Effect of an Intensive Weight-Loss Lifestyle Intervention on Kidney Function: A Randomized Controlled Trial

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Abstract

Background

Large randomized trials testing the effect of a multifactorial weight-loss lifestyle intervention including Mediterranean diet (MedDiet) on renal function are lacking. Here, we evaluated the 1-year efficacy of an intensive weight-loss intervention with an energy-reduced MedDiet (erMedDiet) plus increased physical activity (PA) on renal function.

Methods

Randomized controlled "PREvención con DIeta MEDiterránea-Plus" (PREDIMED-Plus) trial conducted in 23 Spanish centers comprising 208 primary care clinics. Overweight/obese (n=6719) adults aged 55-75 years with metabolic syndrome were randomly assigned (1:1) to an intensive weight-loss lifestyle intervention with an erMedDiet, PA promotion and behavioral support (intervention) or usual-care advice to adhere to an energy-unrestricted MedDiet (control) between Sept-2013 and Dec-2016. The primary outcome was 1-year change in estimated glomerular filtration rate (eGFR). Secondary outcomes were changes in urine albumin-to-creatinine ratio (UACR), incidence of chronic kidney disease (CKD, eGFR<60 ml/min/1.73m^2 or stage 3 CKD) and micro-macroalbuminuria (UACR≥30 mg/g), and reversion of stage 3 to 2 CKD (eGFR between 60-<90 ml/min/1.73m^2) or micro-macroalbuminuria.

Results

After 1-year eGFR declined by 0.66 and 1.25 ml/min/1.73m^2 in the intervention and control groups, respectively (mean difference, 0.58 ml/min/1.73m^2; 95%CI, 0.15 to 1.02). There were no between-group differences in mean UACR or micro-macroalbuminuria changes. CKD incidence and reversion of stage 3 to 2 CKD were 40% lower (HR 0.60; 0.44 to 0.82) and 92% higher (HR 1.92; 1.35 to 2.73), respectively, in the intervention group.

Conclusions

The PREDIMED-Plus lifestyle intervention is an effective approach for preserving renal function and preventing/delaying CKD progression in overweight/obese adults.

Trial Registration

This study was registered at the International Standard Randomized Controlled Trial. isrctn.com Identifier: ISRCTN89898870. Registration date: 24 July 2014-Retrospectively registered.

Background

Chronic kidney disease (CKD) represents a global health burden associated with increased risk of cardiovascular morbidity, premature death, and decreased quality of life (1). CKD is a heterogeneous condition marked by a decline in glomerular filtration rate (eGFR) and/or albuminuria-characterized kidney damage (2) wherein progression is considerably accelerated when obesity or related cardiovascular risk factors are present (3). The incidence of CKD is shown to rise in association with the increasing rates of obesity and population ageing (1,2). Thus, effective public health strategies to reduce excessive body weight and CKD progression are urgently needed.

Among modifiable lifestyle factors, diet may play a role in the prevention and progression of CKD (4,5). Limited epidemiological evidence suggests that dietary patterns, such as the Mediterranean diet (MedDiet), the Dietary Approaches to Stop Hypertension diet, or the Alternative Healthy Eating Index, are associated with a decreased risk of, or progression to, CKD (6–10). However, few randomized clinical trials (RCTs) have evaluated the long-term effect of a dietary intervention on CKD (11–14). The PREvención con DIetaMEDiterránea (PREDIMED) trial, conducted in older individuals at high cardiovascular risk, showed that both an *ad libitum* MedDiet and advice to follow a low-fat diet improved eGFR-based renal function after 1-year of intervention (13), without differences in weight changes between groups. In the DIRECT trial, all three weight loss energy-reduced diets (erMedDiet, low-fat, and low-carbohydrate) showed similar benefits on eGFR in overweight/obese participants (11). The findings of these trials

focused specifically on dietary patterns are consistent with a secondary analysis of the only available large-scale RCT, the Look AHEAD, which tested the effectiveness of a lifestyle weight-loss program on kidney function in obese diabetic patients (12). This trial reported a 31% decreased risk of CKD in the intensive weight-loss intervention group (low-fat diet plus exercise) compared to the control group (12). In light of these findings, we hypothesize that weight-loss through a multifactorial lifestyle intervention combining an erMedDiet and physical exercise might be an optimal strategy to prevent or delay CKD progression. So far, no large well-conducted RCTs on this matter are available and warrants further research.

Therefore in the context of the PREDIMED-Plus study, a large lifestyle clinical trial comparing an erMedDiet plus increased physical activity (PA) and behavioral support to an *ad libitum* MedDiet in participants with metabolic syndrome (MetS) (15,16), we examined the 1-year effectiveness of this multifaceted intensive lifestyle intervention program on renal function and kidney disease progression.

Methods

Study Design and Participants

The analysis was conducted within the framework of the PREDIMED-Plus trial. The design and methods have been previously published (15,16) and the protocol is available at http://predimedplus.com. Briefly, PREDIMED-Plus is an ongoing, 6-year, multicenter, parallel RCT conducted in Spain evaluating the long-term effect of a weight-loss intervention based on an erMedDiet, PA promotion and behavioral support (intervention), in comparison with usual-care recommending an energy-unreduced MedDiet (control), on primary cardiovascular (CVD) prevention. Between Sept 2013 until Dec 2016, 6719 participants were recruited in 23 Spanish centers working in 208 primary care clinics of the National Health System. Ethics approval was obtained from the institutional review boards of the 23 participating centers and all participants signed an informed consent.

Eligible participants were men and women aged 55–75 years, free of CVD at enrollment, with a BMI of 27–40 kg/m^2, and harboring the MetS (17). Further details of the inclusion/exclusion criteria can be found elsewhere (15,16).

Randomization and Interventions

Each recruiting center randomly assigned (1:1) candidates to either the intervention or the control using a computer-generated random number internet-based system, stratified by sex, age (< 65, 65–70, > 70 years) and center in blocks of six participants. The randomization procedure was blinded to all staff members and principal investigators.

Participants allocated to the intervention received intensive training to follow an erMedDiet, together with PA promotion and behavioral support aimed to achieve and maintain weight loss (15,16). Trained staff delivered three visits/month (an individual motivational interview, a telephone call and a group session) to provide dietary and PA counseling and to achieve weight loss success.

Participants in the control group received nutritional educational sessions every 6 months (an individual visit, a telephone call and a group session) on an *ad libitum* MedDiet with the same written dietary material and instructions used in the PREDIMED study (18), along with general lifestyle recommendations for managing MetS. No specific advice for increasing PA or weight loss was provide.

All participants received free extra-virgin olive oil (1 liter/month) and nuts (125 g/month) to reinforce their adherence to the MedDiet. Details about the interventions are available at web site http://predimedplus.com and somewhere else (15,16).

Measurements

At baseline and 1-year, participants completed a general medical questionnaire (socio-demographic variables, educational achievement, lifestyle factors, history of illnesses and medication use), a 17-item questionnaire to assess the degree of adherence to the erMedDiet (modified version of the previously validated 14-item questionnaire used in the PREDIMED trial) (19), a 143-item semi-quantitative food-frequency questionnaire (20), a validated REGICOR Short Physical Activity Questionnaire (21), and the validated Spanish version of the Nurses' Health Study questionnaire to assess sedentary behaviors (22). At each visit, weight,

height, waist circumference and blood pressure were measured. At baseline and 1-year, blood samples and spot morning urine were collected after an overnight fast, and routine biochemical analyses including fasting glucose, lipid profile, serum creatinine (SCr), and urinary creatinine and albumin concentrations were performed.

Outcomes

The primary end-point of the present study was the 1-year change in kidney function, assessed as changes in SCr-based eGFR from baseline calculated using the CKD-Epi Eq. (23). Secondarily, we assessed change from baseline to 1-year in urine albumin-to-creatinine ratio (UACR). Urinary creatinine and albumin concentrations were determined in spot morning urine samples and UACR was calculated (mg/g). To avoid the influence of extreme outliers of UACR at baseline (n = 15, 0.4%) or at 1-year assessment (n = 23, 0.6%), we truncated maximum values at 500 mg/g. Other secondary outcomes included incidence of CKD and micro- and macroalbuminuria, and reversion of stage 3 to 2 CKD and micro- and macroalbuminuria after 1-year of intervention. CKD was defined as an eGFR < 60 ml/min/1.73 m^2 (stage 3 or greater). Stage 2 CKD was defined as slightly decreased eGFR between 60-<90 ml/min/1.73 m^2. Given the small number of participants with UACR ≥ 300 mg/g at baseline [n = 31 (0.8%); 11 in the intervention group and 20 in the control group] or at the 1-year assessment [n = 45 (1.2%); 19 in the intervention group and 26 in the control group], cut-points of UACR ≥ 30 mg/g were used to define micro- and macroalbuminuria regardless of sex. Incident cases of CKD or micro- and macroalbuminuria were determined when participants did not meet the criteria for the kidney outcome at baseline met the criteria at 1-year. Conversely, participants who met the criteria for the kidney outcome at baseline but not at 1-year were considered to have reverted from stage 3 to 2 CKD or micro- and macroalbuminuria.

Statistical Analyses

For the present interim analysis, a sample size of 5990 participants (intervention, n = 2956; control, n = 3034) assessed at 1-year provided more than 80% power at a 5% significance level (one-sided) to detect a difference of 0.58 ml/min/1.73 m^2 in the main outcome (1-year change in eGFR) between groups, assuming a common SD (of the difference in mean changes) of 8.5 ml/min/1.73 m^2. Data are shown as mean (SD), number (percentage) or mean (95%CI) unless otherwise indicated. The analysis for the primary (eGFR) and secondary (UACR) continuous endpoints were conducted on completers-only and a modified intention-to-treat population (mITT) was utilized as a sensitivity analysis, following a multiple imputation method. The mITT analyses included all participants randomly assigned with a baseline measure of eGFR and/or UACR, regardless of whether they had measurements at the 1-year follow-up visit or not, after exclusion of participants who developed cancer or underwent bariatric surgery. As previously reported (16), all missing data for the eGFR (n = 731, 10.8%) and UACR (n = 1104, 22.8%) at 1-year were estimated from multiple imputation using an iterative Markov chain Monte Carlo method (STATA "mi" command) that simulates multiple values to impute (fill-in) each missing value. Then each imputed dataset was analysed separately and finally resulted were pooled together. We generated 20 imputations for each missing measurement from regression equations to predict these outcomes. The imputation models included as predictors all variables in Table 1, group allocation, and the baseline value of the imputed variable. Analyses of completers included only participants who had both baseline and 1-year measurements, omitting imputed data. For other secondary endpoints, completer analyses were conducted. Continuous outcomes were assessed for normality using both Shapiro-Wilk's test and visual inspection [normal plots (histogram), Q-Q plot (quantile-quantile plot)]. Within- and between- group differences in mean changes at 1-year for eGFR and UACR were evaluated by linear regression analyses adjusting for baseline eGFR or UACR values. We analyzed the full cohort and subgroups stratified according to baseline eGFR (< 60, 60-<90 and ≥ 90 ml/min/1.73 m^2) and UACR (< 30 and ≥ 30 mg/g) values. Stratified analyses by sex, age, BMI, hypertension and diabetes were also performed. We used robust variance estimators to account for intra-cluster correlations, considering as clusters the members of the same household (n = 395 couples). The proportion of participants who met the kidney outcome criteria were compared with chi-square tests. Separate Cox proportional hazards models were used to estimate the adjusted hazard ratio (HR, 95% CIs) of CKD and micro- and macroalbuminuria incidence, and reversion of stage 3 to 2 CKD and micro- and macroalbuminuria in the intervention compared with the control. Models were adjusted for sex, age, baseline BMI, diabetes, systolic and diastolic blood pressure, smoking, educational level, PA, erMedDiet score, oral glucose-lowering agents, lipid-lowering drugs, antihypertensive medication use, and baseline eGFR or UACR values. All models were stratified by recruiting center with robust standard errors to account for intracluster correlations. Person-time of follow-up was calculated as the interval between the randomization date and the date of the 1-year visit.

Table 1
Baseline characteristics of study participants.

	All	Intervention group	Control group
	n = 6719	n = 3335	n = 3384
Mean age (SD), y	65.0 (4.9)	64.9 (4.9)	65.0 (4.9)
Male, n (%)	3450 (51.3%)	1717 (51.5%)	1733 (51.2%)
Mean weight (SD), kg	86.6 (13.0)	86.7 (13.0)	86.5 (12.9)
Mean BMI (SD), kg/m^2	32.6 (3.5)	32.6 (3.4)	32.6 (3.5)
Mean waist circumference (SD), cm			
Men	111.0 (8.8)	110.9 (8.6)	111.1 (9.0)
Women	104.0 (9.2)	104.0 (9.4)	104.0 (9.1)
Mean systolic blood pressure (SD), mm Hg	139.5 (16.9)	139.5 (17.2)	139.5 (16.6)
Mean diastolic blood pressure (SD), mm Hg	81.0 (10.0)	80.9 (10.0)	80.8 (9.9)
Current smokers, n (%)	846 (12.6%)	453 (13.6%)	393 (11.6%)
Former smokers, n (%)	2901 (43.2%)	1390 (41.7%)	1511 (44.6%)
Mean physical activity (SD), MET/min/day	353.5 (329.6)	338.9 (315.3)	367.8 (342.7)
Mean erMedDiet (SD), 0 to 17-items	8.5 (2.7)	8.4 (2.6)	8.5 (2.7)
Medications, n (%)			
Lipid-lowering drugs	3458 (51.5%)	1751 (52.5%)	1707 (50.4%)
Oral blood glucose-lowering drugs	1736 (25.8%)	884 (26.5%)	852 (25.2%)
Insulin treatment	1725 (4.5%)	135 (4.0%)	144 (4.3%)
Antihypertensive drugs	5254 (78.2%)	2588 (77.6%)	2666 (78.8%)
ARBs	2429 (36.2%)	1201 (36.0%)	1228 (36.3%)
ACEis	2009 (29.9%)	963 (28.9%)	1046 (30.9%)
Education, n (%)			
Primary school	3293 (49.0%)	1594 (47.8%)	1699 (50.2%)
First-degree high school	1936 (28.8%)	1013 (30.4%)	923 (27.3%)
High school or university	1490 (22.2%)	728 (21.8%)	762 (22.5%)
Obesity (BMI ≥ 30 kg/m^2), n (%)	4932 (73.4%)	2445 (73.3%)	2487 (73.5%)
Hypertension, n (%)	5767 (85.8%)	2865 (85.9%)	2902 (85.8%)
Type 2 diabetes mellitus, n (%)*	2046 (30.4%)	1022 (30.6%)	1024 (30.3%)
Family history of premature CHD, n (%)	1126 (16.8%)	538 (16.1%)	588 (17.4%)
Mean fasting glucose (SD), mg/dl	113.5 (29.3)	113.3 (28.4)	113.7 (30.2)

Data are mean (SD) or n (%). BMI=, body mass index. erMedDiet = energy restricted Mediterranean diet. ARBs = angiotensin-type 2 receptor blocker. ACEis = angiotensin converting enzyme inhibitors. *Current diabetes was defined as previous diagnosis of diabetes, glycated haemoglobin (HbA1c) ≥ 6.5%, use of antidiabetic medication, or having fasting glucose > 126 mg/dl in both the screening visit and baseline visit.

	All	Intervention group	Control group
Mean LDL cholesterol (SD), mg/dl	119.2 (32.9)	119.4 (32.8)	119.2 (33.0)
Mean HDL cholesterol (SD), mg/dl	48.1 (11.8)	48.0 (11.9)	48.3 (11.8)
Mean triglycerides (SD), mg/dl	152.4 (77.8)	151.4 (77.1)	153.3 (78.5)

Data are mean (SD) or n (%). BMI=, body mass index. erMedDiet = energy restricted Mediterranean diet. ARBs = angiotensin-type 2 receptor blocker. ACEis = angiotensin converting enzyme inhibitors. *Current diabetes was defined as previous diagnosis of diabetes, glycated haemoglobin (HbA1c) ≥ 6.5%, use of antidiabetic medication, or having fasting glucose > 126 mg/dl in both the screening visit and baseline visit.

We also performed separate multivariable linear regression analyses to test associations between eGFR and UACR changes (as continuous variables) and changes in body weight, erMedDiet score, TV-viewing time and PA as independent variables at 1 year (both, as continuous and categorical variables). For these analyses, participants from both intervention and control groups were pooled. Multivariable models were adjusted for baseline eGFR or UACR values, group allocation, and the above-mentioned confounders plus changes in systolic and diastolic blood pressure. Statistical significance was set at $p < 0.05$. All analyses were performed using STATA, version 15.0 (StataCorp LP, Tx. USA) using the available March 12th, 2019 PREDIMED-Plus database.

Results

Between Sept 2013 and Dec 2016, 6874 participants were randomly assigned to either the intervention (n = 3406) or the control (n = 3468). For the present study, we excluded participants who developed any type of cancer (n = 65; 36 in the intervention group and 29 in the control group) or underwent bariatric surgery (n = 1 in the intervention group) during the first year, or had missing eGFR (n = 89) and/or UACR (n = 1975) measurements at baseline. A final sample of 6719 participants was analyzed. The sample size for the mITT analyses was 6719 participants for eGFR changes and 4833 participants for UACR changes. For the completer analyses, 5990 participants who had eGFR and 3715 participants who had UACR measurements at baseline and 1 year were included (Supplementary **Figure S1**). There were no significant differences in the baseline characteristics between the intervention and control groups in the current analysis (Table 1).

At 1-year, the intervention group achieved greater reductions in adiposity parameters compared with the control group (**Additional file 1: Table S1**). Mean 1-year weight-loss from baseline was − 3.7 kg (95%CI: -3.8 to -3.5) in the intervention group and − 0.7 kg (95%CI: -0.9 to -0.6) in the control group (between-group comparison, $p < 0.0001$). In terms of compliance with the intervention, beneficial changes in diet, sedentary behaviors and PA were significantly greater in the intervention *vs.* the control group (between-group comparison, $p < 0.0001$) (**Additional file 1: Table S1**). Except for increased fasting glucose and lipid-lowering medications (more prevalent in the control group), 1-year changes in use of insulin and antihypertensive agents, including angiotensin-converting enzyme inhibitors (ACEis) and angiotensin-type 2 receptor blocker (ARBs), were similar between the two groups (**Additional file 1: Table S2**). Table 2 shows the 1-year intervention effects on eGFR and UACR for the entire study population and by pre-specified subgroups. Completer analysis indicated mean baseline SCr was 74.57 μmol/L (95%CI: 73.99 to 75.19) and 74.26 μmol/L (95%CI: 73.65 to 74.86), while eGFR was 84.28 ml/min/1.73 m^2 (95%CI: 83.78 to 84.78) and 84.16 ml/min/1.73 m^2 (95%CI: 83.65 to 84.66), in the intervention and control groups, respectively. SCr was unchanged in the intervention group (0.14 μmol/L (95% CI:-0.23 to 0.50, $p = 0.51$)) and increased by 0.70 μmol/L (95%: 0.32 to 1.09, $p < 0.001$) in the control group after 1 year (between-group comparison, $p = 0.03$). After 1 year, eGFR changed by -0.66 ml/min/1.73 m^2 (95%CI: -0.96 to -0.36) in the intervention group and by -1.25 ml/min/1.73 m^2 (95%CI: -1.56 to -0.94) in the control group (delta mean difference, 0.58 ml/min/1.73 m^2 (95%CI: 0.15 to 1.02); $p = 0.008$). Mean baseline UACR were 15.32 mg/g (95%CI: 13.32 to 17.32) and 18.24 mg/g (95%CI: 15.87 to 20.64) in the intervention and control groups, respectively. Mean 1-year changes were 2.27 mg/g (95%CI: 0.61 to 3.93) in the intervention group and 3.01 mg/g (95%CI: 1.33 to 4.69) in the control group (between-group comparison, $p = 0.53$) (Table 2). Analyses were repeated with all values, including extreme outliers for UACR, and results were similar (data not shown).

Table 2. Baseline and 1-year change in kidney function markers by group: modified intention-to-treat (MI) and completers-only.

	Intervention group		Control group		Intervention *vs* control			
					Between-group difference			
Variable	**mITT (MI)**	**Completers-only**	**mITT (MI)**	**Completers-only**	**mITT (MI)**	**p value**	**Completers-only**	**p value**
eGFR, ml/min/1.73m^2	n=3335	n=2956	n=3384	n=3034				
Baseline	84.38 (83.91 to 84.85)	84.28 (83.78 to 84.78)	84.20 (83.72 to 84.67)	84.16 (83.65 to 84.66)				
1-year change	-0.68 (-1.01 to -0.37)	-0.66 (-0.96 to -0.36)	-1.26 (-1.58 to -0.93)	-1.25 (-1.56 to -0.94)	0.61 (0.16 to 1.06)	0.007	0.58 (0.15 to 1.02)	0.008
eGFR categories								
≥90 ml/min/1.73m^2	n=1455	n=1277	n=1440	n=1290				
Baseline	96.07 (95.83 to 96.31)	95.98 (95.73 to 96.23)	95.92 (95.70 to 96.14)	95.91 (95.66 to 96.15)				
1-year change	-3.06 (-3.49 to -2.70)	-3.07 (-3.44 to -2.70)	-3.79 (-4.22 to -3.37)	-3.79 (-4.19 to -3.39)	0.73 (0.17 to 1.30)	0.01	0.72 (0.17 to 1.26)	0.01
60-<90 ml/min/1.73m^2	n=1673	n=1492	n=1719	n=1539				
Baseline	78.27 (77.88 to 78.67)	78.33 (77.92 to 78.75)	78.80 (78.41 to 79.19)	78.77 (78.35 to 79.18)				
1-year change	0.64 (0.17 to 1.11)	0.57 (0.11 to 1.04)	-0.04 (-0.51 to 0.44)	0.09 (-0.38 to 0.56)	0.54 (-0.12 to 1.19)	0.11	0.49 (-0.18 to 1.15)	0.15
<60 ml/min/1.73m^2	n=207	n=187	n=225	n=205				
Baseline	51.58 (50.52 to 52.64)	51.86 (50.71 to 52.96)	50.38 (49.24 to 51.50)	50.66 (49.51 to 51.80)				
1-year change	5.30 (3.83 to 6.78)	5.25 (3.71 to 6.79)	5.50 (4.13 to 6.87)	5.36 (3.92 to 6.79)	-0.20 (-2.21 to 1.80)	0.84	-0.11 (-2.21 to 1.99)	0.9
UACR, mg/g	n=2384	n=1800	n=2449	n=1915				
Baseline	16.30 (14.35 to 18.24)	15.32 (13.32 to 17.32)	17.81 (15.69 to 19.92)	18.24 (15.87 to 20.64)				
1-year change	2.43 (0.76 to 4.11)	2.27 (0.61 to 3.93)	2.86 (1.16 to 4.57)	3.01 (1.33 to 4.69)	-0.43 (-2.66	0.70	-0.74 (-3.09 to 1.60)	0.53

					to 1.79)			
UACR categories								
<30 mg/g	n=2179	n=1649	n=2215	n=1724				
Baseline	6.31 (6.08 to 6.55)	6.48 (6.20 to 6.75)	6.65 (6.42 to 6.89)	6.72 (6.46 to 6.99)				
1-year change	2.59 (1.24 to 3.95)	2.04 (1.43 to 2.66)	3.98 (2.52 to 5.44)	4.08 (2.90 to 5.27)	-1.38 (-3.16 to 0.38)	0.12	-2.04 (-3.36 to -0.71)	0.003
≥30 mg/g	n=205	n=151	n=234	n=191				
Baseline	122.44 (105.69 to 139.18)	111.92 (94.49 to 129.35)	123.39 (106.50 to 140.28)	120.59 (102.97 to 138.21)				
1-year change	1.76 (-11.72 to 15.26)	5.93 (-11.81 to 23.68)	-8.67 (-20.45 to 3.11)	-7.63 (-21.27 to 6.02)	10.43 (-7.46 to 28.34)	0.25	13.56 (-8.68 to 35.81)	0.23

Data are means (95% CI). To convert eGFR from ml/min/1.73 m^2 to ml/s/1.73 m^2, multiply by 0.01667. eGFR= estimated glomerular filtration rate. UACR= urinary albumin–creatinine ratio. mITT= modified intention-to-treat. MI= multiple imputation. P values for between-groups differences were calculated using linear regression models adjusting for corresponding baseline values with robust standard errors to account for intra-cluster correlations.

Overall, analyses stratified by sex, age, BMI, hypertension and diabetes status revealed similar trends (**Additional file 1: Table S3**). The subgroup analyses according to baseline eGFR (< 60, 60-<90 and ≥ 90 ml/min/1.73 m^2) and UACR (< 30 and ≥ 30 mg/g) values are shown in Table 2. Regarding eGFR changes, significant between-group differences were found among participants with normal eGFR (≥ 90 ml/min/1.73 m^2, p = 0.01), with a mean difference of 0.72 ml/min/1.73 m^2 (95%CI: 0.17 to 1.26) (P = 0.01). Even though there were no statistically significant between-group differences among participants with an initial eGFR of 60-<90 ml/min/1.73 m^2, eGFR improved by 0.64 ml/min/1.73 m^2 in the intervention group, while it did not significantly change (-0.04 ml/min/1.73 m^2) in the control group (between-group comparison, p = 0.11). Although eGFR levels greatly increased in both groups (~ 5 ml/min/1.73 m^2) among participants with CKD (eGFR < 60 ml/min/1.73 m^2), no differences were found between-group (p = 0.90). The analysis revealed a non-significant group_intervention*eGFR_category interaction effect (p for interaction = 0.80). Regarding UACR changes, our data indicated lesser impairment in the intervention group compared to the control group in those participants with normal UACR (< 30 mg/g) (delta mean difference, -2.04 mg/g (95%CI: -3.36 to -0.71); p = 0.003). However, change in UACR levels was not different between groups in participants with UACR > 30 mg/g (p = 0.23). In this case, the group intervention*UACR_category interaction term was statistically significant (p for interaction < 0.001) (Table 2). The results of the mITT analyses using a multiple imputation method were similar to the main analyses using complete cases (Table 2).

Additionally, we also repeated the main analyses after controlling for the same set of potential confounders used in the multivariable model that adjusted for CKD risk, but results remained unchanged (data not shown).

One-year CKD prevalence was 1.9% lower in the intervention group than in the control group (p = 0.003) (Table 3). Compared with the control group, the intervention group showed a higher reversion rate of stage 3 to 2 CKD (10.1%, p = 0.04 vs. the control group) and lower incidence rate of CKD (-1.1%, p = 0.02 vs. the control group). The reversion and incidence rates of micro- and macroalbuminuria were not significantly lower in the intervention group compared to the control group (Table 3).

Table 3. Kidney outcomes by group assignment: completers-only.

	Group assignment, No. (%) of participants		Intervention *vs* Control	
Criteria	**Intervention Group**	**Control Group**	**Between-group difference‡**	**p value**
No.	n=2956	n=3034		
eGFR <60 ml/min/1.73m^2				
Baseline prevalence	187 (6.3%)	205 (6.7%)	-0.4% (-1.68 to 0.82)	0.50
1-y prevalence	180 (6.1%)	244 (8.0%)	-1.9% (-3.25 to -0.65)	0.003
Reversion rate*	80 (42.8%)	67 (32.7%)	10.1% (0.50 to 19.69)	0.04
Incidence rate†	73 (2.6%)	106 (3.7%)	-1.1% (-2.03 to -0.19)	0.02
No.	n=1800	n=1915		
UACR ≥30 mg/g				
Baseline prevalence	151 (8.4%)	191 (10.0%)	-1.6% (-3.44 to 0.27)	0.09
1-y prevalence	183 (10.2%)	229 (12.0%)	-1.8% (-3.81 to 0.22)	0.08
Reversion rate*	40 (26.5%)	60 (31.4%)	-4.9% (-14.68 to 4.83)	0.32
Incidence rate†	72 (4.4%)	98 (5.7%)	-1.3% (-2.79 to 0.16)	0.08

Data are n (%). Abbreviations: eGFR, estimated glomerular filtration rate; UACR, urinary albumin–creatinine ratio. *P* values for between-groups differences were calculated using linear regression models. *Reversion rate indicates the n (%) of participants who met the criterion for the kidney outcome at baseline [eGFR <60 ml/min/1.73m^2 (stage 3 CKD or greater) or UACR ≥30 mg/g] but not at the 1-year assessment [eGFR between 60-<90 ml/min/1.73m^2 (stage 2 CKD) or UACR <30 mg/g]. †Incidence rate indicates the n (%) of participants who did not meet the criterion for the kidney outcome at baseline (eGFR ≥60 ml/min/1.73m^2 or UACR <30 mg/g) but met the criterion at the 1-year assessment (eGFR <60 ml/min/1.73m^2 or UACR ≥30 mg/g). ‡Data are percentage (95% CI). P values for differences between groups by Chi-square tests.

The multivariable-adjusted HR of CKD incidence and reversion of stage 3 to 2 CKD in the intervention group was 0.60 (95%CI: 0.44 to 0.82, p = 0.001) and 1.92 (95%CI: 1.35 to 2.73, p < 0.001), respectively, compared to the control group (Fig. 1). Results were similar when the data was analyzed using a composite definition to ascertain the CKD incidence and reversion of stage 3 to 2 CKD (i.e., both outcomes accompanied by at least an additional 10% change in eGFR from baseline) in order to minimize the possibility of including individuals with baseline eGFR values very close to 60 ml/min/1.73 m^2. This was done to mitigate subsequent changes in the eGFR category due to random variation of estimated eGFR (data not shown). No between-group differences in the incidence or reversion of micro- and macroalbuminuria were observed (Fig. 1).

Multivariable-linear regression analyses in the full cohort showed weight loss (p < 0.001) and improved erMedDiet (p = 0.002) were each independently associated with increased eGFR at 1 year after controlling for cofounders. When changes in weight and other lifestyle variables (erMedDiet score, TV-viewing time and PA) were accounted for as predictors in the same model, these associations remained significant (p ≤ 0.03) (Table 4).

Table 4. Associations of 1-year changes in weight, MedDiet, TV-viewing, and PA with kidney function markers changes: completers-only

		Δ in eGFR, ml/min/1.73m^2				Δ in UACR, mg/g		
Models	**No.**	**Coefficients β (95% CI)**	**P value**	**R^2**	**No.**	**Coefficients β (95% CI)**	**P value**	**R^2**
Model 1[a]	5872			0.13	3647			0.04
Δ in weight, kg		-0.11 (-0.17 to -0.05)	<0.001			0.64 (0.31 to 0.96)	<0.001	
Model 1[a]	5872			0.13	3647			0.04
Δ in weight, %		-0.09 (-0.14 to -0.04)	<0.001			0.55 (0.27 to 0.83)	<0.001	
Model 2[a]	5812			0.13	3613			0.04
Δ in MedDiet score, item		0.12 (0.04 to 0.19)	0.002			-0.01 (-0.36 to 0.33)	0.9	
Model 3[a]	5786			0.13	3659			0.04
Δ in TV-viewing time, hours/d		-0.04 (-0.19 to 0.11)	0.63			1.17 (0.25 to 2.10)	0.01	
Model 4[a]	5832			0.13	3625			0.03
Δ in total leisure-time PA, METs-min/d		0.00 (-0.00 to 0.001)	0.09			-0.00 (-0.004 to 0.003)	0.9	
Model 5[a]	5766			0.13	3587			0.04
Δ in weight, kg		-0.09 (-0.15 to -0.03)	0.002			0.67 (0.31 to 1.02)	<0.001	
Δ in MedDiet score, items		0.08 (0.01 to 0.16)	0.03			0.20 (-0.18 to 0.59)	0.29	
Δ in TV-viewing time, hours/d		-0.01 (-0.16 to 0.14)	0.9			1.08 (0.16 to 1.99)	0.02	
Δ in total leisure-time PA, METs.min/d		0.00 (-0.00 to 0.001)	0.27			0.001 (-0.003 to 0.005)	0.71	

Data are regression coefficients β (95% CI) from multivariate linear regression. Abbreviations: MedDiet= Mediterranean diet; PA= physical activity; eGFR, estimated glomerular filtration rate; UACR, urinary albumin–creatinine ratio. [a]Each model was analyzed independently and adjusted for baseline eGFR or baseline UACR, for treatment group (intervention/control group), sex (men/women), age (< 65/≥65 years), baseline BMI(continuous), diabetes (yes/no), systolic and diastolic blood pressure (continuous), smoking (never, current, or former smoker), educational level (primary/secondary education or academic/graduate), lipid-lowering drugs (yes/no), antihypertensive use (yes/no), center (categorized into quartiles by number of participants), and changes in systolic and diastolic blood pressure. Robust standard errors to account for intra-cluster correlations were used.

Greater increases in eGFR were observed when participants in the lowest weight loss categories were compared to those in the highest categories (5–10% and ≥ 10% loss) (p for trend = 0.004), and for those with an erMedDiet adherence score (≥ 7 point increase) (p for trend = 0.01) (**Additional file 1: Table S4**). Considering UACR as the outcome, only weight loss (p < 0.001) and reduction in TV-viewing time (p = 0.01) were independently associated with decreased UACR. The associations were similar when

all predictor variables were entered into the same model ($p \leq 0.02$) (Table 4). Compared to participants who gained weight or remained weight-stable (< 1% weight loss), those who lost 1–5%, 5–10% and > 10% body weight showed a graded decrease in UACR levels (p for trend = 0.006). An opposite pattern of association with AUCR was observed with greater increases in TV-viewing time (p for trend = 0.49) (**Additional file 1: Table S4**). There were no significant interactions between intervention assignment and these variables with eGFR or UACR (**Additional file 1: Figure S2**).

Discussion

The novel results of our RCT indicate an intensive lifestyle intervention aimed at weight loss based on an erMedDiet and increased PA is effective for preserving renal function and preventing/delaying CKD progression in overweight/obese adults with MetS. Weight loss and high erMedDiet adherence were both independently associated with improvements in kidney function.

In our study eGFR declined in both groups at 1-year but, compared to the control group, the eGFR decline rate was about 0.6 ml/min/1.73m² lower in the intervention group, which experienced a mean weight loss of just 4.2%. These favorable effects on eGFR were similar by sex, age, BMI, hypertension and diabetes status. Of note, 86% and 78% of participants had hypertension and used antihypertensive agents, respectively, making it difficult to assess the role of hypertension on renal function.

In healthy individuals, an eGFR decline of about 1 ml/min/1.73m²/year generally reflects the natural aging process (2). Accordingly, the observed mean rate of eGFR decline in the intervention group was < 1 ml/min/1.73 m^2 at 1-year. It should be noted that our population was comprised of older individuals with overweight/obesity and MetS, which are well-known risk factors for accelerated eGFR decline over and above that imposed by natural ageing.(2,3) Our findings reinforce the importance of weight loss through a healthy lifestyle on preserving renal function, particularly among this vulnerable population group.

We also found that the intervention effect on eGFR changes was closely related to initial eGFR in magnitude and direction. The presence of obesity-related comorbidities alongside aging could partly explain the highest eGFR decline found in subjects with an initial eGFR ≥ 90 ml/min/1.73 m^2. Another explanation could be that small changes in SCr above or below the normal range could have a relatively higher influence on eGFR fluctuations (24). In our study, eGFR increased significantly by 0.57 ml/min/1.73 m^2 only in the intervention group participants with initial eGFR of 60-≤90 ml/min/1.73 m^2. This suggests that the treatment benefits observed on eGFR were more pronounced in participants with modestly impaired renal function at baseline, which emphasizes the importance of early lifestyle interventions in populations at risk.

We also found that at 1 year UACR increased less in normoalbuminuric participants in the intervention group, although no benefit was observed among those with established micro- or macro albuminuria. Possibly a greater and sustained weight loss over a longer period of time is necessary to reduce UACR in obese participants with UACR ≥ 30 mg/g. These findings are interesting from a public health perspective, since a minimal increase in the UACR within the normal range has been associated with increased CVD in high-risk individuals (25). Despite differences in the populations studied, methodology and dietary approaches used, our results are in line with the Look AHEAD findings (12), which showed a protective effect of an intensive weight loss lifestyle intervention with a low-fat diet on CKD progression in diabetic participants. Furthermore, our trial provides new data suggesting that weight loss together with lifestyle changes including a MedDiet intervention may reverse early CKD progression from stage 3 to 2 CKD. However, the results also show that the lifestyle intervention had no beneficial effects on the incidence or reversion of micro- and macroalbuminuria. Further RCTs with longer follow-up and a re-evaluation of the PREDIMED-Plus cohort after longer follow-up time are needed to confirm these findings.

It is likely that the renal-protective effects observed in our study result from a synergistic action from improvement in lifestyle and adiposity parameters. In line with previous findings (26), we showed that weight loss was independently associated with improved kidney function (eGFR and UACR). This supports a direct effect of obesity as a renal risk factor in older individuals with metabolic disturbances. It has been suggested that renin–angiotensin system activation and resultant oxidant stress and inflammation may partly explain obesity-linked kidney dysfunction (27), which supports the weight loss-related benefit observed in our study. We surmise that such a beneficial effect on renal function is likely to be indirectly mediated by the weight loss-induced improvement in cardiometabolic risk factors —insulin resistance, HbA1c, triglycerides, and HDL-cholesterol— achieved by the intervention group after 1-year follow-up (28,29). Furthermore, our study is in line with previous reports (11,13) suggesting that

increased adherence to the erMedDiet may slow the progression of kidney dysfunction, as previously reported in older individuals at high cardiovascular risk (13). This may be partially explained by the antioxidant and anti-inflammatory effects of this healthy dietary pattern and its individual components on several cardiometabolic risk markers (30–32). Additionally, in prior PREDIMED reports we showed that an *ad libitum* MedDiet protects against kidney dysfunction-related comorbidities, such as hypertension (33), diabetes (34), and MetS (35). In our study, increased TV-viewing time was also independently associated with UACR worsening, confirming the negative impact of sedentary behaviors on metabolism and kidney function (36–38). Nonetheless, PA was unrelated to changes in kidney function. Despite using validated questionnaires (21), the use of self-reported PA instead of more objective measures could partially explain this finding. At any rate, observational studies in this field have shown mixed results (38,39). Of note, our interventions had minimal impact on medication changes, including antihypertensive agents such as ARBs and ACEis, both considered renoprotective because of their blood pressure-lowering and anti-proteinuric effects (40,41).

Besides the short follow-up, our study has other limitations. First, our population consisted of overweight/obese older Mediterranean individuals with MetS, which prevents generalization of the findings to other populations. Second, kidney function markers were determined only once at baseline and 1 year, and their known biological variability may have led to some degree of misclassification. We also did not directly measure eGFR using an optimal marker, such as inulin, iothalamate or iohexol, or 24-hours urinary creatinine clearance, as these procedures are costly and time consuming and are not suited to the routine detection of kidney disease. Also, spot morning urine samples were used for the estimation of the albumin excretion rate (expressed as UACR), whereas a 24 hour urine collection is considered the gold standard for the determination of albuminuria. Third, although the analyses were adjusted by several confounders that can affect SCr concentrations, we cannot exclude the possibility of residual confounding. We acknowledge that a large weight loss may reduce the muscle mass and SCr causing an increase in eGFR. Surprisingly, we found that SCr was unchanged in the intervention group experiencing a relatively modest weight loss (-3.7 kg) and increased by 0.70 μmol/L in the control group after 1 year. Besides, < 5% weight loss over 1 year yielded no significant decreases in SCr (**Additional file 1: Table S4**). By applying methods for determination of body composition, we previously demonstrated that the achieved weight loss was due to a reduction of body fat. Thus, we hypothesize that the SCr change observed in the intervention group is unlikely to be influenced by the modest weight loss-induced muscle mass reduction. In fact, a recent pooled analysis of seven RCTs concluded that in patients experiencing a weight reduction of ~ 2 kg, the creatinine-based CKD-EPI equation was unaffected and could be applied (42). This issue requires further study and confirmation. Lastly, only a small number of subjects had eGFR < 30 ml/min/1.73 m^2 (n = 12) and/or UACR ≥ 300 mg/g (n = 31), which limits the ability to assess the interventions impact on eGFR and UACR in advanced CKD stages.

Conclusions

The PREDIMED-Plus lifestyle intervention appears to be an effective approach for preserving renal function and preventing/delaying CKD progression in overweight/obese adults with MetS. We hypothesize that long-term renoprotective effects in response to the lifestyle intervention, if sustained over time, may eventually lead to a decreased incidence of kidney failure, CVD events, and mortality in the future.

Abbreviations

CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; MedDiet, Mediterranean diet; RCT, randomized clinical trial; PREDIMED, PREvención con DIetaMEDiterránea; erMedDiet, energy-reduced MedDiet; PREDIMED-Plus, PREvención con DIeta MEDiterránea-Plus; PA, physical activity; CVD, cardiovascular disease; MetS, metabolic syndrome; SCr, serum creatinine; UACR, urine albumin-to-creatinine ratio; mITT, modified intention-to-treat; ACEis, angiotensin-converting enzyme inhibitors; ARBs, angiotensin-type 2 receptor blocker; HR, hazard ratio.

Declarations

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Availability of data and materials: The dataset (including data dictionaries) of PREDIMED-Plus is available to external investigators in order to make possible the replication of the main analyses used for the published article. However, due to the restrictions imposed by the Informed Consent and the Institutional Review Boards (IRB), bona fide investigators interested in analyzing the PREDIMED-Plus dataset may submit a brief proposal and statistical analysis plan to the corresponding author (JS-S) at jordi.salas@urv.cat. Upon approval from the Steering Committee and IRBs, the data will be made available to them using an onsite secure access data enclave. The study protocol is available at http://predimedplus.com/.

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Figures

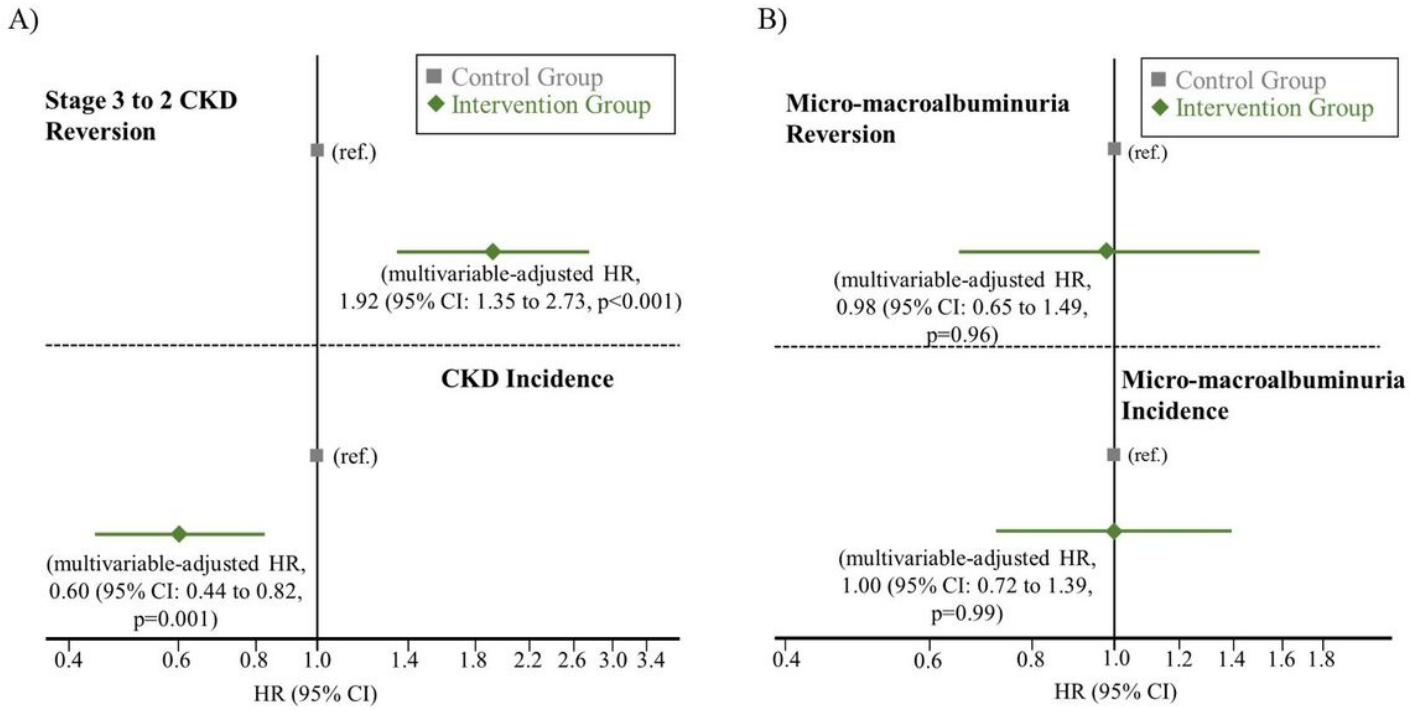
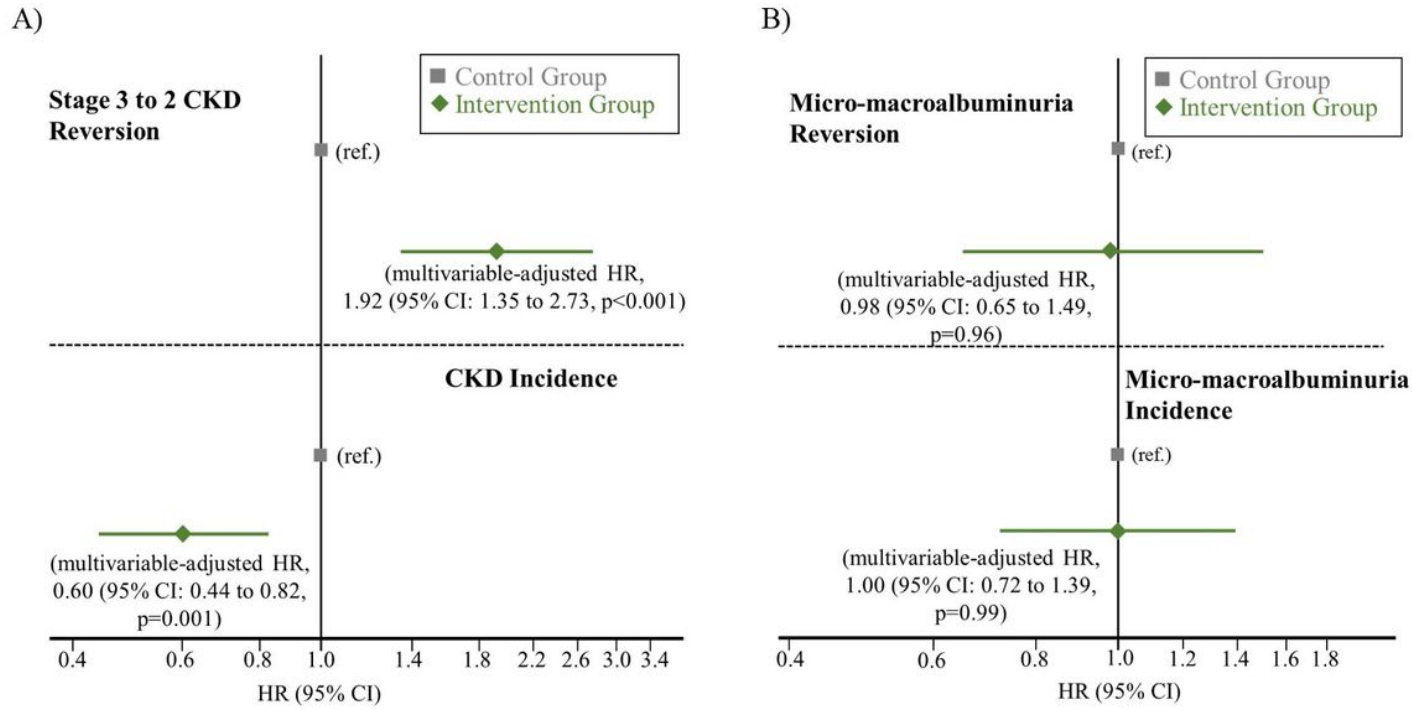


Figure 1

A) Hazard ratio (HR, 95% CI) of 1-year reversion to stage 2 CKD (eGFR between 60-<90 ml/min/1.73m2) among participants who had CKD (eGFR<60 ml/min/1.73m2 or stage 3 CKD) at baseline (top) and incidence of CKD among participants who did not have CKD (eGFR≥60 ml/min/1.73m2) at baseline (bottom) in the intervention group compared with the control group; B) HR (95% CI) of 1-year reversion of micro- and macroalbuminuria among participants who had micro- and macroalbuminuria (UACR≥30 mg/g) at baseline (top) and incidence of micro- and macroalbuminuria among participants who did not have micro- and macroalbuminuria (UACR<30 mg/g) at baseline (bottom) in the intervention group compared with the control group. The Cox proportional hazards models were adjusted for sex (men/women), age (continuous), baseline BMI (continuous), diabetes (yes/no), systolic and diastolic blood pressure (continuous), smoking (never, current, or former smoker), educational level (primary/secondary education or academic/graduate), physical activity in MET-min/day (continuous), erMedDiet score (0-17), oral glucose-lowering agents (yes/no), lipid-lowering drugs (yes/no), antihypertensive use (yes/no) and for corresponding baseline

eGFR or UACR values. All models were stratified by recruitment center. Robust standard errors to account for intracluster correlations were used.



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A) Hazard ratio (HR, 95% CI) of 1-year reversion to stage 2 CKD (eGFR between 60-<90 ml/min/1.73m2) among participants who had CKD (eGFR<60 ml/min/1.73m2 or stage 3 CKD) at baseline (top) and incidence of CKD among participants who did not have CKD (eGFR≥60 ml/min/1.73m2) at baseline (bottom) in the intervention group compared with the control group; B) HR (95% CI) of 1-year reversion of micro- and macroalbuminuria among participants who had micro- and macroalbuminuria (UACR≥30 mg/g) at baseline (top) and incidence of micro- and macroalbuminuria among participants who did not have micro- and macroalbuminuria (UACR<30 mg/g) at baseline (bottom) in the intervention group compared with the control group. The Cox proportional hazards models were adjusted for sex (men/women), age (continuous), baseline BMI (continuous), diabetes (yes/no), systolic and diastolic blood pressure (continuous), smoking (never, current, or former smoker), educational level (primary/secondary education or academic/graduate), physical activity in MET-min/day (continuous), erMedDiet score (0-17), oral glucose-lowering agents (yes/no), lipid-lowering drugs (yes/no), antihypertensive use (yes/no) and for corresponding baseline eGFR or UACR values. All models were stratified by recruitment center. Robust standard errors to account for intracluster correlations were used.

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