



Effect of an intensive lifestyle intervention on cystatin C–based kidney function in adults with overweight and obesity: From the PREDIMED-Plus trial

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Abstract. Martínez-Montoro JI, Cornejo-Pareja I, Díaz-López A, Sureda A, Toledo E, Abete I, et al. Effect of an intensive lifestyle intervention on cystatin C–based kidney function in adults with overweight and obesity: From the PREDIMED-Plus trial. *J Intern Med.* 2024;1–16.

Background. Large-scale trials evaluating a multi-component lifestyle intervention aimed at weight loss on kidney function are lacking.

Methods. This was a post hoc analysis of the “PREvención con DIeta MEDiterránea-Plus” (PREDIMED-Plus) randomized controlled trial, including patients with overweight/obesity and metabolic syndrome, measured cystatin C and creatinine. Participants were randomly assigned (1:1) to an intensive weight loss lifestyle intervention (intervention group [IG]) consisting of an energy-restricted Mediterranean diet (MedDiet), physical activity promotion and behavioral support, or a control group (CG) receiving ad libitum MedDiet recommendations. The primary outcome was between-group differences in cystatin C–based kidney function (cystatin C–based estimated glomerular filtration rate—eGFRcys—and combined cystatin C–creatinine-based eGFR—eGFRcys) change from baseline to 12 and 36 months.

Secondary outcomes included between-group differences in creatinine-based eGFR (eGFRcr) and urinary albumin-to-creatinine ratio (UACR) change and the predictive capacity of these formulas at baseline for new-onset chronic kidney disease (CKD).

Results. A total of 1909 participants (65 ± 5 years, 54% men) were included. Twelve-month decline in eGFRcys, eGFRcr-cys, and eGFRcr was greater in the CG compared to the IG, with between-group differences of −1.77 mL/min/1.73 m² [95% confidence interval −2.92 to −0.63], −1.37 [−2.22 to −0.53], and −0.91 [−1.74 to −0.71], respectively. At 36 months, the decline in eGFRcr-cys and eGFRcr was greater in the CG. No between-group differences in UACR were found. Significant adjusted areas under the curve for baseline eGFR-cys and eGFRcr-cys were observed for incident CKD at 36 months, which were similar to those for eGFRcr and UACR.

Conclusions. In older adults with overweight/obesity and metabolic syndrome, the PREDIMED-Plus intervention may be an optimal approach to preserve kidney function.

Keywords: cystatin C, lifestyle intervention, Mediterranean diet, obesity, kidney function

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Introduction

The prevalence of chronic kidney disease (CKD) is increasing worldwide and has become one of the leading causes of morbidity and mortality in the last decades [1, 2]. This heterogeneous condition marked by a decline in estimated glomerular filtration rate (eGFR) and/or albuminuria-characterized kidney damage is more prevalent in the population over 60 years old because kidney function physiologically declines with aging and/or in populations with an increasing prevalence of comorbid conditions, such as obesity, type 2 diabetes (T2D), and metabolic syndrome. The coexistence of these factors not only further increases the risk of CKD onset and progression but also the risk of cardiovascular disease (CVD), the main cause of morbimortality among this population [3]. Therefore, effective strategies focused on the prevention of CKD development and progression are needed. This requires a multidisciplinary, lifestyle change-focused approach, including weight loss strategies supported by solid scientific evidence, such as using healthy dietary recommendations and physical activity promotion.

Weight loss has been considered essential in the prevention of CKD and also in delaying its progression in individuals with obesity and T2D [4–6]. Moreover, there is increasing evidence that supports the efficacy of lifestyle interventions involving changes to dietary habits or exercise promotion in CKD prevention and management [7–12]. In this regard, the recent 2020 KDOQI guidelines recommend the Mediterranean diet (MedDiet) as one of the existing healthy dietary patterns of choice in any stage of CKD (stages 1–5) [13] due to its demonstrated renal-protective effects against CKD progression and its ability to modulate associated cardiovascular risk factors [14]. However, few well-powered randomized clinical trials (RCTs) have evaluated the long-term effect of a MedDiet-based dietary intervention on parameters associated with kidney function [15–17]. Our group has been at the forefront and has contributed top-level evidence in this field [15, 18]. To our knowledge, only our large-scale PREvención con Dieta MEDiterránea-Plus (PREDIMED-Plus) multicentric trial has explored the benefits on kidney function

of a multicomponent lifestyle intervention aimed at weight loss in CVD primary prevention [19]. We recently found that, compared to individuals in the control group (CG), an intensive weight loss lifestyle intervention using an energy-restricted MedDiet (erMedDiet) and physical activity over 1 year resulted in a lower risk of CKD incidence and, at the same time, reversed CKD [19].

The evaluation and interpretation of kidney function in clinical trials on dietary interventions aimed at weight loss may be challenging when GFR is not directly measured because the limitations of different endogenous biomarkers used, especially creatinine, may impact some outcomes. Although other markers, such as cystatin C, are not influenced by muscle mass, protein intake, or physical activity, they might also be affected by important changes in body weight and other non-GFR-related factors [20]. It should be noted that in all previous studies, including the PREDIMED-Plus trial, kidney function was estimated by creatinine-based formulas (eGFR_{cr}) [15–17, 19]. Although not yet widely used, the current guidelines recommended the use of equations combining creatinine and cystatin C (eGFR_{cr-cys}) because these equations are more accurate than those using only creatinine or cystatin C [21]. However, it should be pointed out that, in older adults with overweight/obesity at high cardiovascular risk, it is not well established which is the best eGFR formula or biomarker to estimate GFR or incident CKD. The use of cystatin C–based estimated glomerular filtration rate (eGFR_{cys}) or eGFR_{cr-cys} may improve the accuracy of CKD diagnosis and GFR staging, with effects on clinical decision-making, particularly in adult populations with obesity without serious coexisting conditions.

In this study, we aimed to assess the 12- and 36-month effects of an intensive lifestyle intervention (aiming at weight loss based on an erMedDiet together with the promotion of physical activity and behavioral intervention) on creatinine-based and cystatin C–based eGFR estimates in older adults with overweight or obesity and metabolic syndrome. We also aimed to compare the ability of these GFR estimating equations using cystatin C and creatinine in predicting incident CKD.

Methods

Study design and participants

This work was conducted within the framework of the PREDIMED-Plus study (ISRCTN89898870), an

ongoing 6-year, multicenter, randomized, parallel-group, primary prevention trial aiming to evaluate the effects of an intensive lifestyle intervention (including an erMedDiet, physical activity, and behavioral support) on incident cardiovascular events and weight loss, compared to usual care and ad libitum MedDiet recommendations. Participants were randomly allocated in a 1:1 ratio to one of the two study arms, using a computer-based system with stratification (center, sex, and age) in blocks of six participants. Detailed information regarding the design and methods of this study can be found elsewhere [22].

The PREDIMED-Plus trial enrolled 6874 community-dwelling participants who were recruited from 23 Spanish centers between September 2013 and December 2016. Eligibility criteria comprised age 55–75 for men and 60–75 for women, a body mass index (BMI) ≥ 27 and < 40 kg/m², and the presence of at least three criteria for the diagnosis of metabolic syndrome [23]. Participants were also free of established CVD at the time of enrollment. In the current study, we analyzed data from the LIKIDI subproject, performed in 5 out of the 23 PREDIMED-Plus recruiting centers, where serum cystatin C levels were determined in a subsample of 1909, 1645, and 1445 participants at baseline, 1 year, and 3 years of follow-up, respectively.

Intervention

Participants in the intensive lifestyle intervention group (IG) followed an erMedDiet plus physical activity promotion and behavioral support, with specific weight loss goals. The follow-up of the IG included individual and group interview sessions three times per month for the first year and twice per month from the second year. Participants in this group were provided for free extra-virgin olive oil (1 L per month). On the other hand, participants in the CG received the usual healthcare recommendations of ad libitum MedDiet used in the PREDIMED study [24]. Participants in the CG were invited to group sessions every 6 months and were also provided extra-virgin olive oil (6 L every 6 months) in each session. Further details of the PREDIMED-Plus intervention can be found in the study protocol (available at <https://www.predimedplus.com/en/project/>) and our previous publication [25].

Outcome assessments

The primary outcome of this post hoc analysis of the PREDIMED-Plus trial was to evaluate the effect of an intensive lifestyle intervention (based on erMedDiet, physical activity promotion, and behavioral support) on changes in cystatin C–based kidney function (i.e., eGFR_{cys} and eGFR_{cr-cys}) at 12 and 36 months compared to usual care and MedDiet recommendations (CG). Secondary outcomes included the assessment of between-group differences in changes in kidney function based on eGFR_{cr} and urinary albumin-to-creatinine ratio (UACR) and the predictive capacity of these formulas and UACR at baseline for new-onset CKD.

Serum creatinine and cystatin C concentrations were measured in fasting conditions at baseline, 12 months, and 36 months of follow-up. Serum creatinine was measured by routine enzymatic methods, and serum cystatin C was measured by nephelometry assay (Atellica NEPH 630, BN II and BN ProSpec, Siemens Healthcare Headquarters) using the Atellica CH CYSC_2 (Siemens Healthcare GmbH), with a limit of quantitation of 0.25 mg/L and an intra- and inter-assay coefficient of variation $< 10\%$. The kidney function was assessed by eGFR indirectly estimated from both endogenous filtration markers, creatinine (eGFR_{cr}), cystatin C (eGFR_{cys}), or creatinine–cystatin C (eGFR_{cr-cys}) using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [21]. At the same time points, urinary creatinine and albumin concentrations were determined from spot morning urine samples, and the UACR was calculated (mg/g). New-onset CKD at 12 and 36 months of follow-up was defined as progression to CKD stage 3 or greater (eGFR_{cr} < 60 mL/min/1.73 m² of body-surface area) and/or progression of albuminuria (UACR ≥ 30 mg/g) in participants free of both conditions (eGFR_{cr} < 60 mL/min/1.73 m² of body-surface area and UACR ≥ 30 mg/g) at baseline [21].

Other relevant measurements

Sociodemographic and clinical variables, including age, sex, lifestyle factors, educational achievement, history of illnesses, medication use, a 17-item questionnaire to assess the degree to the erMedDiet [26], and a validated REGICOR Short Physical Activity Questionnaire [27], were collected for this PREDIMED-Plus trial subpopulation. At each visit

(baseline, 12 and 36 months), weight, height, BMI (calculated as weight in kg divided by the square of height in meters), waist circumference, and blood pressure were measured. At the same time points, fasting blood samples were obtained, and serum was separated and immediately frozen at -80° . Biochemical parameters, including glucose, HbA1c, triglycerides, total cholesterol, and high-density lipoprotein cholesterol, were determined by standardized methods. Low-density lipoprotein cholesterol was calculated using Friedewald's formula [28].

Statistical analysis

The current analysis was conducted using the PREDIMED-plus database updated to February 2, 2024. Statistical analyses were primarily performed using the SPSS program (version 22.0.0 for Windows, SPSS Iberica). Analysis of descriptive baseline characteristics was carried out and reported as means \pm SD and percentages (number) for continuous and categorical variables, respectively. The normal distribution of variables was evaluated by the Kolmogorov–Smirnov test. Baseline differences among groups were evaluated using the Student's *t*-test for independent samples, and categorical variables were compared using the Chi-squared test. Longitudinal within-group changes were analyzed using paired Student's *t*-test, and longitudinal between-group changes were analyzed using unpaired Student's *t*-test. The association between creatinine-based and cystatin C–based equations (continuous exposure variable) with incident CKD was analyzed with logistic regression models to calculate the odds ratio (OR) and 95% confidence interval (CI). Stratified analyses by sex, age, and decrease in GFR (eGFRcr <60 mL/min/1.73 m²) were also performed. An adjusted model was also fitted, including baseline age, sex, BMI, diabetes mellitus, hypertension, dyslipidemia, current smoking, treatment with angiotensin-converting enzyme (ACE) inhibitors, treatment with angiotensin II receptor blockers (ARBs), IG, and weight loss as covariates.

As a secondary analysis, receiver-operating characteristic (ROC) curves, area under the ROC curve (AUC), sensitivity, specificity, and likelihood ratios were calculated to determine biochemical parameters predicting 12- and 36-month incident CKD. The optimal cut-off points for each biochemical parameter of kidney function measurement were

determined by the point of convergence for the highest sensitivity and specificity. ROC analysis and their comparison were performed using the MedCalc program (version 22.020—32 bits for Windows, MedCalc Software Ltd). Statistical significance was set at *p*-value <0.05 .

Results

Baseline characteristics of the study population

The flow chart of participants included in the present analysis is shown in Fig. S1. The baseline clinical and biochemical characteristics of the study participants according to the two trial arms are shown in Table 1. A total of 1909 participants (964 in the CG and 945 in the IG) were included in this analysis. No differences among groups were observed in the studied variables, except for higher use of ACE inhibitors and a small but significant difference in physical activity in the CG. The prevalence of CKD estimated through eGFRcr and albuminuria at baseline was similar among the groups.

Adherence to the lifestyle intervention

Changes in the 17-item erMedDiet score, dietary and energy intake, and physical activity are shown in Table S1. An overall improvement in the general pattern of food consumption was found in both the CG and IG. As expected, we found that the increase in adherence to the erMedDiet was higher in participants in the IG compared to those in the CG ($p < 0.001$).

In addition, compared to participants in the CG, those in the IG showed a higher reduction in energy intake and a higher increase in physical activity at 12 and 36 months of follow-up ($p < 0.001$).

Weight loss

Greater body weight losses were achieved by participants in the intensive lifestyle intervention compared to those in the CG. Mean weight loss differences were -0.4 kg (3.4) in the CG and -3.9 kg (3.8) in the IG (between-group differences, -3.44 kg [95% CI -3.77 to -3.11 ; $p < 0.001$]) at 12 months. From baseline to 36 months, mean weight loss differences were -0.7 kg (4.6) in the CG, and -3.3 kg (3.2) in the IG (between-group differences, -2.69 kg [95% CI -3.11 to -2.26 ; $p < 0.001$]).

Table 1. Baseline characteristics of the study population.

	All (n = 1909)	Control group (n = 964)	Intervention group (n = 945)	p-value
Age, years	65.0 (5)	65.2 (5)	64.9 (5)	0.272
Men, n (%)	1032 (54.1)	522 (54.1)	510 (54)	0.963
Weight, kg	86.9 (12.6)	86.4 (12.5)	87.5 (12.6)	0.070
BMI, kg/m ²	32.5 (3.4)	32.4 (3.4)	32.6 (3.4)	0.130
Waist circumference, cm				
Men	111.0 (8.6)	111.1 (8.6)	110.9 (8.7)	0.801
Women	104.9 (9.7)	104.5 (9.6)	105.2 (9.7)	0.313
Systolic blood pressure, mm Hg	145.1 (18.8)	145.3 (18.7)	144.9 (18.8)	0.655
Diastolic blood pressure, mm Hg	83.9 (10.9)	83.8 (10.9)	84.0 (10.8)	0.767
<i>Comorbidities</i>				
Obesity (BMI ≥ 30 kg/m ²), n (%)	1396 (73.1)	692 (71.8)	704 (74.5)	0.197
Type 2 diabetes mellitus, n (%)	469 (24.6)	222 (23)	247 (26.1)	0.236
Hypertension, n (%)	1616 (84.5)	812 (84.2)	801 (84.8)	0.833
Dyslipidemia, n (%)	1248 (65.4)	646 (67.0)	602 (63.7)	0.136
<i>Chronic kidney disease (CKD)</i>				
eGFRcr < 60 mL/min/1.73 m ² and/or UACR ≥ 30 mg/g, n (%)	230 (12.1)	120 (12.5)	110 (11.7)	0.594
eGFRcr < 60 mL/min/1.73 m ² , n (%)	87 (4.6)	44 (4.6)	43 (4.6)	0.985
UACR > 30 mg/g, n (%)	168 (9.8)	90 (10.4)	78 (9.2)	0.392
<i>Educational level</i>				
Higher education	380 (19.9)	194 (20.1)	186 (19.7)	0.921
High school	586 (30.7)	292 (30.3)	294 (31.1)	
Primary school	943 (49.4)	478 (49.6)	465 (49.2)	
Current smokers, n (%)	58 (4.3)	25 (3.6)	33 (4.9)	0.263
erMedDiet, 0–17 items	8.5 (2.6)	8.5 (2.7)	8.4 (2.6)	0.489
Physical activity, MET-min/week	2563 (2318)	2672 (2379)	2451 (2249)	0.038
<i>Medications, n (%)</i>				
<i>Glucose-lowering drugs</i>				
Metformin	444 (24.3)	211 (22.9)	233 (25.7)	0.236
SGLT2is	43 (2.4)	24 (2.6)	19 (2.1)	0.478
GLP-1 RAs	29 (1.6)	13 (1.4)	16 (1.8)	0.540
Insulin	95 (5.2)	52 (5.6)	43 (4.8)	0.392
<i>Antihypertensive drugs</i>				
ACEis	651 (35.7)	360 (39.3)	291 (32.2)	0.002
ARBs	626 (34.4)	300 (32.7)	326 (36.1)	0.133
Thiazides	704 (38.7)	364 (39.7)	340 (37.6)	0.361
<i>Lipid-lowering drugs</i>				
eGFRcr, mL/min/1.73 m ²	913 (50)	466 (51.0)	447 (49.4)	0.623
eGFRcys, mL/min/1.73 m ²	85.02 (13.0)	84.92 (13.0)	85.13 (12.9)	0.719
eGFRcr-cys, mL/min/1.73 m ²	72.71 (18.3)	72.52 (18.4)	72.91 (18.3)	0.642
UACR, mg/g	78.59 (15.0)	78.44 (15.1)	78.74 (15.0)	0.658
Fasting glucose, mg/dL	17.87 (48.6)	17.54 (44.7)	18.21 (52.3)	0.777
HbA1c, %	114.0 (28.8)	113.2 (28.8)	114.9 (28.8)	0.182
Total cholesterol, mg/dL	6.1 (0.9)	6.01 (0.9)	6.01 (0.9)	0.376
HDL cholesterol, mg/dL	199.0 (37.9)	199.1 (39.0)	198.8 (36.7)	0.878
HDL cholesterol, mg/dL	47.4 (11.5)	47.6 (11.1)	47.2 (11.8)	0.430

(Continued)

Table 1. (Continued)

	All (n = 1909)	Control group (n = 964)	Intervention group (n = 945)	p-value
LDL cholesterol, mg/dL	121.8 (33.4)	122.1 (34.1)	121.4 (32.7)	0.652
Triglycerides, mg/dL	154.5 (82.1)	154.3 (83.3)	154.7 (80.9)	0.908

Note: Continuous variables are expressed as mean (standard deviation, SD). Qualitative variables are expressed as n (%). Differences between groups assessed by unpaired samples tests (Student's *t*-test or Chi-squared test).

Abbreviations: ACEis, angiotensin-converting enzyme inhibitors; ARBs, angiotensin II receptor blockers; BMI, body mass index; eGFRcr, creatinine-based estimated glomerular filtration rate; eGFRcys, cystatin C-based estimated glomerular filtration rate; eGFRcr-cys, creatinine-based and cystatin C-based estimated glomerular filtration rate; erMedDiet, energy-restricted Mediterranean diet; GLP-1 RAS, glucagon-like peptide receptor agonists; HDL, high-density lipoprotein; HbA1c, glycated hemoglobin; LDL, low-density lipoprotein; SGLT2is, sodium-glucose cotransporter 2 inhibitors; UACR, urinary albumin-to-creatinine ratio.

Effect of a lifestyle intervention on kidney function assessed by cystatin C-based formulas

Changes in kidney function according to the study groups are shown in Table 2. Notably, participants in the CG showed a 12-month increase in serum cystatin C levels, whereas no significant changes in serum cystatin C concentrations were observed in the IG. However, between-group differences regarding changes in this biomarker did not remain significant after 36 months. Twelve-month kidney function decline based on eGFRcr, eGFRcys, and eGFRcr-cys equations was greater in the CG compared to the IG, with between-group differences of -0.91 mL/min/1.73 m² [95% CI -1.74 to -0.71 ; $p = 0.034$], -1.77 [95% CI -2.92 to -0.63 ; $p = 0.002$], and -1.37 [95% CI -2.22 to -0.53 ; $p = 0.001$], respectively. Indeed, as opposed to the CG, no significant changes were observed in eGFRcr or eGFRcr-cys from baseline to 12 months in the IG. At 36 months, the decline in eGFRcr-cys and eGFRcr was greater in the CG, compared to the IG, with between-group differences of -1.14 mL/min/1.73 m² [95% CI -2.10 to -0.18 ; $p = 0.020$] and -0.99 [95% CI -1.87 to -0.11 ; $p = 0.028$], respectively. No between-group differences regarding UACR were found at 12 or 36 months. Changes in eGFRcr, eGFRcys, eGFRcr-cys, and UACR across specific subgroups (i.e., sex, age, and baseline eGFR) at 12 and 36 months are shown in Table S2. No differences were found across these subgroups (all p -values for interaction >0.05).

Association between creatinine-based and cystatin C-based equations and incident CKD

Incident CKD (defined as eGFRcr <60 mL/min/1.73 m² and/or UACR ≥ 30 mg/g in participants without CKD at baseline) was 10.3%

at 12 months and 15.7% at 36 months in the study population.

ORs for incident CKD according to baseline creatinine- and cystatin C-based equations and UACR are shown in Table 3. In the adjusted models, we observed an OR for estimating the risk of 12-month incident CKD of 0.979 (95% CI 0.963–0.995, $p = 0.009$), 0.982 (95% CI 0.971–0.993, $p = 0.001$), 0.977 (95% CI 0.963–0.990, $p = 0.001$), and 1.121 (95% CI 1.091–1.152, $p < 0.001$) for eGFRcr, eGFRcys, eGFRcr-cys, and UACR, respectively.

On the other hand, ORs for estimating the risk of 36-month incident CKD were 0.968 (95% CI 0.954–0.981, $p < 0.001$), 0.983 (95% CI 0.974–0.992, $p < 0.001$), 0.973 (95% CI 0.962–0.985, $p < 0.001$), and 1.102 (95% CI 1.076–1.129, $p < 0.001$) for eGFRcr, eGFRcys, eGFRcr-cys, and UACR, respectively.

Predictive capacity of GFR estimating equations using cystatin C and creatinine, and UACR for 12- and 36-month incident CKD

The predictive capacity of baseline eGFRcr, eGFRcys, eGFRcr-cys, and UACR for incident CKD was evaluated (Table 4, Fig. 1). We observed statistically significant adjusted AUC for baseline eGFRcys (0.699, $p < 0.001$) and eGFRcr-cys (0.702, $p < 0.001$) for predicting incident CKD at 12 months. Although eGFRcr is commonly used for the categorization of CKD, we did not observe an increase in the ability of eGFRcr (AUC) to predict 12-month CKD, as compared to eGFRcys or eGFRcr-cys.

Similarly, for predicting incident CKD at 36 months, we found significant AUCs for baseline

Table 2. Changes in anthropometric and kidney function parameters according to the study groups.

	Control group (n = 964)				Intervention group (n = 945)				Control versus intervention between-groups difference					
	Baseline	12 months	p ^a	36 months	p ^b	Baseline	12 months	p ^c	36 months	p ^d	Δ Baseline—12 months	p ^e	Δ Baseline—36 months	p ^f
Weight, kg	86.43 (12.5)	86.06 (12.9)	<0.001	85.66 (13.1)	<0.001	87.47 (12.6)	83.57 (12.5)	<0.001	83.78 (13.0)	<0.001	-0.420 (3.4) vs. -3.858 (3.8)	<0.001	-0.661 (4.6) vs. -3.347 (3.2)	<0.001
BMI, kg/m ²	32.35 (3.4)	32.26 (3.6)	0.005	32.23 (3.8)	0.008	32.59 (3.4)	31.21 (3.5)	<0.001	31.36 (3.7)	<0.001	-0.116 (1.3) vs. -1.411 (1.4)	<0.001	-0.156 (1.7) vs. -1.168 (1.7)	<0.001
Waist circumference, cm	108.07 (9.6)	107.49 (9.9)	<0.001	107.79 (10.3)	0.150	108.27 (9.6)	103.77 (9.8)	<0.001	104.34 (10.1)	<0.001	-0.652 (4.4) vs. -4.552 (5.1)	<0.001	-0.267 (5.4) vs. -3.608 (5.8)	<0.001
Creatinine, mg/L	0.84 (0.2)	0.84 (0.2)	0.543	0.86 (0.2)	<0.001	0.83 (0.2)	0.83 (0.2)	0.076	0.85 (0.2)	0.001	0.003 (0.12) vs. -0.007 (0.12)	0.094	0.026 (0.12) vs. 0.016 (0.14)	0.109
Cystatin C, mg/L	1.06 (0.2)	1.08 (0.2)	<0.001	1.12 (0.3)	<0.001	1.05 (0.2)	1.05 (0.2)	0.152	1.09 (0.2)	<0.001	0.026 (0.16) vs. 0.008 (0.15)	0.018	0.062 (0.18) vs. 0.047 (0.16)	0.095
eGFRcr, mL/min/1.73 m ²	84.92 (13.0)	85.96 (13.2)	0.005	81.75 (13.7)	<0.001	85.13 (12.9)	85.25 (12.6)	0.817	82.81 (13.3)	<0.001	-0.836 (9.0) vs. 0.070 (8.9)	0.034	-3.181 (8.7) vs. -2.193 (9.8)	0.028
eGFRcys, mL/min/1.73 m ²	72.52 (18.4)	69.99 (17.2)	<0.001	67.13 (17.1)	<0.001	72.91 (18.3)	72.26 (17.6)	0.042	68.83 (16.8)	<0.001	-2.620 (11.9) vs. -0.849 (11.8)	0.002	-5.585 (12.5) vs. -4.447 (12.9)	0.088
eGFRcr-cys, mL/min/1.73 m ²	78.44 (15.1)	76.70 (14.7)	<0.001	73.93 (14.7)	<0.001	78.74 (15.0)	78.61 (14.6)	0.305	75.48 (14.4)	<0.001	-1.692 (8.6) vs. -0.320 (8.8)	0.001	-4.549 (9.0) vs. -3.406 (9.5)	0.020
UACR, mg/g	17.54 (44.7)	23.40 (54.8)	<0.001	25.70 (58.29)	0.001	18.21 (52.3)	21.68 (59.2)	<0.001	24.37 (63.25)	<0.001	6.337 (41.1) vs. 4.978 (37.5)	0.507	7.918 (50.5) vs. 8.019 (51.2)	0.972

Note: Data are represented as mean (standard deviation). Differences assessed by paired (°) and unpaired (°) samples Student's *t*-test.

Abbreviations: BMI, body mass index; eGFRcr, creatinine-based estimated glomerular filtration rate; eGFRcr-cys, creatinine- and cystatin C-based estimated glomerular filtration rate; eGFRcys, cystatin C-based estimated glomerular filtration rate; UACR, urinary albumin-to-creatinine ratio.

^aKidney function and anthropometric parameters are compared in the control group at baseline and 12 months.

^bKidney function and anthropometric parameters are compared in the control group at baseline and 36 months.

^cKidney function and anthropometric parameters are compared in the intervention group at baseline and 12 months.

^dKidney function and anthropometric parameters are compared in the intervention group at baseline and 36 months.

^eDifference (Δ) baseline-12 months in kidney function and anthropometric parameters between groups.

^fDifference (Δ) baseline-36 months in kidney function and anthropometric parameters between groups.

Table 3. Odds ratio for the predictive capacity of baseline kidney function parameters and equations for 12- and 36-month incident chronic kidney disease (CKD).

Kidney function parameters and equations	OR for incident CKD at 12 months ^a			OR for incident CKD at 36 months ^b		
	OR	95% CI	<i>p</i>	OR	95% CI	<i>p</i>
eGFRcr crude model	0.973	0.959–0.988	<0.001	0.963	0.951–0.975	<0.001
eGFRcr-adjusted model ^c	0.979	0.963–0.995	0.009	0.968	0.954–0.981	<0.001
eGFRcys crude model	0.978	0.968–0.988	<0.001	0.979	0.971–0.987	<0.001
eGFRcys-adjusted model ^c	0.982	0.971–0.993	0.001	0.983	0.974–0.992	<0.001
eGFRcr-cys crude model	0.972	0.960–0.984	<0.001	0.969	0.959–0.979	<0.001
eGFRcr-cys-adjusted model ^c	0.977	0.963–0.990	0.001	0.973	0.962–0.985	<0.001
UACR crude model	1.128	1.101–1.156	<0.001	1.110	1.086–1.135	<0.001
UACR-adjusted model ^c	1.121	1.091–1.152	<0.001	1.102	1.076–1.129	<0.001

Abbreviations: CI, confidence interval; eGFRcr, creatinine-based estimated glomerular filtration rate; eGFRcys, cystatin C–based estimated glomerular filtration rate; eGFRcr-cys, creatinine- and cystatin C–based estimated glomerular filtration rate; OR, odds ratio; UACR, urinary albumin-to-creatinine ratio.

^a12-Month incidence of CKD was defined when eGFRcr < 60 mL/min/1.73 m² and/or UACR ≥ 30 mg/g in participants without CKD at baseline.

^b36-Month incidence of CKD was defined when eGFRcr < 60 mL/min/1.73 m² and/or UACR ≥ 30 mg/g in participants without CKD at baseline.

^cAdjusted model for age, sex, body mass index, diabetes mellitus, hypertension, dyslipidemia, current smoker, treatment with angiotensin-converting enzyme inhibitors, treatment with angiotensin II receptor blockers, intervention group, and weight loss.

eGFRcys (0.670, *p* < 0.001) and eGFRcr-cys (0.679, *p* < 0.001). No significant differences among the adjusted AUC of eGFRcys, eGFRcr-cys, eGFRcr, and UACR were detected (Table 4, Fig. 2). Thus, cystatin C–based equations were better predictors of long-term incident CKD (with respect to 12-month incident CKD), as no differences between the AUC for these formulas and baseline UACR were found for the prediction of incident CKD at 36 months. In contrast, for 12-month incident CKD, the AUC for baseline UACR was significantly greater than the AUCs for baseline eGFRcys and eGFRcr-cys.

Discussion

The novel results of our RCT indicate that a 3-year weight loss intensive lifestyle intervention based on an erMedDiet and physical activity, compared with advice to follow an ad libitum MedDiet without weight loss goals, resulted in a lower decline in eGFRcr-cys in adults with overweight/obesity and metabolic syndrome. We also found that cystatin C–based eGFR equations were precise for predicting 12- and 36-month incident CKDs, with accuracy similar to that of eGFRcr at 12 months and comparable to UACR and eGFRcr at 36 months. Therefore, they may have a relevant role in the pre-

diction of CKD, alongside the parameters that are commonly used for the categorization of CKD.

These results are in line with our earlier findings regarding the effects of a 1-year PREDIMED-Plus intervention on kidney function assessed by a creatinine-based eGFR equation [19]. Direct measurement of GFR using plasma or urinary clearance of exogenous filtration markers is more precise than eGFR, although its use is limited in clinical practice due to the complexity of this procedure [21]. However, it should be noted that the assessment and interpretation of kidney function in dietary interventions aimed at weight loss is challenging when GFR is not directly measured, as both diet and changes in body composition may impact especially creatinine but also cystatin C levels. Therefore, using an additional marker that is less affected by the potential changes in muscle mass induced by a lifestyle intervention [29], together with creatinine, strengthens our results, suggesting that the PREDIMED-Plus lifestyle intervention preserves kidney function in adults with overweight and obesity after 3 years of follow-up. Indeed, the use of two biomarkers (i.e., cystatin C and creatinine) for the estimation of GFR increases the accuracy, given that each has its benefits and limitations as filtration markers [21]. On the other

Table 4. Predictive capacity of baseline creatinine- and cystatin C-based kidney function for 12- and 36-month incident chronic kidney disease, according to different kidney injury parameters and equations.

Incident CKD	AUC*	95% CI	Cut-off value	Sensitivity%	Specificity%	p	p ^a	p ^b	p ^c
12 months									
eGFRcr	0.577	0.552–0.601	≤79.32	40.37	77.38	0.0029	–	–	–
eGFRcr adjusted ^d	0.693	0.668–0.716	>0.139	51.28	79.16	<0.001	–	–	–
eGFRcys	0.609	0.584–0.633	≤67.43	58.02	62.61	<0.001	0.2431	–	–
eGFRcys adjusted ^d	0.699	0.675–0.722	>0.196	66.88	67.04	<0.001	0.3122	–	–
eGFRcr-cys	0.609	0.584–0.633	≤73.73	50.31	68.28	<0.001	0.0988	0.8751	–
eGFRcr-cys adjusted ^d	0.702	0.678–0.725	>0.108	64.10	69.00	<0.001	0.1989	0.7752	–
UACR	0.712	0.687–0.735	>8.25	61.49	75.26	<0.001	0.0004	0.0035	0.0046
UACR adjusted ^d	0.771	0.747–0.793	>0.107	68.53	73.76	<0.001	0.0003	0.0034	0.0027
36 months									
eGFRcr	0.602	0.578–0.626	≤79.32	41.90	78.84	<0.001	–	–	–
eGFRcr adjusted ^d	0.678	0.653–0.702	>0.198	52.30	75.04	<0.001	–	–	–
eGFRcys	0.608	0.584–0.632	≤67.61	58.43	63.76	<0.001	0.4441	–	–
eGFRcys adjusted ^d	0.670	0.646–0.695	>0.171	61.00	66.25	<0.001	0.9461	–	–
eGFRcr-cys	0.621	0.597–0.645	≤73.73	51.78	69.80	<0.001	0.1020	0.1706	–
eGFRcr-cys adjusted ^d	0.679	0.654–0.703	>0.192	54.81	73.38	<0.001	0.6207	0.2359	–
UACR	0.667	0.641–0.691	>8.21	54.15	76.41	<0.001	0.0517	0.1207	0.2265
UACR adjusted ^d	0.720	0.695–0.745	>0.165	64.81	68.82	<0.001	0.0711	0.0515	0.1174

Abbreviations: AUC, area under the ROC curve; CI, confidence interval; eGFRcr, creatinine-based estimated glomerular filtration rate; eGFRcys, cystatin C-based estimated glomerular filtration rate; eGFRcr-cys, creatinine- and cystatin C-based estimated glomerular filtration rate; UACR, urinary albumin-to-creatinine ratio.

^aComparison of ROC curves vs. eGFRcr ROC curve.

^bComparison of ROC curves vs. eGFRcys ROC curve.

^cComparison of ROC curves vs. eGFRcr-cys ROC curve.

^dAdjusted model for age, sex, body mass index, diabetes mellitus, hypertension, dyslipidemia, current smoker, treatment with angiotensin-converting enzyme, treatment with angiotensin II receptor blockers, intervention group and weight loss.

*12-month incidence of chronic kidney disease was defined by eGFRcr < 60 mL/min/1.73 m² and/or UACR ≥ 30 mg/g in participants without CKD at baseline.

**36-month cumulative incidence of chronic kidney disease was defined by eGFRcr < 60 mL/min/1.73 m² and/or UACR ≥ 30 mg/g at 12 months and/or 36 months in participants without CKD at baseline.

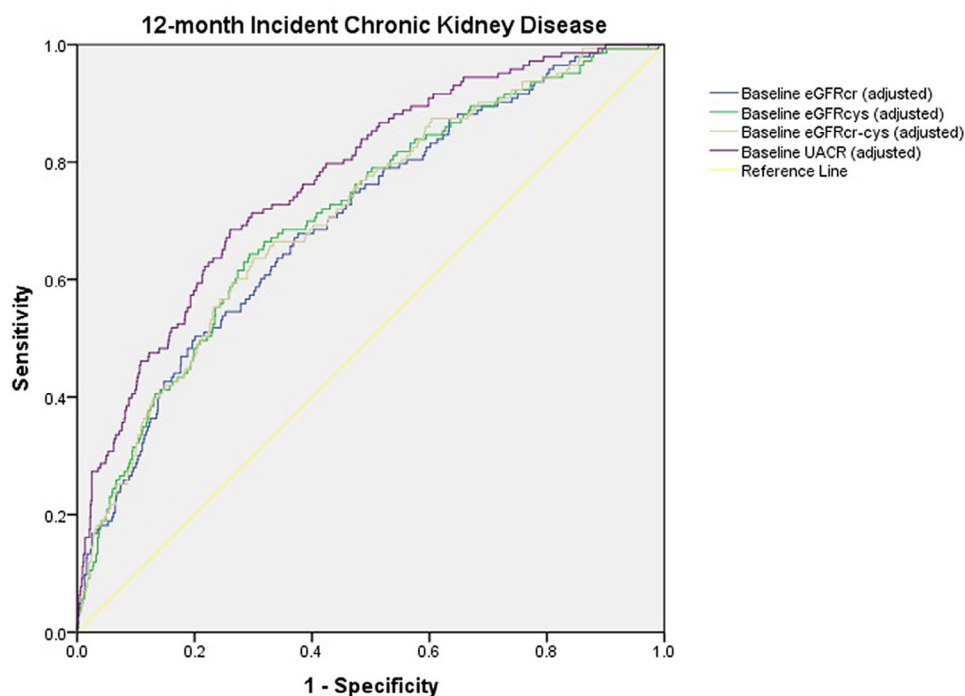


Fig. 1 Receiver-operating characteristic analysis for the evaluation of the predictive capacity of baseline creatinine-based and cystatin C–based kidney function for 12-month incident chronic kidney disease. eGFRcr-cys, creatinine-based and cystatin C–based estimated glomerular filtration rate; eGFRcr, creatinine-based estimated glomerular filtration rate; eGFRcys, cystatin C–based estimated glomerular filtration rate; UACR, urinary albumin-to-creatinine ratio.

hand, changes in weight loss may also have an impact on body-surface area, although this influence may be less pronounced in the context of modest weight loss, as occurred in the present study.

In line with our findings, results from the CORDIO-PREV study showed that a dietary intervention fostering the adherence to a MedDiet in patients with coronary heart disease resulted in a lower decline of eGFRcr, especially in those with mildly impaired eGFRcr, compared to a low-fat diet [17]. However, this intervention did not aim at weight loss [17]. In the PREDIMED study, a primary prevention study conducted in patients at high cardiovascular risk, an improvement in kidney function (evaluated by eGFRcr) was reported in both group arms of participants following a MedDiet enriched either with virgin olive oil or nuts or low-fat diet recommendations [15]. On the other hand, a recent ancillary analysis of the LIFE RCT showed that a physical activity and exercise intervention in sedentary older adults slowed the decline in eGFRcys after 2 years, compared to a health education control intervention [30]. However, to our knowledge, this

is the first RCT exploring the effect of a multicomponent lifestyle intervention aimed at weight loss in primary prevention of CVD on cystatin C–based kidney function.

Normal aging is associated with a decline in eGFR of approximately 1 mL/min/1.73 m² per year (although it can be slightly different in the presence of risk factors, such as obesity, T2D, or hypertension) [31, 32]. In our study, a mean decline of <1 mL/min/1.73 m² in the IG according to all formulas was shown at 12 months. However, greater between-group differences were found regarding 12-month changes in eGFRcys and eGFRcr-cys, compared to eGFRcr. In fact, in contrast to the CG, no significant changes were observed in eGFRcr or eGFRcr-cys from baseline to 12 months in the IG. However, as expected, even the IG presented a significant decline in eGFR measured by the different formulas at 36 months, although it was smaller than the decline observed in the CG.

On the other hand, between-group differences at 36 months remained for changes in eGFRcr from

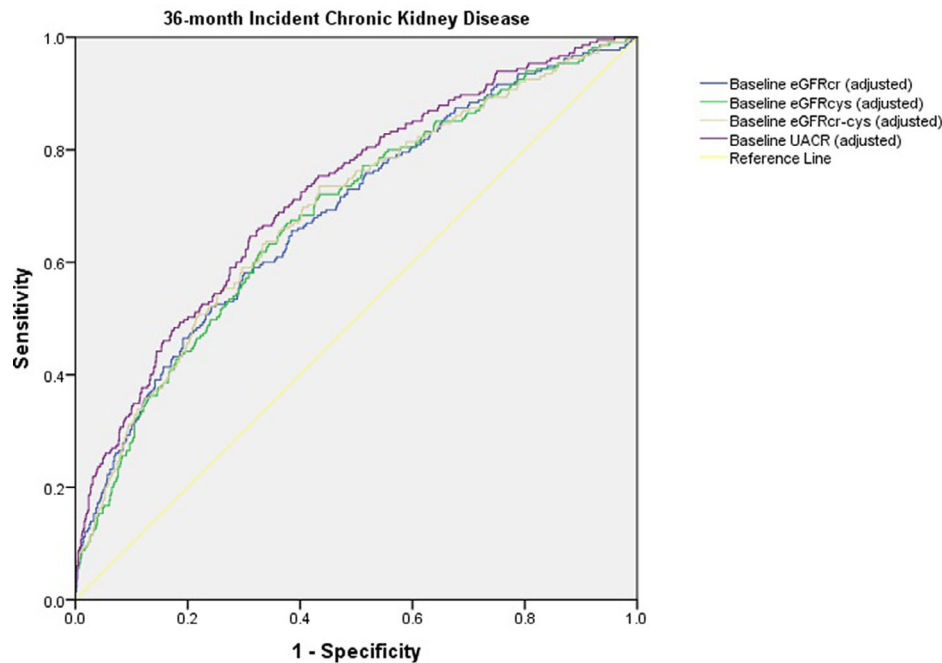


Fig. 2 Receiver-operating characteristic analysis for the evaluation of the predictive capacity of baseline creatinine-based and cystatin C–based kidney function for 36-month incident chronic kidney disease. eGFRcr-cys, creatinine-based and cystatin C–based estimated glomerular filtration rate; eGFRcr, creatinine-based estimated glomerular filtration rate; eGFRcys, cystatin C–based estimated glomerular filtration rate; UACR, urinary albumin-to-creatinine ratio.

baseline. These differences were slightly attenuated for eGFRcr-cys and did not remain significant for eGFRcys. These results may be influenced, in part by the attenuation of between-group differences regarding weight loss, and show that some divergencies may be found among creatinine-based and cystatin C–based formulas. Therefore, these findings point out the need to use formulas including both creatinine and cystatin C, that is, eGFRcr-cys, to assess kidney function.

Some additional differences between the estimation of GFR by creatinine-based and cystatin C–based equations were detected in our population. Therefore, the overall mean values of eGFRcys were lower than eGFRcr. It is known that obesity is associated with increased levels of serum cystatin C, which can lead to an underestimation of GFR using eGFRcys formula [20]. Moreover, although the influence of diet on cystatin C is thought to be minimal [20], it cannot be ruled out that the consumption of olive oil or other components of the MedDiet, due to its anti-inflammatory properties, may have had an effect on cystatin C. There-

fore, the use of both creatinine and cystatin C by the eGFRcr-cys may provide the most accurate measure of GFR for most community-dwelling patients, including people with overweight or obesity [20], especially in weight loss conditions as in the PREDIMED-Plus trial. Moreover, this estimation has been reported to improve creatinine-based formulas in patients with CKD or in the elderly population [33–35].

Notably, a significant increase in serum cystatin C was observed in the CG, whereas cystatin C values remained unchanged after the intensive lifestyle intervention at 12 months. Previous studies reported independent associations between CVD risk and circulating cystatin C levels [36]. Moreover, cystatin C–based estimates of kidney function have been shown to better predict CVD compared to eGFRcr [37–40]. Additionally, some studies have shown an improved prediction of mortality by the use of cystatin C in eGFR formulas [41, 42]. Therefore, our results may add valuable information to previous studies that assessed the effects of dietary interventions on creatinine-based kidney function, although further research is needed.

Improvements in UACR were observed for both the IG and CG. However, no between-group differences regarding this parameter were detected. Similar to our findings, results from the CORDIOPREV RCT reported a lack of significant effects of the interventions on UACR [17]. Moreover, in our previous analysis at 1 year of follow-up, we did not find between-group differences in UACR [19]. These results may be explained, in part, by the widespread use of renoprotective medications in our study population, with blood pressure-lowering and antiproteinuric effects, including ACE inhibitors and ARBs [43]. In fact, a higher proportion of subjects in the CG were on ACE inhibitors compared to the IG within this subpopulation of the PREDIMED-Plus trial. In addition, this difference might also have influenced baseline eGFR, as this type of hypertensive medication can have an initial hemodynamic effect (i.e., reduction of eGFR due to the induced vasodilatation in efferent arterioles and decrease in intraglomerular pressure, followed by a stabilization of eGFR over time) [44].

On the other hand, we found a significant and relevant accuracy of eGFR_{cys} and eGFR_{cr-cys} for predicting incident CKD without significant differences compared to eGFR_{cr} at 12 months and to UACR and eGFR_{cr} at 36 months. Similarly, the OR for incident CKD was significant according to baseline UACR and creatinine-based and cystatin C–based equations at 12 and 36 months. Considering that the definition of new-onset CKD was based solely on eGFR_{cr} and UACR (and not on equations using cystatin C), our results suggest that baseline GFR estimated using cystatin C equations may also serve as a useful and accurate marker for the estimation of the risk of long-term new-onset CKD. It should be noted that only a limited number of previous studies have evaluated the accuracy of cystatin C–based formulas for predicting CKD. In this regard, a prospective study, including 5422 participants with a mean follow-up of 4.7 years, showed that serum cystatin C, together with microalbuminuria, was an independent risk factor for the development of incident CKD [45]. Moreover, the estimation of cystatin C–based kidney function may provide a more precise prediction of end-stage CKD than formulas based solely on creatinine [41]. In fact, eGFR_{cys} has been reported to be more sensitive than eGFR_{cr} for predicting microalbuminuria [46]. On the other hand, other studies found that eGFR_{cr-cys} was more appropriate than eGFR_{cr} to predict hard outcomes (i.e., combination of death, need for renal replacement therapy, or

halving of eGFR) but not declines in GFR without these events [47]. However, these exploratory findings of our study should be cautiously interpreted, and larger, dedicated studies with a longer follow-up are needed to evaluate the predictive capacity of cystatin C–based equations for new-onset CKD in older patients with obesity/overweight and metabolic syndrome.

Strengths and limitations

We acknowledge that this study has some limitations. First, it was conducted in participants with overweight and obesity, with a mean age of 65 years; therefore, our results may show a limited generalizability to other populations. Second, GFR was not directly measured but calculated indirectly by the clearance of serum cystatin C and creatinine. Third, it should be noted that this was a post hoc analysis from the PREDIMED-Plus trial, and dedicated, long-term clinical trials that primarily evaluate the effects of lifestyle interventions on cystatin C–based kidney function are needed to confirm these results. Finally, the design of our study does not allow us to distinguish the effects of each component of the lifestyle intervention (weight loss, erMedDiet, or physical activity) on changes in renal function, although because of mechanistic plausibility, probably all components may have influenced our findings. On the other hand, this study has also important strengths. Thus, this trial included a large population with close long-term follow-up (36 months). In fact, to our knowledge, this is the first large RCT demonstrating that a multicomponent lifestyle intervention aimed at weight loss using a healthy energy-reduced diet and physical activity recommendations preserves kidney function in the long term. Moreover, unlike most previous studies, we used the GFR estimating equation that uses the combination of creatinine and cystatin C (eGFR_{cr-cys}), which has been recently recommended to be used, when available, by the KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of CKD, as it is more accurate than eGFR_{cr}.

Conclusion

In older adults with overweight or obesity and metabolic syndrome, sustained weight loss through an intensive lifestyle program combining an erMedDiet and physical activity might be an optimal approach to preserve kidney function in the long term. In this population, cystatin C–based equations presented significant and relevant pre-

dictive values, which were similar to eGFRcr and UACR in predicting 36-month incident CKD.

Author Contributions

José Ignacio Martínez-Montoro: Writing—original draft; conceptualization; review and editing. **Isabel Cornejo-Pareja:** Writing—original draft; conceptualization; formal analysis; review and editing. **Andrés Díaz-López:** Formal analysis; writing—review and editing. **Antoni Sureda:** Visualization—review and editing. **Estefania Toledo:** Visualization—review and editing. **Itziar Abete:** Visualization—review and editing. **Nancy Babio:** Visualization. **Josep A. Tur:** Visualization. **Miguel A. Martínez-Gonzalez:** Visualization. **J. Alfredo Martínez:** Visualization. **Montse Fitó:** Visualization. **Jordi Salas-Salvadó:** Review and editing; funding acquisition; supervision. **Francisco J. Tinahones:** Review and editing; funding acquisition; conceptualization; supervision.

Conflict of interest statement

The authors declare no conflicts of interest.

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PI16/00501, PI16/00533, PI16/00381, PI16/00366, PI16/01522, PI16/01120, PI17/00764, PI17/01183, PI17/00855, PI17/01347, PI17/00525, PI17/01827, PI17/00532, PI17/00215, PI17/01441, PI17/00508, PI17/01732, PI17/00926, PI19/00957, PI19/00386, PI19/00309, PI19/01032, PI19/00576, PI19/00017, PI19/01226, PI19/00781, PI19/01560, PI19/01332, PI20/01802, PI20/00138, PI20/01532, PI20/00456, PI20/00339, PI20/00557, PI20/00886, PI20/01158); the Special Action Project entitled: Implementación y evaluación de una intervención intensiva sobre la actividad física Cohorte PREDIMED-Plus grant to JS-S. Funding for open access charge: Universidad de Málaga/CBUA.

Data availability statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Ethics statement

This study was approved by the Research Ethics Committees of all PREDIMED-Plus participant centers and was conducted according to the principles of the Declaration of Helsinki. All participants gave their signed informed consent prior to the study inclusion. Trial Registration: ISRCTN89898870.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Supplemental Table S1: 12- and 36-month changes in energy expenditure in leisure-time physical activity, 17-point Mediterranean diet score, energy and dietary intake by treatment group.

Supplemental Table S2: Changes in kidney function parameters across specific subgroups (sex, age, and eGFR at baseline).

Supplemental Figure S1. Flowchart of the study participants. ■