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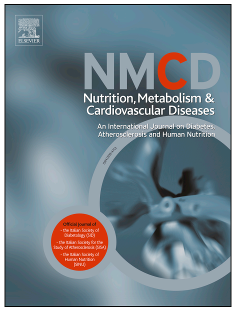

Association Between Dairy Product Consumption and Hyperuricemia in an Elderly Population With Metabolic Syndrome

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ASSOCIATION BETWEEN DAIRY PRODUCT CONSUMPTION AND HYPERURICEMIA IN AN ELDERLY POPULATION WITH METABOLIC SYNDROME.

List of abbreviations:

BMI: body mass index
CKD: chronic kidney disease
CVD: cardiovascular diseases
FFQ: food frequency questionnaire
IQR: interquartile range
MedDiet: Mediterranean diet
MetS: metabolic syndrome
PA: physical activity
PREDIMED-Plus study: Prevención con Dieta Mediterránea-Plus study
PR: prevalence risk
OR: Odds Ratio
SUA: serum uric acid
T2D: type 2 diabetes

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Supplementary tables and list of PREDIMED-PLUS study researchers are available from the "Online Supporting Material" link in the online posting of the article and from the same link in the online table of contents at jn.nutrition.org

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ABSTRACT

Background and aims: The prevalence of hyperuricemia has increased substantially in recent decades. It has been suggested that it is an independent risk factor for weight gain, hypertension, hypertriglyceridemia, metabolic syndrome, and cardiovascular disease. Results from epidemiological studies conducted in different study populations have suggested that high consumption of dairy products is associated with a lower risk of developing hyperuricemia. However, this association is still unclear. The aim of the present study is to explore the association between the consumption of total dairy products, their subtypes and the risk of hyperuricemia in an elderly Mediterranean population with metabolic syndrome.

Methods and results: Baseline cross-sectional analyses were conducted on 6,329 men/women (mean age 65y) with overweight/obesity and metabolic syndrome from the PREDIMED-Plus cohort. Dairy consumption was assessed using a food frequency questionnaire. Multivariable-adjusted Cox regressions were fitted to analyze the association between quartiles of consumption of total dairy products, subtypes and the prevalence of hyperuricemia. Participants in the upper quartile of total dairy (multiadjusted prevalence ratio (PR)=0.84; 95% CI:0.75-0.94; *P*-trend 0.02), low-fat dairy products (PR=0.79; 95% CI:0.70-0.89; *P*-trend <0.001), total milk (PR=0.81; 95% CI:0.73-0.90; *P*-trend<0.001), low-fat milk (PR=0.80; 95% CI:0.72-0.89; *P*-trend<0.001 respectively), low-fat yogurt (PR=0.89; 95% CI: 0.80-0.98; *P*-trend 0.051) and cheese (PR=0.86; 95% CI:0.77-0.96; *P*-trend 0.003) presented a lower prevalence of hyperuricemia. Whole-fat dairy, fermented dairy and yogurt consumption were not associated with hyperuricemia.

Conclusions: High consumption of total dairy, total milk, low-fat dairy, low-fat milk, low-fat yogurt and cheese is associated with a lower risk of hyperuricemia.

Keywords: dairy products, milk, yogurt, cheese, hyperuricemia.

INTRODUCTION

Serum uric acid (SUA) is the final product of human purine metabolism (1). Although much SUA is produced endogenously, it has been estimated that one-third of total SUA levels results from dietary purine metabolism (2,3). Hyperuricemia is defined as an increased concentration of uric acid in blood. In most cases, epidemiologic investigations have considered the upper normal range of concentration equal to 6 mg/dl for women and 7 mg/dl for men (4). Hyperuricemia has emerged as a major public health concern due to the increased prevalence during the recent years. According to epidemiologic studies, the prevalence of hyperuricemia over the last few decades has rapidly increased worldwide in low, middle-income (5,6) and developed countries (4). Estimations of hyperuricemia prevalence are around 8-25% in Chinese population, 11-17% in Western population, near 26% in Japan and 21% in US population (4,7–9).

Hyperuricemia has been strongly associated with metabolic syndrome (MetS) (10), hypertension (11), type 2 diabetes mellitus (12) or renal function decline (13). Furthermore, high plasma uric acid and hyperuricemia have been associated with body mass index (BMI), waist circumference (14,15) and obesity (16). Routine measurement of SUA levels amongst obese people have been recommended as a measure to prevent hyperuricemia and its related complications (17,18).

Hyperuricemia is modulated by various dietary factors. Evidences has shown that the frequent consumption of sweetened beverages, alcoholic drinks and purine-rich animal foods (i.e. fish and meat) is associated with an increased risk of hyperuricemia, whereas these associations have not been reported in the case of purine-rich vegetable foods (19,20). Meanwhile high intakes of dairy products, coffee, vegetables and legumes have been associated with lower SUA concentrations (23–27).

Dairy products have long been investigated for their interesting food matrix, proteins, fatty acid profiles, vitamin and mineral content (25). Some epidemiologic studies (23,24,28) and randomized clinical trials (29–31) have suggested the potential role of dairy products consumption in decreasing SUA levels and the risk of hyperuricemia. However, these studies did not take into account the potential differences amongst subtypes of dairy products and the association with SUA levels.

The main aim of the present study was to assess the relation between the consumption of dairy products and its different subtypes with the prevalence of hyperuricemia in an aged Mediterranean population with overweight/obesity and MetS.

MATERIALS AND METHODS

Study design and participants

The present study is a secondary analysis conducted within the framework of the PREDIMED-Plus study, an ongoing, 6-year, parallel group, multi-center, randomized controlled clinical trial for the CVD primary prevention involving 6,874 participants recruited in 23 Spanish recruiting centers. Participants were overweight/obese, aged between 55-75 years in the case of men and 60-75 years in the case of women, and with MetS. All participants provided written informed consent and institutional review boards of each participating center approved the final protocol and procedures. The trials' main objective is to compare the effect of two lifestyle interventions on long-term weight loss and maintenance and CVD incidence and mortality. The design of the trial has been described in detail elsewhere (29) and the study protocol is available on the PREDIMED-Plus website (30). The study was registered at the International Standard Randomized Controlled Trial (ISRCT; http://www.isrctn.com/ISRCTN89898870) under number 89898870. Registration date: July 24th, 2014.

The present study is cross-sectional and analyses baseline data from all the randomized

PREDIMED-Plus participants. For this analysis we excluded 55 participants who had not completed the food frequency questionnaire (FFQ) and 188 participants who reported total energy intake values outside the specified limits (500-3,500 kcal/day for women and 800-4,000 kcal/day for men) (31). Participants without SUA information were also excluded (n=304). The final sample for the present analysis included information from 6,329 participants. The data were analyzed using the available complete PREDIMED-Plus database, dated 17 September 2018.

Dietary and lifestyle assessment

At baseline, trained dietitians administered a 143-item semi-quantitative FFQ (32) in a face-to-face visit. The FFQ contained 15 items relating to dairy products with nine possible categories of consumption, which ranged from never or almost never to >6 portions/day for each item. Total dairy products included all types of milk, yogurt and cheese; low-fat dairy products included semi-skimmed/skimmed milk and low-fat yogurt; and whole-fat dairy products included whole-fat milk, whole-fat yogurt and cheese. Dairy food consumption was also categorized in dairy subtypes: milk (total, low-fat and whole-fat), yogurt (total, low-fat and whole-fat), cheese (petit Suisse, ricotta, cream cheese, cottage cheese and semi-cured and cured cheeses such as cheddar, manchego and Emmental) and total fermented dairy products (all types of yogurt and cheese). The information collected was converted into grams per day, multiplying serving sizes by consumption frequency and dividing the result by the period assessed. Food groups and energy intake were estimated using Spanish food composition tables (33,34).

Other covariates

Sociodemographic (age, sex, marital status, educational level) and lifestyle (smoking habit, physical activity, Mediterranean diet adherence) related variables, as well as information regarding personal, family history of illness and medication were recorded at baseline. Trained dietitians conducted all the anthropometric measurements. Weight and height were measured in duplicate, with light clothes and without shoes. Body mass index (BMI) was calculated as weight divided by height squared (kg/m^2). Waist circumference was measured with a tape measure at the mid-point between the last rib and ileac crest. We used a validated semiautomatic oscillometer (Omron HEM-705CP, Hoofddorp, The Netherlands) to measure blood pressure three times with a 5-minute interval between each reading, and the median measurement of the three readings was used. After an overnight fast, blood samples were collected and total serum uric acid, LDL-cholesterol, HDL-cholesterol, triglycerides and plasma glucose concentrations were determined by standard enzymatic methods in automatic analyzers in local laboratories. Hyperuricemia was defined as SUA levels >7mg/dL in men and >6mg/dL in women, as has been defined previously (4). Chronic kidney disease (CKD) was defined according to National Kidney Foundation classification: National kidney foundation practice guidelines for chronic kidney disease: evaluation, classification, and stratification, defined as a glomerular filtration rate <60 $mL/min/1.73m^2$ (35).

Statistical analyses.

Participants were categorized into quartiles of total dairy consumption adjusted by energy intake using the residuals method. Chi-square and one-way ANOVA tests were used for the baseline participants' characteristics. Results are expressed as mean ± SD or median and (P25, P75) for continuous variables. Cox proportional hazards regression with a robust variance estimator and constant follow-up time were fitted to estimate prevalence risk (PR) and 95% confidence interval (95% CI) for hyperuricemia by quartiles of consumption of total dairy products, low and whole-fat dairy products, total, low and whole-fat milk, yogurt and cheese. This method has been described to be more appropriate than logistic regression in cross-sectional studies when the outcome prevalence is >10%, as odds ratios (OR) could overestimate or underestimate the risk in logistic regression (36). Analyses were adjusted for different potential confounders including age, sex, BMI, education (primary education, secondary education and higher education), smoking status, physical activity and different food groups such as fruit, vegetables, meat, fish, olive oil, cereals, legumes, nut and alcohol consumption (grams per day adding a quadratic term), medication treatment for lowering SUA (yes/no) and CKD. All models were stratified by the recruiting center, and robust variance estimators to account for intra-cluster correlations (considering members of the same household as clusters) were used.

To assess the linear trend, the median values for each quartile of total dairy products and each subtype were assigned and used as continuous variables in the Cox regression models.

Interaction analyses with quartiles of total and different dairy products and subtypes and several potentially effect-modifying variables such as sex, alcohol consumption, smoking habit and CKD were tested by comparing the model with and without the product term using the likelihood ratio test. Sensitivity analysis excluding those participants who reported CKD at baseline (*n=450*) and those individuals taking medication to reduce SUA levels (*n=534*) were tested. OR is a preferred analysis to estimate associations when investigating chronic disease where the onset of disease is difficult to determine or studying long lasting risk factors. Hence, we repeated the analyses using logistic regression models as a sensitivity analysis. All the analyses were performed using Stata (15.0, StataCorp LP, Tx. USA).

RESULTS

The baseline characteristics of the participants according to energy-adjusted quartiles of total dairy product consumption are presented in **Table 1**. The median (P25, P75) consumption of total dairy products from the lowest to the highest quartile were 124 (66, 168), 253 (230, 273), 343 (317, 373) and 578 (530, 645) grams per day respectively. Compared with participants in the lowest quartile of total dairy consumption, those located in the highest were more likely to be older (P-value <0.001) and women (P-value <0.001), and there were fewer smokers (P-value <0.001). Compared with participants in the lowest quartile, those in the top quartile had lower systolic and diastolic blood pressure levels (P-value 0.005 and <0.001 respectively), triglyceride and SUA concentrations (P-value <0.001), and higher HDL-cholesterol plasma levels (P-value <0.001). The prevalence of hyperuricemia was also lower among those in the top quartile of total dairy product consumption (P-value <0.001).

Table 2 shows the unadjusted and multiadjusted PRs (95% CIs) for the prevalence of hyperuricemia across quartiles of total dairy product consumption and specific subtypes**.** After adjusting for several potential confounders, the consumption of total and low-fat dairy products was associated with a lower prevalence of hyperuricemia (Q4 vs Q1 PR= 0.84; 95% CI: 0.75-0.94; *P-trend*= 0.02 and (Q4 vs Q1 PR= 0.79; 95% CI: 0.70-0.89; P-trend <0.001 respectively). Total milk and low-fat milk consumption was associated with a lower risk of having hyperuricemia (Q4 vs Q1 PR= 0.81; 95% CI: 0.73-0.90; *P-trend* <0.001 and (Q4 vs Q1 PR= 0.80; 95% CI: 0.72-0.89; P-trend <0.001 respectively). No associations were found when comparing extreme quartiles of whole-fat dairy product and whole-fat milk consumption.

Table 3 shows the unadjusted and multiadjusted PRs (95% CIs) for the prevalence of hyperuricemia according to quartiles of consumption of total fermented dairy products and different specific dairy subtypes. High consumption of low-fat yogurt (Q4 vs Q1 PR= 0.89; 95% CI: 0.80-0.98; P-trend= 0.051) and cheese (Q4 vs Q1 PR= 0.86; 95% CI: 0.77-0.96; P-trend= 0.003) were associated with a lower prevalence of hyperuricemia. Total fermented dairy and total yogurt consumption were not associated with the prevalence of hyperuricemia.

Sensitivity analyses

We reanalyzed the results excluding those individuals taking medication to reduce SUA (*n=534*) levels and results remain in the same line. Total dairy (Q4 vs Q1 PR: 0.79; 95%CI: 0.71 to 0.88), low-fat dairy (Q4 vs Q1 PR: 0.75; 95%CI: 0.67 to 0.84), whole-fat dairy (Q4 vs Q1 PR: 0.99; 95%CI: 0.90 to 1.11), total yogurt (Q4 vs Q1 PR: 0.93; 95%CI: 0.83

to 1.04), low-fat yogurt (Q4 vs Q1 PR: 0.85; 95%CI: 0.76 to 0.94), whole-fat yogurt (Q4 vs Q1 PR: 1.05; 95%CI: 0.94 to 1.17), total milk (Q4 vs Q1 PR: 0.81; 95%CI: 0.73 to 0.90), low-fat milk (Q4 vs Q1 PR: 0.80; 95%CI: 0.72 to 0.89), whole-fat milk (Q4 vs Q1 PR: 0.96; 95%CI: 0.86 to 1.06), cheese (Q4 vs Q1 PR: 0.85; 95%CI: 0.76 to 0.95) and total fermented dairy products (Q4 vs Q1 PR: 0.91; 95%CI: 0.82 to 1.02).

No interactions were observed between the different types of dairy products and prevalence of hyperuricemia by sex, age, alcohol consumption or CKD (All, P>0.05). A sensitivity analysis excluding all individuals with CKD revealed the same magnitude of associations (data not shown).

DISCUSSION

In this cross-sectional study involving individuals with overweight/obesity and MetS from the PREDIMED-Plus cohort, we evaluated the consumption of total dairy products and their different subtypes in relation to the prevalence risk of hyperuricemia.

Our results showed an inverse association between the consumption of total dairy products, cheese, low-fat yogurt, total milk and low-fat milk and the prevalence of hyperuricemia.

Our results regarding the consumption of total dairy products and the association between SUA levels and/or hyperuricemia risk, are in line with previous studies (20)(37). In a cross-sectional analysis in the context of the NHANES-III cohort, the frequent consumption of total dairy products (>2 servings/day) was associated with lower plasma concentrations of SUA when comparing highest versus lowest quintiles (<0.5 servings/day). In addition, data from a case-control study conducted over 2,076 healthy participants from Scotland reported an inverse association between dairy consumption and urate concentrations (37). Importantly, in a 4-week randomized clinical trial conducted in 158 healthy post-menopausal nuns, those randomized to a dairy-supplemented diet maintained their SUA levels, whereas those allocated to a dairy-free diet experienced an increase in SUA levels during the intervention (26).

Our studies are partially in agreement with previous studies, with respect to specific dairy subtypes and SUA levels. Data from 14,809 participants (6,932 men and 7,877 women) aged 20 years and older in the Third National Health and Nutrition Examination Survey showed that those who consumed at least one serving/day of milk and yogurt had lower SUA levels compared to those who did not (20). Similarly, those who consumed yogurt at least once a day had lower serum uric acid levels than those who did not consume yogurt. In the NHANES III study, cheese consumption was not associated with SUA levels. Nonetheless, cheese and milk consumption were associated with lower levels of SUA in the AusDiab and Tromsø studies, and yogurt was only inversely associated with SUA concentrations in the AusDiab study when comparing highest versus lowest consumption categories (38). Moreover, in a randomized controlled cross-over trial conducted in 16 healthy males, milk intake was shown to have significant acute urate-lowering effects compared to soy milk beverages (27).

The mixed results from the different observational studies and clinical trials regarding the consumption of the different subtypes of dairy products could be explained through the differences in the categorization of dairy products included in each dairy food group with respect to its nutritional contents (20). In the same line, it is important to highlight that the amount of dairy product consumed differed between studies, and differences in the baseline characteristics of the sample populations may also contribute to the differences observed between the aforementioned studies.

Several mechanisms have been suggested to explain these associations. Casein and lactalbumin from dairy products have been shown to reduce SUA in healthy subjects through their uricosuric effect after consumption (28). Dairy products contain orotic acid, which may reduce serum urate by promoting renal uric acid excretion. The renal transporter URAT1 transports urate and orotate, and the competition between them could also be responsible for uricosuria after dairy-product consumption (21)(27). Moreover, dairy products are rich in lactose and galactose, which can activate the urate transporter/channel (hUAT) (39), thereby reducing levels of uric acid in plasma.

We observed a strong inverse relation between consumption of total dairy products, especially low-fat dairy products, and the prevalence of hyperuricemia. High consumption of low-fat dairy may also reflect an avoidance of other lifestyle factors that contribute to hyperuricemia. Furthermore, high dairy-product consumption may reflect adherence to a healthier diet and lifestyle (40). Experimental studies are warranted to clarify which compounds might modulate SUA concentrations.

In our study, we also reported lower blood pressure, LDL cholesterol concentrations, plasma triglycerides and higher levels of HDL cholesterol in those individuals located in the highest quartiles of dairy consumption, as has been previously reported (41–46). In relation to the plasma HDL cholesterol, results from epidemiological studies and clinical trials are inconsistent (43,45,46). Further evidence from randomized clinical trials in this population is required in order to establish strong cause-effect relationships. A number of limitations should be considered while interpreting the results of this study. The inherent nature of cross-sectional studies does not allow us to address causality, and a possible reverse causality bias could directly affect the interpretation of our findings. The results from this study cannot be extrapolated to other populations, since our population comprised of elderly Spanish individuals with obesity and MetS. Although, all the questionnaires were administered by trained dietitians, possible measurement errors are unavoidable. Nevertheless, the strengths of the study also warrant acknowledgement, such as the large sample sizeand the information given in relation to all the different dairy product subtypes recorded. Finally, the robustness of our results is strengthened by the adjustment of the models to take into account a large number of potential confounders, and the sensitivity analysis performed.

In conclusion, our results suggest that frequent consumption of dairy products, specifically milk, low-fat yogurt and cheese, are associated with a lower prevalence of hyperuricemia in a Spanish elderly population with overweight/obesity and MetS. The increasing burdens of hyperuricemia and obesity, further emphasizes the importance of an urgent need for the development of prevention and management strategies for hyperuricemia. Population-based epidemiological research aimed at evaluating the dietary determinants of hyperuricemia and gout should be encouraged.

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Contribution statement

G.M-S, N.B and J.S-S had full access to all the data for the present study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: N.B and J.S-S. Statistical analyses: G.M-S and N.B-T. Drafting the manuscript: G.M-S, N.B and J.S-S. All authors have critically reviewed the manuscript for important intellectual content and approved the final version.

CONFLICT OF INTEREST STATEMENT

Mena-Sánchez G – Declares no conflicts of interest.

Babio N - Declares that she has received payments from Danone S.A. for scientific and technical consulting, but not for the preparation of this study. She is one of the members of the Scientific Advisory Board of the EU program for the promotion of milk and milk products within the framework of appropriate dietary practices.

Becerra-Tomás N – Declares no conflicts of interest.

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Supplementary Table 1. Baseline characteristics of the PREDIMED-PLUS participants across energy-adjusted quartiles (Q1 vs. Q4) of total milk, total yogurt and cheese consumption.

	Total milk		Total yogurt		Cheese	
	Q1	**Q4**	**Q1**	**Q4**	**Q1**	**Q4**
	n=1,583	n=1,582	n=1,583	n=1,582	n=1,583	n=1,582
g/day, median (P25, P75)	28 (1, 68)	488 (454, 511)	3 (0, 7)	130 (126, 305)	7 (3, 11)	53 (47, 65)
Women, % (n)	40.4 (640)	57.2 (905)*	37.3 (590)	60.4 (955)*	40.5 (641)	53.8 (851)*
Age, years	64.4±5.0	65.4±5.0*	64.7±5	66.6±4.7*	64.7±5	65±4.8*
BMI, kg/m^2	32.6±3.4	32.6±3.4	32.5±3.4	32.6±3.4	32.4±3.4	32.7±3.5
Waist circumference, cm						
Males	111.4±8.7	111.1±8.7	111.2±9	110.6±8.4	110.9±8.7	111.4±8.9
Females	104.1±9.3	104.2±9.2	104±9.4	103.9±9.2	103.8±9	104.1±9.3
Systolic blood pressure, mmHg	139.6±16.5	138.8±17	140.5±16.6	138.4±17.1*	140.5±16.5	138.7±16.4*
Diastolic blood pressure, mmHg	81.2±10	80.5±9.6*	81.2±10	80.3±9.9*	81.7±9.9	80.5±9.7*
Fasting plasma glucose, mg/dL	112.6±27.5	115.8±31.9*	114.4±29.5	112.4±28.2	113.4±27.9	113.4±30.5
Plasma triglycerides, mg/dL	156.1±82.7	151.2±72.6	156.9±83.5	146.8±67.5*	160.3±83	147.5±77.7*
Plasma LDL-cholesterol, mg/dL	121.5±33.4	121.2±44	119.6±40.9	121.9±33	121.1±42	122.6±44.2
Plasma HDL-cholesterol, mg/dL	47.7±12	48.2±11.6*	46.6±11.4	49.1±11.8*	46.4±11.3	49.3±12.2*
Total plasma cholesterol, mg/dL	198.7±38.9	196.7±36.9	194.8±37.8	199.2±42.5*	196.4±37.6	198.1±38.6
Plasma uric acid, mg/dL	6.7±19	5.9±5.6	6.6±19	6±4.3	6.2±4.2	5.9±1.8
Prevalence of type 2 diabetes, % (n)	23.4 (371)	33.6 (532)	28.2 (446)	26.7 (423)	27.3 (432)	26.1 (413)*
Prevalence of hypertension, % (n)	82.6 (1.308)	82.7 (1.308)	82.9 (1.312)	83.6 (1.322)	82.7 (1.329)	83.1 (1.314)
Prevalence of hyperuricemia, % (n)	36.9 (584)	27.1 (428)*	31.9 (505)	30.2 (478)	33.8 (535)	28.9 (457)*
Physical activity, METs/min/week	2470.4±2133.3	2215.4±2103.6*	2519.6±2468	2555±2236.2*	2559.3±2394.2	2502.2±2374.2*
Smoking habit, % (n)						
Never smoked	38.3 (607)	49.9 (789)*	36.7 (581)	52 (822)*	39 (618)	46.5 (735)*
Former smoker	48.9 (774)	39 (617)*	46.2 (731)	39.6 (627)*	46.4 (734)	42.4 (670)*
Current smoker	12.8 (202)	11.1 (176)*	17.1 (271)	8.4 (133)*	14.6 (231)	11.2 (177)*
Education level, % (n)						
Primary school	43.3 (685)	53.9 (853)*	47 (744)	52.5 (830)*	48.5 (768)	45.8 (725)*
Junior high school	30 (475)	26.6 (421)*	30.7 (486)	27.3 (432)*	30.5 (483)	30 (475)*
High school or university	26.7 (423)	19.5 (308)*	22.3 (353)	20.2 (320)*	21 (332)	24.2 (382)*
Current medication use						
Antihypertensive agents	75.8 (1,200)	78.3 (1,239)	77.7 (1,231)	78 (1,234)	77.6 (1,229)	76 (1,202)
Hyperuricemia medication**	10.9 (172)	6.4 (101)*	10.6 (167)	6.13 (97)*	9.7 (153)	6.5 (102)*
Use of insulin	3 (48)	6.9 (109)*	3.5 (56)	5.1 (80)*	4.2 (66)	4.7 (75)
Anti-diabetic medication	15 (237)	22.8 (361)*	20.5 (325)	17.5 (276)	19.5 (308)	17.6 (278)

Data are presented as mean ± SD unless otherwise indicated. Pearson's chi-square test for categorical variables and one-way ANOVA for continuous variables. *Statistically significant differences between quartiles.
Abbreviations: CI, confidence interval; T2D, type 2 diabetes; PA, physical activity; BMI, body mass index; HDL, high-density lipoprotein-cholesterol¸ LDL, low-density lipoprotein-cholesterol; Q, quartile.
**Medication for hyperuricemia: allopurinol and febuxostat. Quartile cut-offs are based on energy-adjusted total dairy-product consumption, and values are medians and interquartile range (P25, P75). [¶] *P*-value for between-categories comparisons.

Supplementary Table 2. Odds ratios and 95% CI of hyperuricemia across energy-adjusted quartiles of dairy products and its different subtypes in the PREDIMED-Plus sample (model 2).

	Dairy products consumption				
	Q1	**Q2**	**Q3**	**Q4**	***P*-Trend**
Total dairy products	1.00 ref.	0.92 (0.79-1.07)	0.83 (0.71-0.97)	0.75 (0.64-0.89)	0.001
Low-fat dairy products	1.00 ref.	0.86 (0.74-1.01)	0.79 (0.67-0.93)	0.68 (0.57-0.80)	<0.001
Whole-fat dairy products	1.00 ref.	0.87 (0.75-1.02)	0.86 (0.73-1.00)	1.03 (0.87-1.20)	0.261
Total milk	1.00 ref.	0.90 (0.76-1.03)	0.79 (0.70-0.92)	0.70 (0.60-0.83)	<0.001
Low-fat milk	1.00 ref.	0.92 (0.80-1.07)	0.83 (0.72-0.97)	0.68 (0.58-0.80)	<0.001
Whole-fat milk	1.00 ref.	0.97 (0.83-1.13)	0.90 (0.77-1.06)	0.94 (0.80-1.10)	0.466
Total fermented dairy	1.00 ref.	1.09 (0.93-1.27)	1.07 (0.91-1.24)	0.95 (0.81-1.11)	0.416
Total yogurt	1.00 ref.	1.14 (0.98-1.33)	1.06 (0.91-1.24)	0.99 (0.85-1.16)	0.754
Low-fat yogurt	1.00 ref.	0.93 (0.79-1.08)	0.99 (0.85-1.15)	0.83 (0.72-0.98)	0.054
Whole-fat yogurt	1.00 ref.	0.90 (0.77-1.05)	0.83 (0.70-0.97)	1.15 (0.98-1.34)	0.002
Cheese	1.00 ref.	0.97 (0.83-1.13)	0.92 (0.79-1.07)	0.79 (67-0.93)	0.002

Abbreviations: CI, confidence interval, IQR, interquartile range; Q, quartile.
1 Logistic regression: Model 1 (data not shown) was adjusted for: sex, age (years), education level (primary education, secondary education and academic/graduate, physical activity (MET-min/day), BMI (kg/m^2), smoking habit and alcohol intake (adding a quadratic term). Model 2 was also adjusted for hyperuricemia treatment (yes/no), chronic kidney disease (yes/no) and different food items: fruit, vegetable, legume, cereals, meat, fish, olive oil, nuts, cookies and dairy products subtypes (as continuous variables) depending on the interest variable.
Quartiles cut-offs are based in energy-adjusted total dairy consumption, and values are medians and interquartile range (IQR).

Table 1. Baseline characteristics of the PREDIMED-PLUS participants across energy-adjusted quartiles of total dairy products consumption.

	Total dairy products consumption				
	Q1	**Q2**	**Q3**	**Q4**	***p*** [¶]
	n=1,583	n=1,583	n=1,582	n=1,582	
g/day, median (IQR)	124 (66, 168)	253 (230, 273)	343 (317, 373)	578 (530, 645)	
Women, % (n)	35.3 (559)	42.7 (675)	58 (918)	57.3 (907)	<.001
Age, years	64.3±5.0	64.8±4.8	65.1±4.9	65.5±4.9	<.001
BMI, kg/m^2	32.6±3.4	32.5±3.5	32.7±3.4	32.6±3.5	.371
Waist circumference, cm					
Males	111.2±8.9	111.1±8.9	110.8±8.5	111±8.7	.860
Females	104.3±9.5	103.5±9	103.8±9.3	104.3±9.2	.288
Systolic blood pressure, mmHg	140.1±16.6	140.5±16.4	139.1±17.3	138.7±16.8	.005
Diastolic blood pressure, mmHg	81.4±9.9	81.3±9.9	79.9±9.9	80.6±9.8	<.001
Fasting plasma glucose, mg/dL	113.6±29.3	113.7±27.7	112±27.9	115.5±32	.010
Plasma triglycerides, mg/dL	158.8±84.3	153.8±83.8	147.2±68.8	149.5±72.8	<.001
Plasma LDL-cholesterol, mg/dL	120.6±33.2	120.3±40.9	123.8±49.4	120.1±33.5	.037
Plasma HDL-cholesterol, mg/dL	47±11.9	48±11.9	48.6±11.9	48.6±11.7	<.001
Total plasma cholesterol, mg/dL	197.7±38.4	195.9±37.8	198±37.5	197±42	.450
Plasma uric acid, mg/dL	6.8±19	6.1±1.5	6±4.4	5.9±5.6	.079
Glomerular filtration rate, mL/min	84.8±14.5	84.3±14.3	83.4±14.5	83.7±14.3	.004
Prevalence of type 2 diabetes, % (n)	25.1 (397)	26.8 (424)	25.5 (404)	32.8 (519)	<.001
Prevalence of hypertension, % (n)	82.4 (1.305)	84.8 (1.341)	83.3 (1.318)	82.6 (1.307)	.282
Prevalence of hyperuricemia, % (n)	36.5 (577)	33.3 (526)	30.5 (483)	27.4 (434)	<.001
Prevalence of Chronic Kidney Disease, % (n)	6.9 (108)	7 (110)	6.2 (97)	6.7 (105)	.072
Physical Activity, METs/min/week	2527.2±2235.8	2490.2±2362.4	2517.2±2295.1	2296±2202.8	.012
Smoking habit, % (n)					
Never smoked	34.9 (553)	40.7 (644)	50.8 (804)	51.3 (812)	
Former smoker	49.7 (787)	45.9 (726)	38.8 (614)	38.6 (610)	<.001
Current smoker	15.4 (243)	13.4 (212)	10.4 (164)	10.1 (160)	
Education level, % (n)					
Primary school	43.5 (689)	48.7 (771)	51.6 (817)	43.7 (850)	
First-degree high school	30.5 (483)	29.9 (473)	28 (443)	26.7 (423)	<.001
High school or university	26 (411)	21.4 (338)	20.4 (322)	19.5 (309)	
Current medication use					
Antihypertensive agents	76.9 (1,217)	76.9 (1,217)	77.9 (1,233)	78.8 (1,246)	.529
Hyperuricemia medication*	11.3 (179)	9 (143)	7.3 (115)	6.1 (97)	<.001
Use of insulin	2.8 (44)	3.9 (61)	4.7 (75)	6.7 (106)	<.001
Anti-diabetic medication	17 (269)	18.5 (293)	17.6 (278)	22.4 (354)	<.001

Data is presented as mean ± SD unless otherwise indicated. Pearson's chi-square test for categorical variables and one-way ANOVA for continuous variables.
Abbreviations: CI, confidence interval, IQR, interquartile range; T2D, Type 2 Diabetes; PA, Physical Activity.
BMI, Body mass index; HDL, High-density lipoprotein-cholesterol¸ LDL, Low-density lipoprotein-cholesterol; Q. Quartile.
*Medication for hyperuricemia: Alopurinol and febuxostat.
Quartiles cut-offs are based in energy-adjusted total dairy products consumption, and values are medians and interquartile range (IQR).
[¶] *P*-value for between-categories comparisons.

Table 2. PR and 95% CI[1] of hyperuricemia across energy-adjusted quartiles of total dairy products, low and whole-fat dairy products total milk, low and whole fat milk in the PREDIMED-Plus sample.

	Dairy consumption				
	Q1	**Q2**	**Q3**	**Q4**	***P*-Trend**
Total dairy products					
g/day, median (P25-P75)	124 (66, 168)	253 (230, 273)	343 (317, 373)	578 (530, 645)	
Hyperuricemia, % (n)	36.5 (577)	33.3 (526)	30.5 (483)	27.4 (434)	
Unadjusted model	1.00 ref.	0.91 (0.83-0.99)	0.83 (0.75-0.92)	0.76 (0.75-0.92)	<.001
Model 1	1.00 ref.	0.94 (0.85-1.03)	0.86 (0.78-0.96)	0.81 (0.73-0.91)	<.001
Model 2	1.00 ref.	0.94 (0.86-1.04)	0.88 (0.79-0.97)	0.84 (0.75-0.94)	.002
Low-fat dairy products					
g/day, median (P25-P75)	15 (0, 60)	191 (159, 204)	264 (237, 310)	518 (490, 586)	
Hyperuricemia, % (n)	36.7 (581)	34 (538)	30.5 (483)	26.4 (418)	
Unadjusted model	1.00 ref.	0.93 (0.85-1.02)	0.83 (0.75-0.92)	0.74 (0.67-0.82)	<.001
Model 1	1.00 ref.	0.93 (0.85-1.02)	0.85 (0.77-0.94)	0.77 (0.69-0.85)	<.001
Model 2	1.00 ref.	0.93 (0.84-1.02)	0.87 (0.78-0.96)	0.79 (0.70-0.89)	<.001
Whole-fat dairy products					
g/day, median (P25-P75)	8 (0, 16)	35 (29, 40)	61 (53, 72)	162 (119, 239)	
Hyperuricemia, % (n)	33.5 (530)	30.3 (479)	30.2 (477)	33.8 (534)	
Unadjusted model	1.00 ref.	0.89 (0.81-0.99)	0.89 (0.80-0.99)	0.99 (0.90-1.10)	.341
Model 1	1.00 ref.	0.90 (0.82-1.01)	0.90 (0.81-1.01)	1.02 (0.92-1.12)	.188
Model 2	1.00 ref.	0.91 (0.82-1.01)	0.90 (0.81-0.99)	1.01 (0.91-1.12)	.315
Total milk					
g/day, median (P25-P75)	28 (1, 68)	173 (153, 187)	215 (207, 226)	488 (454, 511)	
Hyperuricemia, % (n)	36.9 (584)	33 (522)	30.7 (486)	27.1 (428)	
Unadjusted model	1.00 ref.	0.90 (0.82-0.99)	0.83 (0.75-0.91)	0.76 (0.68-0.84)	<.001
Model 1	1.00 ref.	0.90 (0.82-1.00)	0.86 (0.77-0.95)	0.79 (0.77-0.95)	<.001
Model 2	1.00 ref.	0.93 (0.85-1.02)	0.86 (0.78-0.95)	0.81 (0.73-0.90)	<.001
Low-fat milk					
g/day, median (P25-P75)	2 (0, 14)	162 (94, 181)	205 (199, 211)	490 (452, 506)	
Hyperuricemia, % (n)	36.5 (578)	33.6 (532)	31.4 (497)	26.1 (413)	
Unadjusted model	1.00 ref.	0.94 (0.85-1.03)	0.85 (0.77-0.93)	0.74 (0.77-0.93)	<.001
Model 1	1.00 ref.	0.95 (0.79-0.96)	0.87 (0.79-0.96)	0.77 (0.69-0.86)	<.001
Model 2	1.00 ref.	0.97 (0.89-1.07)	0.88 (0.80-0.98)	0.80 (0.72-0.89)	<.001
Whole-fat milk					
g/day, median (P25-P75)	0 (0)	0 (0)	7 (5, 9)	35 (16, 182)	
Hyperuricemia, % (n)	32.8 (519)	32 (506)	31 (491)	31.7 (504)	
Unadjusted model	1.00 ref.	0.96 (0.87-1.06)	0.92 (0.83-1.02)	0.96 (0.87-1.07)	.633
Model 1	1.00 ref.	0.98 (0.88-1.10)	0.95 (0.83-1.09)	0.98 (0.85-1.11)	.930
Model 2	1.00 ref.	0.96 (0.87-1.07)	0.92 (0.83-1.02)	0.96 (0.86-1.06)	.531

Abbreviations: CI, confidence interval, IQR, interquartile range; Q, quartile.

[1]Cox regression Model 1 was adjusted for: sex, age (years), education level (primary education, secondary education and academic/graduate, physical activity (MET-min/day), BMI (kg/m^2), smoking habit and alcohol intake (adding a quadratic term). Model 2 was also adjusted for hyperuricemia treatment (yes/no), chronic kidney disease (yes/no) and different food items: fruit, vegetable, legume, cereals, meat, fish, olive oil, nuts, cookies and dairy products subtypes (as continuous variables) depending on the interest variable.

Quartiles cut-offs are based in energy-adjusted total dairy consumption, and values are medians and interquartile range (IQR).

Table 3. PR and 95% CI[1] of hyperuricemia across energy-adjusted quartiles of total fermented dairy products and its different subtypes in the PREDIMED-Plus sample.

	Fermented dairy consumption				
	Q1	**Q2**	**Q3**	**Q4**	***P*-Trend**
Total fermented dairy					
g/day, median (P25-P75)	24 (14, 34)	68 (58, 78)	122 (101, 136)	176 (158, 315)	
Hyperuricemia, % (n)	32.5 (514)	33.1 (523)	32.2 (510)	29.9 (473)	
Unadjusted model	1.00 ref.	1.00 (0.91-1.11)	0.97 (0.88-1.08)	0.92 (0.83-1.02)	.080
Model 1	1.00 ref.	1.03 (0.93-1.14)	1.00 (0.91-1.11)	0.95 (0.85-1.05)	.243
Model 2	1.00 ref.	1.04 (0.94-1.15)	1.02 (0.92-1.12)	0.95 (0.85-1.06)	.271
Total yogurt					
g/day, median (P25-P75)	3 (0, 7)	48 (21, 52)	94 (59, 114)	130 (126, 305)	
Hyperuricemia, % (n)	31.9 (505)	33.6 (532)	31.9 (505)	30.2 (478)	
Unadjusted model	1.00 ref.	1.03 (0.94-1.14)	0.98 (0.89-1.08)	0.94 (0.84-1.04)	.156
Model 1	1.00 ref.	1.05 (0.95-1.16)	1.00 (0.91-1.11)	0.98 (0.88-1.08)	.527
Model 2	1.00 ref.	1.07 (0.97-1.18)	1.01 (0.92-1.12)	0.98 (0.88-1.08)	.496
Low-fat yogurt					
g/day, median (P25-P75)	0 (0)	5 (3, 9)	53 (51, 56)	125 (122, 130)	
Hyperuricemia, % (n)	33.5 (530)	32.3 (511)	32.7 (518)	29.1 (461)	
Unadjusted model	1.00 ref.	0.96 (0.87-1.06)	0.97 (0.88-1.08)	0.87 (0.79-0.97)	.018
Model 1	1.00 ref.	0.90 (0.81-1.01)	0.96 (0.87-1.06)	0.87 (0.78-0.96)	.046
Model 2	1.00 ref.	0.94 (0.86-1.04)	0.98 (0.89-1.09)	0.89 (0.80-0.98)	.051
Whole-fat yogurt					
g/day, median (P25-P75)	0 (0)	2 (0, 3)	9 (7, 11)	57 (43, 117)	
Hyperuricemia, % (n)	32.7 (518)	30.7 (486)	29.1 (461)	35.1 (555)	
Unadjusted model	1.00 ref.	0.92 (0.83-1.02)	0.89 (0.80-0.98)	1.04 (0.95-1.16)	.022
Model 1	1.00 ref.	0.92 (0.82-1.03)	0.87 (0.76-0.99)	1.05 (0.94-1.17)	.008
Model 2	1.00 ref.	0.93 (0.84-1.03)	0.89 (0.80-0.98)	1.08 (0.98-1.19)	.004
Cheese					
g/day, median (P25-P75)	7 (3, 11)	20 (17, 23)	32 (29, 37)	53 (47, 65)	
Hyperuricemia, % (n)	33.8 (535)	33.3 (526)	31.7 (502)	28.9 (457)	
Unadjusted model	1.00 ref.	0.98 (0.89-1.09)	0.93 (0.84-1.03)	0.86 (0.78-0.96)	.002
Model 1	1.00 ref.	0.98 (0.84-1.03)	0.93 (0.84-1.03)	0.86 (0.78-0.96)	.002
Model 2	1.00 ref.	0.99 (0.89-1.09)	0.94 (0.85-1.04)	0.86 (0.77-0.96)	.003

Abbreviations: CI, confidence interval, IQR, interquartile range; Q, quartile.

[1]Cox regression Model 1 was adjusted for: sex, age (years), education level (primary education, secondary education and academic/graduate, physical activity (MET-min/day), BMI (kg/m^2), smoking habit and alcohol intake (adding a quadratic term). Model 2 was also adjusted for hyperuricemia treatment (yes/no), chronic kidney disease (yes/no) and different food items: fruit, vegetable, legume, cereals, meat, fish, olive oil, nuts, cookies and dairy products subtypes (as continuous variables) depending on the interest variable.

Quartiles cut-offs are based in energy-adjusted total dairy consumption, and values are medians and interquartile range (IQR).

Highlights of the core findings within the manuscript titled "ASSOCIATION BETWEEN DAIRY PRODUCT CONSUMPTION AND HYPERURICEMIA IN AN ELDERLY POPULATION WITH METABOLIC SYNDROME".

- Total dairy products consumption is associated with a lower prevalence risk of hyperuricemia.
- Milk, low-fat yogurt and cheese consumption is associated with a lower prevalence risk of hyperuricemia.
- Whole fat dairy products and the different subtypes are not related with hyperuricemia.

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