± 17.1	40.3 ± 16.8	41.3 ± 16.6	<0.01
Other fats, g/day	2.6 ± 6.1	3.1 ± 6.6	3.1 ± 6.8	0.07	2.6 ± 5.9	3.0 ± 6.5	3.2 ± 7.0	0.02
Sugar and sweetened products, g/day	46.9 ± 64.6	53.7 ± 71.6	65.3 ± 86.5	<0.01	47.3 ± 67.0	54.5 ± 75.2	64.0 ± 81.6	<0.01
Alcohol, g/day	11.3 ± 15.8	11.3 ± 15.4	11.1 ± 14.4	0.92	10.5 ± 15.2	11.3 ± 15.5	11.8 ± 14.8	0.04

Abbreviations: *eGFR*, Estimated glomerular filtration rate; *NEAP*, Net Endogenous Acid Production; *T,* tertile; *PRAL*, Potential Renal Acid Load. Values are presented as means ± standard deviations. P-value was calculated by one-way analysis of variance test.

Online supplementary material

Supplementary Table 2. Baseline, one-year, and changes in dietary intake of macronutrients and micronutrients of the study population with data on eGFR at 1-year of follow-up (n= 5874).

	Baseline	**1-year**	**Change**	
	n= 5874	**n=5675**	**n=5675**	P-value
Carbohydrate intake, g/day	240.9 ± 72.5	209.1 ± 0.8	-31.6 ± 0.9	<0.001
Protein intake, g/day	97.7 ± 22.0	95.4 ± 0.3	-2.2 ± 0.3	<0.001
Fat intake, g/day	104.2 ± 28.3	103.7 ± 0.3	-0.7 ± 0.4	0.07
Monounsaturated fatty acids, g/day	54.0 ± 16.1	58.7 ± 0.2	4.5 ± 0.2	<0.001
Polyunsaturated fatty acids, g/day	18.0 ± 6.6	19.0 ± 0.08	1.0 ± 0.1	<0.001
Saturated fatty acids intake, g/day	26.3 ± 8.4	22.8 ± 0.1	-3.5 ± 0.11	<0.001
Fiber intake, g/day	26.1 ± 8.8	29.8 ± 0.1	3.7 ± 0.1	<0.001
Phosphorus intake, mg/day	1759.11 ± 419.9	1780.2 ± 5.5	22.5 ± 5.6	<0.001
Potassium intake, mg/day	4477.0 ± 1079.6	4673.6 ± 13.6	201.3 ± 14.5	<0.001
Magnesium intake, mg/day	420.4 ± 108.2	453.9 ± 1.5	420.0 ± 1.4	<0.001
Calcium intake, mg/day	1034.0 ± 347.0	992.9 ± 4.2	-40.1 ± 4.4	<0.001
Sodium intake, mg/day	2430.0 ± 774.8	2081.1 ± 8.9	-345.8 ± 10.5	<0.001

Abbreviations: *eGFR*, Estimated glomerular filtration rate. Values are presented as means ± standard deviations. P-value was calculated by T-test.

Online supplementary material

Supplementary Table 3. Baseline characteristics of the study population (n= 6,647) according to included or excluded individuals from the analysis of eGFR and UACR.

	eGFR			UACR		
	Excluded n= 773	**Included** n= 5874	p-value	**Excluded** n= 3008	**Included** n= 3639	p-value
PRAL, mEq/day	-5.2 ± 16.1	-5.4 ± 15.6	0.66	-6.0 ± 16.5	-5.0 ± 14.9	0.01
NEAP, mEq/day	37.1 ± 8.6	37.0 ± 8.1	0.66	36.7 ± 8.4	37.2 ± 8.0	0.01
Age, years	64.8 ± 5.0	65.0 ± 4.9	0.27	65.1 ± 4.9	64.9 ± 5.0	0.04
Women, % (n)	400 (51.8)	2818 (48.0)	0.05	54.7 (1646)	43.2 (1572)	<0.01
Intervention group, % (n)	399 (51.6)	2901 (49.4)	0.244	51.2 (1541)	48.3 (1759)	0.02
BMI, kg/m^2	32.8 ± 3.5	32.5 ± 3.4	0.04	32.6 ± 3.5	32.5 ± 3.4	0.11
PA, METS/min/week	1972.6 ± 1842.9	2528.0 ± 2350.4	<0.01	2326.8 ± 2221.1	2576.4 ± 2364.5	<0.01
Smoking status, % (n)			0.24			<0.01
Never smoked	343 (44.4)	2605 (44.4)		47.5 (1430)	41.7 (1518)	
Former smoker	348 (45.0)	2528 (43.0)		40.5 (1219)	45.5 (1657)	
Current smoker	82 (10.6)	741 (12.6)		11.9 (359)	12.8 (464)	
Education level, % (n)			0.10			0.26
Primary education	379 (49.0)	2891 (49.2)		50.3 (1513)	48.3 (1757)	
Secondary education	204 (26.4)	1714 (29.2)		28.3 (850)	29.4 (1068)	
College/University	190 (24.6)	1269 (21.6)		21.4 (645)	22.4 (814)	
Creatinine	0.8 ± 0.2	0.8 ± 0.2	0.18	0.8 ± 0.22	0.8 ± 0.2	0.731
eGFR, ml/min/1.73m^2	84.6 ± 14.6	84.2 ± 14.0	0.47	83.1 ± 14.5	85.2 ±13.6	<0.01
UACR, mg/g	21.7 ± 68.6	16.8 ± 48.9	0.05	18.1 ± 59.4	17.1 ± 48.7	0.58
CKD, % (n)	40 (5.8)	387 (6.6)	0.42	7.3 (214)	5.9 (213)	0.02
Type 2 diabetes, % (n)	250 (32.3)	1797 (30.6)	0.32	32.7 (983)	29.2 (1064)	0.02
Hypertension, % (n)	642 (83.1)	4941 (84.1)	0.45	83.6 (2515)	84.3 (3068)	0.44
Hypercholesterolemia, % (n)	553 (71.5)	4096 (69.7)	0.30	72.4 (2178)	67.9 (2471)	<0.01
Medication use, % (n)						
Lipid-lowering drugs	416 (53.8)	3042 (51.8)	0.29	53.9 (1,622)	50.5 (1836)	0.01
Oral blood glucose-lowering drugs	216 (28.0)	1528 (26.0)	0.25	28.2 (849)	24.6 (895)	<0.01
Insulin treatment	40 (5.17)	239 (4.1)	0.15	4.5 (136)	3.9 (143)	0.23
Antihypertensive drugs	583 (75.4)	4625 (78.7)	0.04	77.3 (2324)	79.3 (2884)	0.05
ARBs	292 (37.8)	2131 (36.3)	0.42	38.0 (1143)	35.2 (1280)	0.02
ACEis	217 (28.1)	1775 (30.2)	0.22	28.0 (843)	31.6 (1149)	<0.01
Dietary assessment						
erMedDiet score, 17-points	8.6 ± 2.7	8.5 ± 2.7	0.39	8.6 ± 2.7	8.5 ± 2.7	0.12
Energy intake, kcal/d	2325.2 ± 569.3	2370.5 ± 548.9	0.03	2343.6 ± 553.7	2383.2 ± 549.1	0.01
Protein intake, % energy	17.1 ± 2.8	16.7 ± 2.8	<0.01	17.2 ± 2.9	16.4 ± 2.7	<0.01
Fat intake, % energy	39.0 ± 6.9	39.6 ± 6.5	0.02	39.3 ± 6.6	39.8 ± 6.5	<0.01
Carbohydrate intake, % energy	41.1 ± 7.1	40.5 ± 6.8	0.02	40.9 ± 6.9	40.3 ± 6.8	<0.01
Fiber intake, g/day	26.1 ± 8.9	26.1 ± 8.8	0.92	26.9 ± 9.0	25.5 ± 8.5	<0.01
Potassium intake, mg/day	4465.2 ± 1078.5	447.0 ± 1079.6	0.78	4587.0 ± 1119.8	4383.5 ± 1036.0	<0.01
Calcium intake, mg/day	1037.0 ± 332.7	1034.0 ± 347.0	0.82	1059.8 ± 346.6	1013.4 ± 342.8	<0.01
Magnesium intake, mg/day	420.5 ± 110.8	420.4 ± 108.2	0.98	429.4 ± 111.00	412.9 ± 105.9	<0.01
Phosphorus intake, mg/day	1761.3 ± 429.4	1759.1 ± 419.9	0.89	1799.6 ± 428.8	1726.1 ± 411.5	<0.01
Sodium intake, mg/day	2386.9 ± 798.4	2430.0 ± 774.8	0.15	2419.3 ± 778.1	2429.6 ± 777.4	0.59

Abbreviations: *ACEis*, Angiotensin-Converting Enzyme Inhibitors; *ARBs*, Angiotensin II receptor blockers; *eGFR*, Estimated Glomerular Filtration Rate; *erMedDiet*, energy-restricted Mediterranean diet, *NEAP*, Net Endogenous Acid Production; *T*, tertile; *BMI*, Body Mass Index; *PRAL*, Potential Renal Acid Load; *PA*, Physical activity; *eGFR*, estimated Glomerular Filtration Rate; *CKD*, Chronic Kidney Disease (eGFR<60 ml/min/1.73m^2); *UACR*, Urine Albumin/Creatinine Ratio. Values are presented as percentages (n) for categorical variables and means ± standard deviations for continuous variables. P-value was calculated by chi-square or one-way analysis of variance test for categorical and continuous variables, respectively.

Online supplementary material

Supplementary Table 4. Multivariable-adjusted β-coefficients and 95% CI for 1-year changes in eGFR (ml/min/1.73m^2) or 1-year changes in UACR (mg/g) across tertiles and per 1-SD increment of baseline PRAL and NEAP stratified by categories of eGFR and UACR.

	T1	T2	T3	p for Trend	Continuous (1 SD‡)
PRAL					
Δ in eGFR, ml/min/1.73m^2					
eGFR categories					
≥ 90 ml/min/1.73m^2					
No.	n= 838	n= 838	n= 837		n= 2513
Model 1	0 (Ref.)	-0.18 (-0.88 to 0.51)	-0.50 (-1.18 to 0.18)	0.151	-0.22 (-0.48 to 0.03)
Model 2	0 (Ref.)	-0.26 (-0.98 to 0.45)	-0.70 (-1.41 to 0.01)	0.056	-0.28 (-0.56 to -0.01)*
60 – 90 ml/min/1.73m^2					
No.	n= 992	n= 991	n= 991		n=2974
Model 1	0 (Ref.)	0.05 (-0.74 to 0.84)	-0.31 (-1.13 to 0.51)	0.463	-0.12 (-0.46 to 0.21)
Model 2	0 (Ref.)	0.04 (-0.75 to 0.84)	-0.43 (-1.28 to 0.42)	0.331	-0.18 (-0.53 to 0.17)
< 60 ml/min/1.73m^2					
No.	n= 129	n= 129	n= 129		n= 387
Model 1	0 (Ref.)	0.03 (-2.67 to 2.74)	-0.77 (-3.30 to 1.77)	0.568	-0.40 (-1.35 to 0.56)
Model 2	0 (Ref.)	0.80 (-1.95 to 3.57)	-0.52 (-3.24 to 2.20)	0.736	-0.24 (-1.30 to 0.81)
Δ in UACR, mg/g					
UACR categories					
< 30 mg/g					
No.	n= 1099	n= 1099	n= 1098		n= 3296
Model 1	0 (Ref.)	-0.13 (-2.06 to 1.80)	0.07 (-1.56 to 1.70)	0.935	0.07 (-0.55 to 0.70)
Model 2	0 (Ref.)	-0.29 (-2.28 to 1.70)	-0.19 (-2.06 to 1.68)	0.835	-0.01 (-0.71 to 0.69)
≥ 30 mg/g					
No.	n= 115	n= 114	n= 114		n=343
Model 1	0 (Ref.)	-11.17 (-38.85 to 6.50)	-24.54 (-50.53 to 1.46)	0.072	-8.54 (-18.15 to 1.07)
Model 2	0 (Ref.)	-8.52 (-36.46 to 19.41)	-30.06 (-58.88 to -1.24)*	0.055	-10.71 (-22.26 to 0.84)
NEAP					
Δ in eGFR, ml/min/1.73m^2					
eGFR categories					
≥ 90 ml/min/1.73m^2					
No.	n= 838	n= 838	n= 837		n= 2513
Model 1	0 (Ref.)	-0.28 (-0.98 to 0.41)	-0.24 (-0.92 to 0.43)	0.494	-0.20 (-0.45 to 0.06)
Model 2	0 (Ref.)	-0.36 (-1.07 to 0.35)	-0.47 (-1.18 to 0.25)	0.207	-0.31 (-0.58 to -0.03)*
60 – 90 ml/min/1.73m^2					
No.	n= 992	n= 991	n= 991		n=2974
Model 1	0 (Ref.)	-0.19 (-0.98 to 0.60)	-0.40 (-1.23 to 0.43)	0.344	-0.15 (-0.49 to 0.19)
Model 2	0 (Ref.)	-0.14 (-0.94 to 0.66)	-0.46 (-1.32 to 0.40)	0.287	-0.18 (-0.54 to 0.18)
< 60 ml/min/1.73m^2					
No.	n= 129	n= 129	n= 129		n= 387
Model 1	0 (Ref.)	-1.15 (-3.81 to 1.50)	-1.10 (-3.73 to 1.54)	0.420	-0.60 (-1.58 to 0.38)
Model 2	0 (Ref.)	-0.55 (-3.29 to 2.18)	-1.07 (-3.85 to 1.71)	0.448	-0.49 (-1.56 to 0.58)
Δ in UACR, mg/g					
UACR categories					
< 30 mg/g					
No.	n= 1099	n= 1099	n= 1098		n= 3296
Model 1	0 (Ref.)	-0.58 (-2.43 to 1.28)	0.11 (-1.66 to 1.89)	0.876	0.10 (-0.55 to 0.75)
Model 2	0 (Ref.)	-0.64 (-2.30 to 1.02)	-0.04 (-1.77 to 1.69)	0.999	0.04 (-0.66 to 0.74)
≥ 30 mg/g					
No.	n= 115	n= 114	n= 114		n=343
Model 1	0 (Ref.)	-9.54 (-37.37 to 18.29)	-27.10 (-37.37 to 18.29)	0.149	-9.56 (-19.69 to 0.56)
Model 2	0 (Ref.)	-11.65 (-39.66 to 6.35)	-29.71 (-61.06 to 1.65)	0.087	-10.39 (-22.44 to 1.66)

Abbreviations: *eGFR*, Estimated glomerular filtration rate; *NEAP*, Net Endogenous Acid Production; *T*, tertile; *PRAL*, Potential Renal Acid Load; *UACR*, Urine albumin/creatinine ratio. Model 1: adjusted for age (years), sex and baseline eGFR or baseline UACR (in continuous, depending on the main outcome). Model 2: additionally adjusted for participating center (categorized into quartiles by number of participants), intervention group (treatment/control), body mass index (kg/m^2), smoking habits (never, current or former smoker), educational level (primary, secondary education or graduate), leisure-time physical activity (METS/min/week in tertiles), diabetes prevalence (yes/no), hypertension prevalence (yes/no) and hypercholesterolemia prevalence (yes/no), ARBs (yes/no), ACEis (yes/no), Mediterranean diet adherence (high/low adherence), energy intake (kcal/day in tertiles), sodium intake (mg/g in tertiles) and high leukocytes levels (yes/no). *p-value < 0.05. ‡One SD= 15.6 mEq/d in PRAL and 8.1 mEq/d in NEAP.

Online supplementary material

Supplementary Table 5. Multivariable-adjusted β-coefficients and 95% CI of 1-year changes in eGFR (ml/min/1.73m2) or in UACR (mg/g) as well as adjusted OR and 95% CIs for ≥10% eGFR decline or ≥10% UACR increase by tertiles of baseline PRAL and NEAP.

	T1	T2	T3	p for Trend
PRAL (mEq/d)				
Δ in eGFR, ml/min/1.73m²	n= 1958	n= 1958	n= 1958	
Model 2	0 (Ref.)	-0.14 (-0.68 to 0.39)	-0.60 (-1.16 to -0.04)*	0.037
eGFR decline ≥10%	n= 296; %= 15.1	n= 304; %= 15.5	n= 346; %= 17.7	
Model 2	1 (Ref.)	1.04 (0.87 to 1.25)	1.25 (1.05 to 1.50)*	0.017
Δ in UACR, mg/g	n= 1213	n= 1213	n= 1213	
Model 2	0 (Ref.)	-1.53 (-4.75 to 1.69)	-2.83 (-6.19 to 0.57)	0.100
UACR increase ≥5%	n= 539; %= 44.4	n= 547; %= 45.1	n= 597; %= 49.2	
Model 2	1 (Ref.)	1.04 (0.88 to 1.23)	1.23 (1.03 to 1.46)*	0.021
NEAP (mEq/d)				
Δ in eGFR, ml/min/1.73m²	n= 1958	n= 1958	n= 1958	
Model 2	0 (Ref.)	-0.27 (-0.80 to 0.26)	-0.51 (-1.08 to 0.06)	0.080
eGFR decline ≥10%	n= 297; %= 15.2	n= 312; %= 15.9	n= 337; %= 17.2	
Model 2	1 (Ref.)	1.06 (0.89 to 1.26)	1.21 (1.01 to 1.46)*	0.044
Δ in UACR, mg/g	n= 1213	n= 1213	n= 1213	
Model 2	0 (Ref.)	-0.72 (-3.77 to 2.33)	-2.23 (-5.58 to 1.11)	0.184
UACR increase ≥5%	n= 550; %= 45.3	n= 539; %= 44.4	n= 594; %= 49.0	
Model 2	1 (Ref.)	0.97 (0.82 to 1.14)	1.18 (0.99 to 1.41)*	0.053

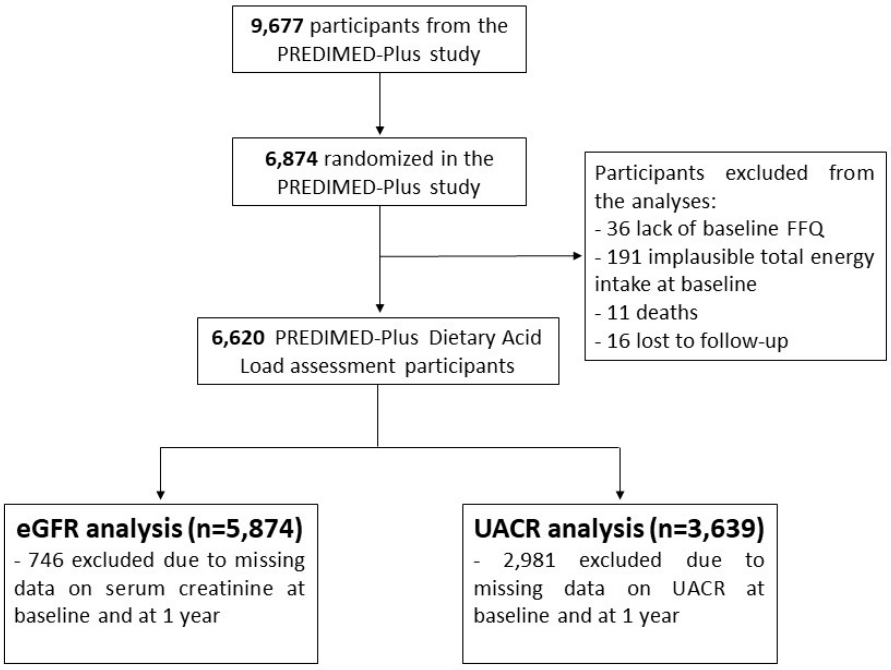
Abbreviations: *eGFR*, Estimated glomerular filtration rate; *NEAP*, Net Endogenous Acid Production; *T*, tertile; *PRAL*, Potential Renal Acid Load; *UACR*, Urine albumin/creatinine ratio. All models were adjusted for age (years), sex, baseline eGFR or baseline UACR (in continuous, in logistic regression models depending on the main outcome), for participating center (categorized into quartiles by number of participants), intervention group (treatment/control), body mass index (kg/m^2), smoking habits (never, current or former smoker), educational level (primary, secondary education or graduate), leisure-time physical activity (METS/min/week in tertiles), diabetes prevalence (yes/no), hypertension prevalence (yes/no) and hypercholesterolemia prevalence (yes/no), ARBs (yes/no), ACEis (yes/no), Mediterranean diet adherence (high/low, ≥/< 12 points), energy intake (kcal/day in tertiles), sodium intake (mg/g in tertiles) and high leukocytes levels (yes/no). *p-value < 0.05.

Supplementary Table 6. Multivariable-adjusted OR (95% CIs) for ≥5% eGFR decline and ≥5% UACR increase by tertiles of baseline PRAL and NEAP and per 1-SD increment.

	T1	T2	T3	p for Trend	Continuous (1 SD‡)
PRAL					
eGFR decline ≥5%					
No. (%)	527 (26.9)	547 (27.9)	578 (29.5)		1652 (28.1)
Model 1	1 (Ref.)	1.05 (0.92 to 1.21)	1.16 (1.01 to 1.34)*	0.037	1.08 (1.02 to 1.14)*
Model 2	1 (Ref.)	1.06 (0.92 to 1.23)	1.20 (1.04 to 1.40)*	0.017	1.10 (1.03 to 1.17)*
UACR increase ≥5%					
No. (%)	580 (47.8)	583 (48.1)	633 (52.2)		1796 (49.4)
Model 1	1 (Ref.)	1.02 (0.87 to 1.19)	1.21 (1.03 to 1.43)*	0.023	1.06 (0.99 to 1.13)
Model 2	1 (Ref.)	1.02 (0.86 to 1.20)	1.19 (1.00 to 1.42)*	0.054	1.05 (0.98 to 1.13)
NEAP					
eGFR decline ≥5%					
No. (%)	532 (27.2)	546 (27.9)	574 (29.3)		1652 (28.1)
Model 1	1 (Ref.)	1.03 (0.90 to 1.19)	1.14 (0.99 to 1.32)	0.062	1.08 (1.02 to 1.14)*
Model 2	1 (Ref.)	1.04 (0.90 to 1.20)	1.18 (1.02 to 1.38)*	0.029	1.10 (1.03 to 1.17)*
UACR increase ≥5%					
No. (%)	589 (48.56)	581 (47.90)	626 (51.61)		1796 (49.4)
Model 1	1 (Ref.)	0.98 (0.83 to 1.15)	1.16 (0.98 to 1.36)	0.076	1.05 (0.98 to 1.12)
Model 2	1 (Ref.)	0.96 (0.82 to 1.14)	1.13 (0.95 to 1.35)	0.148	1.04 (0.97 to 1.12)

Abbreviations: *eGFR*, Estimated glomerular filtration rate; *NEAP*, Net Endogenous Acid Production; *T*, tertile; *PRAL*, Potential Renal Acid Load; *UACR*, Urine albumin/creatinine ratio. Model 1: adjusted for age (years) and sex. Model 2: additionally adjusted for participating center (categorized into quartiles by number of participants), intervention group (treatment/control), body mass index (kg/m^2), smoking habits (never, current or former smoker), educational level (primary, secondary education or graduate), leisure-time physical activity (METS/min/week in tertiles), diabetes prevalence (yes/no), hypertension prevalence (yes/no) and hypercholesterolemia prevalence (yes/no), ARBs (yes/no), ACEis (yes/no), Mediterranean diet adherence (high/low adherence), energy intake (kcal/day in tertiles), sodium intake (mg/g in tertiles) and high leukocytes levels (yes/no). *p-value < 0.05. ‡One SD= 15.6 mEq/d in PRAL and 8.1 mEq/d in NEAP.

Online supplementary material



Supplementary Figure 1. Flow chart of the study population

Chapter 3. Associations between ultra-processed food consumption and kidney function in an older adult population with metabolic syndrome.

Cristina Valle-Hita, Andrés Díaz-López, Nerea Becerra-Tomás, Estefania Toledo, Isabel Cornejo-Pareja, Itziar Abete, Antoni Sureda, Maira Bes-Rastrollo, J Alfredo Martínez, Francisco J Tinahones, Josep A Tur, Tany E Garcidueñas-Fimbres, Francisco París-Pallejá, Albert Goday, Nuria Goñi-Ruiz, Jordi Salas-Salvadó and Nancy Babio.

Overview of the novelty and significance of this publication

What is already known?

- Previous studies have consistently associated the consumption of UPF with several chronic non-communicable diseases. However, there is limited evidence concerning its impact on kidney function or CKD.
- Existing evidence suggests that UPF consumption is inversely associated with kidney function through SCr based-eGFR.

What does this study add?

- For the first time, our study evaluated the cross-sectional and prospective associations between UPF consumption and kidney function using eGFR based on CysC. This biomarker is more accurate and independent of certain risk factors than SCr.
- A negative association between UPF consumption and CysC based-eGFR at baseline and over 3-years of follow-up was observed.
- These results may provide new insights for the design of future evidence-based strategies to prevent kidney dysfunction, and they may also contribute valuable insights for enhancing clinical practices targeting older populations with cardiovascular risk.

Conclusion:

- This study reinforces existing evidence indicating a potentially harmful association between UPF and health, specifically kidney function, in a Mediterranean population at high risk.

UNIVERSITAT ROVIRA I VIRGILI
DIETARY FACTORS AND KIDNEY FUNCTION: INSIGHTS FROM A POPULATION OF OLDER MEDITERRANEAN ADULTS WITH OVERWEIGHT OR OBESITY AND METABOLIC SYNDROME
Cristina Valle Hita

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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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SUMMARY

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

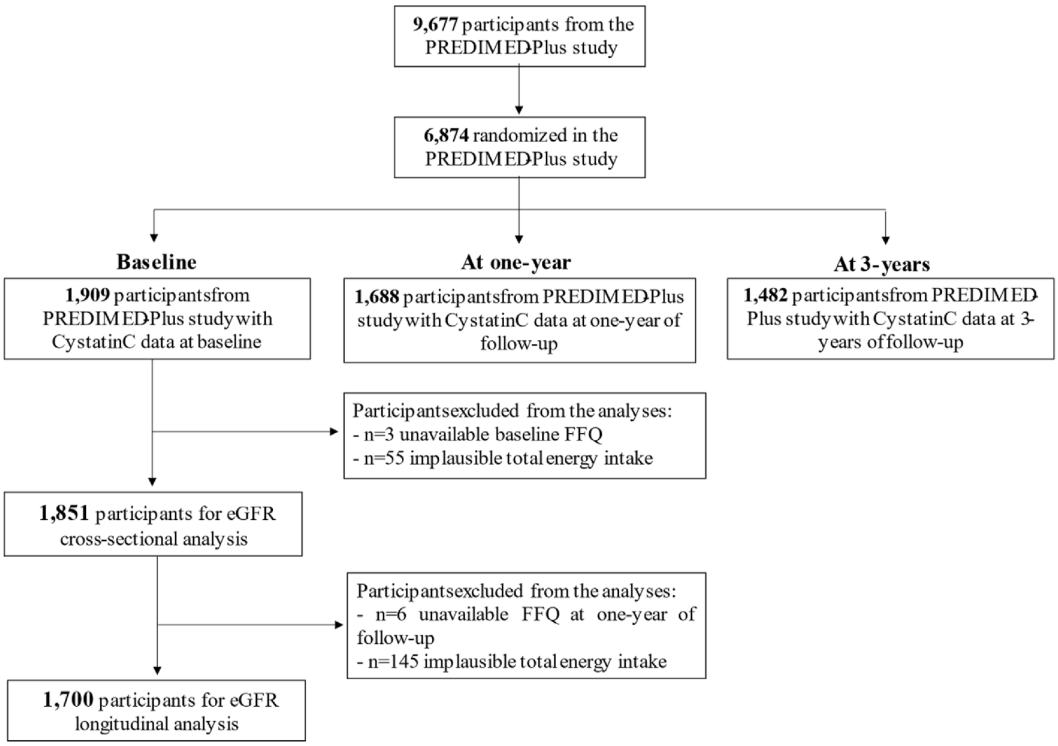

Fig. 1. Flow diagram for study participants. *Abbreviations* eGFR, glomerular filtration rate; FFQ, food frequency questionnaire.

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

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnu.2023.09.028.

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UNIVERSITAT ROVIRA I VIRGILI
DIETARY FACTORS AND KIDNEY FUNCTION: INSIGHTS FROM A POPULATION OF OLDER MEDITERRANEAN ADULTS WITH OVERWEIGHT OR OBESITY AND METABOLIC SYNDROME
Cristina Valle Hita

Online supplementary material

Supplementary Table 1. Baseline characteristics of the PREDIMED-Plus study population according to included or excluded individuals from the analysis.

	Total n= 6874	Included n= 1851	Excluded n= 5023	p-value
Age, years	65.0 ± 4.9	65.0 ± 5.0	64.9 ± 4.9	0.374
Women, n (%)	3335 (48.5)	842 (45.5)	2493 (49.6)	0.002
Intervention group, n (%)	3406 (49.6)	918 (49.6)	2488 (49.5)	0.963
BMI, kg/m^2	32.6 ± 3.5	32.5 ± 3.4	32.6 ± 3.5	0.091
Physical activity, METS/min/week	2463 ± 2301	2568 ± 2321	2424 ± 2293	0.022
Smoking status, n (%)				0.013
Never smoked	3034 (44.1)	764 (41.3)	2270 (45.2)	
Former smoker	2983 (43.4)	851 (46.0)	2132 (42.4)	
Current smoker	857 (12.5)	236 (12.8)	621 (12.4)	
Education level, n (%)				<0.001
Primary education	3357 (48.9)	940 (50.8)	2417 (48.2)	
Secondary education	1986 (28.9)	568 (30.69)	1418 (28.3)	
Academic or graduate	1526 (22.2)	343 (18.5)	1183 (23.6)	
NOVA 4: UPF consumption, % of g/day	8.0 ± 6.8	7.6 ± 6.3	8.1 ± 6.9	0.002
NOVA 3: Processed foods consumption, % of g/day	20.2 ± 10.7	20.8 ± 10.5	20.0 ± 10.7	0.003
NOVA 2: Processed culinary ingredients consumption, % of g/day	2.6 ± 1.2	2.8 ± 1.2	2.6 ± 1.3	<0.001
NOVA 1: Unprocessed and minimally processed foods consumption, % of g/day	69.2 ± 11.8	68.8 ± 11.8	69.3 ± 12.6	0.110
erMedDiet score, 17-points	8.5 ± 2.6	8.5 ± 2.6	8.5 ± 2.7	0.785
Fruits and vegetables consumption (g/d)	730.2 ± 286.7	731.5 ± 295.9	726.6 ± 260.3	0.5304
Energy intake, kcal/d	2416 ± 633	2434 ± 539	2410 ± 664	0.156
Total carbohydrate intake (g/d)	246.5 ± 81.2	245.9 ± 84.1	248.2 ± 72.7	0.3063
Sugar intake, g/day	29.7 ± 69.5	25.5 ± 59.0	31.2 ± 73.0	0.003
Fiber intake, g/day	26.5 ± 9.2	26.3 ± 8.6	26.6 ± 9.4	0.351
Sodium intake (mg/d)	2482.8 ± 867.3	2483.5 ± 890.4	2481.0 ± 802.2	0.916
Phosphorus intake (mg/d)	1788.2 ± 458.2	1800.6 ± 471.9	1754.5 ± 417.1	<0.001
Iron intake (mg/d)	16.8 ± 3.9	16.8 ± 4.5	16.7 ± 3.9	0.689
Glycemic index	53.9 ± 5.2	53.5 ± 5.1	55.0 ± 5.2	<0.001
Cystatin C, mg/dl	1.05 ± 0.23	1.05 (0.2)	1.04 ± 0.16	0.552
eGFR, ml/min/1.73m^2 at baseline	72.7 ± 18.3	72.7 ± 18.4	72.1 ± 15.2	0.811
Type 2 diabetes, n (%)	2093 (30.5)	536 (29.0)	1557 (31.0)	0.103
Hypertension, n (%)	5758 (83.8)	1571 (84.9)	4187 (83.4)	0.130
Hypercholesterolemia, n (%)	4813 (70.0)	1218 (65.8)	3595 (71.6)	<0.001
Medication use, n (%)	16.8 ± 4.4	16.8 ± 4.5	16.7 ± 3.9	0.689
Lipid-lowering drugs	3557 (51.8)	931 (50.3)	2626 (52.3)	0.145
Oral blood glucose-lowering drugs	1779 (25.9)	443 (23.9)	1336 (26.6)	0.025
Insulin treatment	283 (4.1)	88 (4.8)	195 (3.9)	0.106
Antihypertensive drugs	5368 (78.1)	1494 (80.7)	3874 (77.1)	0.001
ARBs	2495 (36.3)	608 (32.9)	1887 (37.6)	<0.001
ACEis	2049 (29.8)	635 (34.3)	1414 (28.2)	<0.001

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/1.73m^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.

In the analyses, there were missing data for NOVA 1 in 36 participants (0.52%), NOVA 2 in 36 participants (0.52%), NOVA3 in 36 participants (0.52%), NOVA 4 in 36 participants (0.52%), erMedDiet adherence in 5 participants (0.7%), fruits and vegetables consumption in 36 participants (0.52%), energy intake in 36 participants (0.7%), total carbohydrate intake in 36 participants (0.52%), fiber intake in 36 participants (0.52%), sugar intake in 36 participants (0.52%), sodium intake in 36 participants (0.52%), phosphorus intake in 36 participants (0.52%), iron intake in 36 participants (0.52%), glycemic index in 36 participants (0.52%), eGFR in 4965 participants (72.2%), CysC in 4965 participants (72.2%),.

Online supplementary material

Supplementary Table 2. Sensitivity analysis of the association between ultra-processed food consumption and kidney function over 3-years of follow-up excluding individuals with T2D, eGFR <60ml/min/1.72m^2 and UACR ≥300mg/g

	Changes in proportions of UPF consumption in the diet after one-year of follow-up (% of g/day)						
	T1	**T2**	**T3**	**T2 vs. T1 difference**	**p-value**	**T3 vs. T1 difference**	**p-value**
eGFR (ml/min/1.73m^2) over 3-years							
Individuals free of T2D	**(n=401)**	**(n=401)**	**(n=400)**				
Baseline	71.69 (69.38 to 73.99)	72.95 (70.81 to 75.09)	72.77 (70.53 to 75.01)				
1-year	70.62 (68.30 to 72.94)	71.68 (69.53 to 73.84)	69.94 (67.69 to 72.19)				
1-year change	-1.07 (-2.23 to 0.10)	-1.27 (-2.43 to -0.11)	-2.83 (-3.99 to -1.67)	-0.20 (-1.85 to 1.44)	0.809	-1.77 (-3.41 to -0.12)	0.035
3-years	67.92 (65.57 to 70.27)	68.11 (65.91 to 70.31)	66.47 (64.18 to 68.77)				
3-years change	-3.77 (-4.99 to -2.55)	-4.84 (-6.07 to -3.62)	-6.29 (-7.52 to -5.07)	-1.08 (-2.80 to 0.65)	0.221	-2.53 (-4.26 to -0.80)	0.004
Individuals with eGFR ≥60ml/min/1.73m^2	**(n=421)**	**(n=421)**	**(n=420)**				
Baseline	79.88 (77.63 to 82.14)	79.05 (76.91 to 81.19)	79.47 (77.27 to 81.67)				
1-year	76.98 (74.70 to 79.25)	75.14 (72.99 to 77.29)	75.35 (73.13 to 77.57)				
1-year change	-2.91 (-4.08 to -1.74)	-3.91 (-5.08 to -2.75)	-4.12 (-5.29 to -2.95)	-1.01 (-2.66 to 0.65)	0.233	-1.22 (-2.87 to 0.44)	0.150
3-years	73.44 (71.13 to 75.75)	71.45 (69.25 to 73.66)	70.67 (68.40 to 72.95)				
3-years change	-6.44 (-7.66 to -5.23)	-7.60 (-8.82 to -6.37)	-8.80 (-10.04 to -7.56)	-1.15 (-2.88 to 0.58)	0.192	-2.35 (-4.09 to -0.62)	0.008
Individuals with UACR <300mg/g	**(n=562)**	**(n=562)**	**(n=561)**				
Baseline	72.09 (69.65 to 74.54)	71.55 (69.24 to 73.86)	71.92 (69.53 to 74.30)				
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)	-2.00 (-3.01 to -1.00)	-2.61 (-3.62 to -1.61)	-0.82 (-2.24 to 0.60)	0.259	-1.43 (-2.85 to -0.004)	0.049
3-years	67.56 (65.07 to 70.05)	66.50 (64.14 to 68.87)	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: T2D, Type 2 diabetes; eGFR, estimated Glomerular Filtration Rate; UPF, Ultra-processed food; T, Tertiles.

Linear Mixed Models were used to assess the longitudinal association between changes in UPF consumption after one-year of follow-up and eGFR over time by excluding individuals with T2D, eGFR <60ml/min/1.72m^2 and UACR ≥300mg/g. 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/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 (g, tertiles), diabetes prevalence (yes/no)(except for analysis excluding individuals with diabetes), 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).

Online supplementary material

Supplementary Table 3. Associations between ultra-processed food consumption and kidney function over 3-years of follow-up stratified by sex and intervention group

	Changes in proportions of UPF consumption in the diet after one-year of follow-up (% of g/day)				
	T2 vs. T1 difference	**p-value**	**T3 vs. T1 difference**	**p-value**	**p-interaction**
eGFR (ml/min/1.73m^2) over 3-years					
Men					0.195
1-year change	-0.77 (-2.80 to 1.26)	0.457	-1.97 (-4.01 to 0.07)	0.059	
3-years change	0.10 (-2.02 to 2.23)	0.924	-2.58 (-4.72 to -0.45)	0.018	
Women					
1-year change	-0.16 (-2.10 to 1.77)	0.869	-0.52 (-2.45 to 1.41)	0.596	
3-years change	-0.48 (-2.53 to 1.57)	0.646	-1.76 (-3.82 to 0.30)	0.094	
Intervention group					0.220
1-year change	-1.95 (-4.00 to 0.10)	0.062	-0.49 (-2.54 to 1.55)	0.636	
3-years change	-0.34 (-2.50 to 1.82)	0.760	-0.03 (-2.20 to 2.13)	0.975	
Control group					
1-year change	-0.90 (-2.85 to 1.06)	0.369	-1.11 (-3.06 to 0.85)	0.268	
3-years change	-2.53 (-4.57 to -0.49)	0.015	-3.52 (-5.59 to -1.45)	0.001	

Abbreviations: eGFR, estimated Glomerular Filtration Rate; UPF, Ultra-processed food; T, Tertiles.

Linear Mixed Models were used to assess the longitudinal association between changes in UPF consumption after one-year of follow-up and eGFR over time stratifying by sex and intervention group. Model was adjusted for age (years), sex (men/women)(except for analysis stratified by sex), 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)(except for analysis stratified by intervention group), body mass index (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 (g, tertiles), diabetes prevalence (yes/no)(except for analysis excluding individuals with diabetes), 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). The n of each group and category was for men T1: n= 312; T2: n= 312; T3: n= 312; for women T1: n= 255; T2: n= 255; T3: n= 254; for intervention group T1: n= 277; T2: n= 276; T3: n= 276; and for control group T1: n= 291; T2: n= 290; T3: n= 290.

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VI. Discussion

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VI. DISCUSSION

Prior evidence has highlighted the potentially crucial relevance of diet to kidney health. The current dissertation aimed to further investigate the associations between different dietary factors - specifically dietary patterns, dietary acid load, and UPF - and kidney function in an older Mediterranean population with overweight or obesity and MetS.

Although each chapter of this doctoral thesis contains a discussion section, a general discussion is presented below to summarize all findings, address important considerations that could not be discussed previously, and provide new scientific evidence that has emerged since the studies of this thesis were published. The overall strengths and limitations derived from this research are also described in this section.

1. General discussion

The results of this dissertation are substantially valuable as they provide new prospective evidence to the existing body of literature in the field of diet, kidney function, and CKD. In particular, the results of the current doctoral thesis showed a beneficial association between healthy dietary patterns, specifically the MedDiet, and kidney function, assessed longitudinally by eGFR, in older Mediterranean adults with underlying comorbidities. In contrast, the dietary acid load indexes PRAL and NEAP demonstrated a prospective negative association with eGFR levels and UACR; which was in line with the detrimental association observed between the consumption of UPF, a food group characterized by a high dietary acid load, and eGFR over 3 years of follow-up.

The findings in **chapter 1** regarding the adherence to a MedDiet and its association with kidney function were consistent with previous scientific literature[199–204] such as the systematic review and meta-analysis led by Hansrivijit et al., which reported that the MedDiet had a relevant impact on the prevention of CKD, with a 10% reduction in the risk of CKD observed for each one-point increase in the MedDiet score[154]. In our longitudinal study, an *a priori* Mediterranean dietary pattern was evaluated using two different approaches - the 17-item erMedDiet and the Trichopoulou-MedDiet - which were based on different scoring criteria. The first mentioned score was obtained from a pre-defined questionnaire that uses absolute values in accordance with established scientific knowledge about the healthy levels of certain food intakes and specific cultural and dietary considerations, whereas the calculation of the Trichopoulou score depends only on the distribution of the study population, as gender-specific median cut-offs are used for the estimation. These score

discrepancies may partly explain why we observed a statistically significant association between changes towards greater adherence to the 17-item erMedDiet score after one year of follow-up and better eGFR as well as 38% lower odds of eGFR decline, but not with the Trichopoulou-MedDiet score.

This prospective study also revealed that the DASH diet score, *a priori* index based on the studied population distribution, was not significantly associated with kidney function outcomes. There is conflicting research regarding the relationship between the DASH diet and kidney function or CKD; while some authors[169] agreed with our non-significant findings, others have observed significant positive associations with eGFR decline[205] or the risk of CKD[156,206]. Given that the DASH diet is relatively similar to the MedDiet and has been widely demonstrated to have a beneficial effect on hypertension[207], a recognized risk factor of CKD, further studies are required to clarify any inconsistencies, which are probably due to differences in the populations studied and the methods used to assess dietary intake.

Traditionally, protein intake has been a major focus in the field of kidney research, and for many years, limiting protein intake has been part of the recommendations for people with some degree of kidney function decline[171,208]. Nevertheless, recent evidence suggests that the source of the protein should be considered as important as the quantity. In fact, in 2017, the Protein Diet Score was developed to assess protein intake on the basis of both total amount and source, using the plant-to-animal protein ratio, and it was found to be positively associated with eGFR[209]. However, this association was not observed in present thesis where we conducted a separate analysis of the two components of the Protein Diet Score and found that only the total protein intake component showed a significant negative association with eGFR, suggesting that the quantity of protein intake may be responsible for this detrimental association. To the best of our knowledge, Møller et al.[209] and the work conducted as part of this thesis are the only studies that have used the Protein Diet Score in relation to kidney function; therefore, additional research with longer follow-up periods is warranted to elucidate the implications of protein intake on CKD prevention.

Both the Mediterranean and DASH diets have been described as healthy, plant-based dietary patterns because they are mainly composed of nutrient-dense foods of plant origin, such as vegetables, fruits, nuts, and legumes, which are also considered alkaline-forming foods. By contrast, these diets are characterized by an extremely low consumption of acid-inducing foods, which include red and processed meats, sugar-sweetened beverages, baked goods, sweets, and convenience foods, among other UPF[158,210,211]. In the introduction section, it was

outlined that diet is a critical contributor to the maintenance of the acid-base status in gastrointestinal tract of humans. Dietary acid load has been proposed as an index of the quality and acidity of dietary patterns[158,210,212]. Given that associations between dietary acid load and an increased risk of CKD have been described previously[183,213], in **chapter 2** we aimed to explore the association between the two most common indexes of dietary acid load, eGFR and UACR. Our results indicated that the PRAL and NEAP indexes were negatively associated with one-year changes in eGFR levels, but not with changes in UACR. In line with this, in our study population, a significant positive association was also reported between both dietary acid load indexes and the odds of eGFR decline after one-year of follow-up as well as between the PRAL index and the odds of UACR increase. These results regarding eGFR and UACR could indicate that dietary acid load may influence kidney function through tubular damage, without affecting the permeability of the glomerulus. The findings of this thesis related to dietary acid load align with the findings of prior cross-sectional studies on eGFR, CKD[214–217], and UACR[215–217]. In addition, to date, only the Atherosclerosis Risk in Communities (ARIC) trial has longitudinally examined the association between dietary acid load and CKD, finding a 13% higher risk of incident CKD among participants with higher PRAL[218], which was in line with our study results. Accordingly, due to the lack of clear evidence, especially in people at high risk, such as older populations with other comorbid conditions, more studies, and ideally prospective longitudinal ones, are urgently needed to verify the associations discussed in the current doctoral thesis.

As mentioned, a group of acid-forming foods is the UPF[178], the consumption of which has increased alarmingly in recent decades[147]. UPF is a relevant source of potentially harmful nutrients and micronutrients, including free sugars, trans fatty acids, and/or sodium[184], which have been extensively related to an increased risk of non-communicable diseases[147,186]. Nonetheless, research into the possible impact of UPF on kidney function is scarce. Therefore, **in chapter 3**, the cross-sectional and prospective associations between UPF and eGFR were investigated in older adults with overweight or obesity and MetS. To the best of our knowledge, this was the first epidemiological study examining these associations using the CysC to estimate eGFR. This biomarker exhibits some advantages over others, such as appearing to be less dependent on important factors in older adults, such as aging, muscle mass, and diet[7,9,219]. The results of this study extend the associations observed by other authors[187–192] regarding the role of UPF on kidney function and CKD, suggesting that both baseline consumption and changes towards higher consumption might decrease eGFR;

hence, UPF consumption could worsen the function of the kidneys. In the long term, this could lead to the development of CKD. In fact, a very recent systematic review and meta-analysis of observational studies observed a 25% increased risk of incident CKD among individuals with the highest consumption of UPF in comparison to those with the lowest consumption[220]. To ensure the accumulation of reliable evidence and to draw robust conclusions, it would be worthwhile in the future to further analyze this association in other populations, also using CysC as a biomarker of eGFR and over longer follow-up periods.

From a mechanistic perspective, several explanations have been proposed for the observed associations between the components of the diet studied in the present doctoral thesis and kidney function. On the one hand, the potential protective impact of the Mediterranean dietary pattern on kidney function could be primarily due to the high content of fiber, vitamins, minerals, phytosterols, and other antioxidant and anti-inflammatory compounds in its foods[160,221]. Furthermore, extra virgin olive oil and nuts are the major sources of dietary fat in the Mediterranean culture; more specifically, these foods contribute substantially to the intake of mono- and polyunsaturated fatty acids[160,221]. All these components may synergistically affect kidney function not only in a direct manner[149,222–226] but also indirectly, as previous scientific evidence has suggested that some of these dietary compounds could modulate inflammatory procedures, endothelial function, oxidative stress[224,225,227–232], blood lipid profiles[224,233,234], insulin resistance[224,225,235,236], and blood pressure[233,234,237]. Therefore, they also have been linked to a reduced risk of some CKD risk factors, including hypertension, obesity, metabolic syndrome, and diabetes[225,231,233,234,238]. On the other hand, the plausible detrimental effect of high acid load diets and UPF may be attributed to the lack of the beneficial compounds mentioned above, particularly the lower fiber content, in addition to the increased amount of simple sugars, trans-fatty acids, phosphate, and/or sodium[184], which have been implicated not only in CKD[239–246] but also in related-comorbidities and mechanisms[246–248], such as gut barrier permeability disturbances[249,250]. Besides, foods with a high acid load, such as UPF, are convenience products that are usually readily available on the market in plastic packaging. Certain constituents of this packaging have recently been suggested to be transferred to the food[251], and may have some adverse health effects, such as changes in the gut microbiota[252,253], inflammatory processes[254], higher risk of obesity or diabetes[252,253,255], and, ultimately, kidney function decline[256,257]. Finally, some other plausible explanations for the potential relationship between dietary acid load and kidney function that have been hypothesized, include activation of the RAAS and the complement pathway,

production of endothelin-1, ammoniagenesis, and oxidative stress, which have been linked to acid retention and metabolic acidosis[44,258].

In brief, the prospective epidemiological studies derived from the current doctoral thesis support the potential role of certain factors of the diet – dietary patterns, dietary acid load, and UPF –on kidney function and CKD. According to our findings, healthy dietary patterns, especially the MedDiet, which is characterized by a high content of nutrient-dense foods with a low dietary acid load, such as fruits, vegetables, nuts, or legumes, and by contrast a low consumption of UPF, may be beneficial for preventing CKD in people with overweight or obesity and MetS. Therefore, even though more studies are still warranted to provide stronger scientific evidence in this area, recommendations to adhere to a diet low in acid load, such as the MedDiet pattern, and to limit the consumption of UPF as much as possible may be prudent, not only for the prevention of the onset and progression of kidney function decline or CKD, but also for the general health of the population and the protection against other non-communicable diseases. Furthermore, from a public health standpoint, dietary guideline design, and clinical practice perspective, these recommendations could be more informative, understandable, and meaningful than advice based solely on individual nutrients.

2. Strengths and limitations

The present doctoral thesis has several strengths and potential limitations that deserve to be addressed. Given the potential limitations, the findings should be interpreted with caution.

Firstly, one of the main **limitations** is the observational nature of the study design, which limits the ability to infer causality; therefore, only associations can be claimed. Secondly, as with any observational study, it is important to recognize that potential confounding factors cannot be entirely ruled out. Nevertheless, the statistical models performed in this investigation were adjusted for a wide range of relevant covariates related to dietary factors as well as kidney function to minimize the risk of confounding bias. Thirdly, given that the population studied was older Mediterranean adults with overweight or obesity and MetS, it might be difficult to extrapolate our findings to other populations. Consequently, to reinforce our conclusions, further research is necessary in populations from other regions and age groups. Fourthly, an FFQ was used to assess exposure to dietary patterns, dietary acid load and UPF. Although this type of questionnaire is widely used in nutritional epidemiological studies for collecting usual dietary intake data, it is sensitive to measurement

errors, recall bias, and misclassification of food and nutrient intake. Nonetheless, it should be mentioned that this FFQ was validated and carefully administered by trained dieticians. In addition, in all the studies comprising this thesis, participants who reported implausible values of energy intake were excluded from the analyses. Finally, it should not be overlooked that the observational studies in this work are based on a randomized clinical trial in which participants underwent a lifestyle intervention program, which might have influenced the results. However, all our analyses were adjusted for the allocation to the intervention group. We also performed interaction tests and subgroup analyses and the results remained consistent. The current investigation also has notable **strengths** that should be highlighted. To begin with, the relatively large sample size and the prospective design should be mentioned. The PREDIMED-Plus has a wide collection of variables that let us adjust the statistical models for an extended range of potential confounding factors. Additionally, the utilization of a validated, semi-quantitative FFQ administrated by trained dieticians was another significant advantage. Additional approaches and sensitivity analyses to the main results were tested to reinforce the robustness of the findings. Finally, it is noteworthy that the optimal and accurate CysC biomarker was available for GFR estimation in the chapter of this thesis that examined the associations between UPF and kidney function.

VII. Conclusions

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VII. CONCLUSIONS

In this section of the current doctoral dissertation, the conclusions drawn from the three original research articles conducted on Mediterranean older adults with overweight or obesity and MetS are presented in response to each hypothesis posited at the beginning of this thesis.

Hypothesis 1: High adherence to *a priori* healthy dietary patterns might be associated with better kidney function in a Mediterranean population of older adults with overweight or obesity and MetS.

- A higher upward change in the adherence to a 17-item erMedDiet score was associated with improvements in eGFR changes and with lower odds of ≥10% eGFR decline after one-year of follow-up. The Trichopoulou-MedDiet and DASH diet scores were not associated with eGFR changes or eGFR decline.
- Higher one-year change toward a greater adherence into the Protein Diet Score was associated with a worsening of eGFR.

Hypothesis 2: Higher dietary acid load might be associated with worse kidney function in a Mediterranean population of older adults with overweight or obesity and MetS.

- PRAL and NEAP were inversely associated with one-year changes in eGFR, but not one-year UACR changes.
- Higher levels of both estimates of dietary acid load were associated with higher odds of ≥10% eGFR decline after one-year of follow-up, and a higher PRAL index was additionally associated with higher odds of ≥10% UACR increase.

Hypothesis 3: Consumption of UPF might decrease kidney function in a Mediterranean population of older adults with overweight or obesity and MetS.

- Higher consumption of UPF was cross-sectionally associated with a lower eGFR and higher odds of decreased kidney function (eGFR<60 ml/min/1.73m^2) at baseline.
- One-year changes towards a higher consumption of UPF were associated with a decrease in eGFR over 3-years of follow-up.

Therefore, the main conclusions of this doctoral thesis support the beneficial association between adherence to the MedDiet and kidney function in older Mediterranean adults with overweight or obesity and MetS. In addition, the results suggest that increased dietary acid load and UPF consumption may have an adverse impact on kidney function.

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VIII. Global and future insights

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VIII. GLOBAL AND FUTURE INSIGHTS

Even though the prevalence, incidence, and mortality rates related to CKD are expected to continue increasing in the coming decades, scientific evidence strongly supports the fact that lifestyle modifications, especially dietary changes, may substantially improve the situation. Consequently, these modifications may reduce these rates, in addition to contributing to a better quality of life for the population, healthier aging, and a reduced burden on the healthcare system.

The findings of the present doctoral thesis provide additional evidence to the existing literature in the field of nutritional epidemiology of kidney function and CKD, which may lead to a better understanding of the associations between the consumption of certain foods or dietary patterns, eGFR, and consequently kidney function and the potential development of the disease. These results could also be of value for the future design or enhancement of dietary guidelines aimed at the prevention of CKD, in conjunction with previous scientific studies available in this area.

As this dissertation may inspire near-future research, our limitations and other important considerations should be addressed beforehand to clarify and confirm the reported associations.

- Randomized controlled clinical trials with long follow-up periods and large samples designed to evaluate the potential impact of different dietary factors on kidney function and CKD would be of great interest to help provide recommendations based on cause-and-effect evidence.
- Since our findings were observed within the framework of a Mediterranean older adult population with underlying comorbidities, additional long-term studies conducted in the general population as well as in individuals under specific conditions, with different ages or in other geographical regions, are needed in the future to extrapolate the results of this investigation.
- Improvements in the methods used to evaluate dietary intake in nutritional epidemiology would greatly aid the comparison of findings from different studies. Some suggestions, that could be helpful in overcoming limitations and enhancing the representation of regular dietary consumption, include collecting data on new food varieties, formulations, and trends; taking into account cooking methods; standardizing food portion sizes; and updating food databases.

- In line with the previous point, to improve the comparability of results among different investigators, a consensus in kidney health research should be reached on the most appropriate and practical methods for assessing kidney function and CKD, in particular regarding the equations and biomarkers used to estimate GFR.
- The potential underlying mechanisms involved in the associations that have been reported in this thesis are not yet clearly understood. Given genetic factors have been suggested to play an important role in CKD, the study of the interplay between diet and genes, known as nutrigenetics, would be an interesting line of research to explore in the future in order to clarify the findings discussed in this work.
- In this sense, the application of Mendelian randomization studies as an alternative to randomized clinical trials with genetic sequencing techniques would be especially promising in the near future, offering a robust framework for the investigation of causality in complex biological pathways between dietary risk factors and kidney health outcomes.
- Omics sciences, and more specifically metabolomics, could also be an appropriate approach to identify potential biomarkers of the dietary components discussed in this thesis and to better understand their impact on metabolism and the pathophysiological mechanisms behind the development of both kidney function and related comorbidities.
- The concept of "brain–gut–kidney axis" has received increasing attention over the past few years[259,260]. Certain nutrients, food groups, and specific types of dietary patterns have been postulated to alter the gut microbiota[259]. In addition, dysbiosis and related metabolites have been linked to various problematic conditions and diseases, such as the loss of kidney function and the onset of CKD[261]. Future investigations examining the impact of the interaction between diet and microbiota on kidney function decline and CKD would therefore be valuable and may enable a better appreciation of further plausible mechanisms behind the associations observed in the current doctoral thesis.

IX. References

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X. Appendices

UNIVERSITAT ROVIRA I VIRGILI
DIETARY FACTORS AND KIDNEY FUNCTION: INSIGHTS FROM A POPULATION OF OLDER MEDITERRANEAN ADULTS WITH OVERWEIGHT OR OBESITY AND METABOLIC SYNDROME
Cristina Valle Hita

X. APPENDICES

1. Scientific contributions

Publications derived from the present work:

Valle-Hita C, Díaz-López A, Becerra-Tomás N, Martínez-González MA, García VR, Corella D, Goday A, Martínez JA, Alonso-Gómez ÁM, Wärnberg J, Vioque J, Romaguera D, López-Miranda J, Estruch R, Tinahones FJ, Lapetra J, Serra-Majem L, Cano-Ibáñez N, Tur JA, Rubín-García M, Pintó X, Delgado-Rodríguez M, Matía-Martín P, Vidal J, Fontao SM, Daimiel L, Ros E, Toledo E, Sorlí JV, Roca C, Abete I, Moreno-Rodriguez A, Crespo-Oliva E, Candela-García I, Morey M, Garcia-Rios A, Casas R, Fernandez-Garcia JC, Santos-Lozano JM, Diez-Espino J, Ortega-Azorín C, Comas M, Zulet MA, Sorto-Sanchez C, Ruiz-Canela M, Fitó M, Salas-Salvadó J, Babio N. ***Prospective associations between a priori dietary patterns adherence and kidney function in an elderly Mediterranean population at high cardiovascular risk.*** Eur J Nutr. 2022 Sep;61(6):3095-3108. doi: 10.1007/s00394-022-02838-7. Epub 2022 Apr 2. PMID: 35366708; PMCID: PMC9363380.

Valle-Hita C, Becerra-Tomás N, Díaz-López A, Vázquez-Ruiz Z, Megías I, Corella D, Goday A, Martínez JA, Alonso-Gómez ÁM, Wärnberg J, Vioque J, Romaguera D, López-Miranda J, Estruch R, Tinahones FJ, Lapetra J, Serra-Majem L, Bueno-Cavanillas A, Tur JA, Martín-Sánchez V, Pintó X, Gaforio JJ, Matía-Martín P, Vidal J, Amengual-Galbarte A, Daimiel L, Ros E, García-Arellano A, Barragán R, Fitó M, Peña-Orihuela PJ, Asencio-Aznar A, Gómez-Gracia E, Martinez-Urbistondo D, Morey M, Casas R, Garrido-Garrido EM, Tojal-Sierra L, Damas-Fuentes M, Goñi E, Ortega-Azorín C, Castañer O, Garcia-Rios A, Gisbert-Sellés C, Sayón-Orea C, Schröder H, Salas-Salvadó J, Babio N. ***Longitudinal association of dietary acid load with kidney function decline in an older adult population with metabolic syndrome.*** Front Nutr. 2022 Sep 30;9:986190. doi: 10.3389/fnut.2022.986190. PMID: 36245494; PMCID: PMC9563235.

Valle-Hita C, Díaz-López A, Becerra-Tomás N, Toledo E, Cornejo-Pareja I, Abete I, Sureda A, Bes-Rastrollo M, Martínez JA, Tinahones FJ, Tur JA, Garcidueñas-Fimbres TE, París-Pallejá F, Goday A, Goñi-Ruiz N, Salas-Salvadó J, Babio N. ***Associations between ultra-processed food consumption and kidney function in an older adult population with metabolic syndrome.*** Clin Nutr. 2023 Oct 2;42(12):2302-2310. doi: 10.1016/j.clnu.2023.09.028. Epub ahead of print. PMID: 37852024.

Other publications:

Valle-Hita C, Salas-Huetos A, Fernández de la Puente M, Martínez MÁ, Canudas S, Palau-Galindo A, Mestres C, Manzanares JM, Murphy MM, Marquès M, Salas-Salvadó J, Babio N. ***Ultra-processed food consumption and semen quality parameters in the Led-Fertyl study.*** Hum Reprod Open. 2024; 2024(1):hoae001. doi: 10.1093/hropen/hoae001. PMID: 38283622; PMCID: PMC10813743.

Nishi SK, Khoury N, **Valle Hita C**, Zurbau A, Salas-Salvadó J, Babio N. ***Vegetable and Fruit Intake Variety and Cardiovascular Health and Mortality: A Systematic Review and Meta-Analysis of Observational Studies.*** Nutrients. 2023 Nov 24;15(23):4913. doi: 10.3390/nu15234913. PMID: 38068771; PMCID: PMC10707746.

Indira Paz-Graniel, Nancy Babio , Stephanie K. Nishi , Miguel Ángel Martínez-González, Dolores Corella, Montserrat Fitó, Alfredo Martínez, Ángel M. Alonso-Gómez, Julia Wärnberg, Jesús Vioque, Dora Romaguera, José López-Miranda, Ramon Estruch, Francisco J. Tinahones, José Manuel Santos-Lozano, J. Luís Serra-Majem, Aurora Bueno-Cavanillas, Josep A. Tur, Vicente Martín Sánchez, Javier Pintó, Miguel Delgado-Rodríguez, Pilar Matía-Martín, Josep Vidal, Cristina Calderon-Sanchez, Lidia Daimiel, Emili Ros, Fernando Fernández-Aranda, Estefania Toledo, **Cristina Valle-Hita**, Jose V. Sorli, Camille Lassale, Antonio Garcia-Rios, Alejandro Oncina-Canovas, Francisco Javier Barón-López, M. Angeles Zulet,Elena Rayó, Rosa Casas, Esther Thomas-Carazo, Lucas Tojal-Sierra, Miguel Damas-Fuentes, Miguel Ruiz-Canela, Sara De las Heras-Delgado, Rebeca Fernandez-Carrión, Olga Castañer, Patricia J. Peña-Orihuela, Sandra Gonzalez-Palacios, Pilar Buil-Cosiales, Albert Goday, and Jordi Salas-Salvadó. ***How Did the COVID-19 Lockdown Pandemic Affect the Depression Symptomatology in Mediterranean Older Adults with Metabolic Syndrome?.*** Depression and Anxiety. 2023. doi: https://doi.org/10.1155/2023/6765950. Article ID 6765950.

Marti A, Fernández de la Puente M, Canudas S, Zalba G, Razquin C, **Valle-Hita C**, Fitó M, Martínez-González MÁ, García-Calzón S, Salas-Salvadó J. ***Effect of a 3-year lifestyle intervention on telomere length in participants from PREDIMED-Plus: A randomized trial.*** Clin Nutr. 2023 Sep;42(9):1581-1587. doi: 10.1016/j.clnu.2023.06.030. Epub 2023 Jul 10. PMID: 37478811.

García S, Pastor R, Monserrat-Mesquida M, Álvarez-Álvarez L, Rubín-García M, Martínez-González MÁ, Salas-Salvadó J, Corella D, Goday A, Martínez JA, Alonso-Gómez ÁM, Wärnberg J, Vioque J, Romaguera D, Lopez-Miranda J, Estruch R, Tinahones FJ, Lapetra J, Serra-Majem L, Riquelme-Gallego B, Pintó X, Gaforio JJ, Matía P, Vidal J, Vázquez C, Daimiel L, Ros E, Sayón-Orea C, Guillem-Saiz P, **Valle-Hita C**, Cabanes R, Abete I, Goicolea-Güemez L, Gómez-Gracia E, Tercero-Maciá C, Colom A, García-Ríos A, Castro-Barquero S, Fernández-García JC, Santos-Lozano JM, Cenoz JC, Barragán R, Khoury N, Castañer O, Zulet MÁ, Vaquero-Luna J, Bes-Rastrollo M, de Las Heras-Delgado S, Ciurana R, Martín-Sánchez V, Tur JA, Bouzas C. ***Metabolic syndrome criteria and severity and carbon dioxide (CO2) emissions in an adult population.*** Global Health. 2023 Jul 13;19(1):50. doi: 10.1186/s12992-023-00948-3. PMID: 37443076; PMCID: PMC10339536.

Fernández de la Puente M, Salas-Huetos A, **Valle-Hita C**, Babio N, Murphy MM, Canudas S, Salas-Salvadó J. ***Is telomere length a biomarker of sperm quality? A systematic review and meta-analysis of observational studies.*** Andrology. 2023 Jun 16. doi: 10.1111/andr.13482. Epub ahead of print. PMID: 37328426.

2. Participation in national and international conferences

Conference: PHD DAY - Institut d'Investigació Sanitària Pere Virgili, Universitat Rovira i Virgili. Reus, Spain. 22 June 2023.
Authors: Valle-Hita C, Díaz-López A, Becerra-Tomás N, Cornejo-Pareja I, Toledo E, Abete I, Sureda A, Bes-Rastrollo M, Alfredo Martínez J, Tinahones FJ, Tur JA, Garcidueñas-Fimbres T, París-Pallejá F, Goday A, Goñi-Ruiz N, Salas-Salvadó J and Babio N.
Title: Associations between ultra-processed food consumption and kidney function in an elderly Mediterranean population with metabolic syndrome.
Format: Flash oral communication.

Conference: XXIX Congreso Nacional de Medicina General y de Familia y V Jornada SEMG Andalucía. Granada, Spain. 14-17 June 2023.
Authors: Valle-Hita C; Díaz López A; Becerra Tomás N; París Pallejá F; Salas Salvadó J; Babio N, PREDIMED-Plus investigators.
Title: Asociación entre el consumo de alimentos ultraprocesados y la función renal en una población mediterránea con síndrome metabólico.
Format: Oral communication.

Conference: Sessió Científica del CCNIEC 2023 ON ES DIRIGEIX LA RECERCA EN NUTRICIÓ? TENDÈNCIES I NECESSITATS DE LA SOCIETAT. Barcelona, Spain. 27 April 2023.

Authors: **Valle-Hita C**, Díaz-López A, Becerra-Tomás N, Cornejo-Pareja I, Toledo E, Abete I, Sureda A, Bes-Rastrollo M, Alfredo Martínez J, Tinahones FJ, Tur JA, Garcidueñas-Fimbres Tany E, Goday A, Goñi-Ruiz N, Salas-Salvadó J and Babio N.

Title: Associations between ultra-processed food consumption and kidney function in an elderly Mediterranean population with metabolic syndrome.

Format: Short oral communication.

Conference: 39th International Symposium on Diabetes and Nutrition. Athens, Greece. 16-19 June 2022.

Authors: **Valle-Hita C**; Becerra-Tomás N, Díaz-López A, Martínez-González MA, Megías I, Corella D, Fitó M, Martínez JA, Alonso-Gómez AM, Wärnberg J, Vioque J, Romaguera D, López-Miranda J, Estruch R, Tinahones FJ, Lapetra J, Serra-Majem L, Bueno-Cavanillas A, Tur JA, Martín Sánchez V, Pintó X, Delgado-Rodríguez M, Matía-Martín P, Vidal J, Vázquez C, Daimiel L, Ros E, Salas-Salvadó J and Babio N

Title: Longitudinal association of Dietary Acid Load with Kidney Function Decline in an older adult population with metabolic syndrome

Format: Oral communication.

Conference: XII Symposium Ciber Fisiopatología de la Obesidad y Nutrición. Virtual Event. 26 – 28 October 2021.

Authors: **Valle-Hita C**, Díaz-López A, Becerra-Tomás N, Martínez-González MA, Martínez-Rodríguez MA, Corella D, Fitó M, Martínez JA, Alonso-Gómez AM, Wärnberg J, Vioque J, Romaguera D, López-Miranda J, Estruch R, Tinahones FJ,Lapetra J, Serra-Majem L Bueno-Cavanillas A, Tur JA, Martín Sánchez V, Pintó X, Delgado-Rodríguez M, Matía-Martín P, Vidal J, Vázquez C, Daimiel L, Ros E, Salas-Salvadó J and Babio N.

Title: Prospective association of a priori dietary patterns and kidney function in the PREDIMED-plus study.

Format: e-Poster.

Conference: 38th International Symposium on Diabetes and Nutrition. Virtual Event. 21 – 24 June 2021.

Authors: **Valle-Hita C**, Díaz-López A, Becerra-Tomás N, Martínez-González MA, Martínez-Rodríguez MA, Corella D, Fitó M, Martínez JA, Alonso-Gómez AM, Wärnberg J,

Vioque J, Romaguera D, López-Miranda J, Estruch R, Tinahones FJ,Lapetra J, Serra-Majem L Bueno-Cavanillas A, Tur JA, Martín Sánchez V, Pintó X, Delgado-Rodríguez M, Matía-Martín P, Vidal J, Vázquez C, Daimiel L, Ros E, Salas-Salvadó J and Babio N.

Title: Prospective association of a priori dietary patterns and kidney function in the PREDIMED-plus study.

Format: e-Poster.

3. Mobility

Length: three months (September – December 2023).

Institution: Guasch group, Department of Public Health, Section of Epidemiology, Faculty of Health and Medical Sciences at University of Copenhagen.

Supervisor: Dr. Marta Guasch.

Objective: To collaborate and participate in the confection of a scientific paper in the context of the Danish National Birth Cohort.

4. Food frequency questionnaire. PREDIMED-Plus Study

ESTUDIO PREDIMED PLUS

Frecuencia de consumo de alimentos

marque así ○ ○ ● ○ así no marque ○ ⊘ ⊗ ✕

Nodo | Paciente | Visita | Fecha actual (Día / Mes / Año) | Número 67066 | 1

Por favor, marque una única opción para cada alimento.

Para cada alimento, marque el recuadro que indica la frecuencia de consumo **por término medio** durante el **año pasado**. Se trata de tener en cuenta también la variación verano/invierno. Por ejemplo, si toma helados 4 veces/semana sólo durante los 3 meses de verano, el consumo promedio al año es 1/semana

	CONSUMO MEDIO DURANTE EL AÑO PASADO								
	NUNCA O CASI NUNCA	AL MES	A LA SEMANA			AL DÍA			
		1 - 3	1	2 - 4	5 - 6	1	2 - 3	4 - 6	6+
I. LÁCTEOS									
1. Leche entera (1 taza, 200 cc)	○	○	○	○	○	○	○	○	○
2. Leche semidesnatada (1 taza, 200 cc)	○	○	○	○	○	○	○	○	○
3. Leche descremada (1 taza, 200 cc)	○	○	○	○	○	○	○	○	○
4. Leche condensada (1 cucharada)	○	○	○	○	○	○	○	○	○
5. Nata o crema de leche (1/2 taza)	○	○	○	○	○	○	○	○	○
6. Batidos de leche (1 vaso, 200 cc)	○	○	○	○	○	○	○	○	○
7. Yogurt entero (1, 125 gr.)	○	○	○	○	○	○	○	○	○
8. Yogurt descremado (1, 125 gr.)	○	○	○	○	○	○	○	○	○
9. Petit suisse (1, 55 gr.)	○	○	○	○	○	○	○	○	○
10. Requesón o cuajada (1/2 taza)	○	○	○	○	○	○	○	○	○
11. Queso en porciones o cremoso (1, porción 25 gr.)	○	○	○	○	○	○	○	○	○
12. Otros quesos: curados, semicurados (Manchego, Bola, Emmental...) (50 gr.)	○	○	○	○	○	○	○	○	○
13. Queso blanco o fresco (Burgos, cabra...) (50 gr.)	○	○	○	○	○	○	○	○	○
14. Natillas, flan, puding (1, 130 cc)	○	○	○	○	○	○	○	○	○
15. Helados (1 cucurucho)	○	○	○	○	○	○	○	○	○

Un plato o ración de 100-150 gr., excepto cuando se indique otra cantidad	NUNCA O CASI NUNCA	AL MES	A LA SEMANA			AL DÍA			
		1 - 3	1	2 - 4	5 - 6	1	2 - 3	4 - 6	6+
II. HUEVOS, CARNES, PESCADOS									
16. Huevos de gallina (uno)	○	○	○	○	○	○	○	○	○
17. Pollo o pavo CON piel (1 ración o pieza)	○	○	○	○	○	○	○	○	○
18. Pollo o pavo SIN piel (1 ración o pieza)	○	○	○	○	○	○	○	○	○
19. Carne de ternera o vaca (1 ración)	○	○	○	○	○	○	○	○	○
20. Carne de cerdo (1 ración)	○	○	○	○	○	○	○	○	○
21. Carne de cordero (1 ración)	○	○	○	○	○	○	○	○	○
22. Conejo o liebre (1 ración)	○	○	○	○	○	○	○	○	○
23. Hígado (ternera, cerdo, pollo) (1 ración)	○	○	○	○	○	○	○	○	○
24. Otras vísceras (sesos, corazón, mollejas) (1 ración)	○	○	○	○	○	○	○	○	○
25. Jamón serrano o paletilla (1 loncha, 30 gr.)	○	○	○	○	○	○	○	○	○
26. Jamón York, jamón cocido (1 loncha, 30 gr.)	○	○	○	○	○	○	○	○	○
27. Carnes procesadas (salchichón, chorizo, morcilla, mortadela, salchichas, butifarra, sobrasada) (50 gr.)	○	○	○	○	○	○	○	○	○
28. Patés, foie-gras (25 gr.)	○	○	○	○	○	○	○	○	○
29. Hamburguesa (una, 50 gr.), albóndigas (3 unidades)	○	○	○	○	○	○	○	○	○
30. Tocino, bacon, panceta (50 gr.)	○	○	○	○	○	○	○	○	○
31. Pescado blanco: mero, lenguado, besugo, merluza, pescadilla,... (1 plato, pieza o ración)	○	○	○	○	○	○	○	○	○
32. Pescado azul: sardinas, atún, bonito, caballa, salmón (1 plato, pieza o ración 130 gr.)	○	○	○	○	○	○	○	○	○
33. Pescados salados: bacalao, salazones (1 ración, 60 gr. en seco)	○	○	○	○	○	○	○	○	○
34. Ostras, almejas, mejillones y similares (6 unidades)	○	○	○	○	○	○	○	○	○
35. Calamares, pulpo, chipirones, jibia (sepia) (1 ración, 200 gr.)	○	○	○	○	○	○	○	○	○
36. Crustáceos: gambas, langostinos, cigalas, etc. (4-5 piezas, 200 gr.)	○	○	○	○	○	○	○	○	○
37. Pescados y mariscos enlatados al natural (sardinas, anchoas, bonito, atún) (1 lata pequeña o media lata normal, 50 gr.)	○	○	○	○	○	○	○	○	○
38. Pescados y mariscos en aceite (sardinas, anchoas, bonito, atún) (1 lata pequeña o media lata normal, 50 gr.)	○	○	○	○	○	○	○	○	○

Por favor, marque una única opción para cada alimento.

Un plato o ración de 200 grs., excepto cuando se indique	CONSUMO MEDIO DURANTE EL AÑO PASADO								
	NUNCA O CASI NUNCA	AL MES	A LA SEMANA			AL DÍA			
		1 - 3	1	2 - 4	5 - 6	1	2 - 3	4 - 6	6 +
III. VERDURAS Y HORTALIZAS									
39. Acelgas, espinacas	○	○	○	○	○	○	○	○	○
40. Col, coliflor, brócoles	○	○	○	○	○	○	○	○	○
41. Lechuga, endivias, escarola (100 gr.)	○	○	○	○	○	○	○	○	○
42. Tomate crudo (1, 150 gr.)	○	○	○	○	○	○	○	○	○
43. Zanahoria, calabaza (100 gr.)	○	○	○	○	○	○	○	○	○
44. Judías verdes	○	○	○	○	○	○	○	○	○
45. Berenjenas, calabacines, pepinos	○	○	○	○	○	○	○	○	○
46. Pimientos (150 gr.)	○	○	○	○	○	○	○	○	○
47. Espárragos	○	○	○	○	○	○	○	○	○
48. Gazpacho andaluz (1 vaso, 200 gr.)	○	○	○	○	○	○	○	○	○
49. Otras verduras (alcachofa, puerro, cardo, apio)	○	○	○	○	○	○	○	○	○
50. Cebolla (media unidad, 50 gr.)	○	○	○	○	○	○	○	○	○
51. Ajo (1 diente)	○	○	○	○	○	○	○	○	○
52. Perejil, tomillo, laurel, orégano, etc. (una pizca)	○	○	○	○	○	○	○	○	○
53. Patatas fritas comerciales (1 bolsa, 50 gr.)	○	○	○	○	○	○	○	○	○
54. Patatas fritas caseras (1 ración, 150 gr.)	○	○	○	○	○	○	○	○	○
55. Patatas asadas o cocidas	○	○	○	○	○	○	○	○	○
56. Setas, níscalos, champiñones	○	○	○	○	○	○	○	○	○

Una pieza o ración	CONSUMO MEDIO DURANTE EL AÑO PASADO								
	NUNCA O CASI NUNCA	AL MES	A LA SEMANA			AL DÍA			
		1 - 3	1	2 - 4	5 - 6	1	2 - 3	4 - 6	6 +
IV. FRUTAS									
57. Naranja (una), pomelo (uno), o mandarinas (dos)	○	○	○	○	○	○	○	○	○
58. Plátano (uno)	○	○	○	○	○	○	○	○	○
59. Manzana o pera (una)	○	○	○	○	○	○	○	○	○
60. Fresas/fresones (6 unidades, 1 plato postre)	○	○	○	○	○	○	○	○	○
61. Cerezas, picotas, ciruelas (1 plato de postre)	○	○	○	○	○	○	○	○	○
62. Melocotón, albaricoque, nectarina (una pieza)	○	○	○	○	○	○	○	○	○
63. Sandía (1 tajada, 200-250 gr.)	○	○	○	○	○	○	○	○	○
64. Melón (1 tajada, 200-250 gr.)	○	○	○	○	○	○	○	○	○
65. Kiwi (1 unidad, 100 gr.)	○	○	○	○	○	○	○	○	○
66. Uvas (un racimo, 1 plato postre)	○	○	○	○	○	○	○	○	○
67. Aceitunas (10 unidades)	○	○	○	○	○	○	○	○	○
68. Frutas en almíbar o en su jugo (2 unidades)	○	○	○	○	○	○	○	○	○
69. Dátiles, higos secos, uvas-pasas, ciruelas-pasas (50 gr.)	○	○	○	○	○	○	○	○	○
70. Almendras (30 gr.)	○	○	○	○	○	○	○	○	○
71. Pistachos (30 gr.)	○	○	○	○	○	○	○	○	○
72. Nueces (30 gr.)	○	○	○	○	○	○	○	○	○
73. Otros frutos secos (30 gr.)	○	○	○	○	○	○	○	○	○

74. ¿Cuántos días a la semana toma fruta como postre?	0 ○	1 ○	2 ○	3 ○	4 ○	5 ○	6 ○	7 ○	

Un plato o ración	CONSUMO MEDIO DURANTE EL AÑO PASADO								
	NUNCA O CASI NUNCA	AL MES	A LA SEMANA			AL DÍA			
		1 - 3	1	2 - 4	5 - 6	1	2 - 3	4 - 6	6 +
V. LEGUMBRES Y CEREALES									
75. Lentejas (1 plato, 150 gr. cocidas)	○	○	○	○	○	○	○	○	○
76. Alubias (pintas, blancas o negras) (1 plato, 150 gr. cocidas)	○	○	○	○	○	○	○	○	○
77. Garbanzos (1 plato, 150 gr. cocidos)	○	○	○	○	○	○	○	○	○
78. Guisantes, habas (1 plato, 150 gr. cocidas)	○	○	○	○	○	○	○	○	○
79. Pan blanco, pan de molde (3 rodajas, 75 gr.)	○	○	○	○	○	○	○	○	○
80. Pan negro o integral (3 rodajas, 75 gr.)	○	○	○	○	○	○	○	○	○
81. Cereales desayuno (30 gr.)	○	○	○	○	○	○	○	○	○
82. Cereales integrales: muesli, copos avena, all-bran (30 gr.)	○	○	○	○	○	○	○	○	○
83. Arroz blanco (60 gr. en crudo)	○	○	○	○	○	○	○	○	○
84. Arroz integral (60 gr. en crudo)	○	○	○	○	○	○	○	○	○
85. Pasta: fideos, macarrones, espaguetis, otras (60 gr. en crudo)	○	○	○	○	○	○	○	○	○
86. Pasta integral (60 gr. en crudo)	○	○	○	○	○	○	○	○	○
87. Pizza (1 ración, 200 gr.)	○	○	○	○	○	○	○	○	○

así no marque

Repita el número de la 1ª hoja y vuelva a marcarlo

3

¿Con que frecuencia consume?	CONSUMO MEDIO DURANTE EL AÑO PASADO								
	NUNCA O CASI NUNCA	AL MES	A LA SEMANA			AL DÍA			
		1 - 3	1	2 - 4	5 - 6	1	2 - 3	4 - 6	6+
88. Alimentos fritos en casa	○	○	○	○	○	○	○	○	○
89. Alimentos fritos fuera de casa	○	○	○	○	○	○	○	○	○

Por favor, marque una única opción para cada alimento.

Una cucharada o porción individual. Para freír, untar, mojar en el pan, aliñar o para ensaladas, utiliza en total:	CONSUMO MEDIO DURANTE EL AÑO PASADO								
	NUNCA O CASI NUNCA	AL MES	A LA SEMANA			AL DÍA			
		1 - 3	1	2 - 4	5 - 6	1	2 - 3	4 - 6	6+
VI. ACEITES Y GRASAS									
90. Aceite de oliva (una cucharada sopera)	○	○	○	○	○	○	○	○	○
91. Aceite de oliva virgen (una cucharada sopera)	○	○	○	○	○	○	○	○	○
92. Aceite de oliva de orujo (una cucharada sopera)	○	○	○	○	○	○	○	○	○
93. Aceite de maíz (una cucharada sopera)	○	○	○	○	○	○	○	○	○
94. Aceite de girasol (una cucharada sopera)	○	○	○	○	○	○	○	○	○
95. Aceite de soja (una cucharada sopera)	○	○	○	○	○	○	○	○	○
96. Mezcla de los anteriores (una cucharada sopera)	○	○	○	○	○	○	○	○	○
97. Margarina (porción individual, 12 gr.)	○	○	○	○	○	○	○	○	○
98. Mantequilla (porción individual, 12 gr.)	○	○	○	○	○	○	○	○	○
99. Manteca de cerdo (10 gr.)	○	○	○	○	○	○	○	○	○
100. Marca de aceite de oliva que usa habitualmente:	— ⓪①②③④⑤⑥⑦⑧⑨ ⓪①②③④⑤⑥⑦⑧⑨ No marque aquí								

CONSUMO MEDIO DURANTE EL AÑO PASADO	NUNCA O CASI NUNCA	AL MES	A LA SEMANA			AL DÍA			
		1 - 3	1	2 - 4	5 - 6	1	2 - 3	4 - 6	6+
VII. BOLLERÍA Y PASTELERÍA									
101. Galletas tipo María (4-6 unidades, 50 gr.)	○	○	○	○	○	○	○	○	○
102. Galletas integrales o de fibra (4-6 unidades, 50 gr.)	○	○	○	○	○	○	○	○	○
103. Galletas con chocolate (4 unidades, 50 gr.)	○	○	○	○	○	○	○	○	○
104. Repostería y bizcochos hechos en casa (50 gr.)	○	○	○	○	○	○	○	○	○
105. Croissant, ensaimada, pastas de té u otra bollería industrial comercial... (uno, 50 gr.)	○	○	○	○	○	○	○	○	○
106. Donuts (uno)	○	○	○	○	○	○	○	○	○
107. Magdalenas (1-2 unidades)	○	○	○	○	○	○	○	○	○
108. Pasteles (uno, 50 gr.)	○	○	○	○	○	○	○	○	○
109. Churros, porras y similares (1 ración, 100 gr.)	○	○	○	○	○	○	○	○	○
110. Chocolates y bombones (30 gr.)	○	○	○	○	○	○	○	○	○
111. Cacao en polvo-cacaos solubles (1 cucharada de postre)	○	○	○	○	○	○	○	○	○
112. Turrón (1/8 de barra, 40 gr.)	○	○	○	○	○	○	○	○	○
113. Mantecados, mazapán (90 gr.)	○	○	○	○	○	○	○	○	○

CONSUMO MEDIO DURANTE EL AÑO PASADO	NUNCA O CASI NUNCA	AL MES	A LA SEMANA			AL DÍA			
		1 - 3	1	2 - 4	5 - 6	1	2 - 3	4 - 6	6+
VIII. MISCELÁNEA									
114. Croquetas, empanadillas, precocinados (una ración)	○	○	○	○	○	○	○	○	○
115. Sopas y cremas de sobre (1 plato)	○	○	○	○	○	○	○	○	○
116. Mostaza (una cucharadita de postre)	○	○	○	○	○	○	○	○	○
117. Mayonesa comercial (1 cucharada sopera = 20 gr.)	○	○	○	○	○	○	○	○	○
118. Salsa de tomate frito, ketchup (1 cucharadita)	○	○	○	○	○	○	○	○	○
119. Picante: tabasco, pimienta, pimentón (una pizca)	○	○	○	○	○	○	○	○	○
120. Sal (una pizca)	○	○	○	○	○	○	○	○	○
121. Mermeladas (1 cucharadita)	○	○	○	○	○	○	○	○	○
122. Azúcar (1 cucharadita)	○	○	○	○	○	○	○	○	○
123. Miel (1 cucharadita)	○	○	○	○	○	○	○	○	○
124. Snacks distintos de patatas fritas: gusanitos, palomitas, maíz, etc. (1 bolsa, 50 gr.)	○	○	○	○	○	○	○	○	○
125. Otros alimentos de frecuente consumo:									
125.1	○	○	○	○	○	○	○	○	○
125.2	○	○	○	○	○	○	○	○	○
125.3	○	○	○	○	○	○	○	○	○

125. Otros alimentos de frecuente consumo (continuación)

125.1 (No marque aquí) 125.2 (No marque aquí) 125.3 (No marque aquí)

Por favor, marque una única opción para cada alimento.

	CONSUMO MEDIO DURANTE EL AÑO PASADO								
	NUNCA O CASI NUNCA	AL MES	A LA SEMANA			AL DÍA			
		1 - 3	1	2 - 4	5 - 6	1	2 - 3	4 - 6	6+
IX. BEBIDAS									
126. Bebidas carbonatadas con azúcar: bebidas con cola, limonadas, tónicas, etc. (1 botellín, 200 cc)	○	○	○	○	○	○	○	○	○
127. Bebidas carbonatadas bajas en calorías, bebidas light (1 botellín, 200 cc)	○	○	○	○	○	○	○	○	○
128. Zumo de naranja natural (1 vaso, 200 cc)	○	○	○	○	○	○	○	○	○
129. Zumos naturales de otras frutas (1 vaso, 200 cc)	○	○	○	○	○	○	○	○	○
130. Zumos de frutas en botella o enlatados (200 cc)	○	○	○	○	○	○	○	○	○
131. Café descafeinado (1 taza, 50 cc)	○	○	○	○	○	○	○	○	○
132. Café (1 taza, 50 cc)	○	○	○	○	○	○	○	○	○
133. Té (1 taza, 50 cc)	○	○	○	○	○	○	○	○	○
134. Mosto (100 cc)	○	○	○	○	○	○	○	○	○
135. Vaso de vino rosado (100 cc)	○	○	○	○	○	○	○	○	○
136. Vaso de vino moscatel (50 cc)	○	○	○	○	○	○	○	○	○
137. Vaso de vino tinto joven, del año (100 cc)	○	○	○	○	○	○	○	○	○
138. Vaso de vino tinto añejo (100 cc)	○	○	○	○	○	○	○	○	○
139. Vaso de vino blanco (100 cc)	○	○	○	○	○	○	○	○	○
140. Vaso de cava (100 cc)	○	○	○	○	○	○	○	○	○
141. Cerveza (1 jarra, 330 cc)	○	○	○	○	○	○	○	○	○
142. Licores, anís o anisetes... (1 copa, 50 cc)	○	○	○	○	○	○	○	○	○
143. Destilados: whisky, vodka, ginebra, coñac (1 copa, 50 cc)	○	○	○	○	○	○	○	○	○

144. ¿A que edad empezó a beber alcohol (vino, cerveza o licores), incluyendo el que toma con las comidas con regularidad (más de siete "bebidas" a la semana)?

Edad (años) — Decena / Unidad

145. ¿Cuántos años ha bebido alcohol con regularidad (más de siete "bebidas" a la semana)?

Años — Decena / Unidad

Si durante el año pasado tomó vitaminas y/o minerales (incluyendo calcio) o productos dietéticos especiales (salvado, aceite de onagra, leche con ácidos grasos omega-3, flavonoides, etc.), por favor indique la marca y la frecuencia con que los tomó:

Marcas de los suplementos de vitaminas o minerales o de los productos dietéticos	CONSUMO MEDIO DURANTE EL AÑO PASADO								
	NUNCA O CASI NUNCA	AL MES	A LA SEMANA			AL DÍA			
		1 - 3	1	2 - 4	5 - 6	1	2 - 3	4 - 6	6+
146.	○	○	○	○	○	○	○	○	○
146.1	○	○	○	○	○	○	○	○	○
146.2	○	○	○	○	○	○	○	○	○

146 (No marque aquí) 146.1 (No marque aquí) 146.2 (No marque aquí)

Muchas gracias por su colaboración