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ORIGINAL RESEARCH

Association Among Polyphenol Intake, Uric Acid, and Hyperuricemia: A Cross-Sectional Analysis in a Population at High Cardiovascular Risk

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BACKGROUND: Dietary polyphenol intake has been associated with a decreased risk of hyperuricemia, but most of this knowledge comes from preclinical studies. The aim of the present study was to assess the association of the intake of different classes of polyphenols with serum uric acid and hyperuricemia.

METHODS AND RESULTS: This cross-sectional analysis involved baseline data of 6332 participants. Food polyphenol content was estimated by a validated semiquantitative food frequency questionnaire and from the Phenol-Explorer database. Multivariable-adjusted linear regression models with serum uric acid (milligrams per deciliter) as the outcome and polyphenol intake (quintiles) as the main independent variable were fitted. Cox regression models with constant follow-up time (t=1) were performed to estimate the prevalence ratios (PRs) of hyperuricemia (≥7 mg/dL in men and ≥6 mg/dL in women). An inverse association between the intake of the phenolic acid class (β coefficient, −0.17 mg/dL for quintile 5 versus quintile 1 [95% CI, −0.27 to −0.06]) and hydroxycinnamic acids (β coefficient, −0.19 [95% CI, −0.3 to −0.09]), alkylmethoxyphenols (β coefficient, −0.2 [95% CI, −0.31 to −0.1]), and methoxyphenols (β coefficient, −0.24 [95% CI, −0.34 to −0.13]) subclasses with serum uric acid levels and hyperuricemia (PR, 0.82 [95% CI, 0.71–0.95]; PR, 0.82 [95% CI, 0.71–0.95]; PR, 0.80 [95% CI, 0.70–0.92]; and PR, 0.79 [95% CI, 0.69–0.91]; respectively) was found. The intake of hydroxybenzoic acids was directly and significantly associated with mean serum uric acid levels (β coefficient, 0.14 for quintile 5 versus quintile 1 [95% CI, 0.02–0.26]) but not with hyperuricemia.

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*A complete list of the PREDIMED-Plus Trial Investigators can be found in the Supplemental Material.

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CONCLUSIONS: In individuals with metabolic syndrome, a higher intake of some polyphenol subclasses (hydroxycinnamic acids, alkylmethoxyphenol, and methoxyphenol) was inversely associated with serum uric acid levels and hyperuricemia. Nevertheless, our findings warrant further research.

Key Words: hyperuricemia ■ polyphenols ■ uric acid

CLINICAL PERSPECTIVE

What Is New?

- The influence of the consumption of different subclasses of polyphenols on both serum uric acid and hyperuricemia in a large sample with metabolic syndrome is evaluated.
- Within a large cohort of older individuals with metabolic syndrome, a higher intake of some polyphenol subclasses (hydroxycinnamic acids, alkylmethoxyphenol, and methoxyphenol) was inversely associated with serum uric acid levels and hyperuricemia.

What Are the Clinical Implications?

- Our findings add new insights into the potential beneficial role of phenolic compounds in serum uric acid levels and the risk of hyperuricemia.
- Our findings could lead to further epidemiological studies in the field of prevention of hyperuricemia and cardiovascular disease.

Nonstandard Abbreviations and Acronyms

FFQ	Food Frequency Questionnaire
PR	prevalence ratio
PREDIMED-Plus	Prevención con Dieta Mediterranea-Plus

Uric acid is the end product of both exogenous dietary purines and their endogenous metabolism.[1] Hyperuricemia is the condition of uric acid in the blood exceeding the normal range and is recognized as a risk factor for various diseases such as gout, urolithiasis, type 2 diabetes, arterial hypertension, metabolic syndrome, as well as cardiovascular disease.[2–7]

A diet rich in plant-based foods, mainly vegetables and fruits, is directly linked to a lower incidence of various health disorders, including hyperuricemia.[8,9] The beneficial effect of this diet is attributable to its richness in antioxidant and anti-inflammatory substances, as well as polyphenols.

Polyphenols are secondary metabolites of plants largely found in foods, including fruits, cereals, vegetables, legumes, cocoa, coffee, tea, and wine.[10] These compounds have been inversely associated with all-cause mortality and the incidence of a wide variety of chronic diseases, including cancer, diabetes, neurodegenerative disease, and cardiovascular disease.[11–19] Many studies have shown that polyphenols may prevent hyperuricemia by inhibiting the enzyme responsible for uric acid production, increasing uric acid excretion and preventing its reabsorption in the kidney, and modulating the gut microbiota composition and improving uric acid excretion through the intestine.[20,21] Most of this knowledge has been obtained from in vitro and in vivo studies or epidemiological studies focused on foods rich in polyphenols.[20,22]

Given their properties, it is expected that a high intake of polyphenols is associated with a lower level of serum uric acid and a lower risk of hyperuricemia and that this relationship differs depending on the classes of polyphenols. In this context, the objective of this study was to assess the association of the intake of the different classes of polyphenols with serum uric acid and hyperuricemia in participants in a large primary cardiovascular prevention trial.

METHODS

Study Population

This study was based on the cross-sectional analysis of baseline data of participants included in the PREDIMED-Plus (Prevención con Dieta Mediterranea-Plus). This is an ongoing 6-year multicenter, parallel-group, primary cardiovascular prevention randomized trial, which is currently being conducted in 23 Spanish recruiting centers (universities, hospitals, and research institutes). The trial was registered at the International Standard Randomized Controlled Trial Number registry (ISRCTN89898870). The study protocol includes more detailed information and is available in previous publications[23–25] and at the website.[26] Because of the confidential nature of the data collected for this study, requests to access the data set from qualified investigators trained in human subject confidentiality protocols should be made to the PREDIMED-Plus trial steering committee.

Participants included women aged 60 to 75 years and men aged 55 to 75 years; with a body mass index between

27.0 and 40.0 kg/m^2; and meeting at least 3 criteria for metabolic syndrome according to the updated harmonized definition of the International Diabetes Federation, the American Heart Association, and the National Heart, Lung, and Blood Institute[27]; and not suffering from cardiovascular disease at the time of enrollment.

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 of the research ethics committees from the participating institutions.

A total of 9677 people were included in a run-in period to identify and select participants with greater probability of complying with the study protocol, of whom 6874 participants were eligible for the study and were included in the trial. After excluding participants with missing data for the main variables, such as serum uric acid, and with data of daily energy intake beyond predefined limits (<500 and >3500 kcal/d for women and <800 and >4000 kcal/d for men),[28] 6332 participants were included in the present analysis (Figure 1). The data were analyzed using the available PREDIMED-Plus database, dated March 12, 2019.

Variables and Data Collection

Data on age, sex, educational levels, anthropometric measurements, dietary habits, and lifestyle, as well as blood samples for biochemical analyses, were collected at the baseline visit. Anthropometric evaluations were measured according to the PREDIMED-Plus protocol. Body mass index was calculated as weight (kilograms) divided by the square of height (square meters).

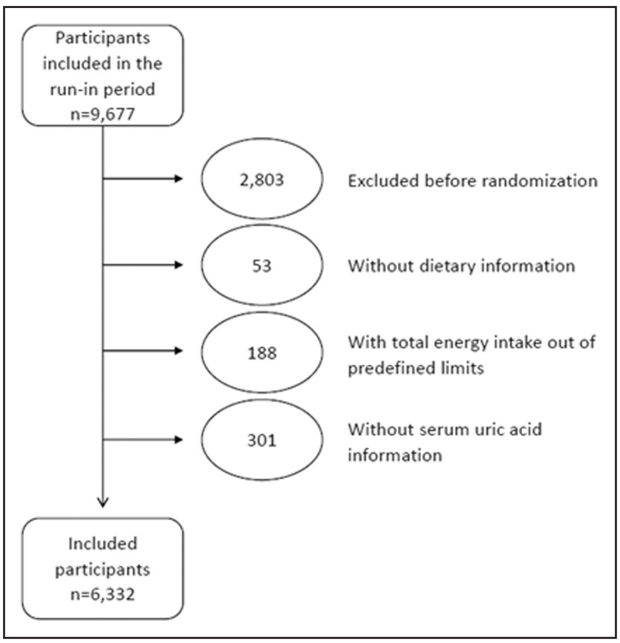

Figure 1. Flowchart of participants from the PREDIMED-Plus (Prevención con Dieta Mediterranea-Plus) trial.

Self-reported information about sociodemographic and lifestyle habits, individual and family medical history, smoking status, medical conditions, and medication use was collected. Biochemical analyses were performed using overnight fasting blood samples by standard enzymatic methods to determine parameters such as fasting plasma glucose, triglycerides, cholesterol, creatinine, or serum uric acid. Blood pressure was measured in triplicate with a validated semiautomatic oscillometer in a seated position. Hyperuricemia was defined as serum uric acid levels ≥7 mg/dL in men and ≥6 mg/dL in women.[29]

Physical activity was evaluated using the validated Regicor Short Physical Activity Questionnaire,[30] and the validated Spanish version of the Nurses' Health Study questionnaire was used to assess sedentary behavior.[31]

Estimation of Dietary Polyphenol Intake

Trained registered dietitians assessed baseline dietary intake with a semiquantitative 143-item Food Frequency Questionnaire,[32] which was 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] We have used aglycone equivalents for polyphenol intake estimation, instead of considering the total amount of individual chemical polyphenol species (glucosides, glucuronides) reported for each food. This procedure standardizes the data of the results of different analytical methods and facilitates cross-study comparisons.[36]

Polyphenol intake was calculated in milligrams per day, using food consumption data from the Food Frequency Questionnaire and the aglycone polyphenols content of each food contained in the Phenol-Explorer database. No retention factors were applied in the calculation of the amount of polyphenol ingested. The data from 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 intake 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 (Qs).

Statistical Analysis

Continuous variables are described as mean and SD, and prevalence is expressed in sample size and percentage.

Linear regression models were performed using serum uric acid (milligrams per deciliter) as the dependent variable and total polyphenol intake and their classes and subclasses in quintiles as the independent variable. Values are shown as β coefficient and 95% CI.

Cox regression models with constant follow-up time (*t*=1) were performed to assess prevalence ratios (PRs) and 95% CIs of hyperuricemia according to quintiles of the intake of energy-adjusted total polyphenols and their classes and subclasses. Cox regression model has been suggested as a better method than logistic regression in cross-sectional studies when the outcome is common (prevalence >10%) because odds ratios could overestimate or underestimate the risk in logistic regression (prevalence of hyperuricemia in our participants: n=2153, 34%); however, their interpretability is similar.[38] We performed a sensitivity analysis in which we performed the same analyses using logistic regression, obtaining odds ratio and 95% CI.

All models were stratified by sex and adjusted for different potential confounders, including age, sex (with the exception of stratified analysis), education level (primary, secondary, or university/graduate), body mass index (weight in kilograms divided by height in square meters), diabetes (yes/no), physical activity (metabolic equivalent tasks per minute per week), antihyperuricemic agents (including allopurinol, oxipurinol, pythic acid, febuxostat, probenecid, sulfinpyrazone, phenylbutazone, benzobromanone [yes/no]), nephropathy (yes/no), smoking habit (yes/no), alcohol consumption (grams per day), basal intake of different food groups (fruits, vegetables, meat, and fish [grams per day]), recruiting center, intervention group, and cluster (subjects randomized in couples).

To assess the linear trend, the median values for each quintile of total polyphenol intake and each class and subclass were assigned and used as continuous variables.

Given the multiple comparisons, to control the expected proportion of discoveries that are false, a false discovery rate test through the Benjamini-Hochberg procedure was made ($P<0.05$). Analyses were performed with the Stata statistical software package version 15.1 (StataCorp, College Station, TX).

RESULTS

Table 1 shows the main characteristics of the 6332 participants from the PREDIMED-Plus study according to quintiles of dietary total polyphenol intake. At baseline, we observed that participants included in the fifth quintile of polyphenol intake were mainly men, with higher levels of physical activity and intake of energy, alcohol, fruit, and vegetables. Participants in the fifth quintile had less diabetes compared with the other quintiles.

The associations between the energy-adjusted dietary intake of polyphenols (comparing the fifth versus the first quartiles) and serum uric acid levels are shown in Figure 2 (and in Table S1). Total polyphenol intake ($\beta_{Q5versusQ1}$, −0.04 [95% CI, −0.15 to 0.08]) tended to be inversely associated with serum uric acid levels. This association was statistically significant for phenolic acid class ($\beta_{Q5versusQ1}$, −0.17 [95% CI, −0.27 to −0.06]). In the same way, some subclasses showed this significant inverse association, including hydroxycinnamic acids ($\beta_{Q5versusQ1}$, −0.19 [95% CI, −0.30 to −0.09]), alkylmethoxyphenols ($\beta_{Q5versusQ1}$, −0.20 [95% CI, −0.31 to −0.10]), and methoxyphenols ($\beta_{Q5versusQ1}$, −0.24 [95% CI, −0.34 to −0.13]). The intake of hydroxybenzoic acids ($\beta_{Q5versusQ1}$, 0.14 [95% CI, 0.02–0.26]) was directly and significantly associated with serum uric acid levels.

In the stratified analysis by sex (Figure S1), flavonols, hydroxybenzoic acids, and other polyphenol (subclass) intake was directly associated with serum uric acid levels in men. In women, the inverse and significant association was maintained with phenolic acid, hydroxycinnamic acids, alkylmethoxyphenols, methoxyphenols, as well as alkylphenols. Women also showed a direct and significant association between the intake of lignans, hydroxypheylpropanoic acids, hydroxyphenylacetic acids, and tyrosols and serum uric acid levels.

We performed Cox proportional models with constant time to study the association between hyperuricemia prevalence and quintiles of polyphenol classes and subclasses as shown in Figure 3 and Table S2. Significant and inverse associations were found for hydroxycinnamic acids ($PR_{Q5versusQ1}$, 0.82 [95% CI, 0.71–0.95]), phenolic acids ($PR_{Q5versusQ1}$, 0.82 [95% CI, 0.71–0.95]), alkylmethoxyphenols ($PR_{Q5versusQ1}$, 0.80 [95% CI, 0.70–0.92]), and methoxyphenols ($PR_{Q5versusQ1}$, 0.79 [95% CI, 0.96–0.91]). In all of them, these significant associations remained in women but not in men (Figure S2). These same results were obtained in the sensitivity analysis in which we calculated odds ratio and 95% CI (Table S3).

In Table 2, we present the main food sources for each polyphenol subclass. The polyphenol subclasses that showed an inverse association with uric acid levels or with the prevalence of hyperuricemia were mainly found in regular coffee and decaffeinated coffee.

DISCUSSION

In the current cross-sectional study in a senior population, our results suggest an inverse association between the intake of the phenolic acids class and hydroxycinnamic acids, alkylmethoxyphenols, and methoxyphenols subclasses with serum uric acid levels and hyperuricemia.

We are not aware of any epidemiological study in which the association between these classes of

Table 1. Baseline Characteristic of Participants by Quintiles of Total Polyphenol Intake

Characteristic	Total polyphenol intake, mg/d					*P* value
	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	
	≤402.7	403.0–507.8	507.8–620.7	620.7–786.5	≥786.6	
N	1327	1327	1326	1327	1326	
Mean±SD, mg/d	324.7±57.9	455.9±30.6	561.8±32.1	699.2±46.3	994.0±216.0	
Age, y	65.26	65.08	65.09	64.97	65.09	0.89
Sex, women (%)	711 (53.58)	676 (50.94)	674 (50.83)	597 (44.99)	551 (41.55)	<0.001
Physical activity, METs/min per wk	2235±2204	2332±2014	2475±2323	2575±2436	2700±2471	<0.001
Total energy intake, kcal/d	1971±460	2207±469	2351±482	2523±482	2773±501	<0.001
Diabetes, yes (%)	378 (28.49)	394 (29.69)	386 (29.11)	366 (27.58)	301 (22.70)	<0.001
BMI, kg/m^2	32.79±3.47	32.52±3.45	32.62±3.48	32.57±3.48	32.22±3.31	0.30
Smokers, n, (%)	163 (12.28)	176 (13.26)	155 (11.69)	159 (11.98)	168 (12.67)	0.76
Alcohol consumption, g/d	7.04±11.62	8.11±11.81	10.35±13.50	13.48±16.15	16.17±18.82	<0.001
Systolic/diastolic blood pressure, mm Hg	139.9±17.6/80.3±10.2	139.9±16.7/80.5±9.8	139.3±16.1/81.0±9.7	139.8±16.9/81.0±10.0	139.3±16.6/81.3±9.9	0.028/0.500
Serum uric acid levels, mg/dL	5.98±1.51	5.93±1.39	5.97±1.46	6.02±1.45	6.08±1.43	0.062
Hyperuricemic, yes (%)	482 (36.32)	474 (35.72)	483 (36.43)	513 (38.66)	502 (37.86)	0.498
Antihyperuricemic agents, yes (%)	95 (7.5)	101 (8.0)	81 (6.4)	86 (6.8)	73 (5.8)	0.194
Nephropathy, yes (%)	78 (5.88)	77 (5.80)	79 (5.96)	83 (6.25)	63 (4.75)	0.521
Fruit and vegetables intake, g/d	501±180	623±193	690±224	759±261	830±332	<0.001
Meat intake, g/d	138±57	145±58	149±57	152±58	154±57	0.917
Fish intake, g/d	91±46	97±46	102±46	108±46	111±49	0.156

BMI indicates body mass index; and METs, metabolic equivalent tasks.

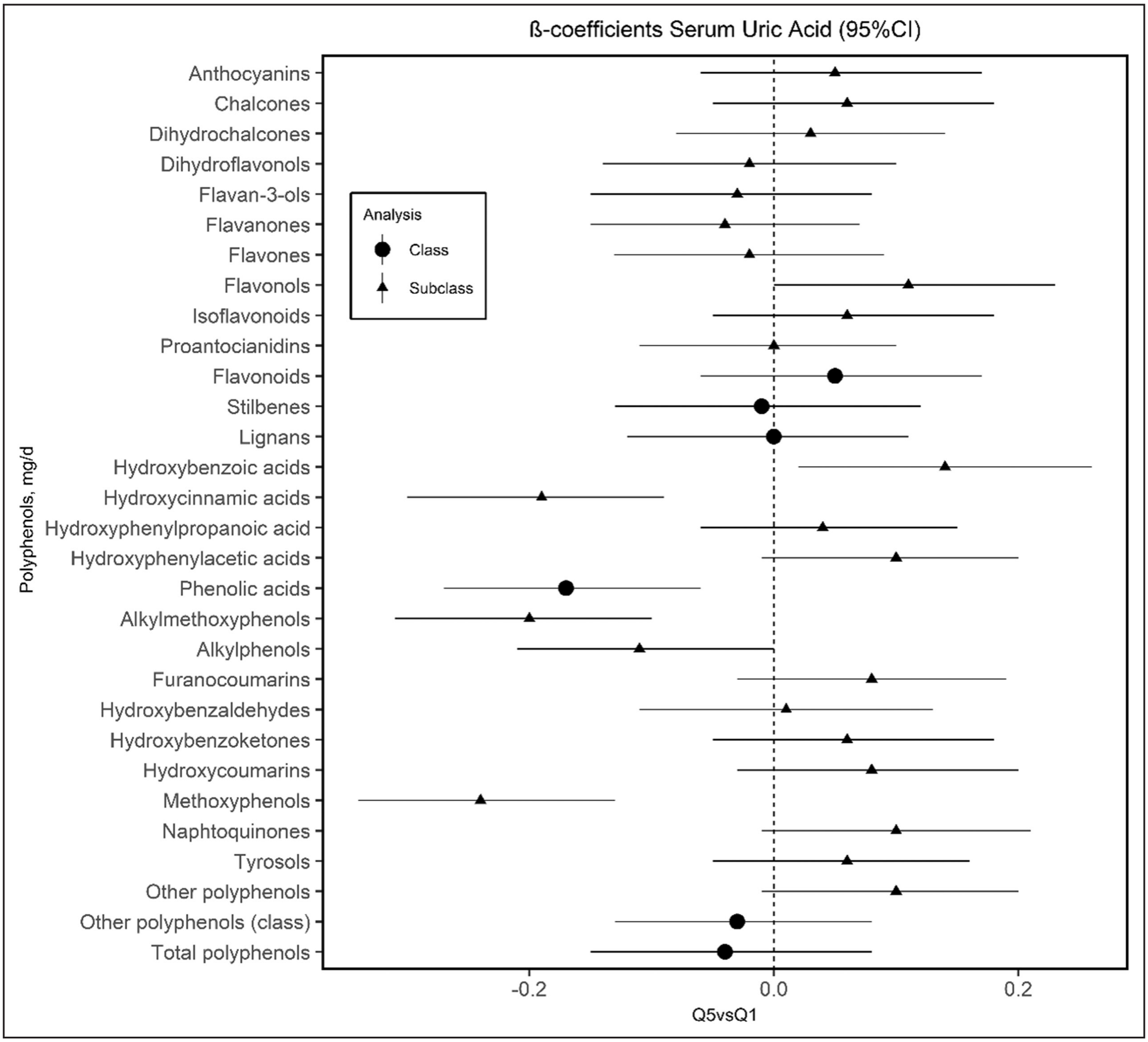

Figure 2. Association between polyphenol intake and serum uric acid levels comparing extreme quintile (Q) in the PREDIMED-Plus (Prevención con Dieta Mediterranea-Plus) trial.

Linear regression analysis evaluating the associations between classes and subclasses of polyphenol intake and serum uric acid levels (standardized β coefficients [95% CIs]). Model body mass index (weight in kilograms divided by height in square meters), diabetes (yes/no), physical activity (metabolic equivalent tasks per minute per week), antihyperuricemic agents (including allopurinol, oxipurinol, pythic acid, febuxostat, probenecid, sulfinpyrazone, phenylbutazone, benzobromanone [yes/no]), nephropathy (yes/no), smoking habit (yes/no), alcohol consumption (grams per day), basal intake of different food groups (fruits, vegetables, meat, and fish [grams per day]), recruiting center, intervention group, and cluster.

polyphenols and uric acid levels or hyperuricemia has been previously reported. Nevertheless, our results are plausible given the results from in vitro and in vivo studies.[20,22]

Different mechanisms by which phenolic compounds could play a role in the prevention or treatment of hyperuricemia have been described in other studies. Within phenolic acids, compounds such as caffeic acid,[39,40] chlorogenic acid,[22] sinapic acid,[41] verbascoside,[42,43] and ferulic acid[21,44] have been shown to decrease serum uric acid by inhibiting xanthine oxidase activity. On the other hand, the antihyperuricemic effect of caffeic acid may be also caused by the fractional excretion of urate activity.[45] These compounds are part of the hydroxycinnamic acid subclass, the most consumed in our cohort.

The main food source in which we can find hydroxycinnamic acids, alkylmethoxyphenol, and methoxyphenol in our population is regular coffee and decaffeinated coffee. There appears to be a clear

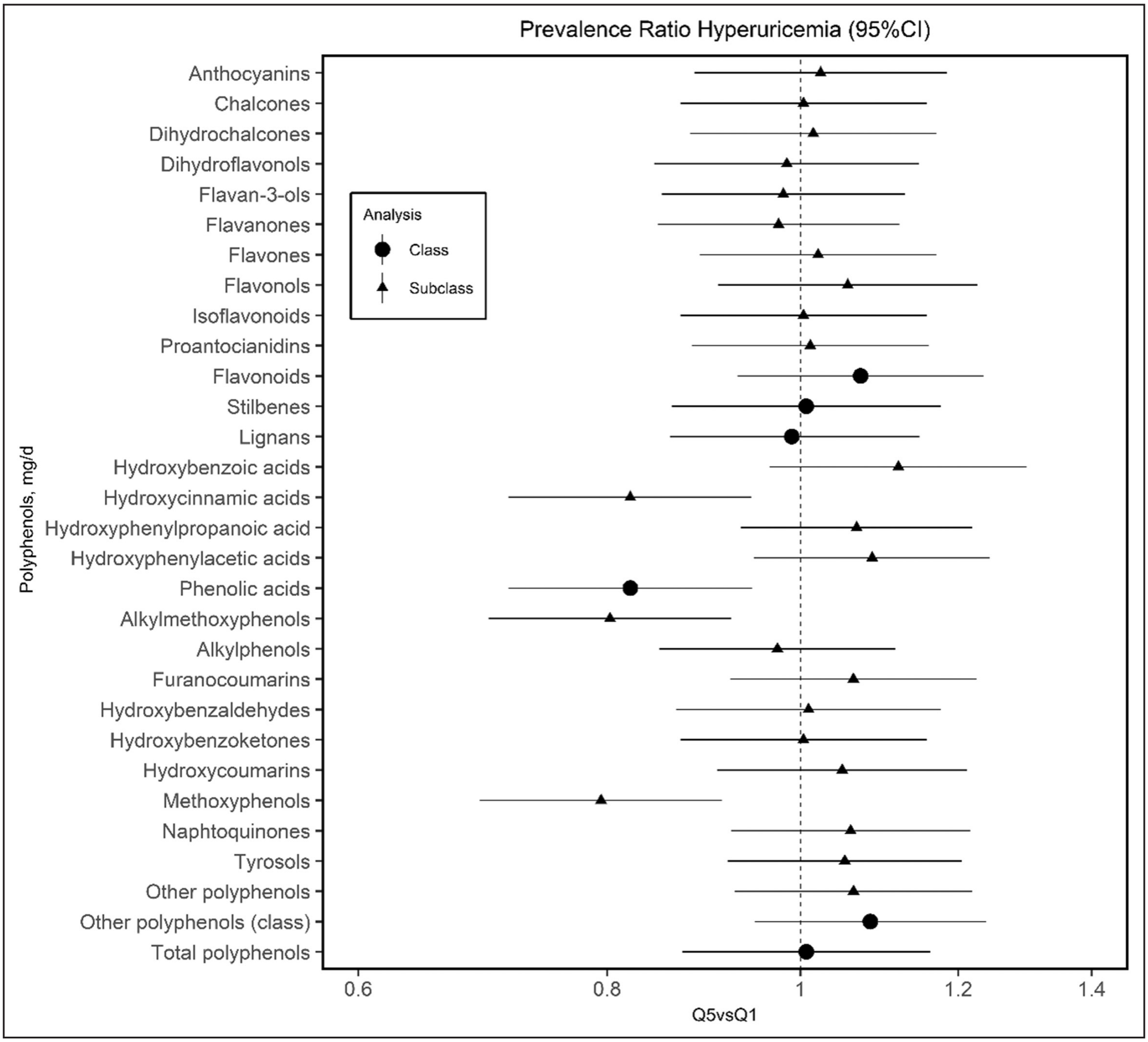

Figure 3. Association between polyphenol intake and hyperuricemia comparing extreme quintile (Q) in the PREDIMED-Plus (Prevención con Dieta Mediterranea-Plus) trial.

Cox regression models with constant follow-up times were performed to assess prevalence ratios and 95% CIs of hyperuricemia according to quintiles of the intake of energy-adjusted total polyphenols and their classes and subclasses. Models were adjusted for age, sex, education level (primary, secondary, or university/graduate), body mass index (weight in kilograms divided by height in square meters), diabetes (yes/no), physical activity (metabolic equivalent tasks per minute per week), antihyperuricemic agents (including allopurinol, oxipurinol, pythic acid, febuxostat, probenecid, sulfinpyrazone, phenylbutazone, benzobromanone [yes/no]), nephropathy (yes/no), smoking habit (yes/no), alcohol consumption (grams per day), basal intake of different food groups (fruits, vegetables, meat, and fish [grams per day]), recruiting center, intervention group, and cluster.

inverse relationship between coffee consumption and serum uric acid concentration.[46] This association has also been found in women, which supports our results.[47] Coffee contains >1000 types of compounds, including phenolic compounds,[48] and this inverse association with serum uric acid appears to be exerted through components of coffee other than caffeine, because the serum uric acid level has been reported to decrease significantly with increasing coffee intake.[49] The phenol chlorogenic acid (hydroxycinnamic acid) might contribute to the inverse coffee–serum uric acid relationship by inhibiting xanthine oxidase,[47,48] and this compound may act in combination with other antioxidants in coffee to decrease oxidative stress.[50] Therefore, it is plausible that various other polyphenols in coffee have the same inhibitory effects.[51]

In regard to the stratified analysis by sex, the statistical significance of the previous subclasses was

Table 2. Contribution of Polyphenol Subclasses to Total Polyphenol Intake and Food Sources

Polyphenol class	Subclass	Contribution, mg/d, mean±SD	Food sources* (% of contribution)
Flavonoids		394.63±217.82	
	Anthocyanins	23.87±20.60	Cherries (37.9), red wine (27.3), strawberries (11.2), grapes (10.6), olives (9.43), onions (2.0)
	Chalcones	0.006±0.012	Beer (100)
	Dihydrochalcones	0.98±0.91	Apples (93.0), fruit juices from concentrate (7.0)
	Dihydroflavonols	1.80±3.40	Red wine (97.6), white wine (1.8)
	Flavan-3-ols	20.10±22.28	Red wine (33.2), apples (22.4), tea (10.4), chocolate (9.9), cherries (7.8), peaches (6.8), cocoa powder (2.5), grapes (1.5), fruit juices from concentrate (1.2), green beans (1.0)
	Flavanones	57.33±54.43	Oranges (59.9), natural orange juice (33.8), fruit juices from concentrate (2.3), tomatoes (2.9), other fruit juices (1.2)
	Flavones	53.62±31.69	Whole grain bread (39.1), bread (30.7), oranges (6.6), artichoke (6.1), natural orange juice (5.2), whole grain cookies (2.2), olives (2.0)
	Flavonols	35.10±14.96	Swiss chard leaves (29.8), onions (24.1), lettuce (11.0), red wine (6.9), olives (4.0), asparagus (3.7), apples (3.3), natural orange juice (3.2), green beans (2.5), cabbage (2.4), chocolate (2.0), tomatoes (1.6), tea (1.4), cherries (1.1)
	Isoflavonoids	0.002±0.004	Beer (100)
	Proanthocyanidins	193.32±172.72	Chocolate (42.3), apples and pears (23.7), cherries and plumb (11.3), cocoa powder (6.3), strawberries (5.1), grapes (4.7), hazelnuts (4.6)
Stilbenes		1.76±3.16	Red wine (92.4), white wine (3.2), grapes (1.7), strawberries (1.2), rose wine (1.1)
Lignans		1.96±0.68	Olive oil (13.0), extra virgin olive oil (12.9), fried potatoes (9.3), seeds (7.7), oranges (7.5), broccoli and cabbage (6.7), green beans (4.2), peaches (3.9), bread (3.5), apples (3.1), asparagus (2.6), red wine (3.2), watermelon (1.8), tomatoes (1.7), whole grain bread (1.7), melon (1.5), peppers (1.4), kiwis (1.3), carrots (1.3), strawberries (1.2)
Phenolic acids		162.36±69.57	
	Hydroxybenzoic acids	20.15±12.07	Swiss chard leaves (23.6), olives (15.2), walnuts (13.9), red wine (16.5), tea (10.8), beer (6.5), apples (2.3), chickpeas (1.4), strawberries (1.3), bananas (1.3), onions (1.1)
	Hydroxycinnamic acids	140.19±12.07	Decaffeinated coffee (35.2), coffee (25.1), potatoes (5.6), olives (5.5), cherries (5.4), apples (4.2), artichoke (3.4), Swiss chard leaves (2.3), red wine (2.2), mushrooms (1.3), peaches (1.2), tomatoes (1.1)
	Hydroxyphenylpropanoic acid	0.89±1.20	Olives (100)
	Hydroxyphenylacetic acids	1.13±1.36	Olives (87.2), red wine (6.6), beer (3.9), extra virgin olive oil (1.5)
Other polyphenols		46.35±26.74	
	Alkylmethoxyphenols	0.94±0.87	Decaffeinated coffee (74.1), coffee (16.3), beer (9.6)
	Alkylphenols	13.56±17.66	Whole grain bread (69.1), whole grain pastries (14.9), breakfast cereals (8.5), pasta (3.3)
	Furanocoumarins	0.37±0.38	Celery stalks (98.4), other fruit juices (1.6)
	Hydroxybenzaldehydes	0.42±0.66	Red wine (79.0), walnuts (14.6), beer (2.6)
	Hydroxybenzoketones	0.002±0.004	Beer (100)
	Hydroxycoumarins	0.09±0.18	Beer (72.0), white wine (28.0)
	Methoxyphenols	0.12±0.12	Decaffeinated coffee (81.4), coffee (18.6)
	Naphtoquinones	0.82±1.12	Walnuts (100)
	Tyrosols	29.38±20.45	Olives (46.7), extra virgin olive oil (36.1), olive oil (4.1), red wine (5.8),
	Other polyphenols (subclass)	0.66±0.53	Coffee (41.9), apples (19.4), olives (15.3), other fruits juice (11.4), decaffeinated coffee (6.0), olive oil (3.1)

*Food sources that contribute >1%.

maintained only in women, showing the inverse association with serum uric acid and hyperuricemia. Lignans, hydroxypheylpropanoic acids, hydroxyphenylacetic acids, and tyrosols in women, and flavonols, hydroxybenzoic acids, and other polyphenols in men, showed a direct significant association with serum uric acid, although not with hyperuricemia.

In general, the effects of the Mediterranean diet appear to be greater in men than in premenopausal women when cardiometabolic changes are considered, although in this study the women were postmenopausal.[52] However, another study reported that flavonoid intake was inversely associated with cardiovascular risk factors in premenopausal women but not in men.[53]

In this study, female participants were postmenopausal, so because of the hormonal deficiency of estrogen that has shown uricosuric effects, women are more susceptible to hyperuricemia at this stage of life.[54,55] For the aforementioned reason, the direct relationships shown for some classes of polyphenols and uric acid in women might be because of reverse causality. Women's habits may have changed because of the diagnosis of hyperuricemia.[56]

This same reverse causality mechanism could explain the significant direct association between hydroxybenzoic acid intake and serum uric acid levels in men, although it was not associated with hyperuricemia. Nevertheless, this subclass was scarcely consumed in our sample, and in previous studies, compounds of this subclass, such as gallic acid, corilagin, or ellagic acid, have shown reduction of uric acid generation and uricosuric activities.[39]

It is interesting to mention that our population comprised elderly individuals with metabolic syndrome, and hyperuricemia could be secondary to an association with obesity, insulin resistance, and dyslipidemia, which are associated with an inflammatory state. However, uric acid is part of the body's antioxidant defenses, and it is still a question whether elevated levels of uric acid are a protective response to damage or a cause of primary disease.[55]

Limitations and Strengths

We acknowledge that several limitations should be considered. First, given the inherent nature of cross-sectional studies, there is a problem in determining the temporal relationship of a presumed cause and effect, and the possibility of reverse causation should be acknowledged. Our population comprised senior Spanish individuals with metabolic syndrome; therefore, our results cannot be extrapolated to the general population. Another limitation is that self-reported dietary information may have led to some misclassification and possible errors in measurement; however, the Food Frequency Questionnaire, administered by trained dietitians, was previously validated in the adult Spanish population and showed good reproducibility and validity.[34] In addition, studies have shown a good correlation between the intake of polyphenol-rich foods and their metabolites excreted in urine.[57–59] Furthermore, we did not have sufficient data to evaluate the effect on gout. Finally, other factors affecting polyphenol content could be a limitation: the estimation of their intake through the Food Frequency Questionnaire; the differences in their absorption and in their bioactivity[60]; the synergies with other polyphenols, nutrients, or compounds[61]; and factors related to climatic stress, geography, and storage conditions or losses during cooking.[62] The grouping for polyphenols instead of considering only individual compounds is another limitation, so important associations for individual compounds may have been missed.

Nevertheless, the strengths of the study are the multicenter design, the large sample size, the availability of blood samples, and the high-quality detailed information collected by qualified personnel. Also, our database was built including all available information on polyphenol content in the Phenol-Explorer database, with a mixture of data extracted from chromatography and chromatography after hydrolysis data, and this was adjusted by energy intake using the residuals method. Another strength of this study is the stratified analysis by sex, allowing us to detect differences with the global analysis. Finally, this is the first epidemiological study to evaluate the influence of polyphenol dietary intake on serum uric acid levels and hyperuricemia. The lack of epidemiologica studies precluded us from comparing our results with others.

In conclusion, in individuals with metabolic syndrome, hydroxycinnamic acids, alkylmethoxyphenol, and methoxyphenol intake were inversely associated with serum uric acid levels and hyperuricemia. Our findings add new insights into the potential beneficial role of phenolic compounds in serum uric acid levels and the risk of hyperuricemia and could lead to further epidemiological studies in the field of cardiovascular disease prevention.

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Supplemental Material

Data S1
Tables S1–S3
Figures S1–S2

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Table S1. Quintiles of polyphenol intake and serum uric acid levels (standardized β-coefficients [95% Confidence Intervals]).

	Q1	Q2 vs.Q1	Q3 vs.Q1	Q4 vs.Q1	Q5 vs.Q1	P trend
TOTAL POLYPHENOLS						
Men	(ref.)	0.08 (-0.07 to 0.24)	0.04 (-0.11 to 0.2)	-0.01 (-0.17 to 0.15)	0.05 (-0.12 to 0.21)	
Women	(ref.)	-0.11 (-0.25 to 0.03)	-0.11 (-0.25 to 0.04)	-0.12 (-0.27 to 0.03)	-0.11 (-0.27 to 0.04)	
Total	(ref.)	-0.01 (-0.11 to 0.1)	-0.04 (-0.14 to 0.07)	-0.07 (-0.18 to 0.04)	-0.04 (-0.15 to 0.08)	0.370
FLAVONOIDS						
Men	(ref.)	0.09 (-0.06 to 0.25)	0.09 (-0.07 to 0.24)	-0.02 (-0.18 to 0.14)	0.12 (-0.04 to 0.29)	
Women	(ref.)	-0.15 (-0.29 to -0.01)	-0.1 (-0.25 to 0.04)	-0.07 (-0.22 to 0.08)	0 (-0.15 to 0.15)	
Total	(ref.)	-0.03 (-0.14 to 0.07)	-0.01 (-0.12 to 0.1)	-0.06 (-0.17 to 0.05)	0.05 (-0.06 to 0.17)	0.291
Anthocyanins						
Men	(ref.)	-0.09 (-0.24 to 0.06)	-0.12 (-0.28 to 0.03)	-0.05 (-0.2 to 0.11)	0.03 (-0.14 to 0.2)	
Women	(ref.)	-0.1 (-0.25 to 0.04)	0.03 (-0.11 to 0.17)	-0.02 (-0.17 to 0.12)	0.06 (-0.1 to 0.22)	
Total	(ref.)	-0.1 (-0.21 to 0.01)	-0.05 (-0.16 to 0.05)	-0.04 (-0.15 to 0.07)	0.05 (-0.07 to 0.17)	0.110
Chalcones						
Men	(ref.)	0.17 (0.02 to 0.32)	-0.05 (-0.21 to 0.1)	0.15 (-0.01 to 0.3)	0.08 (-0.09 to 0.24)	
Women	(ref.)	0.09 (-0.05 to 0.24)	0.05 (-0.09 to 0.2)	0.13 (-0.02 to 0.28)	0.04 (-0.12 to 0.19)	
Total	(ref.)	0.14 (0.03 to 0.24)	0 (-0.11 to 0.11)	0.14 (0.03 to 0.25)	0.06 (-0.05 to 0.18)	0.564
Dihydrochalcones						
Men	(ref.)	0.11 (-0.04 to 0.27)	0 (-0.15 to 0.16)	0.09 (-0.07 to 0.25)	0.1 (-0.07 to 0.26)	
Women	(ref.)	0 (-0.14 to 0.15)	0 (-0.14 to 0.15)	-0.09 (-0.24 to 0.06)	-0.01 (-0.16 to 0.14)	
Total	(ref.)	0.06 (-0.05 to 0.16)	-0.01 (-0.11 to 0.1)	0 (-0.11 to 0.11)	0.03 (-0.08 to 0.14)	0.906
Dihydroflavonols						
Men	(ref.)	-0.06 (-0.21 to 0.1)	-0.23 (-0.39 to -0.08)	-0.04 (-0.19 to 0.12)	-0.1 (-0.28 to 0.08)	
Women	(ref.)	0.07 (-0.07 to 0.21)	0.12 (-0.03 to 0.26)	0.17 (0.02 to 0.31)	0.05 (-0.12 to 0.21)	
Total	(ref.)	-0.01 (-0.11 to 0.1)	-0.07 (-0.18 to 0.03)	0.05 (-0.06 to 0.16)	-0.02 (-0.14 to 0.1)	0.965
Flavan3ols						
Men	(ref.)	-0.16 (-0.32 to -0.01)	-0.06 (-0.21 to 0.1)	0.02 (-0.14 to 0.18)	-0.04 (-0.21 to 0.12)	
Women	(ref.)	-0.12 (-0.27 to 0.02)	-0.02 (-0.17 to 0.12)	0.03 (-0.12 to 0.17)	-0.01 (-0.16 to 0.13)	
Total	(ref.)	-0.15 (-0.25 to -0.04)	-0.05 (-0.15 to 0.06)	0.02 (-0.09 to 0.13)	-0.03 (-0.15 to 0.08)	0.478
Flavanones						
Men	(ref.)	0 (-0.15 to 0.15)	-0.05 (-0.2 to 0.11)	-0.02 (-0.18 to 0.14)	-0.1 (-0.26 to 0.06)	
Women	(ref.)	0.02 (-0.12 to 0.17)	0 (-0.14 to 0.15)	-0.04 (-0.19 to 0.1)	0.04 (-0.11 to 0.19)	
Total	(ref.)	0.01 (-0.09 to 0.12)	-0.02 (-0.13 to 0.08)	-0.03 (-0.14 to 0.08)	-0.04 (-0.15 to 0.07)	0.373
Flavones						
Men	(ref.)	-0.11 (-0.26 to 0.04)	-0.03 (-0.19 to 0.12)	-0.01 (-0.17 to 0.15)	0.01 (-0.15 to 0.17)	
Women	(ref.)	0.11 (-0.03 to 0.25)	-0.06 (-0.2 to 0.09)	0.03 (-0.11 to 0.18)	-0.05 (-0.2 to 0.09)	
Total	(ref.)	0 (-0.11 to 0.1)	-0.04 (-0.15 to 0.06)	0.01 (-0.1 to 0.11)	-0.02 (-0.13 to 0.09)	0.832
Flavonols						
Men	(ref.)	0.08 (-0.08 to 0.23)	0.07 (-0.08 to 0.23)	0.12 (-0.04 to 0.28)	**0.18 (0.01 to 0.35)**	
Women	(ref.)	0.04 (-0.1 to 0.18)	0.15 (0.01 to 0.3)	0.05 (-0.1 to 0.2)	0.04 (-0.11 to 0.2)	
Total	(ref.)	0.05 (-0.06 to 0.15)	0.1 (-0.01 to 0.21)	0.07 (-0.04 to 0.18)	0.11 (0 to 0.23)	0.086
Isoflavonoids						
Men	(ref.)	0.17 (0.02 to 0.32)	-0.05 (-0.21 to 0.1)	0.15 (-0.01 to 0.3)	0.08 (-0.09 to 0.24)	
Women	(ref.)	0.09 (-0.05 to 0.24)	0.05 (-0.09 to 0.2)	0.13 (-0.02 to 0.28)	0.04 (-0.12 to 0.19)	
Total	(ref.)	0.14 (0.03 to 0.24)	0 (-0.11 to 0.11)	0.14 (0.03 to 0.25)	0.06 (-0.05 to 0.18)	0.564
Proantocianidinas						
Men	(ref.)	0.03 (-0.13 to 0.18)	-0.01 (-0.16 to 0.15)	0 (-0.16 to 0.16)	0.07 (-0.08 to 0.23)	
Women	(ref.)	-0.1 (-0.24 to 0.04)	0.03 (-0.12 to 0.17)	-0.02 (-0.16 to 0.13)	-0.07 (-0.21 to 0.07)	
Total	(ref.)	-0.04 (-0.14 to 0.07)	0.01 (-0.1 to 0.11)	-0.01 (-0.12 to 0.1)	0 (-0.11 to 0.1)	0.864
LIGNANS						
Men	(ref.)	-0.09 (-0.25 to 0.06)	-0.12 (-0.28 to 0.03)	-0.12 (-0.28 to 0.04)	-0.16 (-0.32 to 0.01)	
Women	(ref.)	0.01 (-0.14 to 0.15)	0.12 (-0.03 to 0.26)	0.05 (-0.1 to 0.2)	**0.17 (0.02 to 0.32)**	
Total	(ref.)	-0.04 (-0.15 to 0.06)	-0.01 (-0.12 to 0.1)	-0.05 (-0.16 to 0.06)	0 (-0.12 to 0.11)	0.971
STILBENES						
Men	(ref.)	-0.03 (-0.18 to 0.12)	-0.17 (-0.32 to -0.01)	-0.04 (-0.19 to 0.12)	-0.1 (-0.28 to 0.09)	
Women	(ref.)	0.06 (-0.09 to 0.2)	0.1 (-0.04 to 0.25)	0.13 (-0.02 to 0.27)	0.07 (-0.09 to 0.24)	
Total	(ref.)	0 (-0.11 to 0.1)	-0.04 (-0.15 to 0.06)	0.03 (-0.07 to 0.14)	-0.01 (-0.13 to 0.12)	0.908
PHENOLIC ACIDS						
Men	(ref.)	0 (-0.15 to 0.16)	-0.03 (-0.18 to 0.12)	0.1 (-0.06 to 0.25)	-0.04 (-0.2 to 0.11)	
Women	(ref.)	0.04 (-0.11 to 0.18)	0.03 (-0.12 to 0.17)	-0.11 (-0.25 to 0.03)	**-0.28 (-0.42 to -0.14)**	
Total	(ref.)	0.02 (-0.09 to 0.12)	-0.02 (-0.12 to 0.09)	-0.01 (-0.12 to 0.09)	**-0.17 (-0.27 to -0.06)**	**0.001**
Hydroxyphenylacetic acids						

Men	(ref.)	-0.01 (-0.16 to 0.14)	0 (-0.15 to 0.16)	0.04 (-0.12 to 0.19)	-0.01 (-0.17 to 0.14)	
Women	(ref.)	0.11 (-0.03 to 0.25)	0.13 (-0.02 to 0.27)	0.1 (-0.04 to 0.25)	**0.21 (0.07 to 0.35)**	
Total	(ref.)	0.06 (-0.05 to 0.16)	0.06 (-0.04 to 0.17)	0.07 (-0.04 to 0.18)	0.1 (-0.01 to 0.2)	0.114
Hydroxypheylpropanoic acids						
Men	(ref.)	-0.15 (-0.31 to 0)	-0.01 (-0.17 to 0.14)	-0.01 (-0.16 to 0.14)	-0.08 (-0.24 to 0.07)	
Women	(ref.)	0.09 (-0.05 to 0.23)	0.16 (0.01 to 0.3)	0.06 (-0.08 to 0.2)	**0.19 (0.04 to 0.33)**	
Total	(ref.)	-0.04 (-0.14 to 0.07)	0.07 (-0.04 to 0.17)	0.02 (-0.08 to 0.13)	0.04 (-0.06 to 0.15)	0.305
Hydroxybenzoicacids						
Men	(ref.)	0.19 (0.03 to 0.34)	0.03 (-0.13 to 0.18)	0.05 (-0.11 to 0.21)	**0.2 (0.03 to 0.38)**	
Women	(ref.)	0.02 (-0.13 to 0.16)	0.15 (0.01 to 0.3)	0.14 (-0.01 to 0.28)	0.08 (-0.07 to 0.24)	
Total	(ref.)	0.1 (0 to 0.21)	0.09 (-0.02 to 0.19)	0.09 (-0.02 to 0.2)	**0.14 (0.02 to 0.26)**	**0.048**
Hydroxycinnamicacids						
Men	(ref.)	-0.01 (-0.17 to 0.14)	0 (-0.15 to 0.16)	0.12 (-0.04 to 0.27)	-0.1 (-0.26 to 0.05)	
Women	(ref.)	0.15 (0.01 to 0.29)	-0.02 (-0.16 to 0.12)	-0.08 (-0.22 to 0.07)	**-0.28 (-0.42 to -0.14)**	
Total	(ref.)	0.06 (-0.04 to 0.17)	-0.02 (-0.13 to 0.08)	0.01 (-0.09 to 0.12)	**-0.19 (-0.3 to -0.09)**	**0.000**
OTHERS						
Men	(ref.)	-0.02 (-0.18 to 0.13)	0.02 (-0.14 to 0.17)	-0.04 (-0.19 to 0.11)	-0.03 (-0.18 to 0.12)	
Women	(ref.)	0.01 (-0.14 to 0.15)	0.02 (-0.12 to 0.16)	0.01 (-0.14 to 0.15)	-0.01 (-0.16 to 0.13)	
Total	(ref.)	-0.01 (-0.12 to 0.09)	0.01 (-0.09 to 0.12)	-0.03 (-0.13 to 0.08)	-0.03 (-0.13 to 0.08)	0.559
Alkylmethoxyphenols						
Men	(ref.)	0.12 (-0.03 to 0.27)	0.07 (-0.09 to 0.22)	-0.02 (-0.18 to 0.13)	-0.09 (-0.24 to 0.07)	
Women	(ref.)	0.08 (-0.06 to 0.22)	0 (-0.15 to 0.14)	-0.05 (-0.19 to 0.09)	**-0.31 (-0.45 to -0.16)**	
Total	(ref.)	0.09 (-0.01 to 0.19)	0.02 (-0.08 to 0.13)	-0.05 (-0.16 to 0.05)	**-0.2 (-0.31 to -0.1)**	**0.000**
Alkylphenols						
Men	(ref.)	0.01 (-0.15 to 0.16)	-0.13 (-0.29 to 0.03)	-0.02 (-0.18 to 0.13)	-0.04 (-0.2 to 0.11)	
Women	(ref.)	-0.04 (-0.19 to 0.1)	0.01 (-0.13 to 0.15)	-0.04 (-0.18 to 0.1)	**-0.16 (-0.3 to -0.01)**	
Total	(ref.)	-0.02 (-0.13 to 0.08)	-0.07 (-0.18 to 0.04)	-0.05 (-0.16 to 0.06)	-0.11 (-0.21 to 0)	0.069
Furanocoumarins						
Men	(ref.)	0.04 (-0.12 to 0.19)	0.04 (-0.12 to 0.19)	0.13 (-0.02 to 0.28)	0.04 (-0.12 to 0.2)	
Women	(ref.)	0.09 (-0.05 to 0.24)	0.11 (-0.04 to 0.25)	0.08 (-0.06 to 0.22)	0.1 (-0.05 to 0.24)	
Total	(ref.)	0.07 (-0.04 to 0.17)	0.07 (-0.03 to 0.18)	0.11 (0.01 to 0.22)	0.08 (-0.03 to 0.19)	0.367
Hydroxybenzaldehydes						
Men	(ref.)	-0.05 (-0.2 to 0.11)	-0.11 (-0.27 to 0.04)	-0.09 (-0.25 to 0.07)	-0.07 (-0.26 to 0.12)	
Women	(ref.)	0.08 (-0.06 to 0.22)	0.08 (-0.06 to 0.22)	0.12 (-0.03 to 0.26)	0.1 (-0.07 to 0.26)	
Total	(ref.)	0 (-0.1 to 0.11)	-0.03 (-0.14 to 0.08)	-0.01 (-0.11 to 0.1)	0.01 (-0.11 to 0.13)	0.854
Hydroxybenzoketones						
Men	(ref.)	0.17 (0.02 to 0.32)	-0.05 (-0.21 to 0.1)	0.15 (-0.01 to 0.3)	0.08 (-0.09 to 0.24)	
Women	(ref.)	0.09 (-0.05 to 0.24)	0.05 (-0.09 to 0.2)	0.13 (-0.02 to 0.28)	0.04 (-0.12 to 0.19)	
Total	(ref.)	0.14 (0.03 to 0.24)	0 (-0.11 to 0.11)	0.14 (0.03 to 0.25)	0.06 (-0.05 to 0.18)	0.564
Hydroxycoumarins						
Men	(ref.)	0.08 (-0.07 to 0.23)	0.07 (-0.08 to 0.22)	0.11 (-0.05 to 0.26)	0.08 (-0.09 to 0.25)	
Women	(ref.)	0 (-0.14 to 0.15)	0.1 (-0.05 to 0.24)	0.08 (-0.07 to 0.23)	0.05 (-0.1 to 0.21)	
Total	(ref.)	0.04 (-0.06 to 0.15)	0.08 (-0.02 to 0.19)	0.1 (-0.01 to 0.21)	0.08 (-0.03 to 0.2)	0.193
Methoxyphenols						
Men	(ref.)	-0.04 (-0.19 to 0.11)	0.05 (-0.1 to 0.21)	-0.05 (-0.2 to 0.1)	-0.15 (-0.31 to 0)	
Women	(ref.)	0.09 (-0.05 to 0.23)	-0.03 (-0.17 to 0.11)	-0.02 (-0.16 to 0.12)	**-0.31 (-0.45 to -0.17)**	
Total	(ref.)	0.02 (-0.09 to 0.12)	0 (-0.1 to 0.1)	-0.05 (-0.15 to 0.06)	**-0.24 (-0.34 to -0.13)**	**0.000**
Naphtoquinones						
Men	(ref.)	0.1 (-0.05 to 0.26)	0.1 (-0.05 to 0.26)	0.09 (-0.06 to 0.25)	0.12 (-0.04 to 0.27)	
Women	(ref.)	0.05 (-0.09 to 0.2)	0.07 (-0.08 to 0.21)	0.06 (-0.09 to 0.2)	0.12 (-0.03 to 0.26)	
Total	(ref.)	0.08 (-0.03 to 0.18)	0.07 (-0.04 to 0.18)	0.07 (-0.04 to 0.18)	0.1 (-0.01 to 0.21)	0.216
Tyrosols						
Men	(ref.)	-0.09 (-0.25 to 0.06)	0.05 (-0.1 to 0.21)	0 (-0.15 to 0.16)	-0.06 (-0.22 to 0.09)	
Women	(ref.)	0.09 (-0.05 to 0.23)	0.1 (-0.05 to 0.24)	0.07 (-0.08 to 0.21)	**0.18 (0.04 to 0.33)**	
Total	(ref.)	0 (-0.11 to 0.1)	0.08 (-0.02 to 0.19)	0.03 (-0.08 to 0.14)	0.06 (-0.05 to 0.16)	0.268
Other polyphenols						
Men	(ref.)	0.06 (-0.09 to 0.21)	0.2 (0.05 to 0.35)	0.11 (-0.04 to 0.27)	**0.18 (0.02 to 0.33)**	
Women	(ref.)	-0.02 (-0.16 to 0.12)	0.05 (-0.09 to 0.19)	0.15 (0.01 to 0.29)	0.02 (-0.13 to 0.16)	
Total	(ref.)	0.02 (-0.08 to 0.13)	0.13 (0.03 to 0.24)	0.13 (0.03 to 0.24)	0.1 (-0.01 to 0.2)	**0.040**

Linear regression analysis evaluating the associations between classes and subclasses of polyphenol intake and serum uric acid levels (standardized β-coefficients [95% Confidence Intervals]).

Models were adjusted for age, sex, education level (primary, secondary or university/graduate), BMI (kg/m2), diabetes (yes/no), physical activity (METs.min/week), antihyperuricemic agents [including allopurinol, oxipurinol, pythic acid, febuxostat, probenecid, sulfinpyrazone, phenylbutazone, benzobromanone (yes/no)], nephropathy (yes/no), smoking habit (yes/no), alcohol consumption (g/day), basal intake of different food groups [fruits, vegetables, meat and fish (g/day)], recruiting centre, intervention group and cluster.

Table S2. Quintiles of polyphenol intake and hyperuricemia (Prevalence Ratio (PR) [95% Confidence Intervals]).

	Q1	PR Q2vs.Q1	IC95%		PR Q3vs.Q1	IC95%		PR Q4vs.Q1	IC95%		PR Q5vs.Q1	IC95%		P trend
TOTAL POLYPHENOLS														
Men	(ref.)	1.10	0.91	1.32	1.06	0.87	1.28	1.05	0.86	1.27	1.02	0.84	1.24	
Women	(ref.)	0.91	0.75	1.11	0.92	0.75	1.12	0.93	0.76	1.14	1.00	0.81	1.23	
Total	(ref.)	1.01	0.88	1.16	0.98	0.85	1.12	0.98	0.85	1.13	1.01	0.87	1.16	0.996
FLAVONOIDS														
Men	(ref.)	1.14	0.95	1.38	1.12	0.93	1.36	1.05	0.86	1.28	1.10	0.90	1.35	
Women	(ref.)	0.88	0.72	1.08	0.92	0.75	1.13	0.99	0.81	1.22	1.06	0.86	1.30	
Total	(ref.)	1.01	0.88	1.15	1.02	0.89	1.17	1.01	0.88	1.17	1.07	0.93	1.24	0.314
Anthocyanins														
Men	(ref.)	1.07	0.89	1.29	0.97	0.80	1.18	1.04	0.86	1.26	1.02	0.84	1.25	
Women	(ref.)	0.89	0.73	1.09	1.09	0.90	1.33	0.91	0.75	1.12	1.00	0.81	1.24	
Total	(ref.)	0.98	0.86	1.13	1.03	0.90	1.18	0.98	0.85	1.12	1.02	0.88	1.18	0.735
Chalcones														
Men	(ref.)	1.07	0.88	1.28	0.86	0.71	1.05	1.12	0.93	1.35	1.02	0.84	1.24	
Women	(ref.)	1.05	0.86	1.27	1.01	0.83	1.24	1.11	0.91	1.35	0.96	0.78	1.19	
Total	(ref.)	1.06	0.93	1.21	0.93	0.81	1.07	1.12	0.97	1.28	1.00	0.87	1.16	0.900
Dihydrochalcones														
Men	(ref.)	1.10	0.91	1.32	1.09	0.90	1.31	1.06	0.87	1.29	1.14	0.93	1.39	
Women	(ref.)	0.98	0.81	1.19	1.01	0.83	1.23	0.88	0.72	1.09	0.92	0.75	1.14	
Total	(ref.)	1.03	0.91	1.18	1.04	0.91	1.19	0.97	0.84	1.11	1.01	0.88	1.17	0.747
Dihydroflavonols														
Men	(ref.)	1.05	0.87	1.26	0.89	0.74	1.09	0.99	0.82	1.20	0.95	0.77	1.17	
Women	(ref.)	1.04	0.85	1.28	1.15	0.94	1.41	1.18	0.97	1.45	1.00	0.80	1.25	
Total	(ref.)	1.03	0.90	1.18	1.00	0.86	1.14	1.07	0.93	1.23	0.98	0.85	1.15	0.812
Flavan3ols														
Men	(ref.)	0.96	0.79	1.16	0.98	0.81	1.19	1.06	0.88	1.28	1.01	0.84	1.23	
Women	(ref.)	0.90	0.74	1.10	0.96	0.79	1.17	1.05	0.87	1.28	0.96	0.78	1.17	
Total	(ref.)	0.93	0.81	1.07	0.97	0.84	1.11	1.05	0.92	1.20	0.98	0.85	1.13	0.694
Flavanones														
Men	(ref.)	0.98	0.81	1.17	0.94	0.78	1.14	0.94	0.77	1.13	0.93	0.76	1.12	
Women	(ref.)	1.04	0.85	1.27	1.01	0.82	1.23	0.98	0.80	1.21	1.05	0.85	1.28	
Total	(ref.)	1.00	0.88	1.15	0.97	0.85	1.11	0.95	0.83	1.10	0.97	0.85	1.12	0.678
Flavones														
Men	(ref.)	0.92	0.77	1.11	0.95	0.79	1.14	0.98	0.81	1.18	1.01	0.83	1.21	
Women	(ref.)	1.09	0.90	1.32	0.90	0.74	1.11	1.02	0.84	1.25	1.04	0.85	1.27	
Total	(ref.)	1.00	0.87	1.14	0.93	0.81	1.06	0.99	0.87	1.14	1.02	0.89	1.17	0.614
Flavonols														
Men	(ref.)	1.07	0.88	1.29	1.13	0.94	1.37	1.11	0.91	1.36	1.11	0.91	1.37	
Women	(ref.)	1.09	0.90	1.33	1.09	0.89	1.33	1.00	0.81	1.23	1.01	0.81	1.25	
Total	(ref.)	1.07	0.93	1.22	1.10	0.96	1.26	1.04	0.90	1.20	1.06	0.91	1.23	0.717
Isoflavonoids														
Men	(ref.)	1.07	0.88	1.28	0.86	0.71	1.05	1.12	0.93	1.35	1.02	0.84	1.24	
Women	(ref.)	1.05	0.86	1.27	1.01	0.83	1.24	1.11	0.91	1.35	0.96	0.78	1.19	
Total	(ref.)	1.06	0.93	1.21	0.93	0.81	1.07	1.12	0.97	1.28	1.00	0.87	1.16	0.900
Proantocianidinas														
Men	(ref.)	1.11	0.92	1.33	1.08	0.89	1.30	1.08	0.90	1.31	1.05	0.87	1.27	
Women	(ref.)	0.87	0.71	1.06	1.08	0.89	1.31	0.95	0.78	1.17	0.98	0.80	1.20	
Total	(ref.)	0.99	0.87	1.14	1.07	0.94	1.23	1.02	0.89	1.17	1.01	0.88	1.16	0.932
LIGNANS														
Men	(ref.)	0.93	0.78	1.11	0.88	0.73	1.06	0.88	0.73	1.07	0.88	0.72	1.08	
Women	(ref.)	0.97	0.80	1.19	1.12	0.92	1.37	0.94	0.76	1.16	1.14	0.92	1.40	
Total	(ref.)	0.95	0.83	1.09	0.99	0.86	1.13	0.90	0.78	1.04	0.99	0.86	1.15	0.838
STILBENES														
Men	(ref.)	1.06	0.88	1.28	0.97	0.80	1.18	1.01	0.84	1.22	0.96	0.77	1.19	
Women	(ref.)	1.03	0.84	1.26	1.11	0.90	1.36	1.13	0.92	1.39	1.03	0.82	1.30	
Total	(ref.)	1.04	0.90	1.19	1.02	0.89	1.18	1.06	0.92	1.22	1.01	0.86	1.18	0.970
PHENOLIC ACIDS														
Men	(ref.)	1.00	0.83	1.20	0.97	0.80	1.16	1.11	0.93	1.33	0.85	0.70	1.03	
Women	(ref.)	1.00	0.83	1.21	0.99	0.82	1.20	0.86	0.71	1.06	**0.79**	**0.64**	**0.97**	
Total	(ref.)	1.00	0.88	1.14	0.97	0.85	1.11	0.99	0.86	1.13	**0.82**	**0.71**	**0.95**	**0.006**
Hydroxyphenylacetic acids														
Men	(ref.)	0.96	0.79	1.15	1.01	0.83	1.21	1.05	0.87	1.26	1.02	0.85	1.23	
Women	(ref.)	1.06	0.86	1.30	1.14	0.93	1.40	1.01	0.82	1.25	1.15	0.94	1.41	
Total	(ref.)	1.01	0.88	1.16	1.07	0.93	1.23	1.04	0.91	1.19	1.09	0.95	1.24	0.236
Hydroxypheylpropanoic acids														
Men	(ref.)	0.85	0.70	1.03	1.02	0.85	1.23	1.00	0.83	1.19	0.99	0.83	1.19	
Women	(ref.)	1.10	0.90	1.34	**1.24**	**1.02**	**1.51**	1.00	0.82	1.24	1.16	0.96	1.42	

Total	(ref.)	0.95	0.83	1.10	1.12	0.98	1.28	1.00	0.87	1.14	1.07	0.93	1.22	0.329
Hydroxybenzoicacids														
Men	(ref.)	1.19	0.98	1.43	1.13	0.93	1.37	1.02	0.83	1.24	1.21	0.98	1.50	
Women	(ref.)	0.96	0.79	1.18	1.12	0.92	1.36	0.95	0.77	1.17	1.03	0.84	1.28	
Total	(ref.)	1.08	0.94	1.24	1.12	0.98	1.29	0.98	0.85	1.14	1.12	0.97	1.30	0.377
Hydroxycinnamicacids														
Men	(ref.)	1.05	0.88	1.26	1.04	0.87	1.25	1.09	0.91	1.31	0.86	0.71	1.04	
Women	(ref.)	1.09	0.90	1.31	0.93	0.77	1.13	0.90	0.73	1.09	**0.78**	**0.64**	**0.96**	
Total	(ref.)	1.07	0.94	1.22	0.98	0.86	1.12	0.99	0.87	1.13	**0.82**	**0.71**	**0.95**	**0.001**
OTHERS														
Men	(ref.)	0.96	0.80	1.16	1.05	0.87	1.26	0.99	0.83	1.20	1.03	0.86	1.24	
Women	(ref.)	1.10	0.90	1.34	0.99	0.81	1.21	1.00	0.82	1.22	1.16	0.96	1.41	
Total	(ref.)	1.02	0.89	1.17	1.01	0.88	1.16	0.99	0.86	1.14	1.08	0.95	1.24	0.297
Alkylmethoxyphenols														
Men	(ref.)	1.07	0.89	1.28	1.00	0.84	1.21	0.97	0.81	1.17	0.87	0.71	1.05	
Women	(ref.)	1.01	0.83	1.22	0.99	0.82	1.20	0.94	0.78	1.14	**0.74**	**0.60**	**0.91**	
Total	(ref.)	1.03	0.91	1.18	0.99	0.87	1.13	0.95	0.83	1.08	**0.80**	**0.70**	**0.92**	**0.000**
Alkylphenols														
Men	(ref.)	1.07	0.89	1.29	0.92	0.75	1.12	1.02	0.85	1.23	1.00	0.83	1.21	
Women	(ref.)	0.88	0.72	1.08	1.08	0.89	1.30	0.93	0.76	1.14	0.95	0.78	1.16	
Total	(ref.)	0.98	0.86	1.12	0.99	0.87	1.14	0.97	0.84	1.11	0.97	0.85	1.12	0.723
Furanocoumarins														
Men	(ref.)	1.07	0.88	1.29	1.07	0.88	1.29	1.19	0.99	1.43	1.07	0.88	1.30	
Women	(ref.)	1.10	0.90	1.33	1.18	0.97	1.43	1.00	0.81	1.22	1.03	0.84	1.27	
Total	(ref.)	1.08	0.95	1.24	1.12	0.98	1.29	1.10	0.96	1.26	1.06	0.92	1.23	0.818
Hydroxybenzaldehydes														
Men	(ref.)	1.03	0.85	1.24	0.98	0.81	1.19	0.98	0.80	1.18	0.96	0.77	1.19	
Women	(ref.)	1.03	0.85	1.26	1.04	0.85	1.27	0.98	0.80	1.21	1.06	0.85	1.32	
Total	(ref.)	1.02	0.89	1.17	1.00	0.87	1.15	0.97	0.84	1.11	1.01	0.87	1.18	0.963
Hydroxybenzoketones														
Men	(ref.)	1.07	0.88	1.28	0.86	0.71	1.05	1.12	0.93	1.35	1.02	0.84	1.24	
Women	(ref.)	1.05	0.86	1.27	1.01	0.83	1.24	1.11	0.91	1.35	0.96	0.78	1.19	
Total	(ref.)	1.06	0.93	1.21	0.93	0.81	1.07	1.12	0.97	1.28	1.00	0.87	1.16	0.900
Hydroxycoumarins														
Men	(ref.)	1.04	0.86	1.26	0.94	0.77	1.14	1.16	0.96	1.39	1.10	0.90	1.35	
Women	(ref.)	0.95	0.78	1.17	1.04	0.85	1.27	1.04	0.85	1.27	0.95	0.77	1.18	
Total	(ref.)	1.00	0.87	1.14	0.98	0.86	1.13	1.11	0.97	1.27	1.05	0.91	1.21	0.312
Methoxyphenols														
Men	(ref.)	1.02	0.85	1.22	1.04	0.87	1.24	1.01	0.84	1.21	0.84	0.69	1.02	
Women	(ref.)	1.05	0.87	1.26	0.96	0.79	1.16	0.95	0.78	1.15	**0.75**	**0.61**	**0.92**	
Total	(ref.)	1.04	0.91	1.18	0.99	0.87	1.13	0.97	0.85	1.11	**0.79**	**0.69**	**0.91**	**0.000**
Naphtoquinones														
Men	(ref.)	1.01	0.84	1.22	1.06	0.88	1.28	1.03	0.86	1.25	1.09	0.90	1.32	
Women	(ref.)	1.05	0.87	1.28	1.01	0.83	1.24	1.04	0.85	1.26	1.07	0.87	1.30	
Total	(ref.)	1.03	0.90	1.17	1.03	0.89	1.18	1.03	0.90	1.18	1.06	0.92	1.22	0.444
Tyrosols														
Men	(ref.)	0.87	0.72	1.05	1.01	0.84	1.22	1.02	0.85	1.22	0.99	0.82	1.19	
Women	(ref.)	1.05	0.86	1.29	1.09	0.89	1.33	1.02	0.83	1.25	1.13	0.92	1.38	
Total	(ref.)	0.95	0.83	1.09	1.06	0.92	1.21	1.02	0.89	1.16	1.05	0.92	1.21	0.294
Otherpolyphenols														
Men	(ref.)	1.12	0.92	1.35	1.19	0.99	1.43	1.11	0.92	1.34	1.12	0.93	1.36	
Women	(ref.)	0.99	0.81	1.20	1.05	0.86	1.27	1.11	0.91	1.34	0.99	0.81	1.21	
Total	(ref.)	1.05	0.92	1.21	1.13	0.99	1.29	1.11	0.97	1.27	1.06	0.93	1.22	0.442

Cox regression models with constant follow-up time were performed to assess prevalence ratios (PR) and 95% confidence intervals of hyperuricemia according to quintiles of the intake of energy-adjusted total polyphenols and their classes and subclasses.

Models were adjusted for age, sex, education level (primary, secondary or university/graduate), BMI (kg/m2), diabetes (yes/no), physical activity (METs.min/week), antihyperuricemic agents [including allopurinol, oxipurinol, pythic acid, febuxostat, probenecid, sulfinpyrazone, phenylbutazone, benzobromanone (yes/no)], nephropathy (yes/no), smoking habit (yes/no), alcohol consumption (g/day), basal intake of different food groups [fruits, vegetables, meat and fish (g/day)], recruiting centre, intervention group and cluster.

Table S3. Quintiles of polyphenol intake and hyperuricemia (Odds Ratio (OR) [95% Confidence Intervals]).

	Q1	OR Q2vs.Q1	IC95%		OR Q3vs.Q1	IC95%		OR Q4vs.Q1	IC95%		OR Q5vs.Q1	IC95%		P trend
TOTAL POLYPHENOLS														
Men	(ref.)	1.16	0.92	1.47	1.09	0.86	1.38	1.07	0.84	1.37	1.02	0.80	1.31	0.887
Women	(ref.)	0.87	0.68	1.11	0.87	0.68	1.12	0.89	0.69	1.15	1.00	0.77	1.30	0.906
Total	(ref.)	1.01	0.86	1.20	0.97	0.82	1.15	0.97	0.82	1.16	1.01	0.84	1.21	0.909
FLAVONOIDS														
Men	(ref.)	1.24	0.98	1.57	1.20	0.94	1.52	1.08	0.84	1.38	1.16	0.90	1.49	0.615
Women	(ref.)	0.83	0.65	1.06	0.88	0.69	1.13	0.99	0.77	1.27	1.09	0.85	1.41	0.235
Total	(ref.)	1.01	0.85	1.20	1.03	0.87	1.22	1.02	0.85	1.21	1.11	0.93	1.33	0.275
Anthocyanins														
Men	(ref.)	1.10	0.87	1.39	0.95	0.75	1.20	1.06	0.83	1.34	1.03	0.79	1.33	0.971
Women	(ref.)	0.84	0.66	1.08	1.15	0.90	1.47	0.87	0.68	1.12	1.00	0.77	1.31	0.912
Total	(ref.)	0.97	0.82	1.15	1.05	0.88	1.24	0.96	0.81	1.14	1.03	0.86	1.24	0.811
Chalcones														
Men	(ref.)	1.10	0.87	1.39	0.79	0.62	1.01	1.19	0.94	1.51	1.02	0.80	1.31	0.678
Women	(ref.)	1.07	0.84	1.36	1.02	0.79	1.31	1.17	0.91	1.50	0.93	0.71	1.21	0.943
Total	(ref.)	1.09	0.92	1.29	0.90	0.76	1.07	1.18	1.00	1.40	1.00	0.83	1.19	0.666
Dihydrochalcones														
Men	(ref.)	1.17	0.92	1.48	1.15	0.90	1.46	1.10	0.86	1.41	1.23	0.96	1.58	0.222
Women	(ref.)	0.97	0.76	1.23	1.01	0.79	1.29	0.82	0.64	1.07	0.89	0.69	1.15	0.195
Total	(ref.)	1.06	0.89	1.25	1.06	0.90	1.26	0.95	0.80	1.13	1.03	0.86	1.23	0.810
Dihydroflavonols														
Men	(ref.)	1.08	0.85	1.36	0.84	0.66	1.07	0.98	0.77	1.24	0.90	0.68	1.19	0.327
Women	(ref.)	1.06	0.83	1.36	1.24	0.96	1.59	1.29	1.00	1.66	0.97	0.73	1.29	0.421
Total	(ref.)	1.05	0.88	1.24	0.99	0.83	1.18	1.10	0.93	1.31	0.96	0.79	1.17	0.955
Flavan3ols														
Men	(ref.)	0.94	0.74	1.19	0.97	0.76	1.23	1.09	0.86	1.38	1.02	0.79	1.30	0.525
Women	(ref.)	0.85	0.66	1.09	0.94	0.73	1.20	1.08	0.85	1.39	0.93	0.72	1.19	0.759
Total	(ref.)	0.89	0.75	1.06	0.95	0.80	1.12	1.08	0.91	1.28	0.97	0.81	1.15	0.556
Flavanones														
Men	(ref.)	0.97	0.77	1.22	0.91	0.72	1.16	0.90	0.71	1.15	0.89	0.69	1.13	0.276
Women	(ref.)	1.06	0.83	1.35	1.01	0.79	1.29	0.98	0.76	1.25	1.07	0.83	1.38	0.875
Total	(ref.)	1.01	0.85	1.19	0.96	0.81	1.13	0.93	0.78	1.11	0.96	0.81	1.15	0.457
Flavones														
Men	(ref.)	0.88	0.69	1.11	0.92	0.73	1.17	0.97	0.76	1.23	1.01	0.80	1.28	0.653
Women	(ref.)	1.14	0.89	1.45	0.86	0.67	1.10	1.03	0.80	1.32	1.05	0.82	1.35	0.982
Total	(ref.)	0.99	0.84	1.17	0.89	0.75	1.05	0.99	0.84	1.18	1.03	0.87	1.22	0.745
Flavonols														
Men	(ref.)	1.11	0.87	1.40	1.22	0.96	1.55	1.18	0.92	1.51	1.18	0.91	1.54	0.185
Women	(ref.)	1.14	0.89	1.45	1.14	0.89	1.46	0.99	0.77	1.29	1.01	0.77	1.32	0.716
Total	(ref.)	1.10	0.93	1.31	1.16	0.98	1.38	1.07	0.89	1.27	1.09	0.90	1.31	0.543
Isoflavonoids														
Men	(ref.)	1.10	0.87	1.39	0.79	0.62	1.01	1.19	0.94	1.51	1.02	0.80	1.31	0.678
Women	(ref.)	1.07	0.84	1.36	1.02	0.79	1.31	1.17	0.91	1.50	0.93	0.71	1.21	0.943
Total	(ref.)	1.09	0.92	1.29	0.90	0.76	1.07	1.18	1.00	1.40	1.00	0.83	1.19	0.666
Proantocianidinas														
Men	(ref.)	1.17	0.93	1.48	1.12	0.88	1.42	1.14	0.89	1.44	1.07	0.85	1.37	0.703
Women	(ref.)	0.81	0.64	1.04	1.13	0.88	1.44	0.93	0.73	1.20	0.97	0.76	1.25	0.802
Total	(ref.)	0.99	0.83	1.17	1.12	0.95	1.32	1.04	0.87	1.23	1.02	0.86	1.20	0.709
LIGNANS														
Men	(ref.)	0.88	0.70	1.11	0.82	0.65	1.03	0.82	0.64	1.04	0.82	0.63	1.05	0.094
Women	(ref.)	0.96	0.75	1.23	1.20	0.93	1.53	0.91	0.70	1.18	1.23	0.95	1.59	0.232
Total	(ref.)	0.93	0.78	1.09	0.98	0.82	1.16	0.85	0.71	1.02	0.99	0.83	1.18	0.631
STILBENES														
Men	(ref.)	1.11	0.87	1.40	0.95	0.75	1.20	1.01	0.80	1.29	0.91	0.69	1.21	0.463
Women	(ref.)	1.05	0.82	1.35	1.18	0.92	1.51	1.21	0.94	1.56	1.02	0.77	1.36	0.381
Total	(ref.)	1.06	0.89	1.25	1.04	0.87	1.23	1.09	0.92	1.29	1.00	0.82	1.21	0.793
PHENOLIC ACIDS														
Men	(ref.)	0.99	0.79	1.25	0.94	0.75	1.19	1.19	0.94	1.50	**0.78**	**0.61**	**0.99**	**0.263**
Women	(ref.)	1.01	0.80	1.29	1.00	0.78	1.27	0.81	0.63	1.03	**0.70**	**0.55**	**0.90**	**0.001**
Total	(ref.)	1.00	0.85	1.18	0.95	0.81	1.13	0.98	0.83	1.16	**0.74**	**0.62**	**0.88**	**0.002**
Hydroxyphenylacetic acids														
Men	(ref.)	0.92	0.73	1.17	1.00	0.79	1.27	1.08	0.85	1.36	1.03	0.81	1.30	0.438
Women	(ref.)	1.09	0.85	1.39	1.23	0.96	1.57	1.02	0.79	1.31	1.24	0.97	1.59	0.190
Total	(ref.)	1.01	0.86	1.20	1.11	0.93	1.31	1.06	0.90	1.26	1.13	0.96	1.34	0.126
Hydroxypheylpropanoic acids														
Men	(ref.)	0.78	0.61	0.98	1.03	0.82	1.31	0.99	0.79	1.25	0.99	0.78	1.25	0.425
Women	(ref.)	1.15	0.90	1.47	**1.39**	1.09	1.78	1.01	0.78	1.30	1.26	0.99	1.61	0.242
Total	(ref.)	0.93	0.79	1.10	1.19	1.00	1.41	1.00	0.84	1.18	1.11	0.93	1.31	0.168

Hydroxybenzoicacids														
Men	(ref.)	1.30	1.02	1.64	1.19	0.94	1.52	1.01	0.79	1.30	1.35	1.03	1.76	0.293
Women	(ref.)	0.95	0.74	1.21	1.19	0.94	1.52	0.92	0.72	1.19	1.05	0.81	1.36	0.815
Total	(ref.)	1.12	0.95	1.33	1.19	1.01	1.41	0.97	0.81	1.15	1.19	0.99	1.43	0.366
Hydroxycinnamicacids														
Men	(ref.)	1.09	0.86	1.37	1.06	0.84	1.34	1.15	0.91	1.46	0.79	0.62	1.01	0.148
Women	(ref.)	1.15	0.91	1.46	0.90	0.71	1.15	0.85	0.67	1.09	**0.69**	**0.54**	**0.89**	**0.000**
Total	(ref.)	1.12	0.95	1.32	0.97	0.82	1.14	0.99	0.83	1.17	**0.74**	**0.63**	**0.88**	**0.000**
OTHERS														
Men	(ref.)	0.94	0.74	1.19	1.07	0.85	1.35	0.99	0.78	1.25	1.05	0.83	1.32	0.588
Women	(ref.)	1.15	0.90	1.47	0.98	0.77	1.26	1.00	0.78	1.28	1.26	0.99	1.61	0.246
Total	(ref.)	1.03	0.87	1.22	1.02	0.86	1.20	0.98	0.83	1.17	1.13	0.96	1.34	0.277
Alkylmethoxyphenols														
Men	(ref.)	1.12	0.89	1.40	1.00	0.80	1.27	0.95	0.76	1.21	0.80	0.63	1.01	**0.026**
Women	(ref.)	1.02	0.80	1.29	1.00	0.78	1.27	0.92	0.72	1.17	**0.64**	**0.50**	**0.82**	**0.001**
Total	(ref.)	1.06	0.89	1.24	0.98	0.83	1.16	0.92	0.78	1.09	**0.72**	**0.60**	**0.85**	**0.000**
Alkylphenols														
Men	(ref.)	1.12	0.88	1.41	0.87	0.68	1.12	1.03	0.82	1.31	1.00	0.79	1.27	0.810
Women	(ref.)	0.83	0.65	1.06	1.12	0.88	1.42	0.90	0.70	1.15	0.92	0.72	1.18	0.797
Total	(ref.)	0.97	0.82	1.15	0.98	0.83	1.17	0.95	0.80	1.12	0.96	0.81	1.14	0.594
Furanocoumarins														
Men	(ref.)	1.11	0.88	1.40	1.11	0.88	1.40	1.33	1.05	1.68	1.12	0.88	1.43	0.124
Women	(ref.)	1.16	0.91	1.48	1.30	1.02	1.65	0.99	0.77	1.27	1.05	0.81	1.36	0.839
Total	(ref.)	1.13	0.96	1.34	1.20	1.01	1.42	1.16	0.98	1.38	1.10	0.92	1.31	0.255
Hydroxybenzaldehydes														
Men	(ref.)	1.04	0.82	1.31	0.96	0.76	1.22	0.95	0.75	1.21	0.92	0.69	1.21	0.429
Women	(ref.)	1.05	0.82	1.34	1.07	0.83	1.37	0.98	0.76	1.26	1.09	0.82	1.43	0.820
Total	(ref.)	1.03	0.87	1.22	1.00	0.84	1.18	0.95	0.80	1.12	1.01	0.83	1.22	0.695
Hydroxybenzoketones														
Men	(ref.)	1.10	0.87	1.39	0.79	0.62	1.01	1.19	0.94	1.51	1.02	0.80	1.31	0.678
Women	(ref.)	1.07	0.84	1.36	1.02	0.79	1.31	1.17	0.91	1.50	0.93	0.71	1.21	0.943
Total	(ref.)	1.09	0.92	1.29	0.90	0.76	1.07	1.18	1.00	1.40	1.00	0.83	1.19	0.666
Hydroxycoumarins														
Men	(ref.)	1.06	0.84	1.34	0.90	0.71	1.15	1.25	0.99	1.59	1.16	0.90	1.50	0.124
Women	(ref.)	0.93	0.73	1.19	1.06	0.82	1.35	1.07	0.83	1.37	0.92	0.70	1.20	0.986
Total	(ref.)	1.00	0.84	1.18	0.97	0.82	1.16	1.17	0.98	1.38	1.07	0.89	1.28	0.155
Methoxyphenols														
Men	(ref.)	1.04	0.83	1.31	1.06	0.84	1.34	1.01	0.80	1.27	**0.77**	**0.60**	**0.97**	**0.041**
Women	(ref.)	1.09	0.86	1.38	0.94	0.74	1.20	0.93	0.73	1.19	**0.66**	**0.51**	**0.84**	**0.001**
Total	(ref.)	1.06	0.90	1.25	0.99	0.84	1.16	0.95	0.81	1.13	**0.71**	**0.60**	**0.84**	**0.000**
Naphtoquinones														
Men	(ref.)	1.02	0.81	1.29	1.10	0.87	1.39	1.06	0.84	1.34	1.16	0.91	1.48	0.226
Women	(ref.)	1.08	0.85	1.38	1.02	0.80	1.32	1.06	0.83	1.35	1.10	0.86	1.41	0.555
Total	(ref.)	1.04	0.88	1.23	1.04	0.88	1.24	1.05	0.89	1.25	1.10	0.93	1.31	0.316
Tyrosols														
Men	(ref.)	0.80	0.63	1.01	1.02	0.81	1.29	1.02	0.81	1.28	0.98	0.77	1.24	0.470
Women	(ref.)	1.08	0.84	1.38	1.14	0.89	1.46	1.02	0.80	1.32	1.20	0.94	1.53	0.274
Total	(ref.)	0.93	0.78	1.10	1.09	0.92	1.29	1.02	0.86	1.21	1.08	0.91	1.28	0.186
Other polyphenols														
Men	(ref.)	1.18	0.94	1.50	1.31	1.04	1.66	1.17	0.93	1.48	1.20	0.95	1.52	0.190
Women	(ref.)	0.98	0.76	1.25	1.07	0.84	1.37	1.17	0.92	1.49	0.99	0.78	1.27	0.536
Total	(ref.)	1.08	0.91	1.28	1.21	1.02	1.42	1.17	0.99	1.39	1.10	0.93	1.30	0.159

Logistic regression models were performed to assess odds ratios (OR) and 95% confidence intervals of hyperuricemia according to quintiles of the intake of energy-adjusted total polyphenols and their classes and subclasses.

Models were adjusted for age, sex, education level (primary, secondary or university/graduate), BMI (kg/m2), diabetes (yes/no), physical activity (METs.min/week), antihyperuricemic agents [including allopurinol, oxipurinol, pythic acid, febuxostat, probenecid, sulfinpyrazone, phenylbutazone, benzobromanone (yes/no)], nephropathy (yes/no), smoking habit (yes/no), alcohol consumption (g/day), basal intake of different food groups [fruits, vegetables, meat and fish (g/day)], recruiting centre, intervention group and cluster.

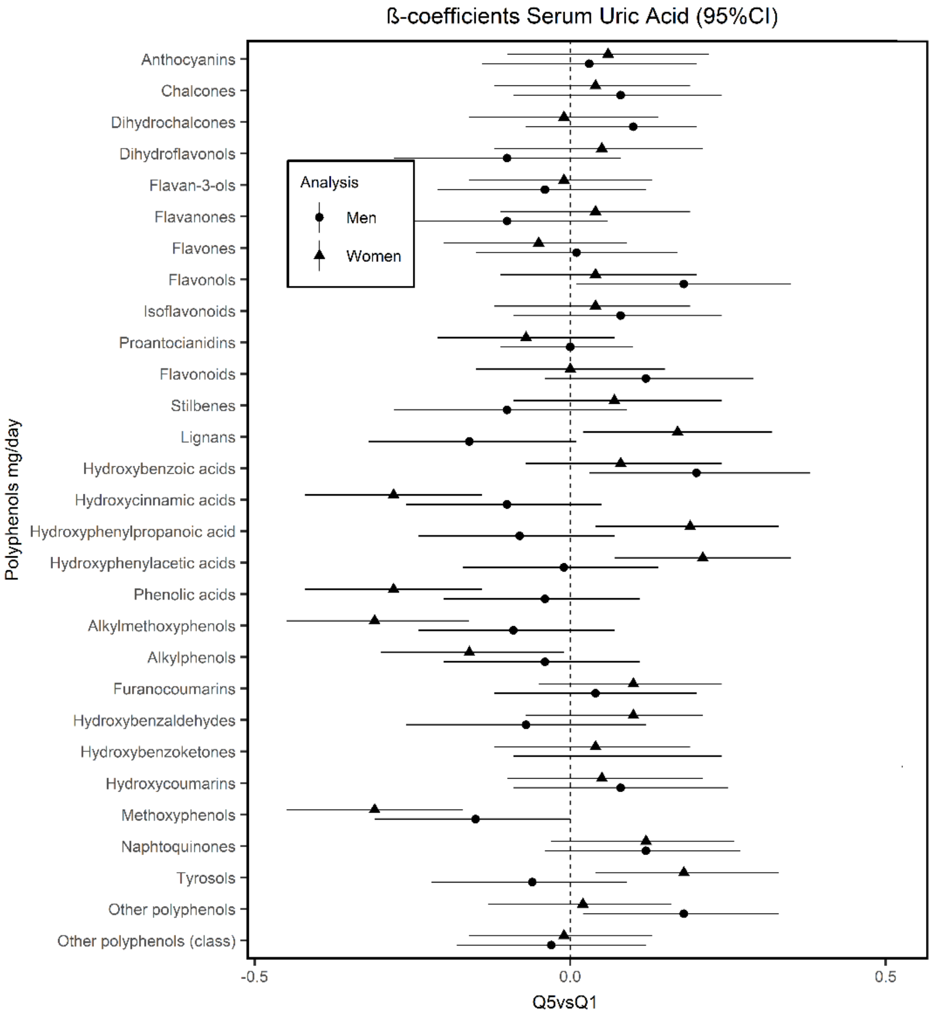

Figure S1. Association between polyphenol intake and serum uric acid levels comparing extreme quintiles by sex in the PREDIMED-Plus trial.

Linear regression analysis evaluating the associations between classes and subclasses of polyphenol intake and serum uric acid levels (standardized β-coefficients [95% Confidence Intervals]).

Models were adjusted for age, sex, education level (primary, secondary or university/graduate), BMI (kg/m2), diabetes (yes/no), physical activity (METs.min/week), antihyperuricemic agents [including allopurinol, oxipurinol, pythic acid, febuxostat, probenecid, sulfinpyrazone, phenylbutazone, benzobromanone (yes/no)], nephropathy (yes/no), smoking habit (yes/no), alcohol consumption (g/day), basal intake of different food groups [fruits, vegetables, meat and fish (g/day)], recruiting centre, intervention group and cluster.

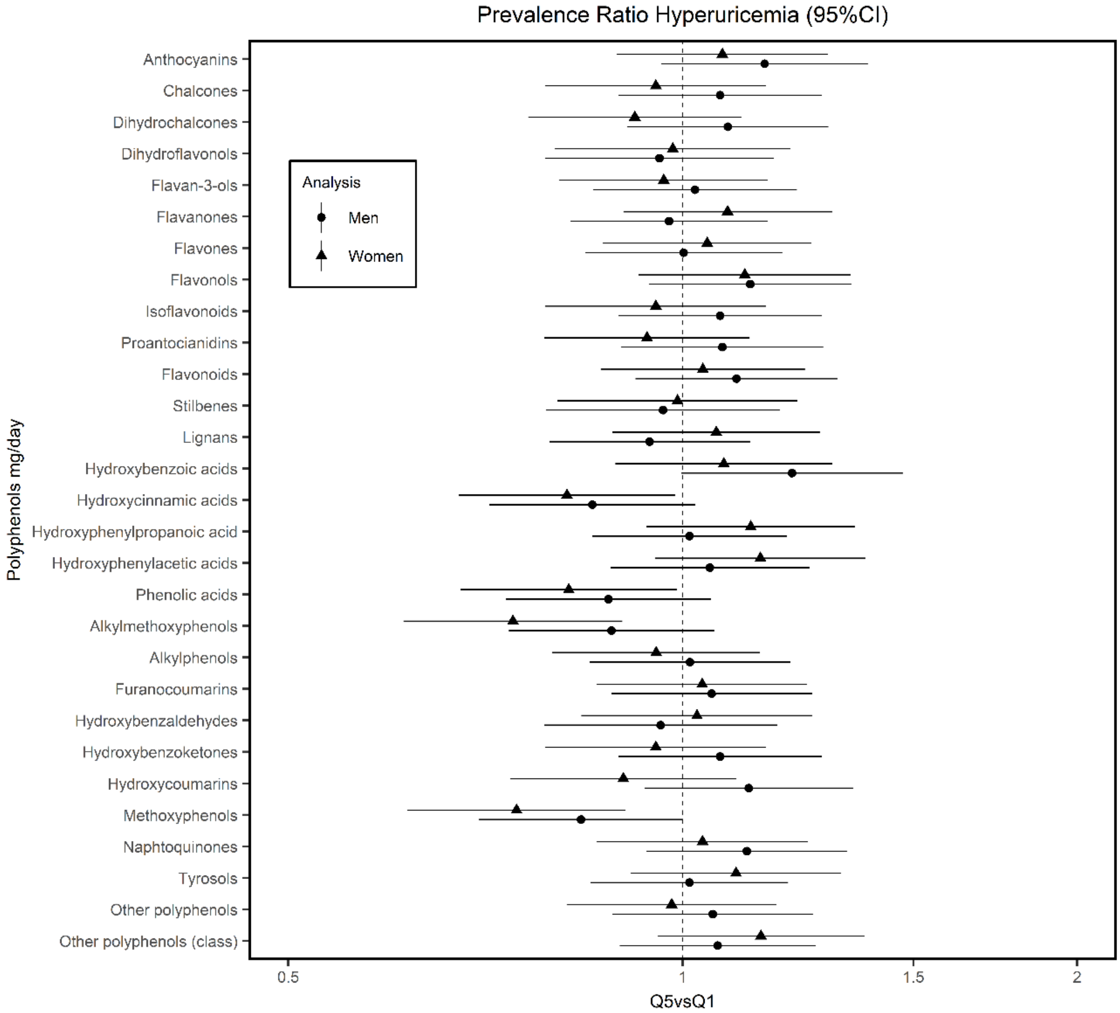

Figure S2. Association between polyphenol intake and hyperuricemia comparing extreme quintiles by sex in the PREDIMED- Plus trial.

Cox regression models with constant follow-up time were performed to assess prevalence ratios (PR) and 95% confidence intervals of hyperuricemia according to quintiles of the intake of energy-adjusted total polyphenols and their classes and subclasses.

Models were adjusted for age, sex, education level (primary, secondary or university/graduate), BMI (kg/m2), diabetes (yes/no), physical activity (METs.min/week), antihyperuricemic agents [including allopurinol, oxipurinol, pythic acid, febuxostat, probenecid, sulfinpyrazone, phenylbutazone, benzobromanone (yes/no)], nephropathy (yes/no), smoking habit (yes/no), alcohol consumption (g/day), basal intake of different food groups [fruits, vegetables, meat and fish (g/day)], recruiting centre, intervention group and cluster.