

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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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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1 **ABSTRACT**

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

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

7 **Methods:** We prospectively analyzed 1868 men and women (55-80 years-old) without
8 MetS at baseline, recruited from different PREDIMED centers between October 2003
9 and June 2009 and followed-up to December 2010. MetS was defined according to
10 updated harmonized criteria. At baseline and yearly thereafter we determined
11 anthropometric variables, dietary habits by a 137-item validated food frequency
12 questionnaire, and blood biochemistry determinations. Multivariable-adjusted hazard
13 ratios (HRs) of MetS or its components were estimated for each of the two upper
14 tertiles (versus the lowest one) of mean consumption of dairy products during the
15 follow-up.

16 **Results:** During a median follow-up of 3.2 years, we documented 930 incident MetS
17 cases. In the multivariable-adjusted model, HRs (95% CIs) of MetS for the comparison of
18 extreme tertiles of dairy product consumption were 0.72 (0.61-0.86) for low-fat dairy,
19 0.73 (0.62-0.86) for low-fat yogurt, 0.78 (0.66-0.92) for whole-fat yogurt, and 0.80
20 (0.67-0.95) for low-fat milk. The respective HR for cheese was 1.31 (1.10-1.56).

21 **Conclusions:** Higher consumption of low-fat dairy products, yogurt (total, low-fat and
22 whole-fat yogurt) and low-fat milk were associated with a reduced risk of MetS in
23 individuals at high cardiovascular risk from a Mediterranean population. Conversely,
24 higher consumption of cheese was related to a higher risk of MetS.

25 This trial was registered at controlled-trials.com as ISRCTN35739639.

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

27 INTRODUCTION

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

32 Diet and lifestyle are recognized as key elements in the prevention (2) and treatment of
33 MetS (3). In recent years a growing body of evidence has shown that the consumption
34 of dairy products may have beneficial effects on risk factors defining the MetS,
35 including atherogenic dyslipidemia (4), hyperglycemia (5), insulin resistance (6) or T2D
36 (7–9), blood pressure (10) and abdominal obesity (11).

37 In epidemiological studies, the association between the total consumption of dairy
38 products and the risk of MetS has been controversial. Some cross-sectional (4,12–15)
39 and prospective studies (5,16,17) have shown an inverse association while others (18,
40 19, 20) have shown no association. Results by sex have also been inconsistent
41 (18,19).

42 Although most studies suggest that total dairy consumption could provide protection
43 against development of MetS, methodological biases or multiple combinations of
44 different types of dairy product with varying nutrient content may have contributed to
45 the controversial results reported. Few studies have analyzed these associations
46 across different dairy product subtypes. Besides, some cross-sectional studies have
47 reported an inverse association (15,19) that was not found when data were analyzed
48 prospectively (5). For example, in the case of cheese consumption, cross-sectional
49 studies showed a positive association with MetS prevalence (19), whereas prospective
50 studies showed a negative one (5,17). Pereira and coworkers (5) showed an inverse
51 association with total consumption of dairy products regardless of their fat content,
52 whereas Louie and coworkers found this inverse association only for whole-fat dairy
53 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

63 **METHODS**

64 ***Study design and participants***

65 The present study was conducted within the framework of the Prevención con Dieta
66 MEDiterránea (PREDIMED) trial, the design of which has been described in detail
67 elsewhere (23,24). The PREDIMED study is a large, parallel-group, multicenter,
68 randomized, controlled field trial, aimed at assessing the effects of the Mediterranean
69 Diet (MedDiet) on the primary prevention of CVD (25). The main results of the trial
70 concerning at the primary endpoint have been published recently (26).
71 Briefly, 7447 community-dwelling men (aged 55–80 years) and women (aged 60–80
72 years) with no previously documented CVD were recruited. They were eligible if they
73 had either T2D, or at least three of the following cardiovascular risk factors:
74 hypertension (systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90
75 mmHg or on antihypertensive medication), high plasma LDL-cholesterol (≥ 160 mg/dL),
76 low plasma HDL-cholesterol (HDL-c) (< 40 mg/dL in men; < 50 mg/dL in women),
77 overweight or obesity (BMI ≥ 25 kg/m²), current smoking, or a family history of
78 premature coronary heart disease (23). From October 2003 to June 2009, participants
79 were randomized to three intervention groups (two of which were advised to follow a
80 MedDiet supplemented with either 1 liter per week of EVOO or 30 g/day of mixed nuts,
81 and were compared to the third group which was advised to follow a control low-fat
82 diet). The study follow-up ended in December 2010. All participants provided their
83 informed consent and the protocol was approved by the institutional review boards of
84 each recruitment center.

85 In the present report, the data were analyzed assuming the design of an observational
86 prospective cohort whose members were selected from all the PREDIMED recruiting
87 centers with biochemical determinations available for a follow-up of at least two years
88 (n=5801). Since our aim was to explore the associations between the consumption of
89 dairy foods and incident MetS, we excluded participants who had diagnoses of MetS
90 (63.9%) at baseline (n=3707). We also excluded participants who had not completed

91 the baseline food frequency questionnaire (FFQ) or who reported extreme total energy
92 intakes with values outside the pre-specified limits (500-3500 kcal/d in women and 800-
93 4000 kcal/d in men). A total of 2094 individuals were assessed. Of these, a total of 226
94 were excluded because of missing data that prevented the presence of MetS incidence
95 from being determined. Thus a total of 1868 participants were included in our
96 longitudinal assessment for MetS incidence. The individual components of MetS –
97 abdominal obesity, hypertriglyceridemia, low-HDL-cholesterol, high blood pressure,
98 and high fasting glucose concentration – were analyzed for a total of 1386, 3539, 3745,
99 337 and 1844 participants (from 5801 initially one) , respectively.

100

101 *Outcome*

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

106 MetS was defined in accordance with the updated harmonized criteria of the
107 International Diabetes Federation and the American Heart Association/National Heart,
108 Lung and Blood Institute(1). Individuals were diagnosed with MetS if they had three or
109 more of the following components: hypertriglyceridemia [≥ 150 mg/dl (≥ 1.7 mmol/L)] or
110 drug treatment for elevated triglycerides; low concentrations of HDL-c [< 50 mg/dl (< 1.3
111 mmol/L) and < 40 mg/dL (< 1.03 mmol/L) in women and men, respectively] or drug
112 treatment for low HDL-c; elevated blood pressure (systolic ≥ 130 mmHg and/or diastolic
113 ≥ 85 mmHg) or being treated for hypertension; high fasting plasma glucose [≥ 100 mg/dl
114 (≥ 5.5 mmol/L)] or drug treatment for hyperglycemia; and elevated waist circumference
115 for European individuals (≥ 88 cm in women and ≥ 102 cm in men).

116

117 ***Dietary assessment***

118 At baseline and yearly during follow-up, dietary intake was quantified by trained
119 dietitians with a face-to-face delivered a 137-item semi-quantitative food-frequency
120 questionnaire (FFQ) validated for the PREDIMED study (27). In the validation study,
121 the FFQ was administered twice to explore reproducibility at 1 year, and four 3-day
122 dietary records for the different seasons of the year were used as gold standard. The
123 reproducibility of the FFQ used in PREDIMED for food groups, and energy and nutrient
124 intake, explored by the Pearson correlation coefficient (r), ranged from 0.50 to 0.82,
125 and the intra-class correlation coefficient (ICC) ranged from 0.63 to 0.90. The validity
126 indexes of the FFQ in relation to the dietary records for food groups, energy and
127 nutrient intake ranged (r) from 0.24 to 0.72, while the range of the ICC was between
128 0.40 and 0.84. Regarding dairy product consumption, the reproducibility and validity of
129 FFQs were 0.81 (ICC 0.89), and 0.72 (ICC 0.84), respectively.

130 Dairy product consumption was assessed yearly using 15 items of the FFQ. In order to
131 assess habitual dietary intakes over the previous year, frequencies of consumption
132 were measured in 9 categories (ranging from never/almost never to >6 servings/day)
133 for each food item. These responses to individual dairy items were then converted into
134 mean daily consumptions (grams/day) during the follow-up by multiplying the typical
135 portion sizes (in grams) by the consumption frequency for each food and making the
136 appropriate division for the period assessed to obtain daily consumptions. Total dairy
137 foods category included semi-skim/skim milk and skim yogurt, whole milk, condensed
138 milk, whole yogurt, custard and all types of cheeses: petit Suisse, ricotta, cottage, semi-
139 cured/cured cheeses such as Cheddar, Manchego, Emmental, etc.). Low-fat dairy foods
140 included semi-skim/skim milk and skim yogurt, whole-fat dairy foods (whole milk and
141 whole yogurt), and total dairy foods, including all of the above. Consumption of dairy
142 products was also categorized by subtype: milk (including total, low-fat and whole-fat
143 milk), yogurt (including total, low-fat and whole-fat yogurt), and cheese. Energy and
144 nutrient intake and food groups were calculated from Spanish food composition tables

145 (28,29). We adjusted dairy consumption for total energy intake using the nutrient
146 residual method (30).

147 **Measurements**

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

157 Blood samples were collected after an overnight fast, coded, shipped to a central
158 laboratory, and stored at -80°C until analysis. Biochemical analysis was performed in
159 local laboratories. Glucose was measured by the glucose-oxidase method, cholesterol
160 by esterase-oxidase-peroxidase (CHOD-PAP), triglycerides by glycerol-phosphate
161 oxidase-peroxidase (GPO-PAP), and HDL cholesterol by direct measurement. All local
162 laboratories satisfied external quality-control requirements. When triglycerides were
163 <300 mg/dL, low density lipoprotein cholesterol was calculated using the Friedewald
164 formula so that the LDL cholesterol was not underestimated. A concordance study of
165 nine laboratories was conducted. From each study, a mean of 200 samples were
166 analyzed for total cholesterol, high density lipoprotein cholesterol, and triglycerides
167 using the IMIM laboratory as reference. The IMIM laboratory used ABX-Horiba
168 commercial kits (ABX-Horiba, Montpellier, France) in a PENTRA-400 autoanalyzer
169 (ABX-Horiba). One center was unable to provide samples for the concordance study.
170 The analysis of concordance of lipid measurements showed a coefficient of
171 determination R^2 and an intra-class correlation coefficient (95% confidence interval),
172 between 0.85 and 0.97, and 0.85 (0.77-0.90) and 0.97 (0.95-0.98) for total cholesterol,

173 respectively; between 0.819 and 0.92, and 0.81 (0.78-0.83) and 0.92 (0.89-0.95) for
174 HDL cholesterol, respectively; between 0.81 and 0.99, and 0.81 (0.73-0.87) and 0.99
175 (0.99-0.99) for triglycerides, respectively; and between 0.82 and 0.96, and 0.82 (0.74-
176 0.88) and 0.99 (0.99-0.99) for glucose, respectively.

177 **Statistical analysis**

178 We averaged the intake reported during the baseline interview and the yearly
179 consumption during the follow-up. Then, participants were categorized into tertiles of
180 the mean consumption of total dairy products and different subtypes during the follow-
181 up. To better represent the long-term consumption of dairy products and to minimize
182 within-person variation, we used the mean energy-adjusted dairy consumption for all
183 analyses based on assessments from items of all FFQs which were administered at
184 baseline and yearly during the follow-up for those participants who did not develop
185 MetS. For those who did develop MetS, and given that participants can alter their
186 dietary pattern after developing MetS, we only used data from all the available FFQs
187 until the year before MetS was diagnosed. The baseline characteristics of the
188 participants are expressed using mean \pm SD or median [IQR] for continuous variables,
189 and number and percentages for categorical variables. Chi square and one-way
190 ANOVA tests were used to assess differences in the baseline characteristics of the
191 study population.

192 Multivariable time-dependent Cox proportional regression models were fitted to assess
193 the hazard ratios (HRs) of developing MetS and its components during follow-up
194 according to tertiles of consumption of total, low-fat, and whole-fat dairy products; milk,
195 low-fat milk and non-reduced milk; total yogurt, low-fat and non-reduced fat yogurt, and
196 cheese. Both upper tertiles were compared with the lowest tertile (reference). The
197 assumption of proportional hazards was tested using time-dependent covariates.
198 The time variable was the interval between randomization and the date of the last follow-
199 up, or the last recorded clinical event (MetS incidence) of participants who were still alive,

200 whichever occurred first. Participants who were free of MetS or who were lost during
201 follow-up were censored at the date of the last visit.

202 Three different Cox regression models were adjusted for potential confounding factors.
203 Model 1 was adjusted for intervention group, sex, age (year), leisure time physical
204 activity (MET-day), BMI (kg/m²), current smoker (yes/no), former smoker (yes/no) and
205 hypoglycemic, hypolipidemic, antihypertensive and insulin treatment at baseline. Model
206 2 was additionally adjusted for the mean consumption during the follow-up of
207 vegetables (g/d), fruit (g/d), legumes (g/d), cereals (g/d), fish (g/d), red meat (g/d),
208 alcohol (g/d and quadratic term), biscuits (g/d), olive oil (g/d) and nuts (g/d). Model 3
209 was adjusted for model 2 plus the prevalence of MetS components at baseline:
210 abdominal obesity (yes/no), hypertriglyceridemia (yes/no), low HDL-cholesterol
211 (yes/no), hypertension (yes/no) and high fasting plasma glucose (yes/no).

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

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

225 All analyses were performed with SPSS software (version 19.0; SPSS).
226

227 RESULTS

228 After a median of 3.2 years of follow-up (IQR: 1.9-5.8), 930 participants without MetS at
229 baseline (53.8% women) developed new-onset MetS. Of those not showing the specific
230 MetS components at baseline, 43.4% of 1040 participants developed abdominal
231 obesity during follow-up; 27.7% of 1770 developed hypertriglyceridemia; 24.5% of 1810
232 developed low-HDL-cholesterol; 82.2% of 240 developed high blood pressure, and
233 41.4% of 1268 developed high fasting glucose concentration.

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

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

245

246 *Consumption of total dairy products and incidence of metabolic syndrome*

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

252

253 *Consumption of dairy product subtypes and incidence of metabolic syndrome*

254 **Table 3** shows the HRs of incident MetS across tertiles of consumption of specific
255 subtypes of dairy products (yogurt, cheese and milk) also adjusted for potential
256 confounders. Among the subtypes of dairy products, consumers in tertile 3 of low-fat
257 yogurt [HR: 0.73; 95% CI:0.62,0.86; P-trend = 0.004], whole-fat yogurt [HR: 0.78; 95%
258 CI: 0.66,0.92; P-trend = 0.003], and low-fat milk [HR: 0.80; 95% CI: 0.67,0.95]; P-trend
259 = 0.007] had lower risk of developing MetS compared to participants in the lowest tertile
260 of consumption. Compared to participants in the lowest tertile of consumption of
261 cheese, those in the highest tertile had an increased risk of incident MetS [HR: 1.31;
262 95% CI: 1.10,1.56; P-trend <0.001]. No statistical interactions were found between the
263 consumption of total dairy products or subtypes and sex or intervention group.

264

265 *Yogurt consumption and metabolic syndrome and its components*

266 Figure 1 shows the multivariable-adjusted HR of each MetS component in subjects
267 who were initially free of MetS in extreme categories of total yogurt, whole-fat and low-
268 fat yogurt consumption (tertile 3 versus tertile 1). With the exception of high blood
269 pressure, participants in the highest tertile of total yogurt consumption had a
270 significantly lower risk of developing each of the MetS components than those in the
271 lowest tertile. However, the linear trend was significant only for high fasting glucose (P
272 for trend= 0.004). Compared with participants in the lowest tertile, participants in the
273 highest tertile of whole-fat yogurt consumption had a lower risk of several components
274 of the MetS: abdominal obesity [HR: 0.80; 95% CI: 0.65,0.98; P-trend=0.048],
275 hypertriglyceridemia [HR: 0.74; 95% CI: 0.64,0.86; P-trend <0.001], low HDL-
276 cholesterol [HR: 0.73; 95% CI: 0.63,0.85; P-trend <0.001], high blood pressure [HR:
277 0.62; 95% CI: 0.44,0.86; P-trend=0.001], and high fasting plasma glucose [HR: 0.80;
278 95% CI: 0.66,0.94; P-trend=0.005]. The associations with low-fat yogurt were in the
279 same direction as those with total and whole-fat yogurt, but inverse associations were
280 limited to hypertriglyceridemia [HR: 0.73; 95% CI: 0.63,0.85; P-trend=0.18], low HDL-

281 cholesterol [HR: 0.76; 95% CI: 0.66,0.88; P-trend=0.35] and high fasting plasma
282 glucose [HR: 0.81; 95% CI: 0.68,0.96; P-trend=0.004].

283

284 *Consumption of dairy products, dairy product subtypes and metabolic syndrome*
285 *components*

286 Supplemental Table 1 shows HRs for the components of incident MetS across tertiles
287 of consumption of total dairy products and subtypes. An increased consumption of total
288 milk and low-fat milk was significantly associated with a lower incidence of low HDL-
289 cholesterol and high fasting glucose. Low-fat dairy consumption was inversely
290 associated with high fasting glucose, hypertriglyceridemia, and low HDL-cholesterol
291 (see Supplemental Table 1).

292 *Consumption of dairy products, subtypes of dairy products and incidence of metabolic*
293 *syndrome based on the number of MetS components at baseline*

294 A sensitivity analysis based on the number of MetS components at baseline found that
295 in those individuals that had only one component or none at all there was no significant
296 association between total dairy or its subtypes and MetS incidence, except for cheese
297 (P-trend <0.05). In those individuals with two MetS components at baseline, there were
298 still significant inverse associations between low-fat dairy, low-fat yogurt and whole-fat
299 yogurt consumption and MetS incidence. A positive association was observed between
300 cheese consumption and MetS development (see Supplemental Table 2).

301 **DISCUSSION**

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

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

322 Our results for the type of product and fat content are discordant with those reported by
323 the prospective CARDIA study (5), in which an inverse association between the
324 consumption of whole-fat dairy products and cheese and MetS was observed in
325 individuals above 18 years of age. We observed a direct association between the
326 consumption of cheese and incident MetS. Unlike our findings, individuals in the BMES
327 study (20) who consumed more whole-fat dairy or low-fat dairy products showed a

328 decreased or an increased risk of developing MetS, respectively. The population in our
329 study consisted of older individuals at high cardiovascular risk, while the study subjects
330 were younger in both the CARDIA and the BMES studies. This may partly explain the
331 contradictory results. It should be pointed out that only the CARDIA study analyzed the
332 associations between MetS and dairy product subtypes, although they were classified
333 differently than in our study. This may help explain the divergent results.

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

337 Numerous biological mechanisms may mediate the relationship between dairy
338 consumption and risk of MetS.

339 Dairy products are an important source of calcium. Calcium in milk products interacts
340 with saturated fatty acid to form calcium-fatty acid soaps, thereby increasing fecal fat
341 excretion (35) and thus, improving the HDL:LDL-cholesterol ratio. Lorenzen and
342 coworkers (36) also showed that, unlike calcium from supplements, calcium from milk
343 and low-fat yogurt reduced the triglyceride content of chylomicrons postprandially (36).
344 Intervention studies have also shown that calcium intake decreases blood pressure
345 (37,38), and that milk-derived bioactive peptides have antihypertensive properties (39).
346 Milk-derived bioactive peptides have increasingly been shown to play an important role
347 in preventing MetS by regulating insulinemia, blood pressure, dyslipidemia and central
348 fat accumulation(39–41). Nutrients from dairy products may act synergistically on
349 metabolic pathways that have a beneficial impact on MetS. It has been reported that
350 insulin concentrations are lower in those subjects consuming diets high in dairy
351 products than in subjects consuming diets low in dairy products (41), which suggests
352 that calcium or other nutrients that make up dairy products have beneficial effects on
353 glucose metabolism. Although some studies (40) have suggested beneficial
354 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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Table 1. Baseline characteristics of study individuals at high cardiovascular risk by tertiles of total dairy consumption¹

	Total dairy consumption (g/day) ²			P-value ³
	T1 ≤287 n=622	T2 287-449 n=623	T3 ≥450 n=623	
Total dairy consumption, median [P25-P75], (g/day)	207 [142-250]	354 [322-393]	577 [518-661]	
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 ;.

¹Data are expressed as means (standard deviation) or medians [IQR, range interquartile] for continuous variables and percentage and number (n) for categorical variables.

²Tertile cut-offs are based on energy-adjusted mean of total dairy consumption during the follow-up.

³P value for differences between tertiles were calculated by chi-square or ANOVA tests for categorical and for continuous variables, respectively.

⁴All 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)			P- trend
	T1 ¹	T2	T3	
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.

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

²Cox regression model 1 adjusted for intervention group, sex, age (year), leisure time physical activity (MET-day), BMI (kg/m²), current smoker (yes/no), former smoker (yes/no) and use of hypoglycemic, hypolipidemic, antihypertensive and insulin treatment at baseline.

³Cox 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).

⁴Cox 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 syndrome¹ 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			P- trend
	T1 ²	T2	T3	
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 (46.2)	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.

¹The MetS components were defined using updated harmonizing criteria.

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

³Cox regression model1: Cox regression model adjusted for intervention group, sex, age (year), leisure time physical activity (MET-day), BMI (kg/m²), current smoker (yes/no), former smoker (yes/no) and use of hypoglycemic, hypolipidemic, antihypertensive and insulin treatment at baseline.

⁴Cox 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).

⁵Cox 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

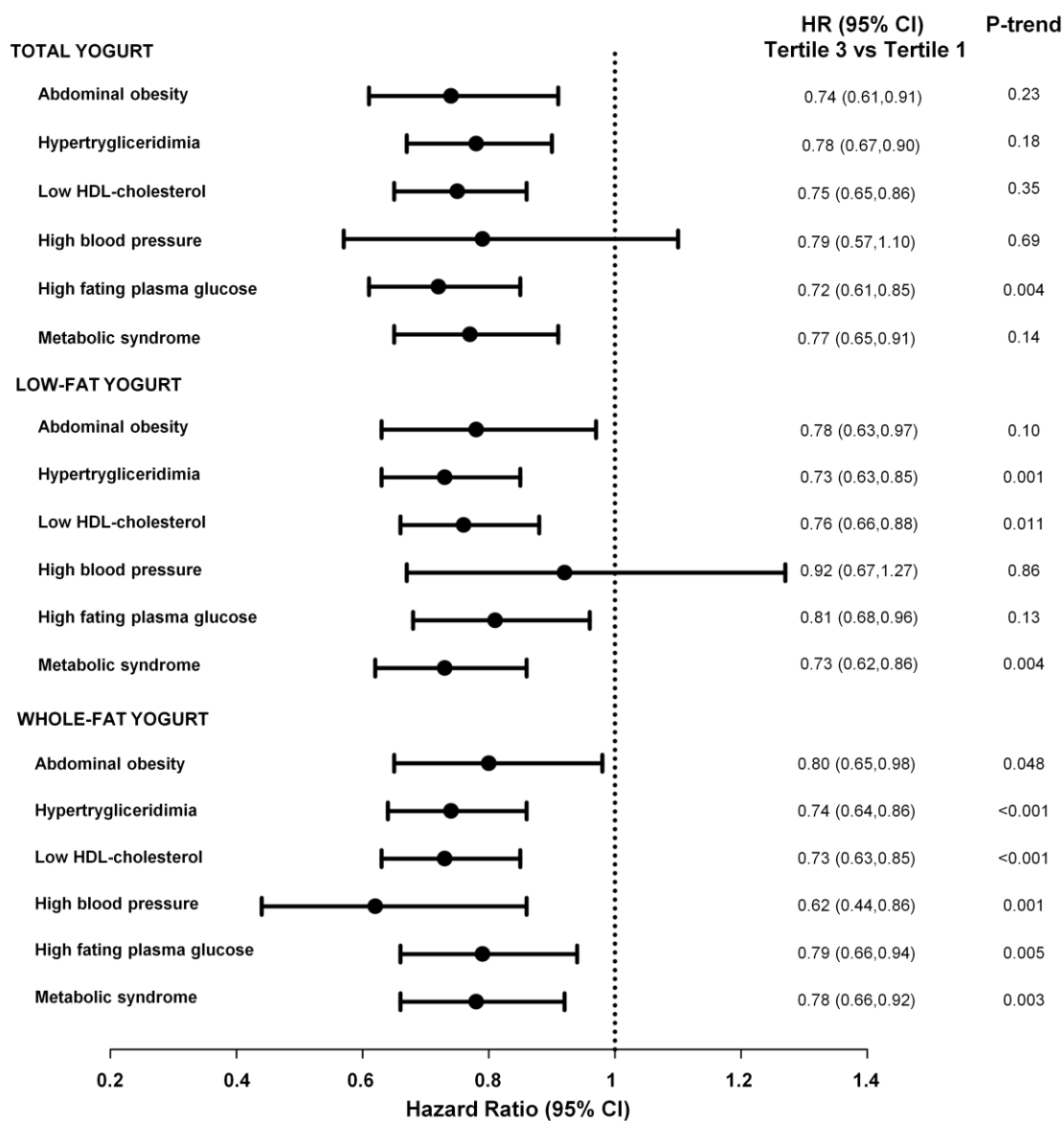
Figure 1. Hazard ratios (95% CI) of MetS and its components comparing tertile 3 vs tertile 1 of yogurt consumption in elderly individuals at high cardiovascular risk

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/m²), 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 components² across energy-adjusted tertiles of specific dairy consumption³ 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
<i>Low-fat dairy</i>				
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
<i>Whole-fat dairy</i>				
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
<i>Low-fat milk</i>				
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
<i>Whole-fat milk</i>				
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/m²), 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 ratios¹ (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)

¹Cox regression model adjusted for intervention group, sex, age (year), leisure time physical activity (MET-day), BMI (kg/m²), 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.

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

Abbreviations: T, Tertile

*P-trend <0.05

[†]P-trend <0.01