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

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i. Supplemental Table 1, Supplemental Table 2 and a complete list of PREDIEMD investigators 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.

ii. Abbreviations used: CVD: Cardiovascular diseases; EVOO**:** Extra virgin olive oil; FFQ: Food frequency questionnaire; ICC: Intra-class correlation coefficient; MedDiet: Mediterranean Diet; MetS: Metabolic syndrome; T2D: Type 2 diabetes.

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ABSTRACT

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

Objective: Therefore, we aimed to evaluate the associations between consumption of dairy products (total and different subtypes) and incident MetS in a Mediterranean population at high cardiovascular risk.

Methods: We prospectively analyzed 1868 men and women (55-80 years-old) without MetS at baseline, recruited from different PREDIMED centers between October 2003 and June 2009 and followed-up to 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 determinations. Multivariable-adjusted hazard ratios (HRs) of MetS or its components were estimated for each of the two upper tertiles (versus the lowest one) of mean consumption of dairy products during the follow-up.

Results: During a median follow-up of 3.2 years, 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 were associated with a reduced risk of MetS in individuals at high cardiovascular 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.

Key words: Dairy products, metabolic syndrome, PREDIMED-study.

INTRODUCTION

Metabolic syndrome (MetS) 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 diseases (CVD) (1).

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 the MetS, including atherogenic dyslipidemia (4), hyperglycemia (5), insulin resistance (6) or T2D (7–9), blood pressure (10) and abdominal obesity (11).

In epidemiological 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 while others (18, 19, 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 development of MetS, methodological 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. Besides, 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 and coworkers (5) showed an inverse association with total consumption of dairy products regardless of their fat content, whereas Louie and coworkers found this inverse association only for whole-fat dairy products (20).

54 To the best of our knowledge, of the four prospective studies published to date on the
55 relationship between dairy product consumption and MetS incidence, three were
56 conducted in healthy adult populations (5,17,20) and only one in older individuals (21),
57 in whom MetS is more prevalent and potentially has more repercussions on health
58 (22). In addition, only one study explored the associations for different dairy subtype
59 products (5). Therefore, the aim of the present study was to examine the relationship
60 between the consumption of dairy products (whole or low-fat options) and risk of MetS
61 in an older Mediterranean population in the frame of the PREDIMED study.
62

METHODS

Study design and participants

The present study was conducted within the framework of the Prevención con DIeta MEDiterránea (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 (MedDiet) on the primary prevention of CVD (25). The main results of the trial concerning at the primary endpoint have been published recently (26).

Briefly, 7447 community-dwelling men (aged 55–80 years) and women (aged 60–80 years) with no previously documented CVD were recruited. They were eligible if they had either T2D, or at least three of the following cardiovascular risk factors: hypertension (systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg or on antihypertensive medication), high plasma LDL-cholesterol (≥ 160 mg/dL), low plasma HDL-cholesterol (HDL-c) (< 40mg/dL in men; < 50mg/dL in women), overweight or obesity (BMI ≥ 25kg/m^2), current smoking, or a family history of premature coronary heart disease (23). From October 2003 to June 2009, participants were randomized to three intervention groups (two of which were advised to follow a MedDiet supplemented with either 1 liter per week of EVOO or 30 g/day of mixed nuts, and were compared to 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 at least two years (n=5801). Since our aim was to explore the associations between the consumption of dairy foods and incident MetS, we excluded participants who had diagnoses of MetS (63.9%) at baseline (n=3707). We also excluded participants who had not completed

the baseline food frequency questionnaire (FFQ) or who reported extreme total energy intakes with values outside the pre-specified 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 initially one) , respectively.

Outcome

The primary endpoint of the PREDIMED trial was a combination of several major cardiovascular clinical events (myocardial infarction, stroke or cardiovascular 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 American Heart Association/National Heart, Lung and Blood Institute(1). Individuals were diagnosed with MetS if they had three or more of the following components: hypertriglyceridemia [≥150mg/dl (≥1.7 mmol/L)] or drug treatment for elevated triglycerides; low concentrations of HDL-c [<50mg/dl (<1.3 mmol/L) and <40mg/dL (<1.03 mmol/L) in women and men, respectively] or drug treatment for low HDL-c; elevated blood pressure (systolic ≥130mmHg and/or diastolic ≥ 85mmHg) or being treated for hypertension; high fasting plasma glucose [≥100mg/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 face-to-face delivered a 137-item semi-quantitative food-frequency questionnaire (FFQ) validated for the PREDIMED study (27). In the validation study, the FFQ was administered twice to explore reproducibility at 1 year, and four 3-day 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 (r), ranged from 0.50 to 0.82, and the intra-class 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, energy and nutrient intake ranged (r) from 0.24 to 0.72, while 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 using 15 items of the FFQ. In order to assess habitual dietary intakes over the previous year, frequencies of consumption were measured in 9 categories (ranging from never/almost never to >6 servings/day) for each food item. These responses to individual dairy items were then converted into mean daily consumptions (grams/day) during the follow-up by multiplying the typical portion sizes (in grams) by the consumption frequency for each food and making the appropriate division for the period assessed to obtain daily consumptions. Total dairy foods category included semi-skim/skim milk and skim yogurt, whole milk, condensed milk, whole yogurt, custard and all types of cheeses: petit Suisse, ricotta, cottage, semi-cured/cured cheeses such as Cheddar, Manchego, Emmental, etc.). Low-fat dairy foods included semi-skim/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: milk (including total, low-fat and whole-fat 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 using the nutrient residual method (30).

Measurements

Participants completed at baseline and yearly: *a)* a questionnaire about lifestyle variables, medical history and medication use; *b)* a 14-item validated questionnaire (31) designed to assess adherence to the MedDiet; *c)* a validated 137 item semi-quantitative FFQ (27); and *d)* the validated Spanish version (32) of the Minnesota Leisure-Time Physical Activity Questionnaire. In addition, anthropometrical variables and blood pressure were determined by trained staff. Blood pressure was measured in triplicate using a validated semiautomatic oscillometer with a 5-minute interval between measurements and the subject in a sitting position (Omron HEM-705CP, Hoofddorp, The Netherlands).

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 (CHOD-PAP), triglycerides by glycerol-phosphate oxidase-peroxidase (GPO-PAP), and HDL cholesterol by direct measurement. All local laboratories satisfied external quality-control requirements. When triglycerides were <300 mg/dL, low density lipoprotein cholesterol was calculated using the Friedewald formula so that the LDL cholesterol was not underestimated. A concordance study of nine laboratories was conducted. From each study, a mean of 200 samples were analyzed for total cholesterol, high density lipoprotein cholesterol, and triglycerides using the IMIM laboratory as reference. The IMIM laboratory used ABX-Horiba commercial kits (ABX-Horiba, Montpellier, France) 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 a coefficient of determination R^2 and an intra-class correlation coefficient (95% confidence interval), 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 from items of 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 using mean ± SD or median [IQR] for continuous variables, and number and percentages for categorical variables. Chi square and one-way 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 hazard ratios (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 non-reduced milk; total yogurt, low-fat and non-reduced fat yogurt, and cheese. Both upper tertiles were compared with the lowest tertile (reference). The assumption of proportional hazards was tested using time-dependent covariates.

The time variable was the interval between randomization 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 (year), leisure time physical activity (MET-day), BMI (kg/m^2), current smoker (yes/no), former smoker (yes/no) and hypoglycemic, hypolipidemic, antihypertensive and insulin treatment at baseline. Model 2 was additionally adjusted for the mean consumption during the follow-up of vegetables (g/d), fruit (g/d), legumes (g/d), cereals (g/d), fish (g/d), red meat (g/d), alcohol (g/d and quadratic term), biscuits (g/d), olive oil (g/d) and nuts (g/d). Model 3 was adjusted for model 2 plus the prevalence of MetS components at baseline: 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 the MetS or had one, or who had two components. This was done to prevent possible bias effects because it is easier for those who already have two criteria to meet the diagnostic definition than those with one or none.

All analyses were performed with SPSS software (version 19.0; SPSS).

RESULTS

After a median of 3.2 years 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-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 363g/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 were 207 g/d, 70 g/d, and 30 g/d, respectively.

Table 1 shows the general characteristics of the study participants according to their mean consumption categories of total dairy products (tertiles) during the follow-up. Compared to 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 triglycerides 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 metabolic syndrome

Table 2 shows the multivariable-adjusted HRs (95% CIs) for MetS incidence across tertiles of consumption of total dairy products. 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 to those in the bottom tertile.

Consumption of dairy product subtypes and incidence of metabolic syndrome

Table 3 shows the HRs of incident MetS across tertiles of consumption of specific subtypes of dairy products (yogurt, cheese and milk) also adjusted for potential confounders. 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 lower risk of developing MetS compared to participants in the lowest tertile of consumption. Compared to 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 metabolic syndrome and its components

Figure 1 shows the multivariable-adjusted HR of each MetS component in subjects who were initially free of MetS in extreme categories of total yogurt, whole-fat and low-fat yogurt consumption (tertile 3 versus tertile 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 for 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 the MetS: 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].

Consumption of dairy products, dairy product subtypes and metabolic syndrome components

Supplemental Table 1 shows HRs for the components of incident MetS across tertiles of consumption of total dairy products and subtypes. 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 (see Supplemental Table 1).

Consumption of dairy products, subtypes of dairy products and incidence of metabolic syndrome 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 individuals that 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 two 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 (see Supplemental Table 2).

DISCUSSION

In this longitudinal assessment of the PREDIMED cohort, an older Mediterranean population at high cardiovascular 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 using 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, while consumption of low-fat yogurt related inversely to high triglycerides, 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 the design of the studies as, unlike the present study, most prior 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 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 years of age. We observed a direct association between the consumption of cheese and incident MetS. Unlike our findings, individuals in the BMES 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 cardiovascular risk, while the study subjects were younger in both the CARDIA and the BMES 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 than 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 relationship between dairy consumption and risk of MetS.

Dairy products are an important source of calcium. Calcium in milk products interacts with saturated fatty acid to form calcium-fatty acid soaps, thereby increasing fecal fat excretion (35) and thus, improving the HDL:LDL-cholesterol ratio. Lorenzen and coworkers (36) also showed that, unlike calcium from supplements, calcium from milk and low-fat yogurt reduced the triglyceride 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 have increasingly 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 beneficial associations between dairy consumption and body weight or body composition, clinical

355 trials data are not supportive (42). Recently, however, a high consumption of total and
356 whole-fat yogurt was associated with a lower risk of being overweight/obese (43). It has
357 also been suggested that probiotics from yogurt beneficially influence the
358 inflammatory/anti-inflammatory balance of microbiota, which might mediate the lower
359 risk of presenting overweight/obesity (44).
360 In our study, whole yogurt protected against all MetS components. Although
361 nutritionally yogurt is comparable to milk, added ingredients and fermentation may
362 improve its nutritional value (45) and provide it with unique properties that enhance the
363 bioavailability of some nutrients (46,47). As far as fat is concerned, dairy products
364 contain mostly SFA in addition to high proportions of oleic, stearic, rumenic and trans-
365 palmitoleic acids. The results of recent meta-analyses have questioned the role of SFA
366 on CVD risk (48). Likewise, there is meta-analytical evidence that high intakes of total
367 dairy products and most dairy subtypes do not increase the risk of CVD (49) . In our
368 study cheese was directly associated with an increased risk of MetS, which may be partly
369 explained by the fact that it is rich in sodium, has a higher energy density than other dairy
370 products and higher phosphorus content compared with other dairy products (19).
371 In elderly individuals, MetS is an important health problem with potentially more
372 repercussions on health than in other population groups (22). According to our results,
373 dairy products are a food group with a high-nutritional value which could prevent MetS
374 development. Consequently, the consumption of this food group may be promoted, in
375 elderly individuals, in order to try to attempt to reduce the incidence levels of this
376 disease.
377 Our study has several strengths: the use of yearly measurements of diet, a relatively
378 long follow-up period, the analysis of dairy subtypes with different fat contents and the
379 adjustment for a large number of potential confounders for which multiple testing
380 corrections minimised small differences among individuals and potential confounders.

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

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REFERENCES

1. Alberti KGMM, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, Fruchart J-C, James WPT, Loria CM, Smith SC. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International . Circulation. 2009;120:1640–5.

2. Esposito K, Marfella R, Ciotola M, Di Palo C, Giugliano F, Giugliano G, D'Armiento M, D'Andrea F, Giugliano D. Effect of a mediterranean-style diet on endothelial dysfunction and markers of vascular inflammation in the metabolic syndrome: a randomized trial. JAMA. 2004;292:1440–6.

3. Babio N, Toledo E, Estruch R, Ros E, Martínez-González MA, Castañer O, Bulló M, Corella D, Arós F, Gómez-Gracia E, et al. Mediterranean diets and metabolic syndrome status in the PREDIMED randomized trial. CMAJ. 2014;186:E649–57.

4. Azadbakht L, Mirmiran P, Esmaillzadeh A, Azizi F. Dairy consumption is inversely associated with the prevalence of the metabolic syndrome in Tehranian adults. Am J Clin Nutr. 2005;82:523–30.

5. Pereira MA, Jacobs DR, Van Horn L, Slattery ML, Kartashov AI, Ludwig DS. Dairy consumption, obesity, and the insulin resistance syndrome in young adults: the CARDIA Study. JAMA. 2002;287:2081–9.

6. Rideout TC, Marinangeli CPF, Martin H, Browne RW, Rempel CB. Consumption of low-fat dairy foods for 6 months improves insulin resistance without adversely affecting lipids or bodyweight in healthy adults: a randomized free-living cross-over study. Nutr J. 2013;12:56.

7. Tong X, Dong J-Y, Wu Z-W, Li W, Qin L-Q. Dairy consumption and risk of type 2 diabetes mellitus: a meta-analysis of cohort studies. Eur J Clin Nutr. 2011;65:1027–31.

8. Liu S, Choi HK, Ford E, Song Y, Klevak A, Buring JE, Manson JE. A prospective study of dairy intake and the risk of type 2 diabetes in women. Diabetes Care. 2006;29:1579–84.

9. Choi HK, Willett WC, Stampfer MJ, Rimm E, Hu FB. Dairy consumption and risk of type 2 diabetes mellitus in men: a prospective study. Arch Intern Med. 2005;165:997–1003.

10. Toledo E, Delgado-Rodríguez M, Estruch R, Salas-Salvadó J, Corella D, Gomez-Gracia E, Fiol M, Lamuela-Raventós RM, Schröder H, Arós F, et al. Low-fat dairy products and blood pressure: follow-up of 2290 older persons at high cardiovascular risk participating in the PREDIMED study. Br J Nutr. 2008;101:59.

11. Wang H, Troy LM, Rogers GT, Fox CS, McKeown NM, Meigs JB, Jacques PF. Longitudinal association between dairy consumption and changes of body weight and waist circumference: the Framingham Heart Study. Int J Obes (Lond). 2014;38:299–305.

12. Liu S, Song Y, Ford ES, Manson JE, Buring JE, Ridker PM. Dietary calcium, vitamin D, and the prevalence of metabolic syndrome in middle-aged and older U.S. women. Diabetes Care. 2005;28:2926–32.

13. Ruidavets J-B, Bongard V, Dallongeville J, Arveiler D, Ducimetière P, Perret B, Simon C, Amouyel P, Ferrières J. High consumptions of grain, fish, dairy products and combinations of these are associated with a low prevalence of metabolic syndrome. J Epidemiol Community Health. 2007;61:810–7.

14. Elwood PC, Pickering JE, Fehily AM. Milk and dairy consumption, diabetes and the metabolic syndrome: the Caerphilly prospective study. J Epidemiol Community Health. 2007;61:695–8.

15. Kim J. Dairy food consumption is inversely associated with the risk of the metabolic syndrome in Korean adults. J Hum Nutr Diet. 2013;26 Suppl 1:171–9.

16. Lutsey PL, Steffen LM, Stevens J. Dietary intake and the development of the metabolic syndrome: the Atherosclerosis Risk in Communities study. Circulation. 2008;117:754–61.

17. Fumeron F, Lamri A, Abi Khalil C, Jaziri R, Porchay-Baldérelli I, Lantieri O, Vol S, Balkau B, Marre M. Dairy consumption and the incidence of hyperglycemia and the metabolic syndrome: results from a french prospective study, Data from the Epidemiological Study on the Insulin Resistance Syndrome (DESIR). Diabetes Care. 2011;34:813–7.

18. Mennen LI, Lafay L, Feskens EJM, Novak M, Lépinay P, Balkau B. Possible protective effect of bread and dairy products on the risk of the metabolic syndrome. Nutr Res. 2000;20:335–47.

19. Beydoun MA, Gary TL, Caballero BH, Lawrence RS, Cheskin LJ, Wang Y. Ethnic differences in dairy and related nutrient consumption among US adults and their association with obesity, central obesity, and the metabolic syndrome. Am J Clin Nutr. 2008;87:1914–25.

20. Louie JCY, Flood VM, Rangan AM, Burlutsky G, Gill TP, Gopinath B, Mitchell P. Higher regular fat dairy consumption is associated with lower incidence of metabolic syndrome but not type 2 diabetes. Nutr Metab Cardiovasc Dis. 2013;23:816–21.

21. Snijder MB, van Dam RM, Stehouwer CDA, Hiddink GJ, Heine RJ, Dekker JM. A prospective study of dairy consumption in relation to changes in metabolic risk factors: the Hoorn Study. Obesity (Silver Spring). 2008;16:706–9.

22. Ervin RB. Prevalence of metabolic syndrome among adults 20 years of age and over, by sex, age, race and ethnicity, and body mass index: United States, 2003-2006. Natl Health Stat Report. 2009;1–7.

23. Estruch R, Martínez-González MA, Corella D, Salas-Salvadó J, Ruiz-Gutiérrez V, Covas MI, Fiol M, Gómez-Gracia E, López-Sabater MC, Vinyoles E, et al. Effects of a Mediterranean-style diet on cardiovascular risk factors: a randomized trial. Ann Intern Med. 2006;145:1–11.

24. Martínez-González MÁ, Corella D, Salas-Salvadó J, Ros E, Covas MI, Fiol M, Wärnberg J, Arós F, Ruíz-Gutiérrez V, Lamuela-Raventós RM, et al. Cohort profile: design and methods of the PREDIMED study. Int J Epidemiol. 2012;41:377–85.

25. Predimed, Prevención con Dieta Mediterránea [Internet]. [cited 2015 May 25]. Available from: http://www.predimed.org

26. Estruch R, Ros E, Salas-Salvadó J, Covas M-I, Corella D, Arós F, Gómez-Gracia E, Ruiz-Gutiérrez V, Fiol M, Lapetra J, et al. Primary prevention of cardiovascular disease with a Mediterranean diet. N Engl J Med. 2013;368:1279–90.

27. Fernández-Ballart JD, Piñol JL, Zazpe I, Corella D, Carrasco P, Toledo E, Perez-Bauer M, Martínez-González MA, Salas-Salvadó J, Martín-Moreno JM. Relative validity of a semi-quantitative food-frequency questionnaire in an elderly Mediterranean population of Spain. Br J Nutr. 2010;103:1808–16.

28. Moreiras O Cabrera L CA. Tablas de composición de alimentos [Food composition tables]. Madrid, Spain: Ediciones Pirámide; 2005.

29. Mataix VJ. Tabla de composicion de alimentos [Food composition tables]. 4th ed. Granada, spain: Universidad de Granada; 2003.

30. Willett W. Nutritional Epidemiology 2nd ed. 1998 Oxford University Press New York. 1998;

31. Schröder H, Fitó M, Estruch R, Martínez-González MA, Corella D, Salas-Salvadó J, Lamuela-Raventós R, Ros E, Salaverría I, Fiol M, et al. A short screener is valid for assessing Mediterranean diet adherence among older Spanish men and women. J Nutr. 2011;141:1140–5.

32. Elosua R, Marrugat J, Molina L, Pons S, Pujol E. Validation of the Minnesota Leisure Time Physical Activity Questionnaire in Spanish men. The MARATHOM Investigators. Am J Epidemiol. 1994;139:1197–209.

33. Controlling the False Discovery Rate: A Practical and Powerful Approach to Multiple Testing on JSTOR. J R Stat Soc B. 1995;57:289–300.

34. Snijder MB, van der Heijden AA, van Dam RM, Stehouwer CDA, Hiddink GJ, Nijpels G, Heine RJ, Bouter LM, Dekker JM. Is higher dairy consumption

associated with lower body weight and fewer metabolic disturbances? The Hoorn Study. Am J Clin Nutr. 2007;85:989–95.

35. Boon N, Hul GBJ, Stegen JHCH, Sluijsmans WEM, Valle C, Langin D, Viguerie N, Saris WHM. An intervention study of the effects of calcium intake on faecal fat excretion, energy metabolism and adipose tissue mRNA expression of lipid-metabolism related proteins. Int J Obes (Lond). 2007;31:1704–12.

36. Lorenzen JK, Nielsen S, Holst JJ, Tetens I, Rehfeld JF, Astrup A. Effect of dairy calcium or supplementary calcium intake on postprandial fat metabolism, appetite, and subsequent energy intake. Am J Clin Nutr. 2007;85:678–87.

37. Bucher HC, Cook RJ, Guyatt GH, Lang JD, Cook DJ, Hatala R, Hunt DL. Effects of dietary calcium supplementation on blood pressure. A meta-analysis of randomized controlled trials. JAMA. 1996;275:1016–22.

38. Van Mierlo LAJ, Arends LR, Streppel MT, Zeegers MPA, Kok FJ, Grobbee DE, Geleijnse JM. Blood pressure response to calcium supplementation: a meta-analysis of randomized controlled trials. J Hum Hypertens. 2006;20:571–80.

39. Ricci-Cabello I, Olalla Herrera M, Artacho R. Possible role of milk-derived bioactive peptides in the treatment and prevention of metabolic syndrome. Nutr Rev. 2012;70:241–55.

40. Zemel MB, Richards J, Mathis S, Milstead A, Gebhardt L, Silva E. Dairy augmentation of total and central fat loss in obese subjects. Int J Obes (Lond). 2005;29:391–7.

41. Zemel MB, Richards J, Milstead A, Campbell P. Effects of calcium and dairy on body composition and weight loss in African-American adults. Obes Res. 2005;13:1218–25.

42. Lanou AJ, Barnard ND. Dairy and weight loss hypothesis: an evaluation of the clinical trials. Nutr Rev. 2008;66:272–9.

43. Martinez-Gonzalez MA, Sayon-Orea C, Ruiz-Canela M, de la Fuente C, Gea A, Bes-Rastrollo M. Yogurt consumption, weight change and risk of overweight/obesity: The SUN cohort study. Nutr Metab Cardiovasc Dis. 2014;24:1189–96.

44. Verdam FJ, Fuentes S, de Jonge C, Zoetendal EG, Erbil R, Greve JW, Buurman WA, de Vos WM, Rensen SS. Human intestinal microbiota composition is associated with local and systemic inflammation in obesity. Obesity (Silver Spring). 2013;21:E607–15.

45. Adolfsson O, Meydani SN, Russell RM. Yogurt and gut function. Am J Clin Nutr. 2004;80:245–56.

46. Wang H, Livingston KA, Fox CS, Meigs JB, Jacques PF. Yogurt consumption is associated with better diet quality and metabolic profile in American men and women. Nutr Res. 2013;33:18–26.

47. El-Abbadi NH, Dao MC, Meydani SN. Yogurt: role in healthy and active aging. Am J Clin Nutr. 2014;99:1263S – 70S.

48. Chowdhury R, Warnakula S, Kunutsor S, Crowe F, Ward HA, Johnson L, Franco OH, Butterworth AS, Forouhi NG, Thompson SG, et al. Association of dietary, circulating, and supplement fatty acids with coronary risk: a systematic review and meta-analysis. Ann Intern Med. 2014;160:398–406.

49. De Oliveira Otto MC, Mozaffarian D, Kromhout D, Bertoni AG, Sibley CT, Jacobs DR, Nettleton JA. Dietary intake of saturated fat by food source and incident cardiovascular disease: the Multi-Ethnic Study of Atherosclerosis. Am J Clin Nutr. 2012;96:397–404.

50. Hu FB, Stampfer MJ, Rimm E, Ascherio A, Rosner BA, Spiegelman D, Willett WC. Dietary fat and coronary heart disease: a comparison of approaches for adjusting for total energy intake and modeling repeated dietary measurements. Am J Epidemiol. 1999;149:531–40.

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

	Total dairy consumption (g/day)[2]			
Total dairy consumption, median [P25-P75], (g/day)	T1 <=287 n=622 207 [142-250]	T2 287-449 n=623 354 [322-393]	T3 >=450 n=623 577 [518-661]	P-value[3]
Age, years	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, METs.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, mmHg				
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, median [IQR]	56.0 [49.0-66.0]	58.0 [51.0-68.0]	60.0 [53.0-68.2]	0.001
Serum Triglycerides, median [IQR]	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
Metabolic syndrome 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
MedDiet+EVOO	32.6 (203)	35.0 (218)	36.1 (225)	
MedDiet+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/day)	2368 (541)	2264 (527)	2336 (522)	0.002
Food consumption, g/day[4]				
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
Biscuits	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-fat milk	25 ± 68	30 ± 85	61 ± 170	<0.001

Abbreviations: EVOO, extra virgin olive oil; MedDiet, Mediterranean diet; MET, metabolic equivalent task;T, Tertile ;.
[1]Data are expressed as means (standard deviation) or medians [IQR, range interquartile] for continuous variables and percentage and number (n) for categorical variables.
[2]Tertile cut-offs are based on energy-adjusted mean of total dairy consumption during the follow-up.
[3]P value for differences between tertiles were calculated by chi-square or ANOVA tests for categorical and for continuous variables, respectively.
[4]All dietary variables were adjusted for energy.

Table 2. Hazard ratios (95% confidence intervals) of metabolic syndrome incidence across energy-adjusted tertiles of consumption of total, low-fat and whole-fat dairy products in elderly individuals at high cardiovascular risk

	Total dairy consumption (g/day)			
	T1[1]	**T2**	**T3**	P- trend
Total dairy consumption, median [P25-P75]; g/day	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[2]	1.00 ref.	0.82 (0.70,0.97)	0.93 (0.78,1.10)	0.54
Multivariate model 2[3]	1.00 ref.	0.83 (0.70,0.98)	0.89 (0.73,1.07)	0.30
Multivariate model 3[4]	1.00 ref.	0.80 (0.68,0.95)	0.83 (0.69,1.01)	0.11
Whole-fat dairy, median [P25-P75]; g/day	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]; g/day	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

Abbreviations: MetS, Metabolic syndrome; P, percentile; T, Tertile.

[1]Tertile cut-offs are based on energy-adjusted mean total dairy, low-fat or whole-fat dairy consumption during the follow-up.

[2]Cox regression model 1 adjusted for intervention group, sex, age (year), leisure time physical activity (MET-day), BMI (kg/m^2), current smoker (yes/no), former smoker (yes/no) and use of hypoglycemic, hypolipidemic, antihypertensive and insulin treatment at baseline.

[3]Cox regression model 2 additionally adjusted for mean consumption during the follow-up of vegetables (g/d), fruit (g/d), legumes (g/d), cereals (g/d), fish (g/d), red meat (g/d), alcohol (g/d and quadratic term), biscuits (g/d), olive oil (g/d) and nuts (g/d).

[4]Cox regression model 3 additionally adjusted for prevalence of metabolic syndrome components at baseline: 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.

Table 3. Hazard ratios (95% CI) of metabolic syndrome[1] incidence across energy-adjusted tertiles of dairy consumption of specific dairy products (yogurt, cheese and milk) in elderly individuals at high cardiovascular risk.

	Tertiles of specific dairy consumption			
	T1[2]	T2	T3	P- trend
Total yogurt, median [P25-P75]; g/day	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[3]	1.00 ref.	0.81 (0.69,0.96)	1.10 (0.93,1.29)	0.31
Multivariate model 2[4]	1.00 ref.	0.88 (0.74,1.03)	0.75 (0.64,0.89)	0.15
Multivariate model 3[5]	1.00 ref.	0.88 (0.74,1.04)	0.77 (0.65,0.91)	0.14
Low-fat yogurt, median [P25, P75]; g/day	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, median [P25-P75]; g/day	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, median [P25-P75]; g/day	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, median [P25-P75]; g/day	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, median [P25-P75]; g/day	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, median [P25-P75]; g/day	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

Abbreviations: MetS, Metabolic syndrome; P, percentile; T, Tertile.

[1]The MetS components were defined using updated harmonizing criteria.

[2]Tertile cut-offs are based on energy-adjusted mean dairy product consumption during the follow-up.

[3]Cox regression model1: Cox regression model adjusted for intervention group, sex, age (year), leisure time physical activity (MET-day), BMI (kg/m^2), current smoker (yes/no), former smoker (yes/no) and use of hypoglycemic, hypolipidemic, antihypertensive and insulin treatment at baseline.

[4]Cox regression model2: additionally adjusted for the mean consumption of vegetables (g/d), fruit (g/d), legumes (g/d), cereals (g/d), fish (g/d), red meat (g/d), alcohol (g/d and quadratic term), biscuits (g/d), olive oil (g/d) and nuts (g/d).

[5]Cox regression model3: additionally adjusted for MetS components prevalence at baseline: 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.

FIGURE LEGENDS

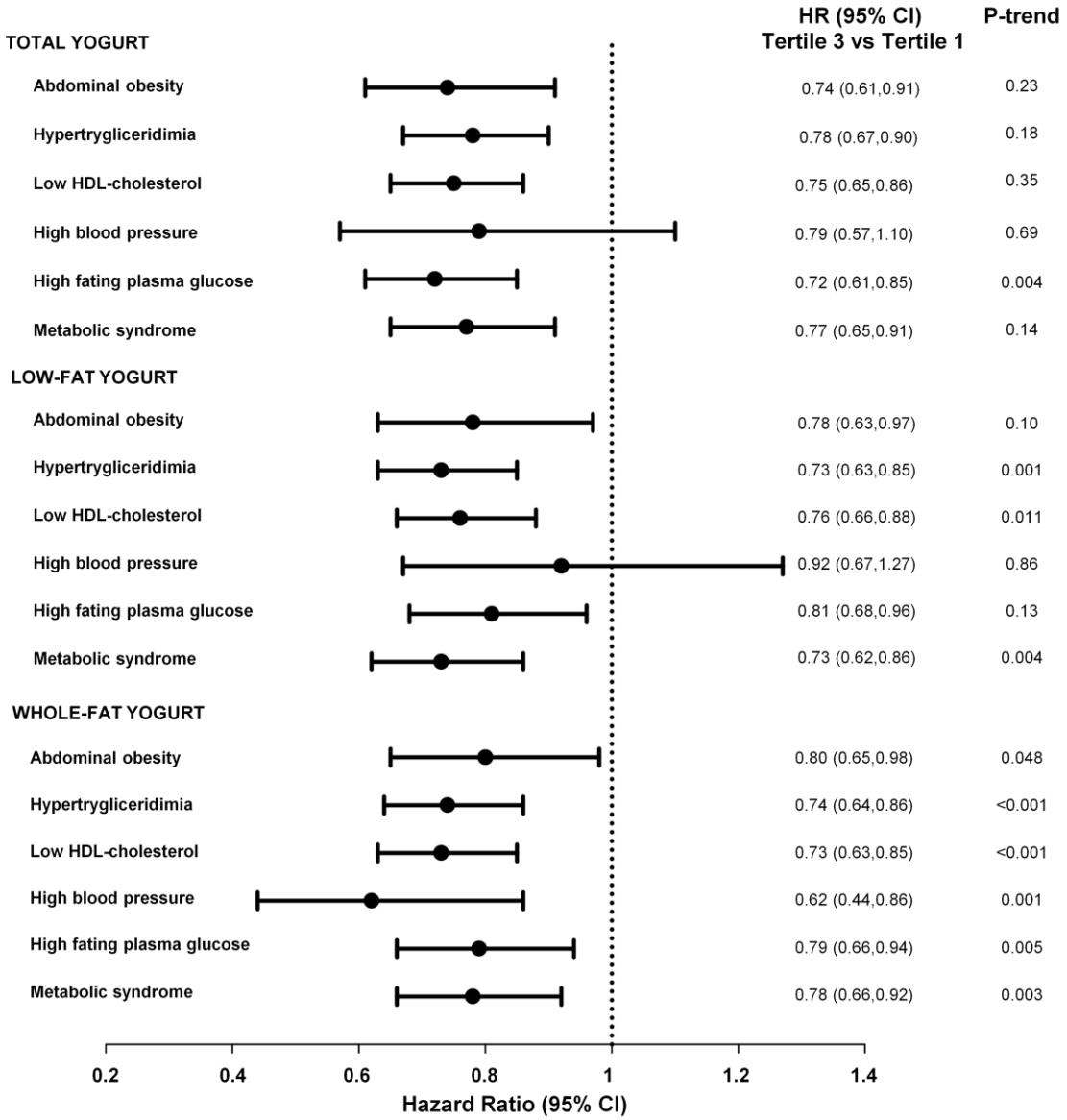
Figure 1. Hazard ratios (95% CI) of MetS and its components comparing tertile 3 vs tertile 1 of yogurt consumption in elderly individuals at high cardiovascular risk

Abbreviations: T, Tertile.

Abdominal obesity (n=1386), hypertriglyceridemia (n=3539), low HDL-cholesterol (n=3745), high blood pressure (n=337) and high fasting plasma glucose (n=1844).

Tertile cut-offs 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 (MET-day), BMI (kg/m^2), current smoker (yes/no), former smoker (yes/no) and use of hypoglycemic, hypolipidemic, antihypertensive and insulin treatment at baseline plus the mean consumption during follow-up of vegetables (g/d), fruit (g/d), legumes (g/d), cereals (g/d), fish (g/d), red meat (g/d), alcohol (g/d and quadratic term), biscuits (g/d), olive oil (g/d) and nuts (g/d). All models were stratified by recruitment center.



Supplemental Table 1. Hazard ratios (95% CI)[1] of MetS components[2] across energy-adjusted tertiles of specific dairy consumption[3] in elderly individuals at high cardiovascular risk

	T1	T2	T3	*P*-trend
Total dairy				
Abdominal obesity	1.00 ref.	0.98 (0.79,1.21)	1.06 (0.83,1.36)	0.55
Hypertriglyceridemia	1.00 ref.	0.70 (0.60,0.81)	0.92 (0.78,1.08)	0.60
Low HDL-cholesterol	1.00 ref.	0.79 (0.68,0.91)	0.87 (0.74,1.03)	0.19
High blood pressure	1.00 ref.	0.86 (0.62,1.19)	0.93 (0.65,1.33)	0.71
High fasting plasma glucose	1.00 ref.	0.88 (0.73,1.04)	0.97 (0.80,1.18)	0.94
Low-fat dairy				
Abdominal obesity	1.00 ref.	1.26 (1.04,1.56)	1.01 (0.81,1.26)	0.92
Hypertriglyceridemia	1.00 ref.	0.78 (0.68,0.91)	0.84 (0.73,0.98)	0.034
Low HDL-cholesterol	1.00 ref.	0.98 (0.85,1.13)	0.85 (0.73,0.99)	0.029
Hypertension	1.00 ref.	0.90 (0.65,1.25)	0.87 (0.63,1.20)	0.41
High fasting plasma glucose	1.00 ref.	0.88 (0.74,1.04)	0.82 (0.69,0.98)	0.033
Whole-fat dairy				
Abdominal obesity	1.00 ref.	0.90 (0.70,1.06)	0.90 (0.73,1.11)	0.59
Hypertriglyceridemia	1.00 ref.	0.81 (0.70,0.94)	0.85 (0.74,0.99)	0.16
Low HDL-cholesterol	1.00 ref.	0.88 (0.77,1.02)	0.87 (0.75,1.01)	0.14
High blood pressure	1.00 ref.	0.94 (0.68,1.32)	0.85 (0.61,1.19)	0.34
High fasting plasma glucose	1.00 ref.	0.89 (0.74,1.07)	1.05 (0.89,1.25)	0.28
Cheese				
Abdominal obesity	1.00 ref.	0.77 (0.62,0.95)	0.95 (0.77,1.18)	0.97
Hypertriglyceridemia	1.00 ref.	0.81 (0.70,0.94)	0.88 (0.76,1.03)	0.16
Low HDL-cholesterol	1.00 ref.	0.86 (0.74,1.00)	0.92 (0.79,1.07)	0.36
High blood pressure	1.00 ref.	0.76 (0.56,1.04)	0.95 (0.68,1.34)	0.86
High fasting plasma glucose	1.00 ref.	0.95 (0.80,1.14)	1.04 (0.87,1.25)	0.61
Total milk				
Abdominal obesity	1.00 ref.	1.02 (0.83,1.26)	1.08 (0.86,1.36)	0.49
Hypertriglyceridemia	1.00 ref.	0.79 (0.68,0.92)	0.92 (0.79,1.08)	0.77
Low HDL-cholesterol	1.00 ref.	0.92 (0.79,1.06)	0.84 (0.72,0.98)	0.035
High blood pressure	1.00 ref.	0.84 (0.60,1.18)	0.81 (0.57,1.15)	0.30
High fasting plasma glucose	1.00 ref.	1.01 (0.85,1.20)	0.84 (0.69,1.01)	0.039
Low-fat milk				
Abdominal obesity	1.00 ref.	1.11 (0.89,1.33)	0.96 (0.78,1.18)	0.66
Hypertriglyceridemia	1.00 ref.	1.00 (0.86,1.15)	0.91 (0.79,1.06)	0.22
Low HDL-cholesterol	1.00 ref.	1.14 (0.99,1.31)	0.81 (0.70,0.95)	0.007
High blood pressure	1.00 ref.	1.20 (0.87,1.65)	0.78 (0.56,1.08)	0.08
High fasting plasma glucose	1.00 ref.	1.13 (0.96,1.33)	0.79 (0.66,0.94)	0.009
Whole-fat milk				
Abdominal obesity	1.00 ref.	0.87 (0.71,1.08)	0.97 (0.78,1.19)	0.91
Hypertriglyceridemia	1.00 ref.	0.78 (0.67,0.90)	0.91 (0.79,1.06)	0.95
Low HDL-cholesterol	1.00 ref.	0.81 (0.69,.93)	0.90 (0.78,1.05)	0.66
High blood pressure	1.00 ref.	0.92 (0.66,1.30)	1.01 (0.72,1.42)	0.16
High fasting plasma glucose	1.00 ref.	0.88 (0.73,1.05)	1.16 (0.97,1.38)	0.028

Abbreviations: CI, confidence interval, MetS, metabolic syndrome; T, tertile.

[1] Cox regression models adjusted for intervention group, sex, age (year), leisure time physical activity (MET-day), BMI (kg/m^2), current smoker (yes/no), former smoker (yes/no) and use of hypoglycemic, hypolipidemic, antihypertensive and insulin treatment at baseline, and mean consumption of vegetables (g/d), fruit (g/d), legumes (g/d), cereals (g/d), fish (g/d), red meat (g/d), alcohol (g/d and quadratic term), biscuits (g/d), olive oil (g/d) and nuts (g/d) during the follow-up. All models were stratified by recruitment center.

[2] The MetS components (abdominal obesity, hypertriglyceridemia, low HDL-cholesterol, high blood pressure and high fasting plasma glucose) were defined according to updated harmonizing criteria.

[3] Tertile cut-offs are based on mean energy-adjusted dairy product consumption during the follow-up.

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Supplemental table 2. Hazard ratios[1] (95%CI) of metabolic syndrome incidence across energy-adjusted tertiles of total dairy consumption and its different subtypes, based on the number of metabolic syndrome components at baseline, in individuals at high cardiovascular risk.

	T3 vs T1[2]	
	0-1 MetS components n=512	**2 MetS components n=1356**
Total dairy	0.78 (0.48,1.27)	0.96 (0.78,1.18)
Low-fat dairy	0.77 (0.50,1.20)	0.77 (0.64,0.93)†
Whole-fat dairy	0.84 (0.61,1.45)	0.99 (0.83,1.18)
Total yogurt	0.89 (0.59,1.35)	0.77 (0.64,0.92)
Low-fat yogurt	0.79 (0.53,1.19)	0.73 (0.61,0.87)†
Whole-fat yogurt	0.77 (0.49,1.20)	0.77 (0.65,0.93)†
Cheese	1.79 (0.13,2.85)*	1.31 (1.09,1.57)*
Total milk	0.99 (0.63,1.54)	0.91 (0.74,1.10)
Low-fat milk	0.92 (0.60,1.43)	0.86 (0.71,1.04)
Whole-fat milk	1.06 (0.69,1.61)	1.12 (0.93,1.34)

[1]Cox regression model adjusted for intervention group, sex, age (year), leisure time physical activity (MET-day), BMI (kg/m^2), current smoker (yes/no), former smoker (yes/no), use of hypoglycemic, hypolipidemic, antihypertensive and insulin treatment at baseline, mean consumption during the follow-up of vegetables (g/d), fruit (g/d), legumes (g/d), cereals (g/d), fish (g/d), red meat (g/d), alcohol (g/d and quadratic term), biscuits (g/d), olive oil (g/d) and nuts (g/d). Stratified by recruitment center.

[2]Tertile cut-offs are based on energy-adjusted mean during the follow-up.

Abbreviations: T, Tertile

*P-trend <0.05

†P-trend <0.01