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Original article

Longitudinal changes in adherence to the portfolio and DASH dietary patterns and cardiometabolic risk factors in the PREDIMED-Plus study



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SUMMARY

Background & aims: The Portfolio and Dietary Approaches to Stop Hypertension (DASH) diets have been shown to lower cardiometabolic risk factors in randomized controlled trials (RCTs). However, the Portfolio diet has only been assessed in RCTs of hyperlipidemic patients. Therefore, to assess the Portfolio diet in a population with metabolic syndrome (MetS), we conducted a longitudinal analysis of one-year data of changes in the Portfolio and DASH diet scores and their association with cardiometabolic risk factors in Prevención con Dieta Mediterránea (PREDIMED)-Plus trial.

Methods: PREDIMED-Plus is an ongoing clinical trial (Trial registration: ISRCTN89898) conducted in Spain that includes 6874 older participants (mean age 65 y, 48% women) with overweight/obesity fulfilling at least three criteria for MetS. Data for this analysis were collected at baseline, six months and one year. Adherence to the Portfolio and DASH diet scores were derived from a validated 143-item food frequency questionnaire. We used linear mixed models to examine the associations of 1-SD increase and quartile changes in the diet scores with concomitant changes in cardiometabolic risk factors.

Results: After adjusting for several potential confounders, a 1-SD increase in the Portfolio diet score was significantly associated with lower HbA1c (β [95% CI]: -0.02 [-0.02 , -0.01], $P < 0.001$), fasting glucose (-0.47 mg/dL [-0.83 , -0.11], $P = 0.01$), triglycerides (-1.29 mg/dL [-2.31 , -0.28], $P = 0.01$), waist circumference (WC) (-0.51 cm [-0.59 , -0.43], $P < 0.001$), and body mass index (BMI) (-0.17 kg/m² [-0.19 , -0.15], $P < 0.001$). A 1-SD increase in the DASH diet score was significantly associated with lower HbA1c (-0.03 % [-0.04 , -0.02], $P < 0.001$), glucose (-0.84 mg/dL [-1.18 , -0.51], $P < 0.001$), triglycerides (-3.38 mg/dL [-4.37 , -2.38], $P < 0.001$), non-HDL-cholesterol (-0.47 mg/dL [-0.91 , -0.04], $P = 0.03$), WC (-0.69 cm [-0.76 , -0.60 cm], $P < 0.001$), BMI (-0.25 kg/m² [-0.28 , -0.26 kg/m²], $P < 0.001$), systolic blood pressure (-0.57 mmHg [-0.81 , -0.32 mmHg], $P < 0.001$), diastolic blood pressure (-0.15 mmHg [-0.29 , -0.01 mmHg], $P = 0.03$), and with higher HDL-cholesterol (0.21 mg/dL [0.09 , 0.34 mg/dL, $P = 0.001$]). Similar associations were seen when both diet scores were assessed as quartiles, comparing extreme categories of adherence.

Conclusions: Among older adults at high cardiovascular risk with MetS, greater adherence to the Portfolio and DASH diets showed significant favourable prospective associations with several clinically relevant cardiometabolic risk factors. Both diets are likely beneficial for cardiometabolic risk reduction.

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1. Introduction

Metabolic syndrome (MetS) is a cluster of cardiometabolic risk factors that continues to be a serious unmet health challenge [1]. Individuals with MetS are at an increased risk of multiple chronic diseases, including cardiovascular disease (CVD) and type 2 diabetes [2,3], which are leading causes of death worldwide [4,5]. Targeting the cardiometabolic risk factors characteristic of MetS (including dyslipidemia, high blood pressure and abnormal glucose control) can help decrease the burden of CVD and diabetes [6–9].

Two dietary patterns that were designed to target specific CVD risk factors include the Portfolio (or Dietary Portfolio) and the Dietary Approaches to Stop Hypertension (DASH) diets, both of which are recommended by international diabetes and CVD clinical practice guidelines [10–15]. The Portfolio diet is a plant-based

dietary pattern that was originally developed to lower low-density lipoprotein cholesterol (LDL-C) [16–21]. The diet limits saturated fat and cholesterol (National Cholesterol Education Program (NCEP) Step II diet [22]), and includes a “portfolio” of 4 cholesterol-lowering foods and nutrients: nuts, plant protein, foods rich in viscous fiber, and phytosterols. An extension of the diet includes adding monounsaturated fats (MUFAs) in the form of olive/canola/soy oil, or avocado [21]. In the randomized controlled trials (RCTs), the Portfolio diet has been shown to significantly reduce LDL-C by 27% (in the intended combination with a NCEP Step II diet), as well as significantly reduce the alternate blood lipid targets non-high-density lipoprotein cholesterol (non-HDL-C) by 14%, apolipoprotein B (apoB) by 15%, and C-reactive protein by 32% [23]. On the other hand, the DASH diet was originally developed to treat high blood pressure and indeed resulted in clinically meaningful

reductions in blood pressure [24]. The DASH diet emphasizes the consumption of fruit, vegetables, low-fat dairy, whole grains, nuts and legumes, and limits red and processed meats, sugary foods and sodium. In RCTs, the DASH diet also significantly reduced cardiometabolic risk factors beyond blood pressure, including LDL-C, glycated hemoglobin (HbA1c) and body weight compared to usual or low-fat diets [25].

After the DASH diet trials were conducted, several DASH diet scores were created to assess if the beneficial effects found in the RCTs translated into less disease outcomes in observational studies of diverse populations [26–29]. However, the Portfolio diet has not yet been assessed in populations outside the hyperlipidemic patients evaluated in the RCTs. Therefore, we have created a Portfolio diet score to assess associations with health outcomes in epidemiological study designs and in other populations. To ascertain whether the findings from RCTs translates to different populations, we examined the associations of one-year changes in the Portfolio and DASH diet scores with cardiometabolic risk factors in a large cohort of older adults with MetS.

2. Materials & methods

2.1. Study design

This one-year longitudinal analysis was conducted within the framework of the Prevención con Dieta Mediterránea (PREDIMED)-Plus trial. PREDIMED-Plus is an ongoing, six-year, multicenter, parallel-group randomized controlled trial conducted in Spain. The trial is evaluating the long-term effects of an energy-reduced Mediterranean diet with enhanced physical activity, behavioural support and weight loss (intervention) compared to an energy-unrestricted Mediterranean diet (control) on the primary prevention of CVD. The overall design, methods and baseline characteristics of PREDIMED-Plus have been reported previously [30,31], and the protocol is available online at <http://predimedplus.com>. Ethics approval was obtained from the institutional review boards of all recruiting centers and all participants provided written informed consent before randomization. The data analyzed for this analysis was obtained from the PREDIMED-plus database of March 12th, 2019. The trial is registered at ISRCTN89898870.

2.2. Participants

Participants include older men (aged 55–75 years) and women (aged 60–75 years) with a body mass index (BMI) between 27 and 40 kg/m² and who fulfilled at least three criteria of the MetS [1]. Approximately 29% also had type 2 diabetes. All participants were free from CVD at enrollment. Further details of the inclusion and exclusion criteria can be found elsewhere [30,31]. Between 2013 and 2016, 6874 participants were recruited from the 23 participating centers in Spain. Participants were randomized in a 1:1 ratio to either the intervention or control group using a computer-generated random number internet-based system. For the present analysis, we excluded participants with implausible energy intake (<500 or >3500 kcal/d for women and <800 or >4000 kcal/d for men) or with missing information on the food frequency questionnaire (FFQ) at baseline. There were 6633 participants after baseline exclusions for all outcomes, except for HbA1c, which was available in 6091 participants.

2.3. Dietary assessment

Dietary data was collected at baseline, six months and one year using a previously validated 143-item semi-quantitative FFQ [32–34]. Trained dietitians administered the FFQ and the energy and food nutrient content were calculated according to the Spanish

Food Tables [35,36]. Participants reported how often, on average, they consumed defined portions of the food items over the previous year through 9 response categories ranging from “never or almost never” to “≥ 6 times per day”.

2.4. Portfolio and DASH diet scores

For the dietary pattern analyses, we used a previously created diet score for the DASH diet [26], and created a score for the Portfolio diet. The DASH diet score includes eight components: fruits, vegetables, whole grains, nuts and legumes, low-fat dairy, sodium (estimated from all foods), red and processed meats and sugar-sweetened beverages. Intake of each food component was ranked into sex-specific quintiles and given positive or reverse points. Positive points were given for foods recommended in the diet (fruits, vegetables, whole grains, nuts and legumes, and low-fat dairy), in which participants in the highest quintile of a food component received five points, and those in the lowest quintile received one point. Reverse points were given for foods or nutrients not recommended in the diet (sodium, red and processed meats, and sugar-sweetened beverages), in which participants in the highest quintile of a food component received one point, and those in the lowest quintile received five points. All food components were counted in servings/d, except for sodium intake (mg/d).

To create the Portfolio diet score, we followed the sex-specific quintile approach from the DASH diet score and gave positive points to food or nutrient components recommended in the diet (plant protein (legumes), nuts (all types), viscous fiber sources (berries, citrus fruit, eggplant, oats), phytosterols (estimated from all plant foods), and MUFAs from plant sources (olive and soy oils)) and reverse points for foods/nutrients not recommended in the diet (high saturated fat and cholesterol sources, including red and processed meats, high fat dairy and butter). All food components were in servings/d, except phytosterol intake (mg/d). The eight individual food/nutrient scores were summed for the DASH diet (score range of 8–40) and the six individual food/nutrient scores were summed for the Portfolio diet (score range of 6–30).

2.5. Assessment of outcomes

All outcomes were determined at baseline, six months and one year. Trained personnel measured anthropometric variables according to the PREDIMED-Plus protocol. Weight and height were measured with electronic calibrated scales and a wall-mounted stadiometer, respectively. BMI was calculated by dividing the weight (kg) by the height squared (m²). Waist circumference (WC) was measured halfway between the last rib and the iliac crest by using an anthropometric tape. BMI and WC were measured in duplicate. Blood pressure was measured in triplicate using a validated semiautomatic oscillometer (Omron HEM-705CP, Netherlands) after 5 min of rest in a seated position.

Blood samples were collected after an overnight fast and biochemical analyses were performed on fasting plasma glucose (FPG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG) and HbA1c. LDL-C was calculated using the Friedewald equation [37]. Non-HDL-C was calculated using the equation from the NCEP Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) [38].

2.6. Assessment of covariates

Questionnaires were administered to participants at baseline, six months and one year to assess information on demographics, disease diagnoses, medication use and lifestyle factors such as

physical activity and smoking. Physical activity was measured using the validated Minnesota-REGICOR Short Physical Activity questionnaire [39]. Participants were considered to have diabetes if they had a previous clinical diagnosis of the condition, had an HbA1c $\geq 6.5\%$, used antidiabetic medication or insulin at baseline, or had a FPG >126 mg/dL in both the screening visit and the baseline visit [40]. Hypertension was defined when systolic blood pressure (SBP) was ≥ 130 mmHg and/or diastolic blood pressure (DBP) was ≥ 85 mmHg, or anti-hypertensive medication was used. Participants were considered to have hypercholesterolemia if their LDL-C was ≥ 130 mg/dL or if they were taking lipid-lowering medications.

2.7. Statistical analyses

Descriptive analysis by quartile of each diet score was conducted by using the chi-square test for categorical variables and ANOVA for continuous variables. We used linear mixed models with a random intercept for each participant and random slope for each visit (categorized as baseline, six months and one year) with an unstructured correlation matrix to examine the associations of changes in intake of the dietary indices with concomitant changes in cardiometabolic outcomes. In all models, we used robust variance estimators to account for intra-cluster correlations ($n = 402$ couples) to account for members of the same household who were randomized together. Cardiometabolic outcomes were truncated at the 1st and 99th percentiles to minimize the influence of outliers. Assumptions of normality were met for all outcomes, except TG, FPG and HbA1c. These three variables were log-transformed.

In each model, we adjusted for the following fixed covariates: sex (male/female), age (continuous), diabetes status (yes/no), intervention group (control/intervention), education (primary/secondary/university), family history of CVD (yes/no), family history of diabetes (yes/no), center (categorized in quartiles by number of participants), hypertension status (yes/no), and hypercholesterolemia status (yes/no), and time-varying covariates: energy intake (continuous), smoking (never/former/current), physical activity (continuous), alcohol intake (continuous), statin therapy (yes/no), diabetes medications (yes/no), fibrate medications (yes/no), and anti-hypertensive medications (yes/no). The Portfolio diet analysis was additionally adjusted for time-varying sodium intake (continuous) for the blood pressure outcomes. We examined associations with the cardiometabolic outcomes with quartiles of change in each score and per-1 SD increase in each score to facilitate comparisons across the scores, as the Portfolio and DASH indices have different score ranges. Tests for linear trend were also conducted by assigning the median value to each quartile. We examined potential interactions with sex, BMI, diabetes status and intervention group. All models are presented as crude (unadjusted) and fully adjusted. All analyses were performed with STATA version 15.0 (StataCorp, College Station, TX, USA). Statistical significance was set at P value < 0.05 .

3. Results

The participants' baseline characteristics are shown in Table 1. Those with better adherence to both the Portfolio and DASH diet scores were more likely to be older, have a lower BMI, be more physically active, have more education, and drink less alcohol, and were less likely to smoke, among others (Table 1). Those with better adherence to the DASH diet score were also more likely to be female (Table 1). The mean score and intake of the Portfolio diet score components in quintile 1 and 5 at each study visit are shown in Supplemental Table 1. The mean score and intake of the DASH diet score components in quintile 1 and 5 at each study visit are shown

in Supplemental Table 2. The average Portfolio diet score did not change from baseline to six months (β coefficients = -0.05 (95% CIs: $-0.16, 0.07$) $P = 0.45$), and significantly increased from baseline to one year of intervention (0.12 (0.00, 0.25), $P = 0.047$). The average DASH diet score also did not change from baseline to six months (0.12 ($-0.01, 0.26$), $P = 0.08$); however, the score did significantly increase from baseline to one year (0.21 (0.06, 0.36), $P = 0.006$), with greater changes observed in the DASH score. A higher percentage of participants, while small, also increased their DASH diet score over the one year compared to the Portfolio diet score (Supplemental Table 3).

As the scoring systems for the Portfolio and DASH diet scores are not based on absolute intakes from the RCTs, we estimated the absolute mean intakes in each quintile at baseline and one year in Supplemental Tables 4 and 5. Intake of plant protein, viscous fibre and phytoosterols did not meet the recommendations of the Portfolio diet RCTs, even in the top quintiles, however, intake of nuts, MUFAs and saturated fat and cholesterol did meet recommendations from the RCTs in specific quintiles at both baseline and at one year (Supplemental Table 4). For the DASH diet score, RCT recommendations for most components (fruit, vegetables, nuts & beans, low fat dairy, sodium, red & processed meats and SSBs) were met in specific quintiles, and these recommendations were met in more quintiles at one year compared to baseline. Whole grain intake is the only component that may be improved in the PREDIMED-plus trial participants to further meet DASH diet recommendations (Supplemental Table 5). Overall, the PREDIMED-Plus participants were more closely meeting DASH diet recommendations compared to the Portfolio diet recommendations.

After adjusting for multiple potential confounders, each 1-SD increase in the Portfolio and DASH diet scores were not associated with either TC or LDL-C (Tables 2 and 3). Each 1-SD increase in the Portfolio diet score was associated with a decrease in TG. This inverse association was substantially stronger for the DASH diet score (Tables 2 and 3). Each 1-SD increase in the Portfolio diet score was not associated with increased HDL-C, however, each 1-SD increase in the DASH diet score was associated with increased HDL-C. Each 1-SD increase in the DASH diet score was also associated with lower non-HDL-C, but this was not significant for the Portfolio diet score (Tables 2 and 3).

When we adjusted for multiple potential confounders, each 1-SD increases in the Portfolio and DASH diet scores were associated with a decrease in HbA1c (Tables 2 and 3). Similar inverse associations were seen with FPG. Each 1-SD increase in the Portfolio diet score was not associated with either SBP or DBP. Conversely, each 1-SD increase in the DASH diet score was associated with both lower SBP and DBP (Tables 2 and 3).

Each 1-SD increases in the Portfolio diet and DASH diet scores over the year were both associated with a lower BMI and WC (Tables 2 and 3), after adjusting for multiple potential confounders. We found similar results when we examined each of the cardiometabolic outcomes comparing extreme quartiles of diet score changes (Tables 2 and 3). A summary of the results per 1-SD increase of the Portfolio and DASH diet scores are shown in Figs. 1 and 2.

For the subgroup analyses (Supplemental Tables 6–16), the associations of the Portfolio diet score with higher HDL-C (Females: 0.23 (0.03, 0.43) mg/dL; Males: -0.01 ($-0.19, 0.17$) mg/dL, $P_{\text{interaction}} = 0.002$) and lower TG (Females: -2.70 ($-4.07, -1.35$) mg/dL, Males: 0.02 ($-1.45, 1.50$) mg/dL, $P_{\text{interaction}} = 0.01$) were significant in females only (Supplemental Tables 8 and 9). The association of the DASH diet score with lower HbA1c (Diabetes: -0.06 ($-0.09, -0.03$) %; No diabetes: -0.02 ($-0.02, -0.01$), $P_{\text{interaction}} < 0.001$) was stronger in participants with diabetes, and associations with lower FPG were stronger in males and those with diabetes (Females: -0.49 ($-0.96, -0.02$) mg/dL; Males: -1.09

Table 1
Baseline characteristics of the 6636 PREDIMED-Plus participants according to quartiles of the Portfolio and DASH diet scores.

Mean (SD)/No. (%) Range	Portfolio Diet Score				DASH Diet Score			
	Q1 (6–14)	Q2 (15–17)	Q3 (18–20)	Q4 (21–30)	Q1 (8–21)	Q2 (22–24)	Q3 (25–27)	Q4 (28–39)
n	1864	1721	1602	1446	2026	1545	1426	1636
Median score	12	16	19	22	19	23	26	30
Age, y	64.4 (4.9)	64.8 (4.9)	65.2 (4.9)	65.7 (4.8) ^a	64.2 (4.9)	65.0 (5.0)	65.2 (4.9)	65.8 (4.8) ^a
Sex, female	933 (50)	827 (48)	764 (48)	685 (47)	921 (45)	712 (46)	737 (52)	839 (51) ^a
European descent	1799 (97)	1682 (98)	1574 (98)	1417 (98)	1973 (97)	1511 (98)	1397 (98)	1591 (97)
Current smoker								
Never	777 (42)	779 (45)	728 (45)	658 (46) ^a	825 (41)	683 (44)	653 (46)	781 (48) ^a
Former	805 (43)	741 (43)	697 (44)	627 (43) ^a	892 (44)	668 (43)	625 (44)	685 (42) ^a
Current	282 (15)	201 (12)	177 (11)	161 (11) ^a	309 (15)	194 (13)	148 (10)	170 (10) ^a
BMI, kg/m ²	32.8 (3.4)	32.6 (3.5)	32.4 (3.5)	32.1 (3.3) ^a	32.8 (3.5)	32.6 (3.4)	32.5 (3.4)	32.1 (3.4) ^a
Allocated to intervention group	910 (49)	872 (51)	782 (49)	731 (51)	1005 (50)	762 (49)	722 (51)	806 (49)
Exercise level, METs/min-week	2196 (2151)	2401 (2310)	2546 (2257)	2793 ^a (2478)	2193 (2154)	2342 (2212)	2528 (2365)	2856 ^a (2444)
Family history of CVD	767 (41)	714 (42)	623 (39)	593 (41)	805 (40)	616 (40)	594 (42)	682 (42)
Family history of diabetes	791 (42)	715 (42)	651 (41)	594 (41)	836 (41)	622 (40)	613 (43)	680 (42)
Highest education attained								
Primary school or less	881 (47)	828 (48)	818 (51)	743 (52) ^a	936 (46)	776 (50)	727 (51)	831 (51) ^a
Complete secondary	558 (30)	533 (31)	443 (28)	379 (26) ^a	645 (32)	426 (28)	420 (29)	422 (26) ^a
University	425 (23)	360 (21)	341 (21)	324 (24) ^a	445 (22)	343 (22)	279 (20)	383 (23) ^a
Hypertension	1730 (93)	1619 (94)	1506 (94)	1356 (94)	1894 (93)	1447 (94)	1344 (94)	1526 (93)
Hypercholesteremia	1400 (75)	1334 (78)	1221 (76)	1079 (75)	1536 (76)	1163 (75)	1070 (75)	1265 (77)
Diabetes	576 (31)	537 (31)	473 (30)	456 (32)	584 (29)	499 (32)	463 (32)	496 (30)
Statin therapy	943 (51)	897 (52)	821 (51)	746 (52)	1036 (51)	782 (51)	714 (50)	875 (53)
Fibrates	69 (4)	65 (4)	57 (4)	52 (4)	74 (4)	70 (5)	41 (3)	58 (4)
Antihypertensive agents	1413 (76)	1349 (78)	1264 (79)	1127 (78)	1539 (76)	1219 (79)	1103 (77)	1292 (79)
Antidiabetic medications	496 (27)	480 (28)	416 (26)	400 (28)	499 (25)	432 (28)	412 (28)	449 (27) ^a
Total energy intake, kcal/d	2098 (530)	2297 (509)	2484 (531)	2657 (464) ^a	2461 (572)	2341 (562)	2318 (533)	2309 (514) ^a
Alcohol intake, g/d	11.7 (16.1)	11.1 (14.8)	11.3 (15.4)	9.8 (13.3) ^a	14.1 (17.4)	11.6 (15.2)	9.4 (13.5)	8.2 (12.0) ^a

Data is shown as mean (SD) or N (%), unless otherwise stated.

BMI, body mass index; CVD, cardiovascular disease; DASH, dietary approaches to stop hypertension; MET, metabolic equivalent of task; Q, quartile; SD, standard deviation.

^a Significantly different comparing Q1 to Q4.

(−1.57, −0.62) mg/dL, $P_{\text{interaction}} = 0.02$; Diabetes: −1.89 (−2.89, −0.89) mg/dL; No diabetes: −0.49 (−0.75, −0.24), $P_{\text{interaction}} = 0.002$) (Supplemental Tables 11 and 12). In addition, the association of the DASH diet score with lower SBP was significant only in participants in the active intervention group (Intervention: −0.75 (−1.09, −0.41) mmHg; Control: −0.12 (−0.46, 0.22), $P_{\text{interaction}} = 0.01$), and the association with lower BMI was stronger in males for the DASH diet score than in females (Females: −0.22 (−0.25, −0.18) kg/m²; Males: −0.28 (−0.31, −0.25) kg/m², $P_{\text{interaction}} < 0.001$) (Supplemental Tables 13 and 15). Lastly, the associations of both the Portfolio and DASH diet scores with lower DBP (Females: 0.33 (0.12, 0.54) mmHg; Males: −0.09 (−0.29, 0.10) mmHg, $P_{\text{interaction}} = 0.01$; Females: 0.04 (−0.15, 0.24) mmHg; Males: −0.32 (−0.50, −0.13) mmHg, $P_{\text{interaction}} = 0.001$, for Portfolio and DASH diets, respectively) and WC (Females: −0.08 (−0.18, 0.02) cm; Males: −0.18 (−0.25, −0.10) cm, $P_{\text{interaction}} = 0.03$; Females: −0.05 (−0.15, 0.06) cm; Males: −0.24 (−0.32, −0.16) cm, $P_{\text{interaction}} < 0.001$, for Portfolio and DASH diets, respectively) were significant or stronger in males only (Supplemental Tables 14 and 16).

4. Discussion

Our study analyzed the association of one-year changes in the Portfolio diet and DASH diet scores with changes in cardiometabolic risk factors in a large sample of older Spanish adults with overweight/obesity and MetS. We found that greater adherence to the Portfolio diet score was associated with lower TG, HbA1c, FPG, BMI and WC (Figs. 1 and 2). This is the first time that the Portfolio diet score has been related to improvements in markers of glycemic control and adiposity. We also found that greater adherence to the DASH diet score was associated with lower TG, non-HDL-C, HbA1c, FPG, SBP, DBP, BMI and WC (Figs. 1 and 2). The inverse association for TG was substantially stronger for the

DASH diet than the Portfolio diet. These findings indicate that both dietary patterns are likely beneficial for cardiometabolic disease reduction. The associations for the Portfolio diet and DASH diet scores were largely similar in the subgroup analyses in terms of direction and statistical significance, although the associations for various cardiometabolic risk factors were stronger in some subgroups (including sex, diabetes status, intervention group and BMI category). In addition, the associations of the Portfolio diet with higher HDL-C and lower TG were only significant in females. The differential findings in the subgroup analyses warrants further investigation.

4.1. Context with previous literature

To our knowledge, our study is the first to investigate associations between the Portfolio diet and cardiometabolic risk factors in a longitudinal cohort, therefore, comparison with existing literature outside of the Portfolio diet RCTs is difficult. When compared to the RCTs, both the findings in this study and the trials' results showed significant reductions/inverse associations with TG. However, we observed no inverse associations of the Portfolio diet score with TC, LDL-C or non-HDL-C in this study, which were lipid variables that were significantly reduced in the trials [23]. Furthermore, the RCTs did not assess markers of glycemic control and were not designed as weight loss studies, therefore, comparisons with FPG, HbA1c, BMI and WC are challenging. Nonetheless, we will await the results of the PortfolioEX trial (ClinicalTrials.gov Identifier: NCT02481466) of the effect of the Portfolio diet plus exercise on a surrogate marker of atherosclerotic CVD (magnetic resonance imaging of atherosclerosis (plaque volume)), in which some of the participants have type 2 diabetes and markers of glycemic control were measured. The discrepancies in results between our study and findings in the RCTs are possibly due to less change in the Portfolio Diet score over the one year compared to the DASH diet score,

Table 2
Cardiometabolic changes over one-year according to 1-SD increase and quartiles of change in the Portfolio diet score.

	Q1	Q2	Q3	Q4	P-trend ^a	Per 1-SD increase	P-value ^b
Lipids							
TC (mg/dL)							
Unadjusted model	0 [reference]	0.37 (−0.69, 1.43)	0.47 (−0.62, 1.56)	−0.33 (−1.55, 0.88)	0.80	−0.12 (−0.56, 0.31)	0.58
Multivariable model	0 [reference]	0.37 (−0.67, 1.41)	0.16 (−0.97, 1.28)	0.29 (−1.02, 1.59)	0.71	0.48 (−0.42, 0.52)	0.84
LDL-C (mg/dL)							
Unadjusted model	0 [reference]	0.45 (−0.47, 1.37)	0.64 (−0.31, 1.60)	−0.07 (−1.10, 0.96)	0.82	0.04 (−0.32, 0.42)	0.82
Multivariable model	0 [reference]	0.38 (−0.52, 1.27)	0.19 (−0.78, 1.16)	0.19 (−0.90, 1.27)	0.75	0.08 (−0.32, 0.47)	0.71
HDL-C (mg/dL)							
Unadjusted model	0 [reference]	0.30 (0.03, 0.56) ^d	0.37 (0.09, 0.66) ^d	0.35 (0.03, 0.66) ^d	0.02	0.12 (0.01, 0.24)	0.04
Multivariable model	0 [reference]	0.25 (−0.04, 0.53)	0.33 (0.02, 0.64) ^d	0.36 (0.00, 0.72) ^d	0.03	0.16 (−0.02, 0.25)	0.09
TG (mg/dL)^c							
Unadjusted model	0 [reference]	−1.96 (−4.02, 0.05)	−3.12 (−5.23, −1.01) ^d	−3.70 (−6.07, −1.32) ^d	<0.001	−1.78 (−2.62, −0.92)	<0.001
Multivariable model	0 [reference]	−1.63 (−3.77, 0.51)	−2.16 (−4.48, 0.14)	−2.37 (−5.10, 0.35)	0.04	−1.29 (−2.31, −0.28)	<0.01
Non-HDL-C (mg/dL)							
Unadjusted model	0 [reference]	−0.03 (−1.04, 0.98)	0.03 (−1.01, 1.07)	−0.78 (−1.93, 0.37)	0.23	−0.28 (−0.69, 0.13)	0.18
Multivariable model	0 [reference]	0.01 (−0.97, 1.01)	−0.20 (−1.27, 0.86)	−0.15 (−1.38, 1.07)	0.73	−0.10 (−0.55, 0.35)	0.67
Markers of glycemic control							
HbA1c (%)^c							
Unadjusted model	0 [reference]	−0.01 (−0.03, 0.01)	−0.01 (−0.03, 0.01)	−0.02 (−0.04, −0.00) ^d	0.04	−0.01 (−0.02, −0.00)	0.02
Multivariable model	0 [reference]	−0.03 (−0.05, −0.01) ^d	−0.03 (−0.05, −0.01) ^d	−0.05 (−0.07, −0.02) ^d	<0.001	−0.02 (−0.03, −0.01)	<0.001
FPG (mg/dL)^c							
Unadjusted model	0 [reference]	−0.50 (−1.20, 0.20)	−0.20 (−0.02, 0.51)	−0.94 (1.78, −0.09) ^d	0.01	−0.36 (−0.66, −0.06)	<0.01
Multivariable model	0 [reference]	−0.97 (−1.76, −0.18) ^d	−0.41 (−1.27, 0.45)	−1.32 (−2.33, −0.30) ^d	0.02	−0.47 (−0.83, −0.11)	<0.01
Blood Pressure Measurements							
SBP (mmHg)							
Unadjusted model	0 [reference]	0.09 (−0.41, 0.59)	0.07 (−0.46, 0.60)	−0.03 (−0.61, 0.54)	0.96	−0.02 (−0.19, 0.23)	0.88
Multivariable model	0 [reference]	0.01 (−0.52, 0.54)	0.02 (−0.57, 0.61)	−0.14 (−0.70, 0.68)	0.85	−0.01 (−0.27, 0.24)	0.93
DBP (mmHg)							
Unadjusted model	0 [reference]	−0.06 (−0.35, 0.22)	−0.01 (−0.30, 0.29)	−0.05 (−0.38, 0.27)	0.83	0.004 (−0.13, 0.12)	0.94
Multivariable model	0 [reference]	−0.04 (−0.34, 0.26)	0.11 (−0.22, 0.43)	0.17 (−0.22, 0.56)	0.39	0.07 (−0.06, 0.23)	0.24
Markers of obesity							
BMI (kg/m²)							
Unadjusted model	0 [reference]	−0.09 (−0.13, −0.05) ^d	−0.14 (−0.19, −0.09) ^d	−0.23 (−0.28, −0.17) ^d	<0.001	−0.09 (−0.11, −0.07)	<0.001
Multivariable model	0 [reference]	−0.15 (−0.20, −0.11) ^d	−0.25 (−0.30, −0.20) ^d	−0.41 (−0.47, −0.35) ^d	<0.001	−0.17 (−0.19, −0.15)	<0.001
WC (cm)							
Unadjusted model	0 [reference]	−0.25 (−0.41, −0.10) ^d	−0.40 (−0.57, −0.23) ^d	−0.72 (−0.91, −0.53) ^d	<0.001	−0.28 (−0.35, −0.22)	<0.001
Multivariable model	0 [reference]	−0.46 (−0.63, −0.30) ^d	−0.72 (−0.91, −0.54) ^d	−1.26 (−1.47, −1.04) ^d	<0.001	−0.51 (−0.59, −0.43)	<0.001

We used linear mixed models (with unstructured correlation matrix and robust variance estimators) to conduct this analysis. Multivariable model: sex (male/female), age (continuous), diabetes status (yes/no), intervention group (control/intervention), education (primary/secondary/university), family history of CVD (yes/no), family history of T2DM (yes/no), center (categorized in quartiles by number of participants), hypertension status (yes/no), hypercholesterolemia status (yes/no), energy intake (continuous), smoking (never/former/current), physical activity (continuous), alcohol intake (continuous), lipid-lowering medications (yes/no), diabetes medications (yes/no), fibrate medication use (yes/no), blood-pressure lowering medications (yes/no) and sodium intake (continuous). BMI, body mass index; DBP, diastolic blood pressure; FPG; fasting plasma glucose; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Q, quartile; SBP, systolic blood pressure; SD, standard deviation; TG, triglycerides; TC, total cholesterol; WC, waist circumference.

^a P for trend obtained from assigning the median value to each quartile.

^b P value obtained from per 1-SD increase in β coefficients.

^c As results for both non and log transformed data were similar, the values of the non-transformed data were provided for ease of interpretation. The P-value provided is from the log transformed data analysis.

^d Significantly different compared to Q1.

lower consumption of the foods recommended in the diet, the population being studied and missing foods on the FFQ in our study, as discussed below. However, the single components of the Portfolio diet (i.e. plant protein, nuts, viscous fiber sources, phytosterols and MUFAs) have shown favourable associations with cardiometabolic outcomes, such as TC and LDL-C [41,42], obesity [41,43], blood pressure and TG [43], in addition to associations with a lower risk of CVD and diabetes in prospective cohort studies [44–52].

For the DASH diet, both the findings in this study and those from prior RCTs suggest significant reductions/inverse associations with SBP, DBP, HbA1c and body weight; however, we observed significant associations with higher HDL-C, and lower TG and FPG in this study, which was not reported in the RCTs [25]. Still, the DASH diet has been extensively examined in prospective cohort studies, and

favourable associations with cardiometabolic outcomes have been documented, including higher HDL-C and lower TG [53–55], and lower BP [55], as well as associations with lower incident CVD, diabetes, non-alcoholic fatty liver disease (NALFD), and total mortality [25,56,57].

In our study, greater adherence to the DASH diet was associated with more improvements of cardiometabolic outcomes than the Portfolio diet. The average DASH diet score increased slightly more over the one-year period compared to the Portfolio diet score, with most of this change in the Portfolio diet coming from small increases in nut consumption and reductions in foods high in saturated fat and cholesterol. The recommendations of the DASH diet may also more closely mimic those of the PREDIMED-Plus trial, as highlighted by the 17-point screener used to assess adherence in the main trial [30,31,58]. For example, in the PREDIMED-Plus trial,

Table 3
Cardiometabolic changes over one-year according to 1-SD increase and quartiles of change in the DASH diet score.

	Q1	Q2	Q3	Q4	P-trend ^a	Per 1-SD increase	P-value ^b
Lipids							
TC (mg/dL)							
Unadjusted model	0 [reference]	-1.07 (-2.14, 0.00)	-1.08 (-2.23, 0.09)	-1.75 (-2.99, -0.51) ^d	0.02	-0.53 (-1.00, -0.06)	0.03
Multivariable model	0 [reference]	-0.61 (-1.67, 0.44)	-0.76 (-1.90, 0.39)	-0.74 (-1.96, 0.49)	0.34	-0.18 (-0.64, 0.28)	0.45
LDL-C (mg/dL)							
Unadjusted model	0 [reference]	-0.36 (-1.29, 0.57)	-0.11 (-1.11, 0.88)	-0.19 (-1.26, 0.88)	0.90	0.07 (-0.33, 0.48)	0.72
Multivariable model	0 [reference]	-0.05 (-0.95, 0.86)	0.05 (-0.92, 1.02)	0.24 (-0.79, 1.28)	0.57	0.19 (-0.20, 0.58)	0.34
HDL-C (mg/dL)							
Unadjusted model	0 [reference]	0.35 (0.07, 0.62) ^d	0.49 (0.20, 0.78) ^d	0.74 (0.42, 1.07) ^d	<0.001	0.28 (0.16, 0.40)	<0.001
Multivariable model	0 [reference]	0.16 (-0.13, 0.45)	0.30 (-0.01, 0.61)	0.53 (0.19, 0.87) ^d	<0.01	0.21 (0.09, 0.34)	0.001
TG (mg/dL)^c							
Unadjusted model	0 [reference]	-6.47 (-8.62, -4.30) ^d	-8.43 (-10.7, -6.16) ^d	-13.3 (-15.7, -10.8) ^d	<0.001	-5.06 (-5.98, -4.14)	<0.001
Multivariable model	0 [reference]	-4.57 (-6.86, -2.27) ^d	-6.64 (-9.03, -4.25) ^d	-8.83 (-11.5, -6.19) ^d	<0.001	-3.38 (-4.37, -2.38)	<0.001
Non-HDL-C (mg/dL)							
Unadjusted model	0 [reference]	-1.49 (-2.51, -0.47) ^d	-1.65 (-2.75, -0.55) ^d	-2.60 (-3.78, -1.42) ^d	<0.001	-0.86 (-1.30, -0.41)	<0.001
Multivariable model	0 [reference]	-0.89 (-1.90, 0.11)	-1.20 (-2.29, -0.11) ^d	-1.48 (-2.65, -0.31) ^d	0.03	-0.47 (-0.91, -0.04)	0.03
Markers of glycemic control							
HbA1c (%)^c							
Unadjusted model	0 [reference]	-0.02 (-0.04, -0.01) ^d	-0.05 (-0.07, -0.03) ^d	-0.09 (-0.12, -0.07) ^d	<0.001	-0.04 (-0.05, -0.03)	<0.001
Multivariable model	0 [reference]	-0.02 (-0.04, 0.01)	-0.03 (-0.05, -0.01) ^d	-0.07 (-0.09, -0.04) ^d	<0.001	-0.03 (-0.04, -0.02)	<0.001
FPG (mg/dL)^c							
Unadjusted model	0 [reference]	-1.31 (-2.02, -0.60) ^d	-2.23 (-2.99, -1.47) ^d	-2.99 (-3.82, -2.14) ^d	<0.001	-1.27 (-1.58, -0.94)	<0.001
Multivariable model	0 [reference]	-0.86 (-1.65, -0.05) ^d	-1.61 (-2.46, -0.76) ^d	-2.14 (-3.04, -1.24) ^d	<0.001	-0.84 (-1.18, -0.51)	<0.001
Blood Pressure Measurements							
SBP (mmHg)							
Unadjusted model	0 [reference]	-0.62 (-1.13, -0.10) ^d	-1.12 (-1.77, -0.61) ^d	-2.27 (-2.89, -1.66) ^d	<0.001	-0.81 (-1.04, -0.58)	<0.001
Multivariable model	0 [reference]	-0.42 (-0.96, 0.12)	-0.70 (-1.31, -0.10) ^d	-1.61 (-2.26, -0.98) ^d	<0.001	-0.57 (-0.81, -0.32)	<0.001
DBP (mmHg)							
Unadjusted model	0 [reference]	-0.28 (-0.56, 0.01)	-0.64 (-0.95, -0.32) ^d	-1.17 (-1.51, -0.84) ^d	<0.001	-0.47 (-0.59, -0.34)	<0.001
Multivariable model	0 [reference]	-0.05 (-0.35, 0.24)	-0.12 (-0.45, 0.20)	-0.47 (-0.82, -0.12) ^d	<0.01	-0.15 (-0.29, -0.01)	0.02
Markers of obesity							
BMI (kg/m²)							
Unadjusted model	0 [reference]	-0.22 (-0.26, -0.17) ^d	-0.38 (-0.43, -0.33) ^d	-0.61 (-0.67, -0.55) ^d	<0.001	-0.27 (-0.29, -0.25)	<0.001
Multivariable model	0 [reference]	-0.19 (-0.23, -0.14) ^d	-0.35 (-0.40, -0.29) ^d	-0.57 (-0.64, -0.52) ^d	<0.001	-0.25 (-0.28, -0.23)	<0.001
WC (cm)							
Unadjusted model	0 [reference]	-0.60 (-0.76, -0.43) ^d	-1.17 (-1.35, -0.99) ^d	-1.82 (-2.03, -1.61) ^d	<0.001	-0.77 (-0.85, -0.69)	<0.001
Multivariable model	0 [reference]	-0.45 (-0.63, -0.28) ^d	-1.00 (-1.20, -0.81) ^d	-1.64 (-1.86, -1.43) ^d	<0.001	-0.69 (-0.76, -0.60)	<0.001

We used linear mixed models (with unstructured correlation matrix and robust variance estimators) to conduct this analysis. Multivariable model: sex (male/female), age (continuous), diabetes status (yes/no), intervention group (control/intervention), education (primary/secondary/university), family history of CVD (yes/no), family history of T2DM (yes/no), center (categorized in quartiles by number of participants), hypertension status (yes/no), hypercholesterolemia status (yes/no), energy intake (continuous), smoking (never/former/current), physical activity (continuous), alcohol intake (continuous), lipid-lowering medications (yes/no), diabetes medications (yes/no), fibrate medication use (yes/no), and blood-pressure lowering medications (yes/no). BMI, body mass index; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Q, quartile; SBP, systolic blood pressure; SD, standard deviation; TG, triglycerides; TC, total cholesterol; WC, waist circumference.

^a P for trend obtained from assigning the median value to each quartile.

^b P value obtained from per 1-SD increase in β coefficients.

^c As results for both non and log transformed data were similar, the values of the non-transformed data were provided for ease of interpretation. The P-value provided is from the log transformed data analysis.

^d Significantly different compared to Q1.

dietary advice is given to increase fruit, vegetable and whole grain consumption, and limit sugar-sweetened beverages. While some of these dietary recommendations are included in the Portfolio diet score, they more closely align with the DASH diet, and may explain why the DASH diet score increased more over time compared to the Portfolio diet score. When assessing estimates of absolute intake of the Portfolio and DASH diet recommendations in this study, we also observed that more PREDIMED-Plus participants met the DASH trial recommendations compared to the Portfolio diet recommendations. Both the Mediterranean diet and Portfolio Diet recommend higher nut and extra virgin olive oil consumption, and lower saturated fat consumption, however, the Portfolio diet has more focus on plant protein, high viscous fiber sources and phytosterols, and consumption of these three components was low in the PREDIMED-trial participants, indicating room for improvement.

This smaller change in the Portfolio diet score over the one-year may result in lack of associations with outcomes. For example, a recent study that assessed 10-year longitudinal changes in plant-based diet indices and anthropometric parameters and blood lipids found that the plant-based diet indices did not change overtime, and as a result, few significant associations were observed with the anthropometrics and blood lipids [59]. The small increase in the Portfolio diet score over the study period may explain some of the lack of associations found with several risk factors compared to the DASH diet score in our study. Although in our study, the DASH diet score showed more favourable associations with the cardiometabolic outcomes, their direction was similar for both the DASH and Portfolio diet scores.

Another important consideration when evaluating our findings is the population being studied. All participants in the PREDIMED-

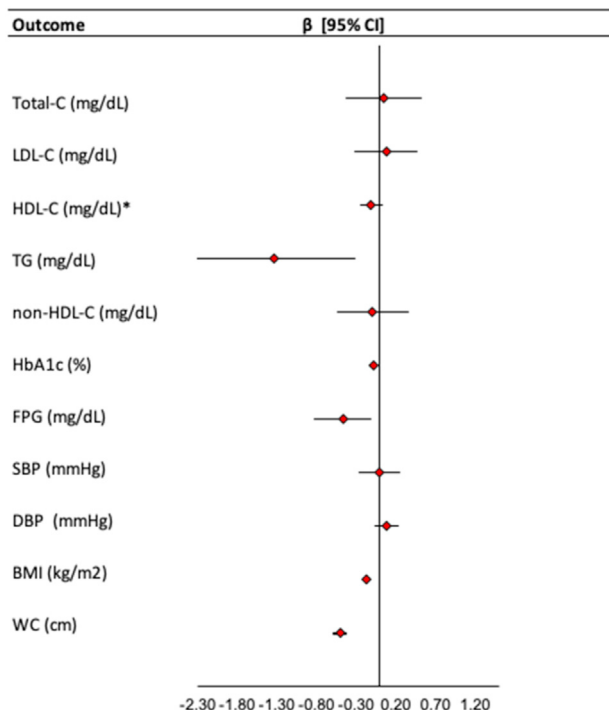


Fig. 1. Summary plot of the longitudinal association between 1- unit SD increase in Portfolio diet and cardiometabolic outcomes over 1-year in PREDIMED-plus. We used linear mixed models (with unstructured correlation matrix and robust variance estimators) to conduct this analysis. Multivariable model: sex (male/female), age (continuous), diabetes status (yes/no), intervention group (control/intervention), education (primary/secondary/university), family history of CVD (yes/no), family history of T2DM (yes/no), center (categorized in quartiles by number of participants), hypertension status (yes/no), hypercholesterolemia status (yes/no), energy intake (continuous), smoking (never/former/current), physical activity (continuous), alcohol intake (continuous), lipid-lowering medications (yes/no), diabetes medications (yes/no), fibrate medication use (yes/no), blood-pressure lowering medications (yes/no) and sodium intake (continuous). BMI, body mass index; DBP, diastolic blood pressure; FPG; fasting plasma glucose; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Q, quartile; SBP, systolic blood pressure; SD, standard deviation; TG, triglycerides; TC, total cholesterol; WC, waist circumference. Data are β -coefficients (95% CIs). *The reciprocal of the actual β -coefficient for HDL-C was provided so that it could be presented on the same scale (benefit vs. harm) as the other outcomes.

Plus trial cohort are older adults with overweight/obesity and MetS. The dyslipidemia present in individuals with MetS is characterized by elevated TG, low levels of HDL-C, high apoB and small LDL particles [60]. High blood pressure, elevated glucose and overweight are also features of the MetS. These metabolic characteristics may explain why many of the associations that are typical of MetS improved with increasing adherence to the diet scores, whereas associations with other outcomes (including TC and LDL-C) did not. The lipid abnormalities in MetS typically do not include elevated TC and LDL-C [60], therefore, there may be less room for improvement of these outcomes in our population. We did not assess small and dense LDL-C particles or apoB; however, non-HDL-C would capture these atherogenic lipoproteins. Greater adherence to the DASH diet score was only significantly associated with non-HDL-C in our study, but the direction of the association was similar for the Portfolio diet score.

The sex-specific differences findings are also noteworthy. We found that the Portfolio diet score was associated with higher HDL-C and lower TG in females only. We also observed that the DASH diet score had stronger associations or was only significantly related with lower DBP and FPG in males. A stronger association with lower BMI and WC was also seen in males compared to

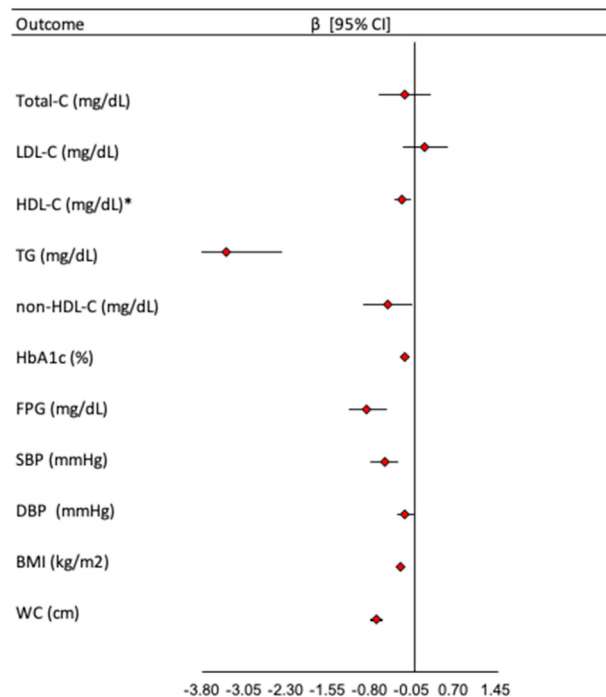


Fig. 2. Summary plot of the longitudinal association between 1- unit SD increase in DASH diet and cardiometabolic outcomes over 1-year in PREDIMED-plus. We used linear mixed models (with unstructured correlation matrix and robust variance estimators) to conduct this analysis. Multivariable model: sex (male/female), age (continuous), diabetes status (yes/no), intervention group (control/intervention), education (primary/secondary/university), family history of CVD (yes/no), family history of T2DM (yes/no), center (categorized in quartiles by number of participants), hypertension status (yes/no), hypercholesterolemia status (yes/no), energy intake (continuous), smoking (never/former/current), physical activity (continuous), alcohol intake (continuous), lipid-lowering medications (yes/no), diabetes medications (yes/no), fibrate medication use (yes/no), and blood-pressure lowering medications (yes/no). BMI, body mass index; DBP, diastolic blood pressure; FPG; fasting plasma glucose; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Q, quartile; SBP, systolic blood pressure; SD, standard deviation; TG, triglycerides; TC, total cholesterol; WC, waist circumference. Data are β -coefficients (95% CIs). *The reciprocal of the actual β -coefficient for HDL-C was provided so that it could be presented on the same scale (benefit vs. harm) as the other outcomes.

females for both diet scores. While in the original Portfolio trials no effect differences by sex were reported [23], women had greater blood pressure reduction in a DASH diet trial compared to men [24], in which the opposite association was shown in our study, where significant associations with lower DBP was observed in males only. Other sex-differences have also been observed in nutrition research. For example, lower carbohydrate quality (higher glycemic index and load) have been associated with stronger risk of type 2 diabetes and CVD in females compared to males [61,62]. Interestingly, sex differences have also been found with the effects of a Mediterranean diet, with men having better responses to the diet [63,64], similar to some of the findings in our study. This highlights the importance of investigating sex-related differences to diets, and warrants further investigation, particularly for the PREDIMED-Plus trial once complete.

Lastly, it is important to consider the clinical relevance of our findings. Based on minimally important differences we have used in previous systematic reviews and meta-analyses conducted by our group [23,25,65,66], many of the effect sizes we saw for the cardiometabolic outcomes are small and may not be clinically relevant. However, the inverse associations found with both diet scores and TG and BMI are considered clinically relevant. Inverse

associations seen with WC and SBP (for the DASH diet score) were also close to clinically relevant reductions [23,25,65,66]. Nevertheless, the beneficial associations found with the cardiometabolic risk factors, despite being small for some outcomes, may still be important as they may favourably impact cardiometabolic disease risk on a population level.

4.2. Strengths and limitations

Strengths of our study include the large sample size and longitudinal design that assessed changes in the diet scores and concomitant changes in cardiometabolic risk factors over one-year. Nevertheless, our study does have some limitations. First, the dietary intake was assessed via self-report. Second, the population included older Mediterranean adults with overweight/obesity and MetS, therefore, the results may not be extrapolated to other populations. Third, one of the key components of the Portfolio diet (i.e., soy foods) was not included in the PREDIMED-Plus FFQ, due to limited consumption of these foods in Spain [33,67]. Future analyses in a population that consumes more soy foods would be needed. Despite adjusting our models for the intervention group, there still may be some bias in our analyses related to the trial intervention/Mediterranean diet that we cannot account for, although this is common to all longitudinal analyses using a clinical trial as a cohort. Some of the beneficial associations we found with the cardiometabolic risk factors were also not considered clinically relevant. Lastly, residual confounding cannot be discounted due to the observational nature of the study design, and therefore causal relations cannot be inferred.

4.3. Conclusion

In conclusion, greater adherence to both the Portfolio and DASH diet scores were associated with improvements in several cardiometabolic risk factors in patients with MetS. As this was the first time that the Portfolio diet score was assessed in a cohort with cardiometabolic risk factors, our findings need to be confirmed in other populations. Future studies should also evaluate the Portfolio diet score with incident CVD and diabetes to assess whether improved cardiometabolic risk observed in prior RCTs and in this study translates into lower clinical events. Overall, our results support existing literature that both dietary patterns may be a useful therapeutic nutrition strategy for preventing and managing CVD and type 2 diabetes.

Statement of authorship

MAM-G, DC, MF, DR, JV, AA-G, JW, JAM, LS-M, RE, FJT, JL, XP, JT, AB, MD-R, PM-M, LD, VMS, JV, CV, ER, JS-S collected the data for the PREDIMED-Plus Trial. **AJG, DJAJ, CWCK, JLS** and **JS-S** designed the study concept. **AJG** wrote the first draft of the manuscript. **AJG** and **PH-A** conducted the statistical analysis. **JLS** and **JS-S** supervised the study. All authors provided interpretation of the data and critical revision of the manuscript for intellectual content. All authors approved the final version of the manuscript.

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Conflict of interest

AJG has done consulting work for SoLo GI Nutrition and has received an honorarium from the Soy Nutrition Institute. **CWCK** has received grants or research support from the Advanced Food Materials Network, Agriculture and Agri-Foods Canada (AAFC), Almond Board of California, American Peanut Council, Barilla, Canadian Institutes of Health Research (CIHR), Canola Council of Canada, International Nut and Dried Fruit Council, International Tree Nut Council Research and Education Foundation, Loblaws Brands Ltd, Pulse Canada and Unilever. He has received in-kind research support from the Almond Board of California, American Peanut Council, Barilla, California Walnut Commission, Kellogg Canada, Loblaws Companies, Nutrartis, Quaker (PepsiCo), Primo, Unico, Unilever, WhiteWave Foods/Danone. He has received travel support and/or honoraria from the American Peanut Council, Barilla, California Walnut Commission, Canola Council of Canada, General Mills, International Nut and Dried Fruit Council, International Pasta Organization, Lantmannen, Loblaws Brands Ltd,

Nutrition Foundation of Italy, Oldways Preservation Trust, Paramount Farms, Peanut Institute, Pulse Canada, Sun-Maid, Tate & Lyle, Unilever and White Wave Foods/Danone. He has served on the scientific advisory board for the International Tree Nut Council, International Pasta Organization, McCormick Science Institute and Oldways Preservation Trust. He is a member of the International Carbohydrate Quality Consortium (ICQC), Executive Board Member of the Diabetes and Nutrition Study Group (DNSG) of the European Association for the Study of Diabetes (EASD), is on the Clinical Practice Guidelines Expert Committee for Nutrition Therapy of the EASD and is a Director of the Toronto 3D Knowledge Synthesis and Clinical Trials foundation. **DJAJ** has received research grants from Loblaw Companies Ltd., the Almond Board of California, Soy Nutrition Institute (SNI), and the Canadian Institutes of Health Research (CIHR). He has received in-kind supplies for trials as a research support from the Almond Board of California, Walnut Council of California, American Peanut Council, Barilla, Unilever, Unico, Primo, Loblaw Companies, Quaker (Pepsico), Pristine Gourmet, Bunge Limited, Kellogg Canada, WhiteWave Foods. He has been on the speaker's panel, served on the scientific advisory board and/or received travel support and/or honoraria from the Loblaw Companies Ltd, Diet Quality Photo Navigation (DQPN), Better Therapeutics (FareWell), Verywell, True Health Initiative (THI), Heali AI Corp, Institute of Food Technologists (IFT), Soy Nutrition Institute (SNI), Herbalife Nutrition Institute (HNI), Herbalife International, Pacific Health Laboratories, Nutritional Fundamentals for Health (NFH), the Soy Foods Association of North America, the Nutrition Foundation of Italy (NFI), the Toronto Knowledge Translation Group (St. Michael's Hospital), the Canadian College of Naturopathic Medicine, The Hospital for Sick Children, the Canadian Nutrition Society (CNS), and the American Society of Nutrition (ASN). He is a member of the International Carbohydrate Quality Consortium (ICQC). His wife, Alexandra L Jenkins, is a director and partner of INQUIS Clinical Research for the Food Industry, his 2 daughters, Wendy Jenkins and Amy Jenkins, have published a vegetarian book that promotes the use of the low glycemic index plant foods advocated here, *The Portfolio Diet for Cardiovascular Risk Reduction* (Academic Press/Elsevier 2020 ISBN:978-0-12-810510-8) and his sister, Caroline Brydson, received funding through a grant from the St. Michael's Hospital Foundation to develop a cookbook for one of his studies. **ER** has received research funding through his institution from the California Walnut Commission, Folsom, CA, USA; was a paid member of its Health Research Advisory Group; and is a nonpaid member of its Scientific Advisory Council. He has also received research support through his institution from Alexion and serves on its Scientific Advisory board, received fees for scientific presentations and travel support from Danone, and travel support from the International Nut Council. **JS-S** serves on the board of (and receives grant support through his institution from) the International Nut and Dried Fruit Council and the Eroski Foundation. He also serves on the Executive Committee of the Instituto Danone, Spain, and on the Scientific Committee of the Danone International Institute. He has received research support from the Patrimonio Comunal Olivarero, Spain, and Borges S.A., Spain. He receives consulting fees or travel expenses from Danone, the Eroski Foundation, the Instituto Danone Spain, and Abbot Laboratories. RE reports grants from Cerveza y Salud, Spain, Fundacion Dieta Mediterranea, Spain and Interprofesional del Vino, Spain. Also, personal fees for given lectures from Brewers of Europe, Belgium, Fundacion Cerveza y Salud, Spain, Pernaud-Ricard, Mexico, Instituto Cervantes, Albuquerque, USA; Instituto Cervantes, Milan, Italy, Instituto Cervantes, Tokyo, Japan, Lilly Laboratories, Spain, and Wine and Culinary International Forum, Spain, and non-financial support to organize a National Congress on Nutrition. Also feeding trials with product from Grand Fountain and

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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.2021.03.016>.

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