The Journal of Nutrition
Nutrition and Disease

Consumption of Yogurt, Low-Fat Milk, and Other Low-Fat Dairy Products Is Associated with Lower Risk of Metabolic Syndrome Incidence in an Elderly Mediterranean Population[1–3]

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Abstract

Background: The association between consumption of dairy products and the risk of developing metabolic syndrome (MetS) is unclear.

Objective: The purpose of this study was to evaluate the associations between consumption of dairy products (total and different subtypes) and incident MetS in a Mediterranean population at high cardiovascular disease risk.

Methods: We prospectively analyzed 1868 men and women (55–80 y old) without MetS at baseline, recruited from different PREDIMED (Prevención con Dieta Mediterránea) centers between October 2003 and June 2009 and followed up until December 2010. MetS was defined according to updated, harmonized criteria. At baseline and yearly thereafter, we determined anthropometric variables, dietary habits by a 137-item validated food-frequency questionnaire, and blood biochemistry. Multivariable-adjusted HRs of MetS or its components were estimated for each of the 2 upper tertiles (vs. the lowest one) of mean consumption of dairy products during the follow-up.

Results: During a median follow-up of 3.2 y, we documented 930 incident MetS cases. In the multivariable-adjusted model, HRs (95% CIs) of MetS for the comparison of extreme tertiles of dairy product consumption were 0.72 (0.61, 0.86) for low-fat dairy, 0.73 (0.62, 0.86) for low-fat yogurt, 0.78 (0.66, 0.92) for whole-fat yogurt, and 0.80 (0.67, 0.95) for low-fat milk. The respective HR for cheese was 1.31 (1.10, 1.56).

Conclusions: Higher consumption of low-fat dairy products, yogurt (total, low-fat, and whole-fat yogurt) and low-fat milk was associated with a reduced risk of MetS in individuals at high cardiovascular disease risk from a Mediterranean population. Conversely, higher consumption of cheese was related to a higher risk of MetS. This trial was registered at controlled-trials.com as ISRCTN35739639. *J Nutr* 2015;145:2308–16.

Keywords: dairy products, metabolic syndrome, milk, yogurt, metabolic syndrome components, PREDIMED study

Introduction

Metabolic syndrome (MetS)[19] comprises a cluster of risk factors, including abnormal obesity, dyslipidemia, increased blood pressure, and high fasting plasma glucose, which markedly increase the risk of type 2 diabetes (T2D) and cardiovascular disease (CVD) (1).

Manuscript received April 1, 2015. Initial review completed May 11, 2015. Revision accepted July 27, 2015.
First published online August 19, 2015; doi:10.3945/jn.115.214593.

Diet and lifestyle are recognized as key elements in the prevention (2) and treatment of MetS (3). In recent years, a growing body of evidence has shown that the consumption of dairy products may have beneficial effects on risk factors defining MetS, including atherogenic dyslipidemia (4), hyperglycemia (5), insulin resistance (6) or T2D (7–9), blood pressure (10), and abdominal obesity (11).

In epidemiologic studies, the association between the total consumption of dairy products and the risk of MetS has been controversial. Some cross-sectional (4, 12–15) and prospective studies (5, 16, 17) have shown an inverse association, whereas others (18–20) have shown no association. Results by sex have also been inconsistent (18, 19).

Although most studies suggest that total dairy consumption could provide protection against the development of MetS, methodologic biases or multiple combinations of different types of dairy product with varying nutrient content may have contributed to the controversial results reported. Few studies have analyzed these associations across different dairy product subtypes. Some cross-sectional studies have reported an inverse association (15, 19) that was not found when data were analyzed prospectively (5). For example, in the case of cheese consumption, cross-sectional studies showed a positive association with MetS prevalence (19), whereas prospective studies showed a negative one (5, 17). Pereira et al. (5) showed an inverse association with total consumption of dairy products regardless of their fat content, whereas Louie et al. (20) found this inverse association only for whole-fat dairy products.

To the best of our knowledge, of the 4 prospective studies published to date on the relation between dairy product consumption and MetS incidence, 3 were conducted in healthy adult populations (5, 17, 20) and only 1 in older individuals (21), in whom MetS is more prevalent and potentially has more repercussions on health (22). In addition, only one study explored the associations for different dairy subtype products (5). Therefore, the aim of the present study was to examine the relation between the consumption of dairy products (whole or low-fat options) and risk of MetS in an older Mediterranean population in the frame of the PREDIMED (Prevención con Dieta Mediterránea) study.

Methods

Study design, participants, and outcome. The present study was conducted within the framework of the PREDIMED trial, the design of which has been described in detail elsewhere (23, 24). The PREDIMED study is a large, parallel-group, multicenter, randomized, controlled field trial aimed at assessing the effects of the Mediterranean diet on the primary prevention of CVD (25). The main results of the trial with respect to the primary endpoint have been published recently (26).

Briefly, 7447 community-dwelling men (aged 55–80 y) and women (aged 60–80 y) with no previously documented CVD were recruited. They were eligible if they had either T2D or ≥3 of the following CVD risk factors: hypertension (systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg or on antihypertensive medication), high plasma LDL cholesterol (≥160 mg/dL), low plasma HDL cholesterol (<40 mg/dL in men; <50mg/dL in women), overweight or obesity (BMI ≥25 kg/m^2), current smoking, or a family history of premature coronary heart disease (23). From October 2003 to June 2009, participants were randomly assigned to 3 intervention groups (2 of which were advised to follow a Mediterranean diet supplemented with either 1 L/wk extra-virgin olive oil or 30 g/d mixed nuts, and were compared with the third group, which was advised to follow a control low-fat diet). The study follow-up ended in December 2010. All participants provided their informed consent and the protocol was approved by the institutional review boards of each recruitment center.

In the present report, the data were analyzed assuming the design of an observational prospective cohort whose members were selected from all the PREDIMED recruiting centers with biochemical determinations available for a follow-up of ≥2 y (n = 5801). Because our aim was to explore the associations between the consumption of dairy foods and incident MetS, we excluded participants who had diagnoses of MetS at baseline (63.9%; n = 3707). We also excluded participants who had not completed the baseline FFQ or who reported an extreme total energy intake with values outside the prespecified limits (500–3500 kcal/d in women and 800–4000 kcal/d in men). A total of 2094 individuals were assessed. Of these, a total of 226 were excluded because of missing data that prevented the presence of MetS incidence from being determined. Thus, a total of 1868 participants were included in our longitudinal assessment for MetS incidence. The individual components of MetS—abdominal obesity, hypertriglyceridemia, low HDL cholesterol, high blood pressure, and high fasting glucose concentration—were analyzed for a total of 1386, 3539, 3745, 337, and 1844 participants (from 5801 participants initially considered with biochemical determinations available for a follow-up of ≥2 y), respectively.

The primary endpoint of the PREDIMED trial was a combination of several major cardiovascular clinical events (myocardial infarction, stroke, or CVD death). In the present analysis, incident MetS and its components were considered as the outcome.

MetS was defined in accordance with the updated harmonized criteria of the International Diabetes Federation and the AHA/National Heart, Lung, and Blood Institute (1). Individuals were diagnosed with MetS if they had ≥3 of the following components: hypertriglyceridemia

[1] This study was funded in part by the Spanish Ministry of Health (PI1001407, PI13/00462, PI052584, and PI071138), Thematic Network G03/140, RD06/0045, the European Regional Development Fund, and the Catalan Nutrition Center of the Institute of Catalan Studies. None of the funding sources played a role in the design, collection, analysis, or interpretation of the data or in the decision to submit the manuscript for publication. The Center of Biomedical Research in Physiopathology of Obesity and Nutrition (CIBEROBN) is an initiative of Health Institute Carlos III (ISCIII), Spain.

[2] Author disclosures: N Babio received consulting fees from Danone. R Estruch served on the board of, and received lecture fees from, the Research Foundation on Wine and Nutrition; served on the boards of the Beer and Health Foundation and the European Foundation for Alcohol Research; received lecture fees from Cerveceros de España and Sanofi-Aventis; and received grant support through his institution from Novartis. E Ros served on the board of, and received travel support and grant support through his institution from the California Walnut Commission; served on the board of the Flora Foundation (Unilever); served on the board of, and received lecture fees from, Roche; served on the board of, and received grant support through his institution from Amgen; received consulting fees from Damm and Abbott Laboratories; received consulting fees, lecture fees, and grant support through his institution from Merck; received lecture fees from Danone, Pace, AstraZeneca, and Rottapharm; received lecture fees and payment for the development of educational presentations and grant support through his institution from Ferrer; received payment for the development of educational presentations from Recordati; and received grant support through his institution from Sanofi-Aventis, Takeda, Daiichi Sankyo, Nutrexpa, Feiraco, Unilever, and Karo Bio. L Serra-Majem is a member of the Scientific Advisory Board and received consulting fees and grant support from the European Hydratation Institute, received lecture fees from the International Nut Council, and received travel support from Nestle. F Arós received payment for the development of educational presentations from Menarini and Astra Zeneca. RM Lamuela-Raventós serves on the board of, and received lecture fees from, the Research Foundation on Wine and Nutrition; received lecture fees from Cerveceros de España; and received lecture fees and travel support from PepsiCo. J Salas-Salvadó served on the board of, and received grant support through his institution from the International Nut and Dried Fruit Council; received consulting fees from Danone; and received grant support through his institution from Eroski and Nestlé. N Becerra-Tomás, MÁ Martínez-González, D Corella, C Sayón-Orea, M Fitó, J Lapetra, E Gómez-Gracia, M Fiol, A Díaz-López, JV Sorlí, and JA Martínez, no conflicts of interest.

[3] Supplemental Tables 1 and 2 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 http://jn.nutrition.org.

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[19] Abbreviations used: CARDIA, Coronary Artery Risk Development in Young Adults; CVD, cardiovascular disease; ICC, intraclass correlation coefficient; MetS, metabolic syndrome; PREDIMED, Prevención con Dieta Mediterránea; T2D, type 2 diabetes.

[≥150 mg/dL (≥1.7 mmol/L)] or drug treatment for elevated TGs; low concentrations of HDL cholesterol [<50 mg/dL (<1.3 mmol/L) and <40mg/dL (<1.03 mmol/L) in women and men, respectively] or drug treatment for low HDL cholesterol; elevated blood pressure (systolic ≥130 mmHg and/or diastolic ≥85 mmHg) or being treated for hypertension; high fasting plasma glucose [≥100 mg/dL (≥5.5 mmol/L)] or drug treatment for hyperglycemia; and elevated waist circumference for European individuals (≥88 cm in women and ≥102 cm in men.

Dietary assessment. At baseline and yearly during follow-up, dietary intake was quantified by trained dietitians with a 137-item semi-quantitative FFQ validated for the PREDIMED study (27). In the validation study, the FFQ was administered twice to explore reproducibility at 1 y; 4 3-d dietary records for the different seasons of the year were used as gold standard. The reproducibility of the FFQ used in PREDIMED for food groups and energy and nutrient intake, explored by the Pearson correlation coefficient, ranged from 0.50 to 0.82, and the intraclass correlation coefficient (ICC) ranged from 0.63 to 0.90. The validity indexes of the FFQ in relation to the dietary records for food groups and energy and nutrient intake ranged from 0.24 to 0.72, whereas the range of the ICC was between 0.40 and 0.84. Regarding dairy product consumption, the reproducibility and validity of FFQs were 0.81 (ICC 0.89), and 0.72 (ICC 0.84), respectively.

Dairy product consumption was assessed yearly with the use of 15 items from the FFQ. In order to assess habitual dietary intake over the previous year, frequencies of consumption were measured in 9 categories (ranging from never/almost never to >6 servings/d) for each food item. These responses to individual dairy items were then converted into mean daily consumption (grams per day) during the follow-up by multiplying the typical portion sizes (grams) by the consumption frequency for each food and making the appropriate division for the period assessed to obtain daily consumption. The total dairy foods category included low-fat/skim milk and skim yogurt, whole milk, condensed milk, whole yogurt, custard, and all types of cheeses, including petit Swiss, ricotta, cottage, and semicured/cured cheeses such as cheddar, Manchego, and Emmentaler). Low-fat dairy foods included low-fat/skim milk and skim yogurt, whole-fat dairy foods (whole milk and whole yogurt), and total dairy foods, including all of the above. Consumption of dairy products was also categorized by subtype, including milk (including total, low-fat and whole milk), yogurt (including total, low-fat and whole-fat yogurt), and cheese. Energy and nutrient intake and food groups were calculated from Spanish food composition tables (28, 29). We adjusted dairy consumption for total energy intake with the use of the nutrient residual method (30).

Measurements. Participants completed the following at baseline and yearly: *1*) a questionnaire about lifestyle variables, medical history, and medication use; *2*) a 14-item validated questionnaire (31) designed to assess adherence to the Mediterranean diet; *3*) a validated 137-item semiquantitative FFQ (27); and *4*) the validated Spanish version (32) of the Minnesota Leisure-Time Physical Activity Questionnaire. In addition, anthropometric variables and blood pressure were determined by trained staff. Blood pressure was measured in triplicate with the use of a validated semiautomatic oscillometer with a 5 min interval between measurements and the subject in a sitting position (Omron HEM-705CP).

Blood samples were collected after an overnight fast, coded, shipped to a central laboratory, and stored at −80°C until analysis. Biochemical analysis was performed in local laboratories. Glucose was measured by the glucose-oxidase method, cholesterol by esterase-oxidase-peroxidase, TGs by glycerol-phosphate oxidase-peroxidase, and HDL cholesterol by direct measurement. All local laboratories satisfied external quality-control requirements. When TGs were <300 mg/dL, LDL cholesterol was calculated with the use of the Friedewald formula so that the LDL cholesterol was not underestimated. A concordance study of 9 laboratories was conducted. From each study, a mean of 200 samples were analyzed for total cholesterol, HDL cholesterol, and TGs with the use of the Medical Research Institute of del Mar laboratory as reference. The Medical Research Institute of del Mar laboratory used ABX-Horiba commercial kits in a PENTRA-400 autoanalyzer (ABX-Horiba). One center was unable to provide samples for the concordance study.

The analysis of concordance of lipid measurements showed an r^2 and an ICC (95% CI) between 0.85 and 0.97, and 0.85 (0.77, 0.90) and 0.97 (0.95, 0.98) for total cholesterol, respectively; between 0.819 and 0.92, and 0.81 (0.78, 0.83) and 0.92 (0.89, 0.95) for HDL cholesterol, respectively; between 0.81 and 0.99, and 0.81 (0.73, 0.87) and 0.99 (0.99, 0.99) for triglycerides, respectively; and between 0.82 and 0.96, and 0.82 (0.74, 0.88) and 0.99 (0.99, 0.99) for glucose, respectively.

Statistical analysis. We averaged the intake reported during the baseline interview and the yearly consumption during the follow-up. Then, participants were categorized into tertiles of the mean consumption of total dairy products and different subtypes during the follow-up. To better represent the long-term consumption of dairy products and to minimize within-person variation, we used the mean energy-adjusted dairy consumption for all analyses based on assessments of items from all FFQs, which were administered at baseline and yearly during the follow-up for those participants who did not develop MetS. For those who did develop MetS, and given that participants can alter their dietary pattern after developing MetS, we only used data from all the available FFQs until the year before MetS was diagnosed. The baseline characteristics of the participants are expressed as mean ± SD or median (IQR) for continuous variables and number and percentages for categorical variables. Chi-square and 1-factor ANOVA tests were used to assess differences in the baseline characteristics of the study population.

Multivariable time-dependent Cox proportional regression models were fitted to assess the HRs of developing MetS and its components during follow-up according to tertiles of consumption of total, low-fat, and whole-fat dairy products; milk, low-fat milk, and whole milk; total yogurt, low-fat yogurt, and whole-fat yogurt; and cheese. Both upper tertiles were compared with the lowest tertile (reference). The assumption of proportional hazards was tested with the use of time-dependent covariates.

The time variable was the interval between random assignment and the date of the last follow-up, or the last recorded clinical event (MetS incidence) of participants who were still alive, whichever occurred first. Participants who were free of MetS or who were lost during follow-up were censored at the date of the last visit.

Three different Cox regression models were adjusted for potential confounding factors. Model 1 was adjusted for intervention group; sex; age (years); leisure time physical activity (metabolic equivalent task · d); BMI (kilograms per meter squared); current smoker (yes/no); former smoker (yes/no); and hypoglycemic, hypolipidemic, antihypertensive, and insulin treatment at baseline. Model 2 was additionally adjusted for mean consumption during follow-up of vegetables, fruit, legumes, cereals, fish, red meat, cookies, olive oil, and nuts (all grams per day), as well as alcohol (grams per day and quadratic term). Model 3 was adjusted for model 2 plus the prevalence of MetS components at baseline, including abdominal obesity (yes/no), hypertriglyceridemia (yes/no), low HDL cholesterol (yes/no), hypertension (yes/no), and high fasting plasma glucose (yes/no).

Statistical interaction between tertiles of total dairy consumption and its different subtypes, and potential effect-modifying variables, such as sex and intervention group, was assessed by including product terms in the models. To assess the linear trend, the median value of each tertile of dairy product and the different dairy subtypes was assigned and used as a continuous variable in the Cox regression models. The level of significance for all statistical tests was $P < 0.05$ for bilateral contrast. The Benjamini-Hochberg method was used to correct P values for multiple comparisons (33).

We also conducted a sensitivity analysis of a number of MetS components at baseline to test the robustness of our results. The main analysis was stratified by those individuals who did not have any components of MetS or had one, or who had 2 components. This was done to prevent possible bias effects, because it is easier for those who already have 2 criteria to meet the diagnostic definition than those with one or none.

All analyses were performed with SPSS software, version 19.0.

Results

After a median of 3.2 y of follow-up (IQR: 1.9, 5.8), 930 participants without MetS at baseline (53.8% women) developed new-onset MetS. Of those not showing the specific MetS components at baseline, 43.4% of 1040 participants developed abdominal obesity during follow-up, 27.7% of 1770 developed hypertriglyceridemia, 24.5% of 1810 developed low HDL

TABLE 1 Baseline characteristics of study individuals at high cardiovascular disease risk by tertiles of total dairy consumption[1]

	Total dairy consumption,[2] g/d			
	T1 (≤287; *n* = 622)	T2 (287–449; *n* = 623)	T3 (≥450; *n* = 623)	*P*[2]
Total dairy consumption, median (P25, P75)	207 (142, 250)	354 (322, 393)	577 (518, 661)	
Age, y	66.0 (6.0)	67.0 (5.9)	67.7 (6.2)	<0.001
Women, % (*n*)	38.7 (241)	52.6 (328)	66.0 (411)	<0.001
Waist circumference, cm				
Women	92.3 ± 10.6	92.43 ± 10.3	92.5 ± 10.8	0.84
Men	98.8 ± 7.9	97.4 ± 7.6	97.5 ± 7.3	0.042
BMI, kg/m^2	28.2 ± 3.4	28.3 ± 3.4	28.6 ± 3.7	0.08
Leisure time physical activity, MET · min/d	297 ± 260	273 ± 258	253 ± 242	0.010
Former smokers, % (*n*)	33.6 (209)	24.7 (154)	19.3 (120)	<0.001
Current smokers, % (*n*)	19.3 (120)	14.6 (91)	13.2 (82)	0.008
Blood pressure, mm Hg				
Systolic	147.6 ± 20.3	145.7 ± 19.6	145.7 ± 21.5	0.18
Diastolic	82.6 ± 10.9	81.9 (10.5)	81.6 ± 10.9	0.25
Biochemistry, mg/dL				
Plasma fasting blood glucose	101.7 ± 27.9	102.5 ± 32.1	107.5 ± 39.0	0.004
Serum HDL cholesterol	56.0 (49.0, 66.0)	58.0 (51.0, 68.0)	60.0 (53.0, 68.2)	0.001
Serum TGs	99.9 (77.0, 122)	95.0 (75.0, 118)	94.0 (73.0, 118)	0.022
Current medication use, % (*n*)				
Use of hypoglycemic agents	12.3 (76)	14.5 (90)	16.4 (102)	0.12
Use hypolipidemic agents	45.0 (280)	46.7 (291)	46.5 (290)	0.66
Use of antihypertensive agents	65.6 (408)	66.6 (415)	63.4 (395)	0.46
Insulin treatment	3.2 (20)	2.7 (17)	7.1 (44)	<0.001
MetS components, % (*n*)				
Abdominal obesity	41.2 (255)	41.4 (256)	49.1 (303)	0.006
Hypertriglyceridemia	6.9 (43)	5.3 (33)	3.4 (21)	0.019
Low HDL cholesterol	2.6 (16)	3.4 (21)	3.1 (19)	0.71
High blood pressure	88.9 (552)	87.3 (543)	85.1 (530)	0.13
High fasting plasma glucose	29.7 (184)	29.7 (183)	35.7 (222)	0.032
Intervention groups, % (*n*)				0.44
Mediterranean diet + EVOO	32.6 (203)	35.0 (218)	36.1 (225)	
Mediterrandean diet + nuts	36.8 (229)	34.5 (215)	31.8 (198)	
Control low-fat diet	30.5 (190)	30.5 (190)	32.1 (200)	
Energy intake, kcal/d	2368 (541)	2264 (527)	2336 (522)	0.002
Food consumption,[3] g/d				
Vegetables	336 ± 122	348 ± 120	343 ± 126	0.23
Fruits	383 ± 154	391 ± 135	397 ± 160	0.24
Legumes	22 ± 9	22 ± 10	23 ± 11	0.40
Meat	128 ± 43	125 ± 40	118 ± 42	<0.001
Fish	111 ± 39	105 ± 35	101 ± 37	<0.001
Cereals	238 ± 71	223 ± 60	210 ± 60	<0.001
Cookies	21 ± 24	21 ± 20	21 ± 22	0.94
Nuts	16 ± 14	16 ± 13	14 ± 13	0.015
Olive oil	46 ± 13	45 ± 13	43 ± 14	<0.001
Alcohol	14 ± 15	9 ± 10	6 ± 9	<0.001
Low-fat dairy	125 ± 88	270 ± 96	485 ± 191	<0.001
Whole-fat dairy	32 ± 58	51 ± 85	79 ± 161	<0.001
Total yogurt	41 ± 44	92 ± 61	122 ± 89	<0.001
Low-fat yogurt	29 ± 40	67 ± 60	95 ± 88	<0.001
Whole-fat yogurt	12 ± 25	25 ± 44	26 ± 51	<0.001
Cheese	27 ± 22	33 ± 23	37 ± 32	<0.001
Total milk	117 ± 82	229 ± 73	442 ± 131	<0.001
Low-fat milk	97 ± 85	203 ± 90	389 ± 176	<0.001
Whole milk	25 ± 68	30 ± 85	61 ± 170	<0.001

[1] Values are means ± SDs or medians (IQRs) unless otherwise indicated. Tertile cutoffs are based on the energy-adjusted mean of total dairy consumption during the follow-up. EVOO, extra virgin olive oil; MET, metabolic equivalent task; MetS, metabolic syndrome; P, percentile; T, tertile.
[2] *P* values for differences between tertiles were calculated by chi-square tests for categorical variables and ANOVA tests for continuous variables.
[3] All dietary variables were adjusted for energy.

cholesterol, 82.2% of 240 developed high blood pressure, and 41.4% of 1268 developed high fasting glucose concentration.

The median consumption during the follow-up of total dairy products in the whole study population was 363 g/d (IQR: 257, 525 g/d), low-fat dairy products being the largest contributors to total dairy consumption (72.5%). The median of consumption of milk, yogurt, and cheese was 207 g/d, 70 g/d, and 30 g/d, respectively.

The general characteristics of the study participants according to their mean consumption categories of total dairy products (tertiles) during the follow-up are shown in **Table 1**. Compared with those in the lowest tertile, participants in the top tertile were more likely to be older women and less likely to smoke, be physically active, and have lower serum concentrations of TGs and higher concentrations of HDL cholesterol. Participants in the highest tertile of dairy consumption also had lower total energy intake and consumed less red meat, fish, cereals, nuts, olive oil, and alcohol.

Consumption of total dairy products and incidence of MetS. The multivariable-adjusted HRs (95% CIs) for MetS incidence across tertiles of consumption of total dairy products are shown in **Table 2**. After adjusting for several potential confounders, subjects in the top tertile of low-fat dairy consumption, but not total dairy or high-fat dairy, had a lower risk of incident MetS [HR: 0.72; 95% CI: 0.61,0.86; *P*-trend = 0.001] compared with those in the bottom tertile.

Consumption of dairy product subtypes and incidence of MetS. The HRs of incident MetS across tertiles of consumption of specific subtypes of dairy products (yogurt, cheese, and milk) also adjusted for potential confounders are shown in **Table 3**. Among the subtypes of dairy products, consumers in tertile 3 of low-fat yogurt [HR: 0.73; 95% CI: 0.62, 0.86; *P*-trend = 0.004], whole-fat yogurt [HR: 0.78; 95% CI: 0.66, 0.92; *P*-trend = 0.003], and low-fat milk [HR: 0.80; 95% CI: 0.67, 0.95); *P*-trend = 0.007] had a lower risk of developing MetS than did participants in the lowest tertile of consumption. Compared with participants in the lowest tertile of consumption of cheese, those in the highest tertile had an increased risk of incident MetS [HR: 1.31; 95% CI: 1.10, 1.56; *P*-trend < 0.001]. No statistical interactions were found between the consumption of total dairy products or subtypes and sex or intervention group.

Yogurt consumption and MetS and its components. The multivariable-adjusted HR of each MetS component in subjects who were initially free of MetS in extreme categories of total, whole-fat, and low-fat yogurt consumption (tertile 3 vs. tertile 1) are shown in **Figure 1**. With the exception of high blood pressure, participants in the highest tertile of total yogurt consumption had a significantly lower risk of developing each of the MetS components than those in the lowest tertile. However, the linear trend was significant only for high fasting glucose (*P*-trend = 0.004). Compared with participants in the lowest tertile, participants in the highest tertile of whole-fat yogurt consumption had a lower risk of several components of MetS, including abdominal obesity [HR: 0.80; 95% CI: 0.65, 0.98; *P*-trend = 0.048], hypertriglyceridemia [HR: 0.74; 95% CI: 0.64, 0.86; *P*-trend < 0.001], low HDL cholesterol [HR: 0.73; 95% CI: 0.63, 0.85; *P*-trend < 0.001], high blood pressure [HR: 0.62; 95% CI: 0.44, 0.86; *P*-trend = 0.001], and high fasting plasma glucose [HR: 0.80; 95% CI: 0.66, 0.94; *P*-trend = 0.005]. The associations with low-fat yogurt were in the same direction as those with total and whole-fat yogurt, but inverse associations were limited to hypertriglyceridemia [HR: 0.73; 95% CI: 0.63, 0.85; *P*-trend = 0.18], low HDL cholesterol [HR: 0.76; 95% CI: 0.66, 0.88; *P*-trend = 0.35], and high fasting plasma glucose [HR: 0.81; 95% CI: 0.68, 0.96; *P*-trend = 0.004].

TABLE 2 HRs (95% CIs) of MetS incidence across energy-adjusted tertiles of consumption of total, low-fat, and whole-fat dairy products in elderly individuals at high cardiovascular disease risk[1]

	Total dairy consumption, g/d			
	T1	T2	T3	*P*-trend
Total dairy consumption, median (P25, P75)	207 (142, 250)	354 (322, 393)	577 (518, 661)	
MetS incidence, *n* (%)	319 (51.3)	293 (47.0)	318 (51.0)	0.24
Crude model	1.00 (ref.)	0.84 (0.72, 0.99)	1.02 (0.87, 1.20)	0.60
Multivariate model 1	1.00 (ref.)	0.82 (0.70, 0.97)	0.93 (0.78, 1.10)	0.54
Multivariate model 2	1.00 (ref.)	0.83 (0.70, 0.98)	0.89 (0.73, 1.07)	0.30
Multivariate model 3	1.00 (ref.)	0.80 (0.68, 0.95)	0.83 (0.69, 1.01)	0.11
Whole-fat dairy, median (P25, P75)	0	18 (12, 25)	94 (53, 179)	
MetS incidence, *n* (%)	327 (47.4)	289 (46.4)	314 (50.4)	0.09
Crude model	1.00 (ref.)	0.88 (0.75, 1.03)	0.95 (0.81, 1.11)	0.85
Multivariate model 1	1.00 (ref.)	0.82 (0.69, 0.96)	0.93 (0.80, 1.09)	0.88
Multivariate model 2	1.00 (ref.)	0.90 (0.76, 1.06)	0.96 (0.81, 1.13)	0.87
Multivariate model 3	1.00 (ref.)	0.92 (0.78, 1.10)	0.99 (0.84, 1.16)	0.92
Low-fat dairy, median (P25, P75)	87 (7, 163)	263 (227, 316)	503 (429, 587)	
MetS incidence, *n* (%)	325 (52.3)	310 (49.8)	295 (47.4)	0.22
Crude model	1.00 (ref.)	0.90 (0.77, 1.06)	0.87 (0.74, 1.02)	0.18
Multivariate model 1	1.00 (ref.)	0.87 (0.74, 1.02)	0.79 (0.67, 0.93)	0.005
Multivariate model 2	1.00 (ref.)	0.90 (0.76, 1.05)	0.78 (0.66, 0.93)	0.005
Multivariate model 3	1.00 (ref.)	0.88 (0.75, 1.03)	0.72 (0.61, 0.86)	0.001

[1] Tertile cutoffs are based on energy-adjusted mean total, low-fat, or whole-fat dairy consumption during the follow-up. Cox regression model 1 adjusted for intervention group; sex; age (year); leisure time physical activity (metabolic equivalent task · day); BMI (kilograms per meter squared); current smoker (yes/no); former smoker (yes/no); and use of hypoglycemic, hypolipidemic, antihypertensive, and insulin treatment at baseline. Cox regression model 2 additionally adjusted for mean consumption during the follow-up of vegetables, fruit, legumes, cereals, fish, red meat, cookies, olive oil, and nuts (all grams per day), as well as alcohol (grams per day and quadratic term). Cox regression model 3 additionally adjusted for prevalence of MetS components at baseline, including abdominal obesity (yes/no), hypertriglyceridemia (yes/no), low HDL cholesterol (yes/no), hypertension (yes/no), and high fasting plasma glucose (yes/no). All models were stratified by recruitment center. MetS, metabolic syndrome; P, percentile; ref., reference; T, tertile.

TABLE 3 HRs (95% CIs) of MetS incidence across energy-adjusted tertiles of consumption of specific dairy products (yogurt, cheese, and milk) in elderly individuals at high cardiovascular disease risk[1]

	Tertiles of specific dairy consumption			
	T1	T2	T3	*P*-trend
Total yogurt,[2] g/d	7 (1, 24)	70 (54,94)	127 (125, 189)	
MetS incidence, *n* (%)	318 (51.1)	283 (45.4)	329 (52.8)	
Crude model	1.00 (ref.)	0.82 (0.69, 0.97)	1.10 (0.95, 1.29)	0.26
Multivariate model 1	1.00 (ref.)	0.81 (0.69, 0.96)	1.10 (0.93, 1.29)	0.31
Multivariate model 2	1.00 (ref.)	0.88 (0.74, 1.03)	0.75 (0.64, 0.89)	0.15
Multivariate model 3	1.00 (ref.)	0.88 (0.74, 1.04)	0.77 (0.65, 0.91)	0.14
Low-fat yogurt,[2] g/d	1 (0, 5)	46 (27, 60)	124 (107, 159)	
MetS incidence, *n* (%)	366 (58.8)	260 (41.7)	304 (48.8)	<0.001
Crude model	1.00 (ref.)	0.56 (0.47, 0.65)	0.74 (0.64, 0.87)	0.004
Multivariate model 1	1.00 (ref.)	0.53 (0.47, 0.64)	0.72 (0.62, 0.85)	0.002
Multivariate model 2	1.00 (ref.)	0.57 (0.49, 0.67)	0.76 (0.65, 0.90)	0.016
Multivariate model 3	1.00 (ref.)	0.56 (0.47, 0.66)	0.73 (0.62, 0.86)	0.004
Whole-fat yogurt,[2] g/d	0	6 (4, 9)	46 (24, 78)	
MetS incidence, *n* (%)	346 (55.6)	310 (49.8)	274 (44.0)	<0.001
Crude model	1.00 (ref.)	0.88 (0.75, 1.03)	0.71 (0.61, 0.84)	<0.001
Multivariate model 1	1.00 (ref.)	0.83 (0.71, 0.98)	0.71 (0.60, 0.83)	<0.001
Multivariate model 2	1.00 (ref.)	0.91 (0.77, 1.07)	0.74 (0.63, 0.87)	<0.001
Multivariate model 3	1.00 (ref.)	0.93 (0.79, 1.10)	0.78 (0.66, 0.92)	0.003
Cheese,[2] g/d	11 (6, 15)	28 (23, 33)	51 (44, 66)	
MetS incidence, *n* (%)	293 (47.1)	280 (44.9)	357 (57.3)	
Crude model	1.00 (ref.)	0.94 (0.79, 1.11)	1.41 (1.20, 1.66)	<0.001
Multivariate model 1	1.00 (ref.)	0.90 (0.76, 1.07)	1.29 (1.10, 1.52)	0.001
Multivariate model 2	1.00 (ref.)	0.94 (0.79, 1.12)	1.34 (1.13, 1.58)	<0.001
Multivariate model 3	1.00 (ref.)	0.93 (0.79, 1.11)	1.31 (1.10, 1.56)	<0.001
Total milk,[2] g/d	120 (35, 162)	222 (205, 250)	462 (380, 504)	
MetS incidence, *n* (%)	313 (50.3)	303 (48.6)	314 (50.4)	0.78
Crude model	1.00 (ref.)	0.97 (0.83, 1.14)	1.04 (0.88, 1.22)	0.57
Multivariate model 1	1.00 (ref.)	0.90 (0.76, 1.06)	0.93 (0.78, 1.10)	0.58
Multivariate model 2	1.00 (ref.)	0.93 (0.79, 1.10)	0.90 (0.75, 1.78)	0.29
Multivariate model 3	1.00 (ref.)	0.90 (0.77, 1.07)	0.85 (0.70, 1.02)	0.11
Low-fat milk,[2] g/d	28 (0, 107)	204 (193, 216)	433 (345, 499)	
MetS incidence, *n* (%)	306 (49.2)	331 (53.1)	293 (47.0)	0.09
Crude model	1.00 (ref.)	1.17 (1.00, 1.37)	0.94 (0.80, 1.11)	0.38
Multivariate model 1	1.00 (ref.)	1.14 (0.98, 1.34)	0.86 (0.73, 1.02)	0.06
Multivariate model 2	1.00 (ref.)	1.16 (0.99, 1.37)	0.85 (0.71, 1.01)	0.040
Multivariate model 3	1.00 (ref.)	1.16 (0.98, 1.36)	0.80 (0.67, 0.95)	0.007
Whole-fat milk,[2] g/d	0	5 (2, 8)	31 (18, 136)	
MetS incidence, *n* (%)	314 (50.5)	288 (462)	328 (52.6)	0.07
Crude model	1.00 (ref.)	0.92 (0.78, 1.08)	1.12 (0.96, 1.31)	0.08
Multivariate model 1	1.00 (ref.)	0.89 (0.75, 1.05)	1.02 (0.87, 1.21)	0.50
Multivariate model 2	1.00 (ref.)	1.00 (0.85, 1.19)	1.10 (0.93, 1.30)	0.21
Multivariate model 3	1.00 (ref.)	1.02 (0.86, 1.21)	1.12 (0.95, 1.33)	0.16

[1] The MetS components were defined with updated harmonizing criteria. Tertile cutoffs are based on energy-adjusted mean dairy product consumption during the follow-up. Cox regression model 1 adjusted for intervention group; sex; age (year); leisure time physical activity (metabolic equivalent task · day); BMI (kilograms per meter squared); current smoker (yes/no); former smoker (yes/no); and use of hypoglycemic, hypolipidemic, antihypertensive, and insulin treatment at baseline. Cox regression model 2 additionally adjusted for mean consumption during the follow-up of vegetables, fruit, legumes, cereals, fish, red meat, cookies, olive oil, and nuts (all grams per day), as well as alcohol (grams per day and quadratic term). Cox regression model 3 additionally adjusted for prevalence of MetS components at baseline, including abdominal obesity (yes/no), hypertriglyceridemia (yes/no), low HDL cholesterol (yes/no), hypertension (yes/no), and high fasting plasma glucose (yes/no). All models were stratified by recruitment center. MetS, metabolic syndrome; ref., reference; T, tertile.
[2] Values are medians; 25th, 75th percentiles in parentheses.

Consumption of dairy products, dairy product subtypes, and MetS components. HRs for the components of incident MetS across tertiles of consumption of total dairy products and subtypes are shown in **Supplemental Table 1.** An increased consumption of total milk and low-fat milk was significantly associated with a lower incidence of low HDL cholesterol and high fasting glucose. Low-fat dairy consumption was inversely associated with high fasting glucose, hypertriglyceridemia, and low HDL cholesterol (Supplemental Table 1).

Consumption of dairy products, subtypes of dairy products, and incidence of MetS based on the number of MetS components at baseline. A sensitivity analysis based on the number of MetS components at baseline found that in those

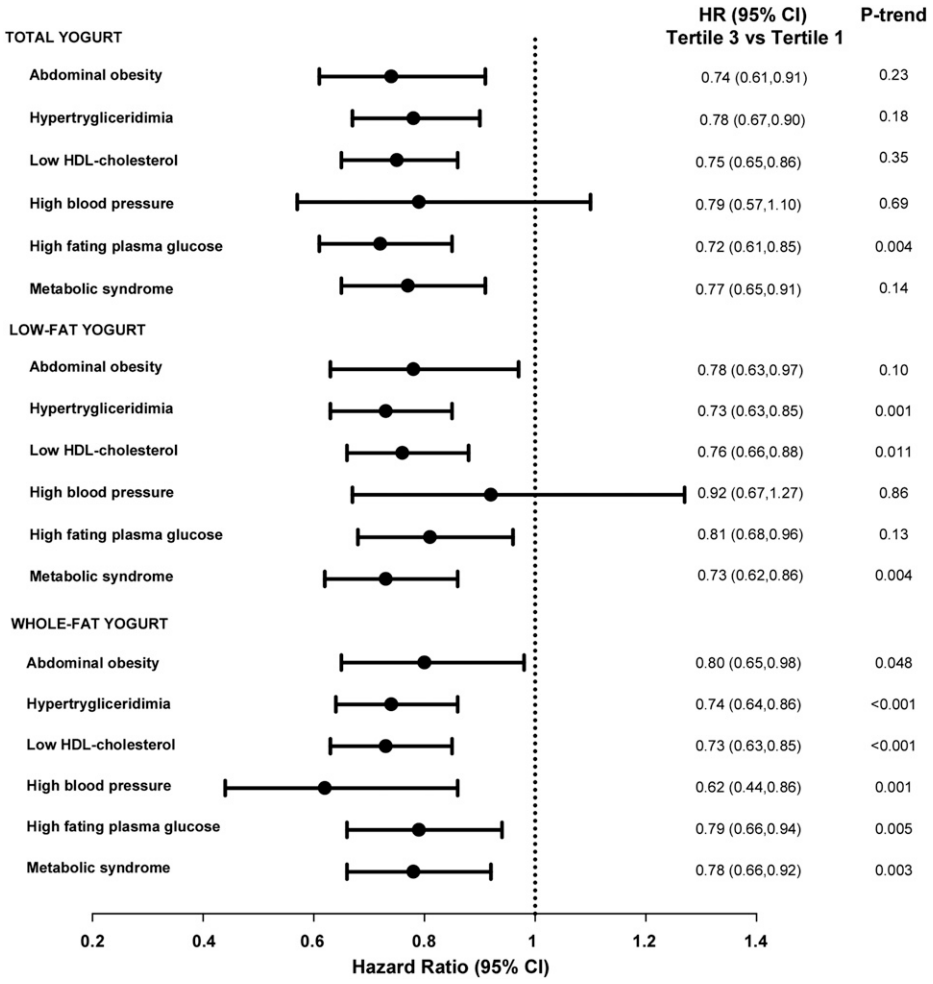

FIGURE 1 HRs (95% CIs) of metabolic syndrome and its components [abdominal obesity (n = 1386), hypertriglyceridemia (n = 3539), low HDL cholesterol (n = 3745), high blood pressure (n = 337), and high fasting plasma glucose (n = 1844)], comparing tertile 3 and tertile 1 of yogurt consumption in elderly individuals at high cardiovascular disease risk. Tertile cutoffs are based on energy-adjusted mean yogurt consumption during the follow-up. Cox regression models adjusted for intervention group; sex; age (years); leisure time physical activity (metabolic equivalent task · day); BMI (kilograms per meter squared); current smoker (yes/no); former smoker (yes/no); and use of hypoglycemic, hypolipidemic, antihypertensive, and insulin treatment at baseline plus mean consumption during follow-up of vegetables, fruit, legumes, cereals, fish, red meat, cookies, olive oil, and nuts (all grams per day), as well as alcohol (grams per day and quadratic term). All models were stratified by recruitment center.

individuals who had only one component or none at all, there was no significant association between total dairy or its subtypes and MetS incidence, except for cheese (P-trend < 0.05). In those individuals with 2 MetS components at baseline, there were still significant inverse associations between low-fat dairy, low-fat yogurt, and whole-fat yogurt consumption and MetS incidence. A positive association was observed between cheese consumption and MetS development (**Supplemental Table 2**).

Discussion

In this longitudinal assessment of the PREDIMED cohort, an older Mediterranean population at high CVD risk, we evaluated the consumption of total and specific dairy products in relation to the risk of developing MetS. The results show that the consumption of low-fat dairy products, yogurt (total, low-fat, and whole yogurt), and low-fat milk is associated with a lower incidence of MetS. These results remained even after we used the Benjamini-Hochberg method to correct P values for multiple comparisons. The association between total dairy consumption and MetS remained in the same direction, although it was not significant (P = 0.11). In contrast, increased consumption of total cheese was directly associated with a higher risk of MetS. Likewise, increased consumption of whole yogurt was also inversely associated with all MetS components, whereas consumption of low-fat yogurt related inversely to high TGs, low HDL cholesterol, and elevated fasting glucose.

Our results are in line with those of other prospective studies showing an inverse association between total dairy product consumption and MetS (5, 16, 17). The results of other cross-sectional (19, 34) and prospective studies (20, 21), however, are not fully consistent. These mixed results can be partially explained by the heterogeneity of dairy products included in the total dairy category. Further reasons for discordant results could relate to the design of the studies, because, unlike in the present study, most previous studies did not use repeated measurements of consumption, and to inherent differences in the characteristics of the population studied.

Our results for the type of product and fat content are discordant with those reported by the prospective CARDIA (Coronary Artery Risk Development in Young Adults) study (5), in which an inverse association between the consumption of whole-fat dairy products and cheese and MetS was observed in individuals above 18 y of age. We observed a direct association between the consumption of cheese and incident MetS. Unlike in our findings, individuals in the Blue Mountain Eyes Study (20) who consumed more whole-fat dairy or low-fat dairy products showed a decreased or an increased risk of developing MetS, respectively. The population in our study consisted of older individuals at high CVD risk, whereas the study subjects were younger in both the CARDIA and the Blue Mountain Eyes Studies. This may partly explain the contradictory results. It should be pointed out that only the CARDIA study analyzed the associations between MetS and dairy product subtypes, although

they were classified differently from in our study. This may help explain the divergent results.

In support of our findings, the protective role of yogurt consumption on MetS has been noted previously in cross-sectional studies (15, 19), but the prospective CARDIA study (5) found no association between yogurt consumption and MetS development.

Numerous biological mechanisms may mediate the relation between dairy consumption and risk of MetS.

Dairy products are an important source of calcium. The calcium in milk products interacts with SFAs to form calcium–FA soaps, thereby increasing fecal fat excretion (35) and, thus, improving the HDL-to-LDL cholesterol ratio. Lorenzen et al. (36) also showed that, unlike calcium from supplements, calcium from milk and low-fat yogurt reduced the TG content of chylomicrons postprandially (36). Intervention studies have also shown that calcium intake decreases blood pressure (37, 38), and that milk-derived bioactive peptides have antihypertensive properties (39). Milk-derived bioactive peptides increasingly have been shown to play an important role in preventing MetS by regulating insulinemia, blood pressure, dyslipidemia, and central fat accumulation (39–41). Nutrients from dairy products may act synergistically on metabolic pathways that have a beneficial impact on MetS. It has been reported that insulin concentrations are lower in those subjects consuming diets high in dairy products than in subjects consuming diets low in dairy products (41), which suggests that calcium or other nutrients that make up dairy products have beneficial effects on glucose metabolism. Although some studies (40) have suggested that there are beneficial associations between dairy consumption and body weight or body composition, clinical trials data are not supportive (42). Recently, however, a high consumption of total and whole-fat yogurt was associated with a lower risk of being overweight/obese (43). It has also been suggested that probiotics from yogurt beneficially influence the inflammatory/anti-inflammatory balance of the microbiota, which might mediate the lower risk of presenting overweight/obesity (44).

In our study, whole-milk yogurt protected against all MetS components. Although nutritionally yogurt is comparable to milk, added ingredients and fermentation may improve its nutritional value (45) and provide it with unique properties that enhance the bioavailability of some nutrients (46, 47). As far as fat is concerned, dairy products contain mostly SFAs, in addition to high proportions of oleic, stearic, rumenic and trans-palmitoleic acids. The results of recent meta-analyses have questioned the role of SFAs on CVD risk (48). Likewise, there is meta-analytical evidence that a high intake of total dairy products and most dairy subtypes do not increase the risk of CVD (49). In our study, cheese was directly associated with an increased risk of MetS, which may be partly explained by the fact that it is rich in sodium and has a higher energy density and phosphorus content than other dairy products (19).

In elderly individuals, MetS is an important health problem with potentially greater repercussions on health than in other population groups (22). According to our results, dairy products are a food group with a high nutritional value that could prevent MetS development. Consequently, the consumption of this food group may be promoted in elderly individuals in order to try to attempt to reduce the incidence of this disease.

Our study has several strengths, including the use of yearly measurements of diet, a relatively long follow-up period, the analysis of dairy subtypes with different fat contents, and adjustment for a large number of potential confounders for which multiple testing corrections minimized small differences among individuals and potential confounders.

The study also has limitations. First, incident MetS was a secondary endpoint of the PREDIMED trial, which make our analyses exploratory in nature. Second, our cohort was made up of elderly participants at high risk of CVD; thus, our findings cannot be generalized to other populations. Third, although diet was assessed by a validated FFQ, potential measurement errors are unavoidable. Nevertheless, to minimize the random measurement error caused by within-person variation and dietary changes during follow-up, we calculated the mean of consumption during the follow-up for dietary variables to better represent long-term habitual dietary consumption when these associations were explored (50). The present study suggests that consumption of low-fat dairy products, all types of yogurt, and low-fat milk is associated with a lower incidence of MetS in older individuals at high CVD risk. Furthermore, increased consumption of whole-fat yogurt is associated with a lower incidence of all MetS components. Conversely, cheese consumption is associated with an increased risk of MetS development.

Acknowledgments

MÁM-G, DC, RE, ER, LS-M, FA, JL, EG-G, MF, and JS-S designed the PREDIMED (Prevención con Dieta Mediterránea) study; NB, NB-T, MÁM-G, DC, RE, ER, CS-O, MF, LS-M, FA, RML-R, JL, EG-G, MF, AD-L, JVS, JAM, and JS-S conducted the research; NB and NB-T analyzed the data; NB, NB-T, and JS-S wrote the manuscript; MÁM-G, DC, RE, ER, MF, LS-M, and JL were the coordinators of subject recruitment an follow-up at the outpatient clinics; and NB and JS-S had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors read and approved the final manuscript.

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