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Total polyphenol intake, polyphenol subtypes and incidence of cardiovascular disease: The SUN cohort study

R.D. Mendonça [a,b,c], N.C. Carvalho [d], J.M. Martin-Moreno [a,e], A.M. Pimenta [a,f], A.C.S. Lopes [b], A. Gea [a,g,h], M.A. Martinez-Gonzalez [a,g,h,i], M. Bes-Rastrollo [a,g,h,*]

[a] University of Navarra, Preventive Medicine and Public Health, Pamplona, Spain
[b] Departament Nutrition, Universidade Federal de Minas Gerais, Brazil
[c] CAPES Foundation, Ministry of Education of Brazil, Brasília, Brazil
[d] Department of Food and Nutrition, University of Campinas, Brazil
[e] Department of Preventive Medicine & INCLIVA, University of Valencia, Spain
[f] Department of Maternal-Child Nursing and Public Health, Universidade Federal de Minas Gerais, Brazil
[g] Navarra's Health Research Institute (IDISNA), Pamplona, Spain
[h] CIBERobn, Institute of Health Carlos III, Madrid, Spain
[i] Harvard TH-Chan School of Public Health, Department of Nutrition, Boston, MA, USA

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Abstract *Background and aims:* Polyphenol-rich diets have been associated with reduced risk of cardiovascular disease (CVD). However, few prospective epidemiological studies have examined the relationship between classes of ingested polyphenols and risk of CVD. Our aim was to evaluate the association between polyphenol intake and risk of major cardiovascular events in a prospective Spanish cohort.
Methods and results: We included 17,065 university graduates (60.7% women, mean age: 37.2 years, age range: 20–89) followed-up for a mean of 10.1 years. Polyphenol intake was assessed at baseline using a validated semi-quantitative 136-item food frequency questionnaire and matching food consumption data with the Phenol-Explorer database. Cox proportional hazards models were used to estimate the adjusted hazard ratios (HR) and 95% confidence intervals (95% CI) for incident cardiovascular events (myocardial infarction, stroke or cardiovascular death). Cherries, chocolate, coffee, apples, and olives were the major sources of variability in polyphenol intake. Participants with higher flavonoids intake (fifth quintile) had a 47% lower incidence of cardiovascular events compared to those in the lowest quintile (HR: 0.53, 95% CI: 0.29–0.98; P for trend = 0.09) after adjusting for potential confounders. The results were non-significant for other polyphenol types.
Conclusion: The intake of flavonoids showed an inverse association with risk of cardiovascular events in a prospective cohort of Spanish middle-aged adult university graduates.
Registration number for clinical trials: NCT02669602 in Clinical Trials.

* Corresponding author. Preventive Medicine and Public Health, University of Navarra, Irunlarrea 1, 31008 Pamplona, Navarra, Spain. Fax: +34 948455740.
E-mail address: mbes@unav.es (M. Bes-Rastrollo).

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Introduction

Cardiovascular diseases (CVDs) are the largest cause of mortality worldwide, accounting for 17.5 million yearly deaths (31% of all-cause global mortality) mainly due to coronary heart disease and stroke [1]. Most CVDs can be prevented by addressing risk factors such as obesity, hypertension, high lipid levels, diabetes, tobacco use, lack of regular physical activity, harmful use of alcohol, and unhealthy diet [2]. Increased intake of dietary polyphenols has been suggested as part of the strategy for cardiovascular disease prevention and reduction of the related risk factors [3].

Polyphenols are secondary plant metabolites, which are compounds produced in metabolic pathways triggered by the plant interactions with environmental factors and that, although important, are not essential for growth and development of a plant. However, secondary plant metabolites, as polyphenols, are generally involved in chemical defense and against pathogens, reproduction, and plant–plant communication [4]. Thousands of polyphenol compounds are found in a variety of plant-derived foods including vegetables, fruits, cocoa, cereal grains, and nuts, as well as their related processed foods (wine, juice and tea) [5].

Dietary polyphenols act on both the inflammatory processes and endothelial dysfunction implicated in the development of CVDs. Potential protective effects of polyphenols against CVD have been attributed to several features including antioxidant properties and free-radical scavenging activities [6]; regulation of the activities of inflammation-related cells and their molecular targets [7]; and induction of nitric oxide (NO) production, which results in the synthesis of vascular-relaxing factors such as prostacyclin (PGI2) and causes inhibition of vasoconstrictor endothelin-1 (ET-1) synthesis [8]. However, the action of dietary polyphenols in the body is quite complex, and their precise mechanism of action is not yet fully understood.

Epidemiological studies have shown associations between polyphenols consumption, especially certain polyphenol types, and risk of chronic diseases [9–14]. However, few longitudinal studies have assessed the effects of total polyphenol intake and the intake of specific classes of polyphenols on CVD. Results from the PREDIMED randomized trial showed that polyphenol-rich diets, such as the Mediterranean diet (Med-Diet), were associated with reduced risk of CVD and mortality [3,12]. In the PREDIMED study, after a one-year intervention with Med-Diet supplemented with extra-virgin olive oil or nuts, a significant increase in total polyphenols excreted in urine and changes in plasma NO levels in the elderly population at high cardiovascular risk were observed [13]. However, it is not known whether this attenuation by polyphenol-rich diets is also present among younger subjects at lower cardiovascular risk.

Our aim was to evaluate whether total intake of polyphenols or of specific polyphenols were associated with the subsequent occurrence of cardiovascular events among middle-aged adults participating in a Spanish prospective cohort study.

Methods

Study population

The "Seguimiento Universidad de Navarra" (SUN) Project is an ongoing prospective cohort study in Spain among university graduates since 1999. The recruitment of participants is permanently open, and participants are followed-up biennially using questionnaires. Details of the design and methods of the SUN Project have been published previously [15].

Through March 2014, the SUN Project dataset included 22,279 participants who had completed the baseline questionnaire. In the present study, we excluded participants with cardiovascular events at baseline (n = 342), those who reported total energy intake values outside of the predefined limits (low: <3347 kJ/d or <800 kcal/d in men and <2092 kJ/d or <500 kcal/d in women; high: >16,736 kJ/d or >4000 kcal/d in men and >14,644 kJ/d or >3500 kcal/d in women; n = 2092) [16], those who were lost to follow-up (n = 1760; retention in the cohort: 91%), and those with ≥9 items missing on the food frequency questionnaire (FFQ; n = 1020). A total of 17,065 participants were included in the final analyses (Fig. 1).

Ethics

This study was conducted according to the principles of the Declaration of Helsinki and was approved by the Institutional Review Board of the University of Navarra. Voluntary completion of the baseline self-administrated questionnaire was considered to imply informed consent.

Ascertainment of cardiovascular events

In both the baseline and follow-up questionnaires, participants were asked whether they had received a medical diagnosis of cardiovascular events. The follow-up questionnaire also requested the date of cardiovascular event diagnoses. The incident cardiovascular events were the composite of incident non-fatal acute coronary syndromes (myocardial infarction with or without ST elevation), non-fatal stroke, or death due to cardiovascular causes. Participants (or their families) who reported any of these diagnoses during follow-up were asked to provide access to their medical records. An expert panel of physicians, blinded with respect to diet and risk factors, reviewed the medical records and adjudicated events based on universal definitions of myocardial infarction [17]. Non-fatal stroke was defined as a focal neurological deficit of sudden onset via a vascular mechanism that lasted more than 24 h. Deaths were reported to our research team by the participant's next of kin, work associates, and postal authorities.

For participants lost to follow-up, the National Death Index was yearly checked to identify deceased cohort members and to obtain causes of death.

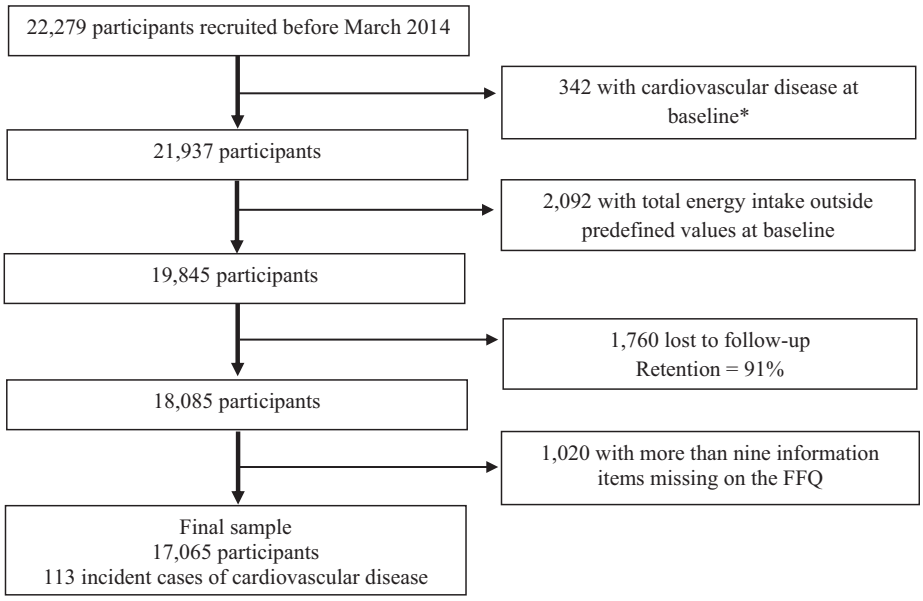

Figure 1 Participants flow chart. The SUN Project, 1999–2016. *Cardiovascular events: stroke, myocardial infarction and coronary artery revascularization. FFQ: food frequency questionnaire.

Polyphenol intake

Polyphenol dietary intake was assessed at baseline using a self-administered 136-item semi-quantitative FFQ, which was previously validated in Spain and subsequently re-evaluated [18,19]. The FFQ grouped the foods into the following categories: fruits (fresh and dried), vegetables, legumes, oils [olive (extra virgin, virgin and pure), sunflower and corn], grains (rice and pasta), breads (white and whole), artisanal (homemade) and industrialized pastries, natural juice, canned and bottle fruits (fruits in syrup and fruits in their juice), breakfast cereals, and pizza. A typical Spanish portion size was presented for each item, and the frequencies of consumption were grouped into nine categories ranging from never/almost never to >6 servings/day. Daily food consumption was estimated by multiplying the portion size by the consumption frequency for each food item.

Data on the polyphenol content in foods were obtained from the Phenol-Explorer database (www.phenol-explorer.eu) [20]. For foods not identified in Phenol-Explorer (leek, thistle, and honey), we used the United States Department of Agriculture (USDA) database (https://www.ars.usda.gov/nutrientdata). Foods with only traces or without polyphenols, such as meat-based foods, were excluded [21].

The recipes and processed foods, including canned goods, were separated according to their ingredients; polyphenol content was calculated on the basis of their ingredients. Several foods that contained refined wheat flour like pizza were included and their polyphenol contents estimated based on their wheat-flour content according to their ingredients by means of composition tables and recipes. Furthermore, a retention factor was applied for cooked and processing foods. The retention factor considers the food cooking and processing when calculating polyphenol content [21]. Domestic cooking practices (i.e., boiling, steaming, frying, microwaving) of plant foods cause considerable losses of the polyphenol content, usually provoked by oxidation, thermal destruction, and leaching into water or oil that is discard [22]. Polyphenols losses due to boiling presented a retention factor of 0.59, while the retention factor due to steaming was 0.67. The retention factors due to microwaving and frying were 0.56 and 0.50, respectively [21]. Total polyphenol intake was calculated as the sum of all individual polyphenol intakes from all food sources reported by the FFQ. Individual polyphenol intake from each food was calculated by multiplying the individual polyphenol content by the daily consumption of each food. Total intake and classes of polyphenols were adjusted for total energy intake using the residual method. Energy-adjusted total intake and classes of polyphenols was computed as specific residuals from the linear regression model where polyphenols intake was the dependent variable and total energy intake the independent. This method provides a measure of polyphenols intake completely uncorrelated with total energy intake [16]. The sample was divided into sex-specific quintiles according to total intake (mg/d).

Assessment of covariates

The baseline questionnaire also included other questions, including sociodemographic information (sex and age), medical history and medication use, anthropometric (weight and height), lifestyle (smoking status, physical activity during leisure time, and hours of television watched per day), adherence to the Med-Diet, snacking between main meals, and consumption of a special diet

(hypocaloric, hypolipidemic, low-sodium, vegetarian, lactose intolerance, or food allergy diets).

Body mass index (BMI) was calculated as the self-reported weight in kilograms divided by the square of height in meters. Physical activity was evaluated using a validated 17-item questionnaire [23].

The intakes of total energy, macronutrients, sodium intake, fiber, and alcohol were calculated as the frequency multiplied by the nutrient composition of specified portion sizes based on FFQ responses. The nutrient databank was updated by a trained team of dieticians using food composition tables for Spain [18,19].

Statistical analyses

To determine the contribution of each food item to the between-person variance in polyphenol intake [16], we constructed a series of nested least-squares linear regression models after stepwise-selection regression analyses. The additional contribution of a given food item was reflected in the change of cumulative R^2.

Follow-up time was defined as the interval between the date of recruitment and the date that the last follow-up questionnaire was returned or the date on which the participant was first classified as having an incident cardiovascular event (myocardial infarction, stroke or cardiovascular death).

We used Cox regression models with age as the underlying time variable. Multivariable Cox regression models were fitted to estimate hazards ratios (HR) and 95% confidence intervals (CIs) of the risk of developing cardiovascular events during the follow-up according to baseline quintiles of total polyphenol intake and of the different types of polyphenols. We used the lowest quintiles as the reference category. Tests of linear trends were performed by determining the median total and classes of polyphenol intake for each category and treating this as a continuous variable in the respective Cox regression model.

The Cox regression models were adjusted for several potential confounders. We adjusted all models for age and year of entry into the cohort. We fitted a model stratified by age (deciles) and recruitment year. The second model was additionally adjusted for baseline BMI (continuous), physical activity (quartiles), hours of watching television (quartiles), smoking status (never, former, current), family history of CVD, cardiovascular drugs use, aspirin use, prevalent diseases (hypertension, hypercholesterolemia, hypertriglyceridemia, diabetes, and cancer), and alcohol intake; the last model was also adjusted for use of dietary supplements, following a special diet at baseline, intake of saturated fatty acids, polyunsaturated fatty acids, monounsaturated fatty acids, and energy-adjusted sodium.

We evaluated the interaction between total and types of polyphenol intake and the relevant variables (sex, age, and BMI) using a likelihood ratio test (two degrees of freedom) that compared the fully adjusted Cox regression model and the same model with interaction product-terms.

Sensitivity analyses were performed, by rerunning the multivariable-adjusted Cox regression models with the following changes: 1) excluding participants with energy intake <5th and >95th percentiles; 2) excluding participants who had prevalent diabetes or cancer at baseline; 3) excluding participants who had hypertension at baseline; 4) excluding early cases of CVD (<2 years); 5) excluding late cases of CVD (≥10 years); 6) excluding participants less than 40 years of age, and 7) excluding adjustment for special diets.

All analyses were performed using Stata/SE version 12.1 (Stata Corp, College Station, USA) with a statistical significance of 5% based on two-tailed tests.

Results

The main baseline characteristics of participants according to quintiles of total polyphenol intake are presented in Table 1. Participants in the fifth quintile of total polyphenol intake compared with those in the first quintile (sex-specific energy-adjusted) were more likely to be older, former smokers, more physically active, have a family history of CVD, and have a chronic disease. They also had higher adherence to the Med-Diet and higher consumption of food sources of polyphenols, such as fruits, vegetables, nuts, coffee, and red wine. Those in the lower quintile of polyphenol intake watched more television and had the highest fat and sodium intake. Moreover, on average, they consumed more meat and meat products and sugar-sweetened-beverages.

The mean total polyphenol intake was 727 (SD 370) mg/d, 384 (SD 269) of which were flavonoids, 298 (SD 171) phenolic acids, 0.9 (SD 1.9) stilbenes, 0.6 (SD 0.4) lignans, and 44 (SD 34) mg other polyphenols. The contributions of different foods to the variability of total and types of polyphenol intake are shown in Table 2. Cherries, chocolate, coffee, apples and olives were among the major contributors to total polyphenol intake variability. Chocolate and fruits were the major contributors to flavonoids; coffee, olives and cherries to phenolic acids; red wine to stilbenes; and olive oils and dried fruits to lignans.

During a total of 171,688 person-years of follow-up [mean follow-up: 10.1 years (SD 4.1)], a total of 113 incident major cardiovascular events were identified. The estimated HRs for the incidence of cardiovascular events according to quintiles of total polyphenol intake and polyphenol types are shown in Table 3.

In the analysis by polyphenol classes, when we assessed quintiles of flavonoid intake, participants with higher flavonoid intake (highest quintile) had a 47% lower incidence of cardiovascular events compared with those in the lowest quintile (multivariate-adjusted HR, 0.53 [95% CI, 0.29−0.98]) with a marginally non-significant linear trend across quintiles (P for trend = 0.09). The results for the other polyphenol classes were not statistically significant (Table 3).

No significant interactions between total intake and types of polyphenol intake and sex age and BMI were observed. The results of the sensitivity analyses described

Table 1 Baseline characteristics of participants according to sex-specific energy-adjusted quintiles of total polyphenol intake. The SUN Project, Navarra, Spain, 1999–2016.

	Quintiles of polyphenols adjusted for total energy intake and sex					*P* for trend[a]
	Q1 (n = 3413)	Q2 (n = 3413)	Q3 (n = 3413)	Q4 (n = 3413)	Q5 (n = 3413)	
Polyphenol intake (mg/d)	396 (134)	526 (149)	653 (149)	812 (156)	1248 (405)	
Female (%)	60.7	60.7	60.7	60.7	60.7	1.00
Age (years)	32.1 (10.3)	35.8 (11.3)	37.6 (11.4)	39.2 (11.7)	41.3 (12.2)	<0.001
Body mass index (kg/m^2)	23.0 (3.4)	23.5 (3.4)	23.6 (3.5)	23.7 (3.5)	23.7 (3.6)	<0.001
Family history of CVD (%)	10.7	12.1	13.6	14.7	16.9	<0.001
Hypertension (%)	7.3	9.3	9.9	11.0	12.6	<0.001
Hypercholesterolemia (%)	11.3	14.5	16.7	18.7	22.7	<0.001
Hypertriglyceridemia (%)	4.3	5.8	6.7	7.2	8.9	<0.001
Diabetes at baseline (%)	1.2	1.4	1.9	2.1	2.3	<0.001
Cancer at baseline (%)	2.3	3.4	3.6	4.3	4.9	<0.001
Drug use at baseline (%)						
Cardiovascular drugs	1.7	2.3	2.6	2.8	3.6	<0.001
Aspirin	2.2	2.6	3.8	3.8	4.8	<0.001
Leisure-time physical activity (METs-h/wk)	25.5 (22.9)	25.3 (22.6)	26.4 (22.4)	27.7 (23.5)	29.5 (25.8)	<0.001
TV watching time (h/d)	1.7 (1.3)	1.6 (1.2)	1.6 (1.1)	1.6 (1.1)	1.5 (1.1)	<0.001
Smoking status (%)						
Never	57.1	50.6	45.9	43.7	41.6	<0.001
Former	15.5	21.6	26.3	28.1	30.9	<0.001
Current	25.1	25.2	25.4	26.0	25.5	0.50
Mediterranean dietary pattern (0–9 points)[b]	3.3 (1.6)	3.8 (1.7)	4.2 (1.7)	4.5 (1.7)	5.0 (1.7)	<0.001
Total energy intake (kcal/d)	2550 (578)	2291 (599)	2275 (595)	2277 (591)	2456 (604)	<0.001
Carbohydrate intake (% energy)	42.3 (6.9)	42.8 (6.9)	42.8 (6.9)	43.8 (6.9)	45.3 (7.7)	<0.001
Protein intake (% energy)	17.9 (3.1)	18.4 (3.1)	18.5 (3.1)	18.3 (3.2)	17.6 (3.1)	<0.001
Fat intake (% energy)	38.5 (6.1)	37.2 (6.0)	36.6 (6.0)	35.6 (6.2)	34.4 (6.7)	<0.001
SFA (% energy)	13.6 (3.0)	12.9 (2.9)	12.5 (2.9)	11.9 (2.9)	11.2 (3.0)	<0.001
MUFA (% energy)	16.2 (3.5)	15.9 (3.5)	15.8 (3.5)	15.5 (3.6)	15.0 (3.7)	<0.001
PUFA (% energy)	5.6 (1.7)	5.3 (1.5)	5.2 (1.4)	5.0 (1.4)	4.8 (1.4)	<0.001
Sodium intake[c] (g/d)	4.2 (2.1)	4.1 (2.5)	4.0 (2.0)	3.8 (1.8)	3.6 (1.9)	0.11
Dietary fiber intake (g/d)	23.9 (9.0)	24.9 (9.4)	27.2 (10.3)	29.1 (11.2)	35.4 (15.4)	<0.001
Fruit consumption (g/d)	216 (171)	269 (193)	313 (205)	371 (247)	557 (438)	<0.001
Vegetable consumption (g/d)	425 (258)	471 (258)	528 (295)	564 (317)	666 (445)	<0.001
Legume consumption (g/d)	23.2 (19.0)	22.5 (16.3)	22.9 (16.7)	22.8 (16.1)	23.7 (19.0)	0.05
Dairy products consumption (g/d)	469 (275)	424 (251)	413 (246)	410 (253)	401 (255)	<0.001
Meat and meat products consumption (g/d)	204 (83)	179 (72)	175 (75)	163 (72)	159 (75)	<0.001
Fish consumption(g/d)	91.1 (63.3)	91.8 (51.0)	98.9 (56.9)	102 (60.6)	108 (61.3)	<0.001
Nuts consumption (g/d)	4.6 (6.2)	5.6 (8.2)	6.8 (9.6)	8.3 (12.7)	11.9 (17.9)	<0.001
Olive oil consumption (g/d)	15.3 (14.3)	14.6 (13.6)	15.0 (12.9)	15.5 (13.4)	16.3 (13.2)	<0.001
Coffee consumption (mL/d)	31.0 (35.5)	55.2 (46.8)	74.7 (52.4)	90.5 (60.6)	117 (86.0)	<0.001
Alcohol consumption (g/d)	4.9 (8.3)	5.7 (8.0)	6.7 (9.3)	7.2 (10.3)	8.8 (12.9)	0.001
Red wine consumption (g/d)	20.1 (48.3)	33.3 (67.4)	49.1 (96.4)	62.3 (124.7)	95.5 (193.2)	<0.001
Sugar-sweetened-beverage consumption (mL/d)	85.1 (162)	66.6 (117)	58.6 (106)	59.0 (113)	60.3 (127)	<0.001
Snacks (%)	37.6	32.4	31.4	32.3	32.1	<0.001
Special diet at baseline (%)	4.6	6.1	8.0	10.5	11.0	<0.001
Use of dietary supplements (%)	17.5	18.2	17.5	19.3	21.7	<0.001

Values are expressed as means and standard deviations or percentage.
Q, quintile; CVD, cardiovascular disease; MET, metabolic equivalents of task; SFA, saturated fatty acid; MUFA, monounsaturated fatty acid; PUFA, polyunsaturated fatty acid.
[a] Chi-square test for trend (categorical variables) and ANOVA (continuous variables) across quintiles of polyphenol intake.
[b] Higher scores indicate greater adherence.
[c] Energy-adjusted.

previously did not substantially change in any of the scenarios (Table 4).

Discussion

In this prospective cohort study of middle-aged Spanish adults, we found that higher flavonoid intake was associated with a lower incidence of cardiovascular events after an average of ten years of follow-up, even after adjusting for other CVD risk factors.

There are several potential reasons to explain that only flavonoids presented a statistical inverse association.

Polyphenols compounds are found in a variety of vegetables, fruits, cocoa, cereal grains, berries and nuts, as well as wine, juice and tea [4,5]. Flavonoids are found most abundantly in fruits, vegetables, cocoa, nuts, wine and tea [4]. In the Spanish population, fruits are the major source of flavonoids [24]; the sources of variability in flavonoids intake in the SUN project were cacao and fruits.

The cardiovascular protective effects of flavonoids have been attributed to improved vascular endothelial function,

Table 2 Main sources of variability of total polyphenols and their classes. The SUN Project, Navarra, Spain, 1999–2016.

Food	Change in R^2	Cumulative R^2
Total polyphenols		
Cherries	0.313	
Chocolate	0.236	0.548
Coffee	0.122	0.671
Apples	0.096	0.767
Olives	0.068	0.835
Flavonoids		
Chocolate	0.437	
Cherries	0.350	0.787
Apples	0.102	0.889
Orange juice	0.029	0.918
Grapes	0.015	0.933
Phenolic acids		
Coffee	0.517	
Decaffeinated coffee	0.233	0.750
Olives	0.102	0.852
Cherries	0.060	0.912
Stilbenes		
Red wine	0.992	
Grapes	0.002	0.994
Strawberries	0.0005	0.994
Lignans		
Olive oil	0.796	
Dried fruits	0.158	0.954
Gazpacho	0.016	0.970
White bread	0.013	0.983
Whole bread	0.004	0.987
Other polyphenols		
Olives	0.589	
Breakfast cereals	0.242	0.831
Olive oil	0.104	0.935
Whole bread	0.052	0.987
Orange juice	0.004	0.991

Note: Cumulative R^2 values were determined from nested regression analyses after stepwise selection.

which may be due to multiple mechanisms [8]. Flavonoids may improve vascular health by enhancing the bioavailability and bioactivity of NO in circulating plasma, which promotes vasodilation, prevents platelet adhesion, and inhibits smooth muscle proliferation in the vessel wall [6–8,25]. Flavonoids can also improve endothelial dysfunction by stimulating the formation of other vascular relaxing factors such as endothelium-derived hyperpolarizing factor (EDHF) and PGI2 [8], and by reducing excessive vascular oxidative stress which prevents the degradation of NO by superoxide anions [6]. Moreover, the protective effect of flavonoids against CVD has been associated in part with their anti-inflammatory properties [26]. The possible mechanisms by which flavonoids block the inflammatory processes involved in CVD include the following: scavenging of free radical species and inhibition of their production [27]; inhibition of the activity/expression of pro-inflammatory enzymes such as inducible NO synthase [28]; and down-regulation of pro-inflammatory mediators (tumor necrosis factor [TNF]-α, interleukin [IL]-1β, and IL-6) [29].

Prior research has shown that polyphenols, mainly flavonoids, play an important role in the prevention of CVD. In a very different Spanish population (a cohort of participants of older ages and at high cardiovascular risk), higher intakes of total polyphenols, lignans, flavonoids and hydroxybenzoic acids were associated with a lower risk of CVD [3] and subjects with high polyphenol intake, especially stilbenes and lignans, exhibited a reduced risk of overall mortality compared to lower intakes, but no significant associations for flavonoids or phenolic acids with all-cause mortality were found [12]. A meta-analysis of 14 prospective cohort studies showed that consumption of flavonoid-rich diets significantly decreased the risk of CVD [30].

The differences between individuals in the absorption and metabolism of plant bioactive compounds and the heterogeneity in their biological response can confound associations between their intake and health benefits. The interindividual variability in response suggests that intake of specific plant bioactive compounds may benefit some subjects more than others [31]. This variability can be attributed to genetic factors (i.e., polymorphis), sex, age, lifestyle and gut microbiota, which may contribute to individual differences in the absorption, distribution, metabolism and excretion of polyphenols [31,32]. For example, ellagitannins are hydrolyzed to ellagic acid under pH condition of small intestine and cecum and ellagic acid is metabolized to urolithins by the gut microbiota in colon. The differences in microbiota composition impact urolithins production and therefore the beneficial effects attributed to the consumption of foods containing ellagitannins [33,34]. Other example of this interindividual variation is conversion of soy isoflavones (daidzin and daidzein) in equol by intestinal bacteria. The frequency of equol production varies among individuals and population, which suggests that health benefits of polyphenols depend on the capability to equol production of each individual [35]. Therefore, interindividual differences in responses to these bioactives may play a confounding role in the epidemiological picture.

Our study had limitations. The estimation of polyphenol intake was performed using an FFQ not specifically designed to collect data regarding polyphenols, and some culinary ingredients rich in polyphenols like herbs and spices were not captured; therefore, we cannot rule out the existence of a certain level of information misclassification (although in principle it would be a non-differential misclassification, since the error would be unrelated to the occurrence or presence of the outcome). However, some validation studies have shown that FFQs are reasonable for estimated polyphenols intake [36] and our FFQ was previously validated and represents the main foods ingested by the studied population [19].

Analyses were based on baseline consumption. We cannot rule out the possibility of changes in polyphenol intake during follow-up. Indeed, eating attitudes among a subsample of participants of the SUN cohort with an FFQ at 10 years of follow-up showed an improvement. Some sociodemographic and clinical characteristics such being female, being middle-aged or had low BMI might predict positive changes [37]. However, when we assessed the

Table 3 Hazard ratio (HR) and 95% confidence intervals (CI) for the risk of cardiovascular events according to baseline intake of total polyphenols and each polyphenol class quintiles, adjusted for energy intake and sex. The SUN Project, Navarra, Spain, 1999–2016.

	Quintiles of polyphenols adjusted for total energy intake and sex					*P* for trend
	Q1	Q2	Q3	Q4	Q5	
Total polyphenols (mg/d) (SD)	396 (134)	526 (149)	653 (149)	812 (156)	1248 (405)	
Incident cases	19	20	19	20	35	
Person-years	34,626	34,841	34,354	34,176	33,693	
Model 1	1 (ref)	0.57 (0.30–1.09)	0.58 (0.31–1.09)	0.50 (0.26–0.93)	0.63 (0.36–1.11)	0.39
Model 2	1 (ref)	0.61 (0.31–1.17)	0.62 (0.33–1.17)	0.49 (0.26–0.95)	0.54 (0.29–0.99)	0.20
Model 3	1 (ref)	0.61 (0.32–1.19)	0.65 (0.35–1.22)	0.54 (0.28–1.05)	0.61 (0.33–1.13)	0.28
Flavonoids (mg/d) (SD)	186 (72)	234 (86)	302 (97)	424 (105)	772 (330)	
Incident cases	21	21	19	26	26	
Person-years	35,179	35,224	34,606	33,611	33,068	
Model 1	1 (ref)	0.71 (0.39–1.32)	0.57 (0.30–1.07)	0.65 (0.36–1.18)	0.49 (0.27–0.91)	0.06
Model 2	1 (ref)	0.72 (0.38–1.36)	0.62 (0.33–1.18)	0.70 (0.38–1.27)	0.49 (0.27–0.91)	0.05
Model 3	1 (ref)	0.73 (0.38–1.39)	0.65 (0.34–1.22)	0.74 (0.41–1.35)	0.53 (0.29–0.98)	0.09
Phenolic acids (mg/d) (SD)	113 (47)	190 (44)	275 (56)	367 (43)	546 (157)	
Incident cases	19	19	21	20	34	
Person-years	33,831	33,876	33,875	34,994	35,113	
Model 1	1 (ref)	0.64 (0.34–1.21)	0.53 (0.28–1.01)	0.64 (0.35–1.18)	0.76 (0.43–1.35)	0.84
Model 2	1 (ref)	0.66 (0.35–1.24)	0.53 (0.28–1.01)	0.58 (0.31–1.09)	0.63 (0.35–1.13)	0.33
Model 3	1 (ref)	0.67 (0.35–1.28)	0.56 (0.30–1.07)	0.63 (0.33–1.18)	0.69 (0.38–1.24)	0.49
Stilbenes (mg/d) (SD)	0.09 (0.08)	0.15 (0.14)	0.27 (0.20)	0.82 (0.64)	3.5 (3.3)	
Incident cases	17	21	12	23	40	
Person-years	35,235	34,262	33,576	33,391	35,224	
Model 1	1 (ref)	0.91 (0.48–1.74)	0.59 (029–1.22)	1.00 (0.53–1.90)	1.31 (0.74–2.32)	0.06
Model 2	1 (ref)	0.85 (0.44–1.66)	0.59 (0.28–1.21)	0.91 (0.47–1.75)	1.01 (0.53–1.95)	0.51
Model 3	1 (ref)	0.87 (0.45–1.69)	0.58 (0.28–1.20)	0.93 (0.48–1.82)	1.08 (0.55–2.10)	0.40
Lignans (mg/d) (SD)	0.29 (0.12)	0.34 (0.12)	0.44 (0.17)	0.67 (0.17)	1.07 (0.37)	
Incident cases	20	16	30	23	24	
Person-years	35,536	34,963	34,195	33,877	33,118	
Model 1	1 (ref)	0.66 (0.34–1.30)	1.08 (0.62–1.89)	0.82 (0.45–1.50)	0.78 (0.43–1.43)	0.57
Model 2	1 (ref)	0.65 (0.33–1.28)	1.10 (0.62–1.96)	0.78 (0.42–1.44)	0.75 (0.40–1.41)	0.47
Model 3	1 (ref)	0.71 (0.36–1.39)	1.29 (0.71–2.35)	1.08 (0.55–2.12)	1.36 (0.62–2.99)	0.31
Other polyphenols (mg/d) (SD)	18.8 (8.2)	24.9 (9.2)	33.8 (10.8)	50.4 (11.7)	90.8 (45.3)	
Incident cases	26	19	18	19	31	
Person-years	35,694	35,099	33,762	34,099	33,035	
Model 1	1 (ref)	0.68 (0.38–1.22)	0.62 (0.33–1.14)	0.68 (0.38–1.24)	1.01 (0.59–1.72)	0.12
Model 2	1 (ref)	0.65 (0.36–1.17)	0.52 (0.28–0.98)	0.56 (0.30–1.05)	0.86 (0.50–1.48)	0.21
Model 3	1 (ref)	0.69 (0.38–1.26)	0.59 (0.32–1.09)	0.68 (0.36–1.31)	1.13 (0.62–2.05)	0.04

Note: Q, quintile. Model 1: Stratified by age (deciles) and recruitment year. Model 2: Adjusted for the factors in Model 1 plus baseline BMI (continuous), physical activity (quartiles), hours of watching television (quartiles), smoking status, family history of cardiovascular disease, cardiovascular drugs intake, aspirin use, prevalent hypertension, prevalent hypercholesterolemia, prevalent hypertriglyceridemia, prevalent diabetes, prevalent cancer, and alcohol intake. Model 3: Adjusted for the factors in Model 2 plus following a special diet at baseline, use of dietary supplements, intake of saturated fatty acids, polyunsaturated fatty acids, monounsaturated fatty acids, and energy-adjusted sodium.

interactions between polyphenols intake and sex, age, and BMI were not statistically significant. In addition, when we excluded late CVD deaths (more than 10 years of follow-up) the results were similar (adjusted HR: 0.68; 95% CI: 0.35–1.31 for total polyphenol and adjusted HR: 0.63; 95% CI: 0.33–1.23 for flavonoids; Table 4).

The number of events in the SUN project was relatively low, which limited the statistical power for assessing the associations between polyphenol intake and cardiovascular events. Therefore, the moderate effects or lack of significance for total polyphenols and some other classes may well be due to the small number of events in this relatively healthy cohort. Residual confounding cannot be totally excluded. Additional unknown or unmeasured confounding factors may still be present. Nevertheless, we adjusted for several potential confounding factors related to lifestyle and diet and usually unmeasured confounders track together with those which are measured. Caution is required when extrapolating our results to the general population because the participants of the SUN project are volunteer university graduates of a Mediterranean population.

A major strength of our study is its novelty, because we assessed a population of young subjects from a Mediterranean country who was at a low cardiovascular risk. This population was very different from previous assessments, including the reports from the PREDIMED trial, conducted only among older subjects who were selected because of their high cardiovascular risk [3,12]. Therefore, from a public health perspective we should recommend healthy dietary patterns rich in polyphenols, specially flavonoids, to prevent CVD even among young-middle aged populations at low cardiovascular risk. Other strengths include its prospective design, the use of validated methods

Table 4 Sensitivity analyses: hazard ratios (95% confidence intervals) for incident cardiovascular diseases according to the total intake and classes of polyphenol, in the SUN Project, Navarra, Spain, 1999–2016.

	Quintiles of polyphenol intake (sex and energy-adjusted intake)		*P* for trend
	Cases/person-years	Q5 vs. Q1 (reference)	
Total polyphenols			
Overall[a]	113/171,688	0.61 (0.33–1.13)	0.28
Energy limits between the fifth and ninety-fifth percentiles	106/173,329	0.70 (0.37–1.33)	0.42
Excluding participants with prevalent diabetes or cancer at baseline	96/163,155	0.63 (0.33–1.20)	0.36
Excluding participants with hypertension at baseline	70/155,218	0.51 (0.22–1.16)	0.28
Excluding early cases of CVD (<2 years)	100/171,671	0.65 (0.33–1.28)	0.43
Excluding late cases of CVD (≥10 years)	103/171,567	0.68 (0.35–1.31)	0.50
Excluding participants <40 years	101/61,046	0.60 (0.31–1.17)	0.29
Excluding adjusted for special diet	113/171,688	0.60 (0.32–1.12)	0.25
Flavonoids			
Overall[a]	113/171,688	0.53 (0.29–0.98)	0.09
Energy limits between the fifth and ninety-fifth percentiles	106/173,329	0.54 (0.29–0.99)	0.10
Excluding participants with prevalent diabetes or cancer at baseline	96/163,155	0.54 (0.27–1.06)	0.13
Excluding participants with hypertension at baseline	70/155,218	0.50 (0.22–1.12)	0.23
Excluding early cases of CVD (<2 years)	100/171,671	0.59 (0.31–1.15)	0.16
Excluding late cases of CVD (≥10 years)	103/171,567	0.63 (0.33–1.23)	0.29
Excluding participants <40 years	101/61,046	0.58 (0.30–1.10)	0.15
Excluding adjusted for special diet	113/171,688	0.52 (0.28–0.97)	0.09
Phenolic acids			
Overall[a]	113/171,688	0.69 (0.38–1.24)	0.49
Energy limits between the fifth and ninety-fifth percentiles	106/173,329	0.68 (0.37–1.26)	0.48
Excluding participants with prevalent diabetes or cancer at baseline	96/163,155	0.71 (0.37–1.35)	0.69
Excluding participants with hypertension at baseline	70/155,218	0.90 (0.38–2.15)	0.47
Excluding early cases of CVD (<2 years)	100/171,671	0.72 (0.39–1.34)	0.52
Excluding late cases of CVD (≥10 years)	103/171,567	0.70 (0.37–1.36)	0.69
Excluding participants <40 years	101/61,046	0.64 (0.34–1.20)	0.50
Excluding adjusted for special diet	113/171,688	0.68 (0.37–1.23)	0.47
Stilbenes			
Overall[a]	113/171,688	1.08 (0.55–2.10)	0.40
Energy limits between the fifth and ninety-fifth percentiles	106/173,329	1.04 (0.52–2.07)	0.43
Excluding participants with prevalent diabetes or cancer at baseline	96/163,155	1.04 (0.51–2.12)	0.32
Excluding participants with hypertension at baseline	70/155,218	0.74 (0.33–1.65)	0.73
Excluding early cases of CVD (<2 years)	100/171,671	1.43 (0.67–3.07)	0.35
Excluding late cases of CVD (≥10 years)	103/171,567	1.04 (0.52–2.10)	0.57
Excluding participants <40 years	101/61,046	1.06 (0.53–2.15)	0.43
Excluding adjusted for special diet	113/171,688	1.04 (0.54–2.01)	0.47
Lignans			
Overall[a]	113/171,688	1.36 (0.62–2.99)	0.31
Energy limits between the fifth and ninety-fifth percentiles	106/173,329	1.41 (0.61–3.25)	0.32
Excluding participants with prevalent diabetes or cancer at baseline	96/163,155	1.43 (0.58–3.51)	0.37
Excluding participants with hypertension at baseline	70/155,218	2.22 (0.79–6.23)	0.09
Excluding early cases of CVD (<2 years)	100/171,671	1.32 (0.59–2.98)	0.24
Excluding late cases of CVD (≥10 years)	103/171,567	1.72 (0.76–3.88)	0.15
Excluding participants <40 years	101/61,046	1.34 (0.59–3.06)	0.39
Excluding adjusted for special diet	113/171,688	1.34 (0.61–2.97)	0.33
Other polyphenols			
Overall[a]	113/171,688	1.13 (0.62–2.05)	0.04
Energy limits between the fifth and ninety-fifth percentiles	106/173,329	1.07 (0.58–1.99)	0.06
Excluding participants with prevalent diabetes or cancer at baseline	96/163,155	1.10 (0.58–2.07)	0.05
Excluding participants with hypertension at baseline	70/155,218	0.90 (0.40–2.03)	0.05
Excluding early cases of CVD (<2 years)	100/171,671	1.40 (0.72–2.71)	0.10
Excluding late cases of CVD (≥10 years)	103/171,567	1.21 (0.65–2.26)	0.10
Excluding participants <40 years	101/61,046	1.12 (0.61–2.08)	0.01
Excluding adjusted for special diet	113/171,688	1.12 (0.62–2.04)	0.04

[a] Adjusted for BMI (continuous), physical activity (quartiles), hours of watching television (quartiles), smoking status, family history of cardiovascular disease, cardiovascular drugs intake, aspirin use, prevalent hypertension, prevalent hypercholesterolemia, prevalent hypertriglyceridemia, prevalent diabetes, prevalent cancer, alcohol intake, following a special diet at baseline, use of dietary supplements, intake of saturated fatty acids, polyunsaturated fatty acids, monounsaturated fatty acids and energy-adjusted sodium and stratified by age (deciles) and recruitment year.

among highly educated subjects who are likely to provide high-quality self-reports, long follow-up period with close tracking of each participant, control of multiple variables as potential confounders, and detailed medical confirmation of cardiovascular events. We also used comprehensive databases to assess polyphenol content as well as considered specific polyphenol types in our analyses.

The results of our study suggest that a higher intake of flavonoids was associated with a lower risk of cardiovascular events in middle-aged, low-risk Mediterranean subjects. Strategies for increasing the consumption of food rich in polyphenols (mainly flavonoids), should be encouraged as part of a preventive approach against cardiovascular events. Further longitudinal studies in different contexts are necessary to confirm our findings.

Conflict of interest

There are no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.numecd.2018.09.012.

References

[1] WHO. Cardiovascular diseases (CVDs) [fact sheet]. 2016. Available online: http://www.who.int/mediacentre/factsheets/fs317/en/ [accessed 05.07.16].
[2] Dahlof B. Cardiovascular disease risk factors: epidemiology and risk assessment. Am J Cardiol 2010;105:3a–9a. https://doi.org/10.1016/j.amjcard.2009.10.007.
[3] Tresserra-Rimbau A, Rimm EB, Medina-Remon A, Martinez-Gonzalez MA, de la Torre R, Corella D, et al. Inverse association between habitual polyphenol intake and incidence of cardiovascular events in the PREDIMED study. Nutr Metab Cardiovasc Dis 2014;24:639–47. https://doi.org/10.1016/j.numecd.2013.12.014.
[4] Manach C, Scalbert A, Morand C, Remesy C, Jimenez L. Polyphenols: food sources and bioavailability. Am J Clin Nutr 2004;79. ISSN: 0002-9165:727–47.
[5] Velderrain-Rodriguez GR, Palafox-Carlos H, Wall-Medrano A, Ayala-Zavala JF, Chen CY, Robles-Sanchez M, et al. Phenolic compounds: their journey after intake. Food Funct 2014;5:189–97. https://doi.org/10.1039/c3fo60361j.
[6] Steffen Y, Gruber C, Schewe T, Sies H. Mono-O-methylated flavanols and other flavonoids as inhibitors of endothelial NADPH oxidase. Arch Biochem Biophys 2008;469:209–19. https://doi.org/10.1016/j.abb.2007.10.012.
[7] Estruch R. Anti-inflammatory effects of the Mediterranean diet: the experience of the PREDIMED study. Proc Nutr Soc 2010;69:333–40. https://doi.org/10.1017/s0029665110001539.
[8] Andriantsitohaina R, Auger C, Chataigneau T, Etienne-Selloum N, Li H, Martinez MC, et al. Molecular mechanisms of the cardiovascular protective effects of polyphenols. Br J Nutr 2012;108:1532–49. https://doi.org/10.1017/s0007114512003406.
[9] Grosso G, Stepaniak U, Micek A, Stefler D, Bobak M, Pajak A. Dietary polyphenols are inversely associated with metabolic syndrome in Polish adults of the HAPIEE study. Eur J Nutr 2016:1–12. https://doi.org/10.1007/s00394-016-1187-z.
[10] Lajous M, Rossignol E, Fagherazzi G, Perquier F, Scalbert A, Clavel-Chapelon F, et al. Flavonoid intake and incident hypertension in women. Am J Clin Nutr 2016;103:1091–8. https://doi.org/10.3945/ajcn.115.109249.
[11] Tresserra-Rimbau A, Guasch-Ferre M, Salas-Salvado J, Toledo E, Corella D, Castaner O, et al. Intake of total polyphenols and some classes of polyphenols is inversely associated with diabetes in elderly people at high cardiovascular disease risk. J Nutr 2016;146:767–77. https://doi.org/10.1016/j.abb.2007.10.012.
[12] Tresserra-Rimbau A, Rimm EB, Medina-Remon A, Martinez-Gonzalez MA, Lopez-Sabater MC, Covas MI, et al. Polyphenol intake and mortality risk: a re-analysis of the PREDIMED trial. BMC Med 2014;12:77. https://doi.org/10.1186/1741-7015-12-77.
[13] Medina-Remon A, Tresserra-Rimbau A, Pons A, Tur JA, Martorell M, Ros E, 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;25:60–7. https://doi.org/10.1016/j.numecd.2014.09.001.
[14] Estruch R, Ros E, Salas-Salvado J, Covas MI, Corella D, Aros F, et al. Primary prevention of cardiovascular disease with a Mediterranean diet. N Engl J Med 2013;368:1279–90. https://doi.org/10.1056/NEJMoa1200303.
[15] Martinez-Gonzalez MA. The SUN cohort study (Seguimiento University of Navarra). Public Health Nutr 2006;9:127–31. https://doi.org/10.1079/PHN2005935.
[16] Willett WC. Nutritional epidemiology. 3rd ed. New York: Oxford University Press; 2012.
[17] Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD. Third universal definition of myocardial infarction. Circulation 2012;126:2020–35. https://doi.org/10.1161/CIR.0b013e31826e1058.
[18] de la Fuente-Arrillaga C, Ruiz ZV, Bes-Rastrollo M, Sampson L, Martinez-Gonzalez MA. Reproducibility of an FFQ validated in Spain. Public Health Nutr 2010;13:1364–72. https://doi.org/10.1017/s1368980009993065.
[19] Martin-Moreno JM, Boyle P, Gorgojo L, Maisonneuve P, Fernandez-Rodriguez JC, Salvini S, et al. Development and validation of a food frequency questionnaire in Spain. Int J Epidemiol 1993;22:512–9. https://doi.org/10.1093/ije/22.3.512.
[20] Perez-Jimenez J, Neveu V, Vos F, Scalbert A. Systematic analysis of the content of 502 polyphenols in 452 foods and beverages: an application of the phenol-explorer database. J Agric Food Chem 2010;58:4959–69. https://doi.org/10.1021/jf100128b.
[21] Rothwell JA, Medina-Remon A, Perez-Jimenez J, Neveu V, Knaze V, Slimani N, et al. Effects of food processing on polyphenol contents: a systematic analysis using phenol-explorer data. Mol Nutr Food Res 2015;59:160–70. https://doi.org/10.1002/mnfr.201400494.
[22] Gunathile KDPP, Ranaweera KKDS, Rupasinghe HPV. Influence of boiling, steaming and frying of selected leafy vegetables on the in vitro anti-inflammation associated biological activities. Plants (Basel) 2018;7(1):22. https://doi.org/10.3390/plants7010022.
[23] Martinez-Gonzalez MA, Lopez-Fontana C, Varo JJ, Sanchez-Villegas A, Martinez JA. 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;8:920–7. https://doi.org/10.1079/PHN2005745.
[24] Zamora-Ros R, Andres-Lacueva C, Lamuela-Raventos RM, Berenguer T, Jakszyn P, Barricarte A, et al. Estimation of dietary sources and flavonoid intake in a Spanish adult population (EPIC-Spain). J Am Diet Assoc 2010;110:390–8. https://doi.org/10.1016/j.jada.2009.11.024.
[25] Squadrito F, Altavilla D, Morabito N, Crisafulli A, D'Anna R, Corrado F, et al. The effect of the phytoestrogen genistein on plasma nitric oxide concentrations, endothelin-1 levels and

endothelium dependent vasodilation in postmenopausal women. Atherosclerosis 2002;163:339–47. https://doi.org/10.1016/S0021-9150(02)00013-8.

[26] Garcia-Lafuente A, Guillamon E, Villares A, Rostagno MA, Martinez JA. Flavonoids as anti-inflammatory agents: implications in cancer and cardiovascular disease. Inflamm Res 2009;58:537–52. https://doi.org/10.1007/s00011-009-0037-3.

[27] Sarkar A, Bhaduri A. Black tea is a powerful chemopreventor of reactive oxygen and nitrogen species: comparison with its individual catechin constituents and green tea. Biochem Biophys Res Commun 2001;284:173–8. https://doi.org/10.1006/bbrc.2001.4944.

[28] Hamalainen M, Nieminen R, Vuorela P, Heinonen M, Moilanen E. Anti-inflammatory effects of flavonoids: genistein, kaempferol, quercetin, and daidzein inhibit STAT-1 and NF-kappaB activations, whereas flavone, isorhamnetin, naringenin, and pelargonidin inhibit only NF-kappaB activation along with their inhibitory effect on iNOS expression and NO production in activated macrophages. Mediators Inflamm 2007;2007:45673. https://doi.org/10.1155/2007/45673.

[29] Leyva-Lopez N, Gutierrez-Grijalva EP, Ambriz-Perez DL, Heredia JB. Flavonoids as cytokine modulators: a possible therapy for inflammation-related diseases. Int J Mol Sci 2016;17:1–15. https://doi.org/10.3390/ijms17060921.

[30] Wang X, Ouyang YY, Liu J, Zhao G. Flavonoid intake and risk of CVD: a systematic review and meta-analysis of prospective cohort studies. Br J Nutr 2014;111:1–11. https://doi.org/10.1017/s0007114513002778x.

[31] Manach C, Milenkovic D, Wiele TV, Rodriguez-Mateos A, Roos B, Garcia-Conesa MT, et al. Addressing the inter-individual variation in response to consumption of plant food bioactives: towards a better understanding of their role in healthy aging and cardiometabolic risk reduction. Mol Nutr Food Res 2017. https://doi.org/10.1002/mnfr.201600557.

[32] Milenkovic D, Morand C, Cassidy A, Konic-Ristic A, Tomás-Barberán F, Ordovas JM, et al. Interindividual variability in biomarkers of cardiometabolic health after consumption of major plant-food bioactive compounds and the determinants involved. Adv Nutr 2017. https://doi.org/10.3945/an.116.013623.

[33] Espín JC, Larrosa M, García-Conesa MT, Tomás-Barberán F. Biological significance of urolithins, the gut microbial ellagic acid-derived metabolites: the evidence so far. Evid Based Complement Altern Med 2013. https://doi.org/10.1155/2013/270418.

[34] Landete JM. Ellagitannins, ellagic acid and their derived metabolites: a review about source, metabolism, functions and health. Food Res Int 2011. https://doi.org/10.1016/j.foodres.2011.04.027.

[35] Setchell KDR, Clerici C. Equol: history, chemistry, and formation. J Nutr 2010. https://doi.org/10.3945/jn.109.119776.

[36] Burkholder-Cooley N, Rajaram S, Haddad E, Fraser GE, Oda K, Jaceldo-Siegl K. Validating polyphenol intake estimates from a food-frequency questionnaire using repeated 24-hour dietary recalls and a unique method-of-triads approach with 2 biomarkers. Am J Clin Nutr 2017. https://doi.org/10.3945/ajcn.116.137174.

[37] Andrade L, Zazpe I, Santiago S, Carlos S, Bes-Rastrollo M, Martínez-Gonazález MA. Ten-year changes in healthy eating attitudes in the SUN Cohort. J Am Coll Nutr 2017;36:319–29. https://doi.org/10.1080/07315724.2016.