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Original article

Polyphenol intake and cardiovascular risk in the PREDIMED-Plus trial. A comparison of different risk equations

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ABSTRACT

Introduction and objectives: Quantification of cardiovascular risk has been based on scores such as Framingham, Framingham-REGICOR, SCORE or Life's Simple 7 (LS7). In vitro, animal, and randomized clinical studies have shown that polyphenols may provide benefits to the vascular system and reduce the inflammatory response. However, some clinical-epidemiological studies have yielded inconsistent results. Our aim was to assess the possible association between intake of the various polyphenol classes and established cardiovascular scores.

Methods: This cross-sectional analysis involved 6633 PREDIMED-Plus study participants. Food polyphenol content was estimated by a semiquantitative food frequency questionnaire, adjusted for total energy intake according to the residual method. The association between polyphenol intake and cardiovascular risk was tested using linear regression analyses.

Results: Total polyphenol and flavonoid intake were directly and significantly associated only with the LS7 scale. Intake of lignans was directly and significantly associated with SCORE and LS7 scales, stilbene intake with SCORE, and phenolic acid intake with Framingham and Framingham-REGICOR scores. Other polyphenol classes were associated in a protective and significant manner in Framingham, SCORE and LS7 scores. In women, intake of all the polyphenol classes, except phenolic acids, showed a protective trend in the results of the Framingham, Framingham-REGICOR scores and LS7 scale.

Conclusions: An inverse association was found between consumption of the 'other polyphenols' class and, especially among women, with estimated cardiovascular risk. The results were similar to those of Framingham, Framingham-REGICOR and LS7 (after eliminating the diet component) and differed from those of SCORE, but the predictors included were limited in the latter case.

Ingesta de polifenoles y riesgo cardiovascular en el ensayo PREDIMED-Plus. Una comparación de diferentes ecuaciones de riesgo

Palabras clave:
Polifenoles
Riesgo cardiovascular
Ecuación cardiovascular

RESUMEN

Introducción y objetivos: La cuantificación del riesgo cardiovascular se basa en puntuaciones como las de Framingham, Framingham-REGICOR, SCORE o Life's Simple 7 (LS7). Los polifenoles pueden proporcionar beneficios al sistema vascular y reducir la respuesta inflamatoria; sin embargo, los estudios clínico-epidemiológicos muestran resultados discordantes. Nuestro objetivo es evaluar la posible asociación entre la ingesta de diferentes clases de polifenoles y las puntuaciones cardiovasculares.

Métodos: Estudio transversal sobre 6.633 participantes del estudio PREDIMED-Plus. El contenido de polifenoles se estimó mediante un cuestionario semicuantitativo de frecuencia alimentaria y se ajustó por la ingesta energética total según el método de residuales. La asociación entre la ingesta de polifenoles y el riesgo cardiovascular se evaluó mediante análisis de regresión lineal.

Resultados: La ingesta total de polifenoles y flavonoides se asoció directa y significativamente con la escala LS7. Igualmente, los lignanos se asociaron directa y significativamente con las escalas SCORE y LS7; los estilbenos, con la SCORE y los ácidos fenólicos, con las de Framingham y Framingham-REGICOR. La clase «otros polifenoles» se asoció de manera significativa con las escalas de Framingham, SCORE y LS7. En las mujeres, la ingesta de todas las clases de polifenoles, excepto los ácidos fenólicos, mostró una tendencia directa en los resultados de Framingham y Framingham-REGICOR e indirecta con la escala LS7.

Conclusiones: Se encontraron asociaciones inversas entre el consumo de la clase «otros polifenoles» y, especialmente en las mujeres, el riesgo cardiovascular estimado. Los resultados fueron similares con las de Framingham, Framingham-REGICOR y LS7 (después de eliminar el componente de dieta) y diferentes con la SCORE, pero los predictores que se incluyen en este son escasos.

Abbreviations

CVD: cardiovascular disease
FFQ: food frequency questionnaire
LS7: Life's Simple 7

INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of death worldwide.[1] It was estimated to cause 17.8 million deaths in 2017[2] and one third occurred in people younger than 70 years.[1] There is clear evidence that intervention strategies have helped to reduce mortality trends but, despite this progress, CVD remains a public health challenge.[3]

The incidence of CVD is largely explained by several risk factors, mostly related to lifestyles, which are in turn potentially modifiable and susceptible to prevention. These includes cigarette smoking, low physical activity levels and unhealthy dietary patterns, all of which can contribute to high blood pressure, high body mass index (BMI), high total cholesterol levels, and high fasting plasma glucose levels.[4] One of the dietary patterns which has shown benefits in relation to CVD is the Mediterranean diet.[5] It is postulated that the beneficial effect of the Mediterranean diet is

due to its richness in antioxidant and anti-inflammatory substances, especially polyphenols.[5–11]

Polyphenols are found in foods including fruits, cereals, vegetables, legumes and cocoa, and beverages such as coffee, tea, and wine.[12] These compounds have been observed to show preventive properties against a wide variety of diseases, including CVD.[13–15] In addition, many studies have shown that polyphenols may have protective effects in the vascular system and in reducing inflammatory responses.[12,16]

In epidemiological studies, the relationship between polyphenol intake and cardiovascular risk factors has been analyzed by various approaches.[7,8,10,17] In almost all of these, an inverse relationship was observed between them, although results varied with regard to the polyphenol classes or subclasses. Nevertheless, the evidence is still too limited to lead to a recommendation for daily polyphenol intake.

The multifactorial nature of CVD events has led to the development of multivariable risk assessment tools or CVD risk scores,[18] including Framingham,[19] Framingham-REGICOR,[20] and SCORE.[21].The Life's Simple 7 (LS7)[22] is an alternative to calculate optimal cardiovascular health and provide a new approach to the previous tools. There is wide variability between scores in terms of in the population on which they are based or in the traits they include, so they are not exempt from limitations and agreement problems.[23]

The aim of this study was to provide a new approach using different cardiovascular risk scores. Since the scores include cardiovascular risk factors (cholesterol, hypertension, smoking, diabetes, overweight/obesity, and other nonmodifiable factors such as age and sex), commonly gathered in the participants included in the PREDIMED-Plus trial, the aim was to assess the possible association between intake of different polyphenol classes and the Framingham, Framingham-REGICOR, SCORE and LS7 instruments.

METHODS

Study population

This study was based on the cross-sectional analysis of the baseline data of participants included in PREDIMED-Plus. This is an ongoing 6-year multicenter, parallel-group, randomized trial, which is currently being conducted in 23 Spanish recruiting centers. The trial was registered at the International Standard Randomized Controlled Trial Registry (ISRCTN89898870). The study protocol includes more detailed information and is available in previous publications[24–26] and at the ISRCT website.[27]

Participants consisted of women aged 60 to 75 years and men aged 55 to 75 years, with a BMI between 27.0 and 40.0 kg/m^2 and meeting at least 3 criteria for metabolic syndrome[28] and with no CVD at enrolment. All participants provided written informed consent, and the study protocol and procedures were approved according to the ethical standards of the Declaration of Helsinki by all the participating institutions.

A total of 9677 people were contacted, of whom 6874 participants were eligible for the study, and were included in the trial. After exclusion of participants with missing data for the main variables and with implausible values for mean daily energy intake (< 500 and > 3500 kcal/d for women, < 800 and > 4000 kcal/d for men), 6633 participants were included in the present analysis (figure 1).

Variables and data collection

Data on age, sex, educational level, anthropometric measurements, dietary habits, and lifestyle were collected at baseline. Anthropometric evaluations were measured according to the PREDIMED-Plus protocol. Physical activity was evaluated using the validated REGICOR Short Physical Activity Questionnaire,[29] while the validated Spanish version of the Nurses' Health Study questionnaire was used to assess sedentary behavior.[30]

Adherence to an energy-reduced Mediterranean diet was assessed with a 17-item questionnaire (17-item erMedDiet), which is a modified version of the previously validated questionnaire used in the PREDIMED trial.[31]

Information on sociodemographic and lifestyle habits, individual and family medical history, smoking status, medical conditions, and medication use was evaluated by self-reported questionnaires. Biochemical analyses were performed using overnight fasting blood samples by standard enzymatic methods. Low-density lipoprotein cholesterol was calculated using the Friedewald formula. Blood pressure was measured in triplicate with a validated semiautomatic oscillometer in a seated position.

Variables included in the cardiovascular risk tools are shown in table 1, detailing their units. The LS7 scores each of 7 healthy habits favourably (plus 1 point).

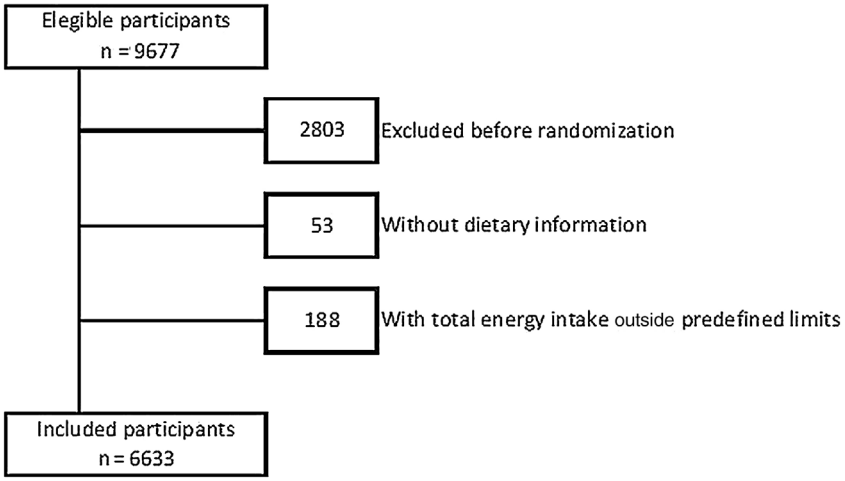

Figure 1. Flowchart of participants from the PREDIMED-Plus trial.

Table 1
Traits included in the estimation of the different cardiovascular risk scores

Scores			
SCORE	REGICOR	Framingham	Life's Simple 7
Age	Age	Age	BMI (< 25 kg/m^2)
Sex	Sex	Sex	Healthy diet (≥ 12 point in 17-item MedDiet questionnaire)
Total colesterol, mmol/L	Total colesterol, mg/dL	Total colesterol, mg/dL	Total colesterol (≤ 200 mg/dL)
Smoking status (current/nonsmoker)	Smoking status (current/nonsmoker)	Smoking status (current/nonsmoker)	No smoking
SBP, mmHg	SBP, mmHg	SBP with treatment, mmHg	BP (SBP ≤ 120 and DBP ≤ 80)
	DBP, mmHg	SBP without treatment, mmHg	Physical activity (≥ 500 METs-h/wk)
	HDL-cholesterol, mg/dL	HDL-cholesterol, mg/dL	Fasting plasma glucose (≤ 100 mg/dL)
	Diabetes	Diabetes	

BMI, body mass index; BP, blood pressure; DBP, diastolic blood pressure; HDL, high-density lipoprotein; SBP, systolic blood pressure.

Estimation of dietary polyphenol intake

Registered study dietitians assessed baseline diet with a semiuantitative 143-item food frequency questionnaire (FFQ),[32] which has been previously validated in the Spanish population.[33,34]

Dietary intake of the aglycone forms of polyphenols was estimated from the European Phenol Explorer database.[35] This procedure standardizes the data of the results of different analytical methods and facilitates cross-study comparisons.[36]

Polyphenol intake was calculated in mg/d (without applying a retention factor) using food consumption data from the FFQ and the aglycone polyphenol content of each food contained in the Phenol Explorer database. The data from the Phenol Explorer contains information on polyphenol concentration obtained from both chromatography and chromatography after hydrolysis analytical methods.

Polyphenol intake values were adjusted for total energy according to the Willett residuals method[37] to obtain intake of polyphenols, which is not correlated to total energy intake, and were categorized in sex-specific quintiles.

Statistical analysis

Descriptive statistics were used to define participants' baseline characteristics. Data are shown as mean and standard deviation (SD) and prevalence is expressed as frequency (No.) and percentage (%). The correlation between the scales was evaluated with Pearson pairwise correlations.

Linear regression models were carried out using CVD risk (Framingham, SCORE, Framingham-REGICOR and LS7) as the dependent variable and total polyphenol intake and the intake of their classes in quintiles as the independent variable.

The original risk equations were evaluated and, subsequently, the included CVD risk factors were eliminated from each equation one by one (total cholesterol, smoking status, BP, diabetes, and high-density lipoprotein cholesterol) and physical activity, BMI, healthy diet, and fasting plasma glucose were eliminated in the case of the LS7.

All regression models were stratified by sex and adjusted for recruiting center, intervention group, and cluster. Values are shown as beta coefficients and 95% confidence intervals (95%CI).

The analyses were performed with the Stata statistical software package version 15.1 (StataCorp LP, United States).

RESULTS

Table 2 shows the main characteristics of the 6633 participants from the PREDIMED-Plus study according to quintiles of total dietary polyphenol intake. Participants included in the fifth quintile of polyphenol intake were mainly men, with the highest score in the 17-item MedDiet questionnaire and higher physical activity and energy dietary intake than in the other quintiles. In addition, participants in the fifth quintile had less diabetes and lower BMI than those in the other quintiles.

The 4 scores were statistically significantly correlated ($P < .001$): the coefficient was 0.849 for Framingham and Framingham-REGICOR, 0.731 for Framingham and SCORE, −0.309 Framingham and LS7 was, 0.602 for Framingham-REGICOR and SCORE, −0.333 for Framingham-REGICOR and LS7, and −0.249 for SCORE and LS7.

The associations between the energy-adjusted dietary intake of polyphenols and cardiovascular risk for the different risk equations are shown in table 3 and in the supplementary tables. Total polyphenol and flavonoid intake were only directly and significantly associated with the LS7 scale. Total polyphenol and flavonoid intake were only directly and significantly associated with the LS7 scale. Regarding Q1 of total polyphenol intake, the participants in Q5 showed an improvement in cardiovascular health of 10% ($\beta_{Q5vs.Q1}$ = 0.10; 95%CI, 0.04-0.17). For those in Q5 of flavonoid intake, the improvement in cardiovascular health was 17% ($\beta_{Q5vs.Q1}$ = 0.17; 95%CI, 0.10-0.24). Similarly, Q5 intake of lignans (in relation to Q1) was associated with an increase in the risk of cardiovascular death of 48% (SCORE: $\beta_{Q5vs.Q1}$ = 0.48; 95%CI, 0.25-0.71) and with an increase in cardiovascular health of 23% (LS7: $\beta_{Q5vs.Q1}$ = 0.23; 95%CI, 0.16-0.30). The Q5 intake in stilbenes was associated with a 38% increase in the risk of cardiovascular death (SCORE: $\beta_{Q5vs.Q1}$ = 0.38; 95%CI, 0.15-0.62), Q5 intake of phenolic acids with a 191% increase in total CVD risk (Framingham: $\beta_{Q5vs.Q1}$ = 1.91; 95%CI, 0.76-3.06) and with a 27% increase in coronary risk (Framingham-REGICOR: $\beta_{Q5vs.Q1}$ = 0.27; 95%CI, 0.00-0.54). Intake of other polyphenols was significantly associated in Framingham ($\beta_{Q5vs.Q1}$ = −1.22; 95%CI, −2.37 to −0.07) and SCORE ($\beta_{Q5vs.Q1}$ = −0.32; 95%CI, −0.55 to −0.08), decreasing total CVD risk by 122% and coronary risk by 8%, respectively.

For the stratified analysis by sex, in women, the intake of all the polyphenol classes, except phenolic acids, showed an indirect association in the results of the Framingham and Framingham-REGICOR scores and a direct association in the LS7 scale. Other polyphenol intake also showed the same result for the SCORE equation. In men, total polyphenol intake was directly associated

Table 2
Baseline characteristics of the PREDIMED-Plus participants according to quintiles of polyphenol intake

Total polyphenol intake (mg/d)						
Range	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	*P*
	(≤ 402.7)	(403.0-507.8)	(507.8-620.7)	(620.7-786.5)	(≥ 786.6)	
No.	1327	1327	1326	1327	1326	
Age, y	65.3 ± 4.9	65.1 ± 5.0	65.1 ± 4.9	65.0 ± 4.9	65.1 ± 4.9	.67
Female sex, %	711 (53.6)	676 (50.9)	674 (50.8)	597 (45.0)	551 (41.6)	< .001
Smokers	163 (12.3)	176 (13.3)	155 (11.7)	159 (12.0)	168 (12.7)	.76
Systolic blood pressure	140 ±18	140 ± 17	139 ± 16	140 ± 17	139 ± 17	.83
Diastolic blood pressure	80.33 ± 10.18	80.58 ± 9.84	80.95 ± 9.72	81.13 ± 10.06	81.33 ± 9.90	.07
HDL-C	48 ± 12	48 ± 12	48 ± 12	49 ± 12	48 ± 12	.16
Total colesterol, mg/dL	197 ± 38	196 ± 38	196 ± 38	197 ± 36	198 ± 38	.58
Presence of diabetes	378 (28.5)	394 (29.7)	386 (29.1)	366 (27.6)	301 (22.7)	< .001
BMI, kg/m^2	32.8 ± 3.5	32.5 ± 3.5	32.6 ± 3.5	32.6 ± 3.5	32.2 ± 3.3	< .001
Blood glucose	114 ± 30	115 ± 32	114 ± 29	113 ± 27	112 ± 27	.06
17-item MedDiet questionnaire (≥ 12 points)	104 (7.8)	150 (11.3)	191 (14.4)	208 (15.7)	273 (20.6)	< .001
Physical activity (METs-h/wk)	38.5 ± 36.7	40.3 ± 33.3	42.5 ± 38.6	44.7 ± 40.5	46.5 ± 41.0	< .001
Total energy intake (kcal/d)	1971 ± 460	2208 ± 470	2351 ± 482	2523 ± 483	2773.36 ± 501.16	<.001
Antihypertensive treatment	1017 (76.7)	1038 (78.2)	1031 (77.8)	1029 (77.5)	1038 (78.3)	.83
Lipid-lowering treatment	700 (52.8)	684 (51.5)	686 (51.7)	663 (50.0)	674 (50.8)	.82
Familiar history of CVD	539 (41.7)	545 (41.9)	539 (41.3)	535 (41.3)	539 (41.4)	.99

BMI, body mass index; CVD, cardiovascular disease; HDL-C, high-density lipoprotein cholesterol.
The data are expressed as No. (%) or mean ± standard deviation.

Table 3
Association between polyphenol intake and cardiovascular risk scores stratified by sex in the PREDIMED-Plus trial

Polyphenol intake	Framingham quintile 5 vs quintile 1			Framingham-REGICOR quintile 5 vs quintile 1		
	All	Men	Women	All	Men	Women
Flavonoids	−0.71 (−1.86; 0.43) (*P* = .222)	−0.02 (−1.61; 1.57) (*P* = .980)	−1.52 (−2.57; −0.47) (*P* = .005)	−0.13 (−0.39; 0.14) (*P* = .344)	0.17 (−0.24; 0.57) (*P* = .418)	−0.45 (−0.71; −0.19) (*P* < .001)
Lignans	0.56 (−0.59; 1.71) (*P* = .341)	1.41 (−0.18; 3.00) (*P* = .083)	−0.31 (−1.37; 0.74) (*P* = .558)	0.04 (−0.23; 0.31) (*P* = .773)	0.40 (−0.01; 0.80) (*P* = .054)	−0.34 (−0.60; −0.08) (*P* = .009)
Stilbenes	0.15 (−1.00; 1.30) (*P* = .798)	0.97 (−0.62; 2.56) (*P* = .231)	−0.65 (−1.70; 0.41) (*P* = .230)	−0.1 (−0.36; 0.17) (*P* = .472)	0.25 (−0.15; 0.66) (*P* = .218)	−0.47 (−0.73; −0.21) (*P* < .001)
Phenolic acids	1.91 (0.76; 3.06) (*P* < .001)	2.79 (1.20; 4.37) (*P* < .001)	0.85 (−0.20; 1.90) (*P* = .114)	0.27 (0.00; 0.54) (*P* = .047)	0.38 (−0.02; 0.79) (*P* = .063)	0.13 (−0.13; 0.39) (*P* = .340)
Other polyphenols	−1.22 (−2.37; −0.07) (*P* = .038)	−0.75 (−2.34; 0.84) (*P* = .353)	−1.79 (−2.84; −0.73) (*P* < .001)	−0.17 (−0.44; 0.09) (*P* = .202)	0.08 (−0.32; 0.49) (*P* = .688)	−0.46 (−0.72; −0.20) (*P* < .001)
Total Polyphenols	−0.13 (−1.28; 1.02) (*P* = .823)	0.97 (−0.62; 2.56) (*P* = .230)	−1.40 (−2.45; −0.35) (*P* = .009)	−0.02 (−0.29; 0.25) (*P* = .879)	0.42 (0.01; 0.82) (*P* = .043)	−0.50 (−0.76; −0.24) (*P* < .001)
Polyphenol intake	**SCORE quintile 5 vs quintile 1**			**Life's Simple 7 quintile 5 vs quintile 1**		
	All	Men	Women	All	Men	Women
Flavonoids	0.12 (−0.12; 0.35) (*P* = .328)	0.31 (−0.05; 0.68) (*P* = .088)	−0.12 (−0.36; 0.12) (*P* = .335)	0.17 (0.10; 0.24) (*P* < .001)	0.18 (0.09; 0.27) (*P* < .001)	0.23 (0.13; 0.33) (*P* < .001)
Lignans	0.48 (0.25; 0.71) (*P* < .001)	0.73 (0.37; 1.09) (*P* < .001)	0.19 (−0.05; 0.43) (*P* = .128)	0.23 (0.16; 0.30) (*P* < .001)	0.23 (0.14; 0.33) (*P* < .001)	0.28 (0.18; 0.38) (*P* < .001)
Stilbenes	0.38 (0.15; 0.62) (*P* < .001)	0.64 (0.28; 1.00) (*P* < .001)	0.13 (−0.12; 0.37) (*P* = .314)	0.03 (−0.04; 0.1) (*P* = .220)	−0.04 (−0.14; 0.05) (*P* = .366)	0.13 (0.03; 0.24) (*P* = .009)
Phenolic acids	0.02 (−0.22; 0.25) (*P* = .899)	−0.01 (−0.37; 0.35) (*P* = .949)	0.03 (−0.21; 0.27) (*P* = .813)	−0.03 (−0.10; 0.03) (*P* = .191)	−0.06(−0.16; 0.03) (*P* = .169)	−0.03 (−0.13; 0.07) (*P* = .605)
Other polyphenols	−0.32 (−0.55; −0.08) (*P* = .008)	−0.30 (−0.66;0.06) (*P* = .102)	−0.32 (−0.56;−0.08) (*P* = .010)	0.06 (−0.01; 0.12) (*P* < .001)	0.11 (0.02; 0.21) (*P* = .015)	0.19 (0.09; 0.29) (*P* < .001)
Total polyphenols	0.10 (−0.13; 0.34) (*P* = .384)	0.29 (−0.70; 0.65) (*P* = .114)	−0.13 (−0.37; 0.12) (*P* = .300)	0.10 (0.04; 0.17) (*P* < .001)	0.11 (0.01; 0.20) (*P* = .024)	0.20 (0.10; 0.30) (*P* < .001)

The table shows the adjusted mean difference in the cardiovascular risk scores for the 5th vs the 1st quintile of polyphenol intake and the *P* for trend. The data are expressed as beta coefficients and 95% confidence intervals. Results from multivariable linear regression models adjusted for recruiting center, intervention group, and cluster.

with the Framingham-REGICOR and LS7 equations. Intake of lignans was directly associated with SCORE and LS7 equations, stilbene intake with SCORE, and intake of other polyphenols with the LS7 scale.

Table 4 shows the main results derived from linear regression models after removal of 1 risk factor at a time from each score. In general, for Framingham, Framingham-REGICOR and SCORE, the inverse associations were maintained even if some risk factors were not taken into account in the equations (for Framingham and Framingham-REGICOR in flavonoids and total polyphenols, and for the 3 equations in other polyphenols). The direct association was reversed in Framingham and Framingham-REGICOR equations when blood pressure was eliminated for lignans and, in Framingham for stilbenes when cholesterol, blood pressure and diabetes were removed. The best cardiovascular health (higher score on LS7 scale) was found when consumption of all polyphenol classes (except for phenolic acids) was highest, regardless of removing traits from the equation, except when a healthy diet was removed.

DISCUSSION

In this cross-sectional study, we evaluated the relationship between intake of different polyphenol classes and estimated cardiovascular risk measured with different tools in the cohort of the PREDIMED-Plus trial.

Previous evidence, mainly from in vivo or in vitro studies, suggests that polyphenol intake reduces CVD probably due to their anti-inflammatory effect, since they lower blood pressure, protect pancreatic cells, improve insulin resistance, inhibit platelet aggregation, reduce very low-density lipoprotein, reduce plasma triglyceride levels, improve nitric oxide homeostasis, antagonize atherogenesis, and improve atherosclerosis.[12,38]

A few previous studies have evaluated the association between the Mediterranean diet[39] and other dietary patterns[40] with cardiovascular risk but none has evaluated the association between polyphenol intake and overall cardiovascular risk measured by risk equations. Previous reports were of associations with individual cardiovascular risk factors, mostly focused on the flavonoid family[41] and on components of the metabolic syndrome.[42–44]

Our results are consistent with those already published from the PREDIMED-Plus trial[9,10] in which intake of stilbenes and lignans showed a direct association, while intake of flavonoids and other polyphenols showed an inverse association with systolic and diastolic blood pressure. All polyphenol classes were directly associated with high-density lipoprotein cholesterol. The direct association between phenolic acids with the equations and their inverse association with LS7 could also be seen in the aforementioned study,[10] in which this family showed a direct and significant association with fasting plasma glucose and, in another study, with higher levels of low-density lipoprotein cholesterol.[45] However, another study reported that phenolic acids showed an inverse association with blood pressure, glucose and lipid metabolism, as well as a stronger independent association with metabolic syndrome.[42] The main source of phenolic acids in our participants was coffee,[10] and some studies have suggested a J-shape relationship between coffee and cardiovascular risk,[45,46] which could partly explain the inconclusive results.

Other polyphenol intakes showed a tendency for a protective effect against CVD risk measured by all scores. One of the main sources of these polyphenols in our participants were olives and olive oil,[10] which have shown health benefits, mainly attributable to their polyphenol content, which include improvements in lipid profile, insulin sensitivity and endothelial function, as well as antiatherosclerotic and antithrombotic properties.[47,48]

Interestingly, in the analyses stratified by sex a stronger protective trend was observed in women (except for the phenolic acid family) and, in most cases, results were statistically significant and in the opposite direction than for men. In general, the effects of the Mediterranean diet appear to be greater in men than in premenopausal women when cardiometabolic changes are considered,[49] although in this trial the women were postmenopausal. However, the results of the present study are in line with those previously observed in the trial.[10] Another study also reported that consumption of foods rich in flavonoids was inversely associated with cardiovascular risk factors in premenopausal women but not in men.[50] As in the aforementioned publication, men's habits may have changed due to diagnosis of high cardiovascular risk. In fact, men showed higher CVD risks, measured with all scales, than women. Therefore, reverse causality may have taken place.

Regarding risk equations, the results were concordant for Framingham, Framingham-REGICOR, and LS7. The SCORE equation has shown direct associations with the intake of all the polyphenol classes (except for other polyphenols in all participants and flavonoids and total polyphenols in women).

Differences between polyphenol classes were assessed by a sensitivity analysis. The healthy diet (adherence to the Mediterranean diet) was eliminated from the LS7 scale to check whether the direct association was due to the correlation between diet and polyphenols. In many cases, the direct association was maintained, although in others (stilbenes, other polyphenols, total polyphenols) the association became inverse. The latter suggests that this scale was in harmony with the results shown in the rest of the scores.

In the present study, the 4 scales showed a significant correlation, in addition to showing similar results when they were related to polyphenol intake. Although no studies have been found that compared the equations in this way, those that compared them with each other have shown variation between these scores. The main differences or limitations of these equations are the variables included and the ages for which they were designed. In addition, the risks measured are different, since Framingham addresses total CVD risk, REGICOR addresses coronary risk, SCORE addresses cardiovascular mortality and LS7 measures cardiovascular health. Discrepancies in the detection of high risk have also been shown, specifically, SCORE and Framingham classify different patients as high risk[51] and REGICOR classifies fewer individuals as high risk than SCORE.[52] In general, most equations work similarly in terms of discrimination, but calibration can vary widely, depending mostly on the population to which it is applied.[53]

Limitations and strengths

We acknowledge that our study may have some limitations. First, and given the cross-sectional design of the study, there is a problem in determining the temporal relationship of a presumed cause and effect. Moreover, our entire study population is at high cardiovascular risk due to the trial protocol. Furthermore, the outcome is not an event, but an estimate of cardiovascular risk and the equations take into account factors that cannot be influenced by polyphenol intake (eg, age, sex, smoking status) and others that have shown benefits (eg, total cholesterol, high-density lipoprotein cholesterol, blood pressure). SCORE is the equation that includes most of these factors. In addition, no adjustment for lifestyle or other dietary factors was made, to compare the results for the equations with others, although LS7 includes physical activity and the results between them were similar. Another limitation is that self-reported dietary

Table 4

Sensitivity analyses for the association between polyphenol intake and cardiovascular risk scores stratified by sex

		Framingham. Quintile 5 vs quintile 1			F-REGICOR. Quintile 5 vs quintile 1			SCORE. Quintile 5 vs quintile 1			Life's Simple 7. Quintile 5 vs quintile 1		
		All	Men	Women	All	Men	Women	All	Men	Women	All	Men	Women
Flavonoids	Original	−0.71 (−1.86; 0.43)	−0.02 (−1.61; 1.57)	−1.52 (−2.56; −0.47)	−0.13 (−0.39; 0.14)	0.17 (−0.24; 0.57)	−0.45 (−0.71; −0.19)	0.12 (−0.12; 0.35)	0.31 (−0.05; 0.68)	−0.12 (−0.36; 0.12)	0.17 (0.10; 0.24)	0.16 (0.07; 0.26)	0.17 (0.08; 0.27)
	Without total cholesterol	−0.84 (−2.11; 0.44)	−0.15 (−1.88; 1.59)	−1.69 (−2.83; −0.55)	−0.21 (−0.55; 0.14)	−0.03 (−0.52; 0.46)	−0.42 (−0.68; −0.16)	0.12 (−0.14; 0.38)	0.35 (−0.06; 0.75)	−0.16 (−0.42; 0.10)	0.18 (0.12; 0.23)	0.17 (0.09; 0.25)	0.18 (0.09; 0.26)
	Without blood preassure	−0.51 (−1.31; 0.29)	−0.35 (−1.45; 0.76)	−0.71 (−1.20; −0.22)	−0.08 (−0.31; 0.14)	0.12 (−0.22; 0.45)	−0.30 (−0.47; −0.13)	0.08 (−0.03; 0.20)	0.16 (−0.02; 0.34)	−0.02 (−0.13; 0.09)	0.16 (0.10; 0.22)	0.16 (0.07; 0.25)	0.16 (0.06; 0.25)
	Without diabetes/ fasting plasma glucose	−0.01 (−0.98; 0.96)	0.54 (−0.78; 1.86)	−0.64 (−1.41; 0.14)	0.03 (−0.20; 0.26)	0.25 (−0.10; 0.60)	−0.20 (−0.39; −0.02)				0.15 (0.09; 0.21)	0.16 (0.08; 0.25)	0.13 (0.05; 0.22)
	Without healthy diet										0.06 (0.00; 0.12)	0.06 (−0.03; 0.14)	0.07 (−0.03; 0.16)
Lignans	Original	0.56 (−0.59; 1.71)	1.41 (−0.18; 3.00)	−0.31 (−1.37; 0.74)	0.04 (−0.23; 0.31)	0.40 (−0.01; 0.80)	−0.34 (−0.06; −0.08)	0.48 (0.25; 0.71)	0.73 (0.37; 1.09)	0.19 (−0.05; 0.43)	0.23 (0.16; 0.30)	0.27 (0.18; 0.36)	0.18 (0.08; 0.28)
	Without total cholesterol	0.60 (−0.68; 1.88)	1.39 (−0.35; 3.13)	−0.21 (−1.35; 0.94)	0.03 (−0.32; 0.37)	0.34 (−0.15; 0.83)	−0.30 (−0.56; −0.03)	0.55 (0.29; 0.81)	0.83 (0.43; 1.23)	0.22 (−0.04; 0.48)	0.22 (0.16; 0.28)	0.25 (0.17; 0.33)	0.18 (0.10; 0.27)
	Without blood preassure	−0.27 (−1.07; 0.54)	−0.08 (−1.19; 1.02)	−0.41 (−0.90; 0.08)	−0.08 (−0.31; 0.15)	0.12 (−0.22; 0.45)	−0.29 (−0.46; −0.12)	0.16 (0.05; 0.28)	0.22 (0.05; 0.40)	0.08 (−0.04; 0.19)	0.04 (−0.02; 0.11)	0.29 (0.21; 0.38)	0.19 (0.10; 0.28)
	Without diabetes/ fasting plasma glucose	0.32 (−0.65; 1.29)	0.67 (−0.65; 1.99)	−0.06 (−0.84; 0.72)	0.00 (−0.23; 0.22)	0.21 (−0.14; 0.57)	−0.24 (−0.43; −0.06)				0.21 (0.15; 0.27)	0.25 (0.17; 0.33)	0.15 (0.07; 0.24)
	Without healthy diet										0.07 (0.00; 0.13)	0.09 (0.00; 0.17)	0.04 (−0.05; 0.13)
Stilbenes	Original	0.15 (−1.00; 1.30)	0.97 (−0.62; 2.56)	−0.65 (−1.70; 0.41)	−0.10 (−0.36; 0.17)	0.25 (−0.15; 0.66)	−0.47 (−0.73; −0.21)	0.38 (0.15; 0.62)	0.64 (0.28; 1.00)	0.13 (−0.12; 0.37)	0.03 (−0.04; 0.10)	−0.02 (−0.11; 0.07)	0.08 (−0.02; 0.18)
	Without total cholesterol	−0.47 (−1.75; 0.81)	0.38 (−1.35; 2.12)	−1.23 (−2.38; −0.08)	−0.32 (−0.66; 0.03)	−0.11 (−0.60; 0.38)	−0.50 (−0.76; −0.23)	0.34 (0.07; 0.60)	0.62 (0.21; 1.02)	0.06 (−0.20; 0.32)	0.07 (0.01; 0.13)	0.02 (−0.06; 0.10)	0.13 (0.04; 0.21)
	Without BP	−0.19 (−0.99; 0.62)	0.23 (−0.87; 1.33)	−0.53 (−1.03; −0.04)	−0.14 (−0.37; 0.09)	0.10 (−0.24; 0.43)	−0.38 (−0.55; −0.21)	0.18 (0.07; 0.30)	0.34 (0.16; 0.51)	0.04 (−0.07; 0.15)	0.04 (−0.02; 0.11)	0.01 (−0.08; 0.10)	0.07 (−0.02; 0.17)
	Without diabetes/ fasting plasma glucose	0.03 (−0.94; 1.00)	0.22 (−1.10; 1.53)	−0.11 (−0.90; 0.67)	−0.10 (−0.33; 0.13)	0.07 (−0.28; 0.42)	−0.28 (−0.47; −0.09)				0.04 (−0.02; 0.10)	0.08 (−0.01; 0.16)	0.00 (−0.09; 0.08)
	Without healthy diet										−0.05 (−0.11; 0.01)	−0.12 (−0.21; −0.04)	0.03 (−0.07; 0.12)
Phenolic acids	Original	1.91 (0.76; 3.06)	2.79 (1.20; 4.37)	0.85 (−0.20; 1.90)	0.27 (0.00; 0.54)	0.38 (−0.02; 0.79)	0.13 (−0.13; 0.39)	0.02 (−0.22; 0.25)	−0.01 (−0.37; 0.35)	0.03 (−0.21; 0.27)	−0.03 (−0.10; 0.03)	−0.07 (−0.16; 0.03)	0.00 (−0.10; 0.10)
	Without total cholesterol	2.18 (0.90; 3.46)	2.98 (1.25; 4.72)	1.14 (−0.01; 2.28)	0.37 (0.03; 0.71)	0.50 (0.02; 0.99)	0.18 (−0.08; 0.44)	−0.01 (−0.27; 0.26)	−0.07 (−0.48; 0.33)	0.04 (−0.21; 0.30)	−0.06 (−0.11; 0.00)	−0.08 (−0.16; 0.00)	−0.03 (−0.12; 0.05)
	Without blood preassure	1.36 (0.56; 2.16)	2.23 (1.13; 3.33)	0.39 (−0.11; 0.88)	0.26 (0.03; 0.49)	0.42 (0.08; 0.75)	0.08 (−0.09; 0.25)	0.08 (−0.04; 0.19)	0.11 (−0.07; 0.29)	0.03 (−0.08; 0.14)	−0.03 (−0.10; 0.03)	−0.07 (−0.16; 0.02)	0.00 (−0.09; 0.09)
	Without diabetes/ fasting plasma glucose	0.40 (−0.57; 1.37)	0.51 (−0.80; 1.83)	0.16 (−0.62; 0.94)	−0.01 (−0.24; 0.22)	−0.04 (−0.39; 0.31)	0.00 (−0.19; 0.19)				0.02 (−0.04; 0.07)	−0.01 (−0.09; 0.07)	0.04 (−0.04; 0.13)
	Without healthy diet										−0.09 (−0.15; −0.03)	−0.11 (−0.20; −0.03)	−0.07 (−0.16; 0.02)

Table 4 *(Continued)*
Sensitivity analyses for the association between polyphenol intake and cardiovascular risk scores stratified by sex

		Framingham. Quintile 5 vs quintile 1			F-REGICOR. Quintile 5 vs quintile 1			SCORE. Quintile 5 vs quintile 1			Life's Simple 7. Quintile 5 vs quintile 1		
		All	Men	Women	All	Men	Women	All	Men	Women	All	Men	Women
Other polyphenols	Original	−1.22 (−2.37; −0.07)	−0.75 (−2.34; 0.84)	−1.79 (−2.84; −0.73)	−0.17 (−0.44; 0.09)	0.08 (−0.32; 0.49)	−0.46 (−0.72; −0.20)	−0.32 (−0.55; −0.08)	−0.30 (−0.66; 0.06)	−0.32 (−0.56; −0.08)	0.06 (−0.01; 0.12)	0.06 (−0.04; 0.15)	0.06 (−0.04; 0.16)
	Without total cholesterol	−1.41 (−2.69; −0.13)	−0.95 (−2.69; 0.79)	−1.97 (−3.12; −0.83)	−0.28 (−0.63; 0.06)	−0.15 (−0.64; 0.33)	−0.45 (−0.71; −0.18)	−0.40 (−0.66; −0.13)	−0.40 (−0.80; 0.01)	−0.38 (−0.64; −0.13)	0.08 (0.02; 0.14)	0.06 (−0.02; 0.14)	0.10 (0.02; 0.18)
	Without blood preassure	−0.12 (−0.92; 0.68)	0.22 (−0.88; 1.32)	−0.47 (−0.96; 0.02)	0.00 (−0.23; 0.23)	0.19 (−0.14; 0.53)	−0.20 (−0.37; −0.03)	−0.06 (−0.17; 0.06)	−0.06 (−0.24; 0.12)	−0.04 (−0.15; 0.07)	0.04 (−0.03; 0.10)	0.04 (−0.05; 0.13)	0.04 (−0.05; 0.13)
	Without diabetes / fasting plasma glucose	−1.62 (−2.59; −0.64)	−1.77 (−3.09; −0.45)	−1.51 (−2.29; −0.73)	−0.25 (−0.48; −0.02)	−0.16 (−0.52; 0.19)	−0.35 (−0.54; −0.17)				0.09 (0.03; 0.15)	0.13 (0.05; 0.22)	0.05 (−0.04; 0.13)
	Without healthy diet										−0.03 (−0.09; 0.03)	−0.03 (−0.12; 0.05)	−0.02 (−0.11; 0.07)
Total polyphenols	Original	−0.13 (−1.28; 1.02)	0.97 (−0.61; 2.56)	−1.40 (−2.45; −0.35)	−0.02 (−0.29; 0.25)	0.42 (0.01; 0.82)	−0.50 (−0.76; −0.24)	0.10 (−0.13; 0.34)	0.29 (−0.07; 0.65)	−0.13 (−0.37;0.12)	0.10 (0.04; 0.17)	0.08 (−0.01; 0.18)	0.13 (0.03; 0.23)
	Without total cholesterol	−0.29 (−1.57; 0.99)	0.66 (−1.07; 2.40)	−1.49 (−2.63; −0.35)	−0.09 (−0.43; 0.25)	0.19 (−0.30; 0.68)	−0.43 (−0.69; −0.17)	0.09 (−0.17; 0.35)	0.28 (−0.13; 0.68)	−0.16 (−0.42; 0.10)	0.12 (0.06; 0.18)	0.11 (0.03; 0.19)	0.13 (0.05; 0.22)
	Without blood preassure	0.14 (−0.66; 0.94)	0.76 (−0.35; 1.86)	−0.58 (−1.07; −0.09)	0.05 (−0.18; 0.27)	0.39 (0.05; 0.72)	−0.32 (−0.50; −0.15)	0.13 (0.02; 0.25)	0.22 (0.05; 0.40)	0.01 (−0.10; 0.12)	0.10 (0.04; 0.17)	0.08 (−0.01; 0.17)	0.12 (0.03; 0.21)
	Without diabetes/ fasting plasma glucose	0.20 (−0.77; 1.17)	0.93 (−0.38; 2.25)	−0.64 (−1.42; 0.14)	0.06 (−0.16; 0.29)	0.37 (0.02; 0.72)	−0.26 (−0.45; −0.08)				0.10 (0.04; 0.15)	0.10 (0.02; 0.18)	0.09 (0.01; 0.18)
	Without healthy diet										−0.01 (−0.08; 0.05)	−0.03 (−0.12; 0.05)	0.01 (−0.08; 0.10)

The table shows the adjusted mean difference in the cardiovascular risk scores for the 5th vs the 1st quintile of polyphenol intake. The data are expressed as beta coefficients and 95% confidence intervals. Results from multivariable linear regression models adjusted for recruiting centre, intervention group and cluster.

information may have led to some misclassification. However, the FFQ used was previously validated in the adult Spanish population and showed good reproducibility and validity.[29] Finally, other factors affecting polyphenol content could be a limitation: the estimation of their intake through the FFQ, the differences in their absorption and in their bioactivity,[54] the synergies with other polyphenols, nutrients or compounds,[55] factors related to climate stress, geography, and storage conditions or losses during cooking.[56] In addition, polyphenols were grouped instead of considering only individual compounds and therefore important associations for individual compounds may have been missed.

On the other hand, our study also has important strengths, such as its multicenter design, the large sample size and the high-quality, detailed information collected by qualified interviewers. Second, our database was built including all available information on polyphenol content in Phenol Explorer, with a mixture of data extracted from chromatography and chromatography after hydrolysis data and this consumption was adjusted using the residuals method. In addition, 4 different scores were used to assess cardiovascular risk, since CVD is a multifactorial disease and we found similar results between the scores. The strength of these findings was reinforced by the results obtained from the sensitivity analysis. Another strength of this study is the analysis stratified by sex, allowing us to detect differences with the overall analysis. Finally, this is the first study to evaluate the influence of polyphenol intake on cardiovascular risk as measured by these 4 different risk equations. The lack of epidemiologic studies precluded us from comparing our results with those of other studies.

CONCLUSIONS

This study shows the association between polyphenol classes and global cardiovascular risk, showing an inverse association between the class of other polyphenols and especially among women. The results were similar for Framingham, Framingham-REGICOR and LS7 (after eliminating diet). SCORE showed different results, but the predictors considered in this equation are limited and do not include some important ones such as diabetes or high-density lipoprotein cholesterol, while it includes other traits with which polyphenols may have no associations.

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WHAT IS KNOWN ABOUT THE TOPIC?

- Polyphenols have shown benefits in improving cardiovascular risk factors, but the evidence is still too limited to support a recommendation for daily polyphenol intake for cardiovascular disease prevention.
- So far, no study has been found that relates polyphenol intake with the cardiovascular risk scores used in this study.

WHAT DOES THIS STUDY ADD?

- This is the first study to evaluate the relationship between the intake of different classes of polyphenols and cardiovascular risk measured by 4 different risk scores.
- The results obtained allowed comparison of these 4 equations with each other.

CONFLICTS OF INTEREST

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APPENDIX. SUPPLEMENTARY DATA

Supplementary data associated with this article can be found in the online version available at https://doi.org/10.1016/j.rec.2021.06.013

REFERENCES

1. The World Health Organization. Cardiovascular Diseases. The World Health Organization; Geneva, Switzerland. Available at: https://www.who.int/health-topics/cardiovascular-diseases/#tab=tab_1. 2016. Accessed 20 Sep 2020.
2. Roth GA, Abate D, Abate KH, et al. Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet.* 2018;392:1736–1788.
3. Thomas H, Diamond J, Vieco A, et al. Global Atlas of Cardiovascular Disease 2000-2016: The Path to Prevention and Control. *Glob Heart.* 2018;13:143–163.
4. Virani SS, Alonso A, Benjamin EJ, et al. American Heart Association Council on Epidemiology and Prevention Statistics Committee and Stroke Statistics Subcommittee Heart Disease and Stroke Statistics-2020 Update: A Report From the American Heart Association. *Circulation.* 2020;141:e139–e596.
5. Willett WC. The Mediterranean diet: science and practice. *Public Health Nutr.* 2006;9:105–110.
6. Billingsley HE, Carbone S. The antioxidant potential of the Mediterranean diet in patients at high cardiovascular risk: an in-depth review of the PREDIMED. *Nutr Diabetes.* 2018;8:13.
7. Tresserra-Rimbau A, Rimm EB, Medina-Remón A, et al. Polyphenol intake and mortality risk a re-analysis of the PREDIMED trial. *BMC Med.* 2014;12:77.
8. Tresserra-Rimbau A, Rimm EB, Medina-Remón A, et al. Inverse association between habitual polyphenol intake and incidence of cardiovascular events in the PREDIMED study. *Nutr Metab Cardiovasc Dis.* 2014;24:639–647.
9. Tresserra-Rimbau A, Castro-Barquero S, Vitelli-Storelli F, et al. Associations between Dietary Polyphenols and Type 2 Diabetes in a Cross-Sectional Analysis of the PREDIMED-Plus Trial: Role of Body Mass Index and Sex. *Antioxidants (Basel).* 2019;8:537.
10. Castro-Barquero S, Tresserra-Rimbau A, Vitelli-Storelli F, et al. Dietary Polyphenol Intake is Associated with HDL-Cholesterol and A Better Profile of other Components of the Metabolic Syndrome: A PREDIMED-Plus Sub-Study. *Nutrients.* 2020;12:689.
11. Bullón-Vela V, Abete I, Zulet MA, et al. Urinary Resveratrol Metabolites Output: Differential Associations with Cardiometabolic Markers and Liver Enzymes in House-Dwelling Subjects Featuring Metabolic Syndrome. *Molecules.* 2020;25:4340.
12. Giglio RV, Patti AM, Cicero AFG, et al. Polyphenols: Potential Use in the Prevention and Treatment of Cardiovascular Diseases. *Curr Pharm Des.* 2018;24:239–258.
13. Rubín-García M, Vitelli-Storelli F, Molina AJ, et al. Association between Polyphenol Intake and Gastric Cancer Risk by Anatomic and Histologic Subtypes: MCC-Spain. *Nutrients.* 2020;12:3281.
14. Vitelli Storelli F, Molina AJ, Zamora-Ros R, et al. Flavonoids and the Risk of Gastric Cancer: An Exploratory Case-Control Study in the MCC-Spain Study. *Nutrients.* 2019;11:967.
15. Pandey KB, Rizvi SI. Plant polyphenols as dietary antioxidants in human health and disease. *Oxid Med Cell Longev.* 2009;2:270–278.
16. Tresserra-Rimbau A, Lamuela-Raventos RM, Moreno JJ. Polyphenols, food and pharma Current knowledge and directions for future research. *Biochem Pharmacol.* 2018;156:186–195.
17. Medina-Remón A, Tresserra-Rimbau A, Pons A, et al. Effects of total dietary polyphenols on plasma nitric oxide and blood pressure in a high cardiovascular risk cohort The PREDIMED randomized trial. *Nutr Metab Cardiovasc Dis.* 2015;25:60–67.
18. Karmali KN, Persell SD, Perel P, et al. Risk scoring for the primary prevention of cardiovascular disease. *Cochrane Database Syst Rev.* 2017;3:CD006887.
19. D'Agostino Sr RB, Vasan RS, Pencina MJ, et al. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. *Circulation.* 2008;117:743–753.
20. Marrugat J, D'Agostino R, Sullivan L, et al. An adaptation of the Framingham coronary heart disease risk function to European Mediterranean areas. *J Epidemiol Community Health.* 2003;57:634–638.
21. Conroy RM, Pyörälä K, Fitzgerald AP, et al. Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. *Eur Heart J.* 2003;24:987–1003.
22. Lloyd-Jones DM, Hong Y, Labarthe D, et al. American Heart Association Strategic Planning Task Force and Statistics Committee. Defining and setting national goals for cardiovascular health promotion and disease reduction: the American Heart Association's strategic Impact Goal through 2020 and beyond. *Circulation.* 2010;121:586–613.
23. Damen JA, Hooft L, Schuit E, et al. Prediction models for cardiovascular disease risk in the general population: systematic review. *BMJ.* 2016;16:353i2416.
24. Martínez-González MA, Buil-Cosiales P, Corella D, et al. PREDIMED-Plus Study Investigators Cohort Profile: Design and methods of the PREDIMED-Plus randomized trial. *Int J Epidemiol.* 2019;48:387–388.
25. Salas-Salvadó J, Díaz-López A, Ruiz-Canela M, et al. Effect of a Lifestyle Intervention Program With Energy-Restricted Mediterranean Diet and Exercise on Weight Loss and Cardiovascular Risk Factors: One-Year Results of the PREDIMED-Plus Trial. *Diabetes Care.* 2019;42:777–788.
26. Sayón-Orea C, Razquin C, Bulló M, et al. Effect of a Nutritional and Behavioral Intervention on Energy-Reduced Mediterranean Diet Adherence Among Patients With Metabolic Syndrome: Interim Analysis of the PREDIMED-Plus Randomized Clinical Trial. JAMA. 019;322:1486-1499.
27. PREDIMED-Plus Website. Available at: http://www.predimedplus.com. Accessed 26 Sep 2020.
28. Alberti KG, Eckel RH, Grundy SM, et al. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. *Circulation.* 2009;120:1640–1645.
29. Molina L, Sarmiento M, Peñafiel J, et al. Validation of the regicor short physical activity questionnaire for the adult population. *PLoS ONE.* 2017;12:e0168148.
30. Martínez-González MA, López-Fontana C, Varo JJ, et al. Validation of the Spanish version of the physical activity questionnaire used in the nurses' health study and the health professionals' follow-up study. *Public Health Nutr.* 2005;8:920–927.
31. Álvarez-Álvarez I, Martínez-González MÁ, Sánchez-Tainta A, et al. Adherence to an Energy-restricted Mediterranean Diet Score and Prevalence of Cardiovascular Risk Factors in the PREDIMED-Plus: A Cross-sectional Study. *Rev Esp Cardiol.* 2019;72:925–934.
32. Fernández-Ballart JD, Piñol JL, Zazpe I, et al. Relative validity of a semi-quantitative food-frequency questionnaire in an elderly Mediterranean population of Spain. *Br J Nutr.* 2010;103:1808–1816.
33. Martin-Moreno JM, Boyle P, Gorgojo L, et al. Development and validation of a food frequency questionnaire in Spain. *Int J Epidemiol.* 1993;22:512–519.
34. De la Fuente-Arrillaga C, Ruiz ZV, Bes-Rastrollo M, et al. Reproducibility of an FFQ validated in Spain. *Public Health Nutr.* 2010;13:1364–1372.
35. Neveu V, Perez-Jimenez J, Vos F, et al. Phenol Explorer: an online comprehensive database on polyphenol contents in foods. *Database (Oxford).* 2010. http://doi.org/10.1093/database/bap024.
36. Balentine DA, Dwyer JT, Erdman JW, et al. Recommendations on reporting requirements for flavonoids in research. *Am J Clin Nutr.* 2015;101:1113–1125.
37. Willett WC, Howe GR, Kushi LH. Adjustment for total energy intake in epidemiologic studies. *Am J Clin Nutr.* 1997;65(4 Suppl):1220S–1228S.

38. Santos CN, Gomes A, Oudot C, et al. Pure Polyphenols Applications for Cardiac Health and Disease. *Curr Pharm Des.* 2018;24:2137–2156.
39. Bédard A, Dodin S, Corneau L, et al. Impact of the traditional Mediterranean diet on the Framingham risk score and the metabolic syndrome according to sex. *Metab Syndr Relat Disord.* 2014;12:95–101.
40. Shahavandi M, Amini MR, Shahinfar H, et al. Major dietary patterns and predicted cardiovascular disease risk in an Iranian adult population. *Nutr Health.* 2020. http://doi.org/10.1177/0260106020952591.
41. do Rosario VA, Schoenaker DAJM, Kent K, Weston-Green K, Charlton K. Association between flavonoid intake and risk of hypertension in two cohorts of Australian women: a longitudinal study. *Eur J Nutr.* 2020. https://doi.org/10.1007/s00394-020-02424-9
42. Grosso G, Stepaniak U, Micek A, et al. Dietary polyphenols are inversely associated with metabolic syndrome in Polish adults of the HAPIEE study. *Eur J Nutr.* 2017;56:1409–1420.
43. Vetrani C, Vitale M, Bozzetto L, et al. Association between different dietary polyphenol subclasses and the improvement in cardiometabolic risk factors: evidence from a randomized controlled clinical trial. *Acta Diabetol.* 2018;55:149–153.
44. Sohrab G, Hosseinpour-Niazi S, Hejazi J, Yuzbashian E, Mirmiran P, Azizi F. Dietary polyphenols and metabolic syndrome among Iranian adults. *Int J Food Sci Nutr.* 2013;64:661–667.
45. Wisnuwardani RW, De Henauw S, Forsner M, et al. Polyphenol intake and metabolic syndrome risk in European adolescents: the HELENA study. *Eur J Nutr.* 2020;59:801–812.
46. Miranda AM, Steluti J, Fisberg RM, et al. Association between Coffee Consumption and Its Polyphenols with Cardiovascular Risk Factors: A Population-Based Study. *Nutrients.* 2017;9:276.
47. Ditano-Vázquez P, Torres-Peña JD, Galeano-Valle F, et al. The Fluid Aspect of the Mediterranean Diet in the Prevention and Management of Cardiovascular Disease and Diabetes: The Role of Polyphenol Content in Moderate Consumption of Wine and Olive Oil. *Nutrients.* 2019;11:2833.
48. Mehmood A, Usman M, Patil P, Zhao L, Wang C. A review on management of cardiovascular diseases by olive polyphenols. *Food Sci Nutr.* 2020;8:4639–4655.
49. Franconi F, Campesi I, Romani A. Is Extra Virgin Olive Oil an Ally for Women's and Men's Cardiovascular Health? *Cardiovasc Ther.* 2020;2020:6719301.
50. Mennen LI, Sapinho D, de Bree A, et al. Consumption of foods rich in flavonoids is related to a decreased cardiovascular risk in apparently healthy French women. *J Nutr.* 2004;134:923–926.
51. Baena Díez J, del Val García J, Salas Gaetgens L, et al. Comparación de los moldelos SCORE y REGICOR para el cálculo del riesgo cardiovascular en sujetos sin enfermedad cardiovascular atendidos en un centro de salud de Barcelona. *Rev Esp Salud Publ.* 2005;79:453–464.
52. Buitrago F, Cañon-Barroso L, Diaz-Herrera N, et al. Comparación de las tablas REGICOR y SCORE para la clasificación del riesgo cardiovascular y la identificación de pacientes candidatos a tratamiento hipolipemiante o antihipertensivo. *Rev Esp Cardiol.* 2007;60:139–147.
53. Cooney MT, Dudina AL, Graham IM. Value and limitations of existing scores for the assessment of cardiovascular risk: a review for clinicians. *J Am Coll Cardiol.* 2009;54:1209–1227.
54. Crozier A, Jaganath IB, Clifford MN. Dietary phenolics: chemistry, bioavailability and effects on health. *Nat Prod Rep.* 2009;26:1001–1043.
55. Jacobs Jr DR, Gross MD, Tapsell LC. Food synergy: an operational concept for understanding nutrition. *Am J Clin Nutr.* 2009;89:1543S–1548S.
56. Diotallevi C, Fava F, Gobbetti M, et al. Healthy dietary patterns to reduce obesity-related metabolic disease: polyphenol-microbiome interactions unifying health effects across geography. *Curr Opin Clin Nutr Metab Care.* 2020;23:437–444.