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5 **Dairy product consumption and risk of type 2 diabetes in an elderly Spanish Mediterranean population**
6 **at high cardiovascular risk**

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25 **ABSTRACT**

26 **Purpose:** The possible effects of dairy consumption on diabetes prevention remain controversial. The aim
27 of this study was to investigate the association between the dairy consumption and type 2 diabetes (T2D)
28 risk in an elderly Mediterranean population at high cardiovascular risk.

29 **Methods:** We prospectively followed 3454 non-diabetic individuals from the PREDIMED study. Dairy
30 consumption was assessed at baseline and yearly using food-frequency questionnaires, and categorised
31 into total, low-fat, whole-fat, and subgroups: milk, yogurt, cheeses, fermented dairy, concentrated full-fat,
32 and processed dairy. Hazard ratios (HRs) were calculated using Cox proportional hazards regression
33 models.

34 **Results:** During a median follow-up of 4.1 years, we documented 270 incident T2D cases. After
35 multivariate adjustment, total dairy product consumption was inversely associated with T2D risk (0.68
36 [95%CI, 0.47-0.98]; P-trend=.040). This association appeared to be mainly attributed to low-fat dairy; the
37 multivariate HRs (95%CIs) comparing the highest versus the lowest tertile consumption were 0.65 (0.45-
38 0.94) for low-fat dairy products and 0.67 (0.46-0.95) for low-fat milk (both P-trend<.05). Total yogurt
39 consumption was associated with a lower T2D risk (HR: 0.60 [0.42-0.86]; P-trend=.002). An increased
40 consumption of total, low-fat dairy and total yogurt during the follow-up was inversely associated with
41 T2D; HRs were 0.50 (0.29-0.85), 0.44 (0.26-0.75) and 0.55 (0.33-0.93) respectively. Substituting one
42 serving/day of a combination of biscuits and chocolate, and whole-grain biscuits and homemade pastries
43 for one serving/day of yogurt was associated with a 40% and 45% lower risk of T2D, respectively. No
44 significant associations were found for the other dairy subgroups (cheese, concentrated full-fat and
45 processed dairy products).

46 **Conclusions:** A healthy dietary pattern incorporating a high consumption of dairy products, and
47 particularly yogurt may be protective against T2D in older adults at high cardiovascular risk.

48

49 **Keywords:** PREDIMED; type 2 diabetes; older adults; dairy; yogurt.

50 INTRODUCTION

51 Type 2 diabetes (T2D) incidence is increasing at an alarming rate worldwide and especially in elderly
52 population [1]. Compelling evidence shows that dietary and lifestyle changes are a key element in the
53 prevention of T2D and obesity-associated metabolic disturbances [2, 3]. Of the many food groups that may
54 offer protection against T2D, dairy products are one of the most frequently investigated. Largely owing to
55 their saturated fat content, dairy products are conventionally perceived as having an adverse impact on health
56 [4]. However, they are nutrient-dense food, and contain high-quality protein, vitamins (A, D, B₂, B₁₂ and
57 menaquinones), and minerals (calcium, magnesium and potassium), which have been shown to have
58 beneficial effects on T2D risk [5].

59 Limited evidence suggests that insulin sensitivity can be improved when dairy consumption is promoted [6,
60 7]. In addition, four meta-analyses of prospective studies have recently reported an overall reduced risk of
61 T2D incidence in subjects with higher dairy consumption, particularly the low-fat variety [8–11].

62 Nonetheless, the results of studies from these meta-analyses have shown mixed results: some have reported
63 inverse associations for low-fat dairy [12–16], milk [17, 18], low-fat or skim milk [12, 13, 19], cheese [13],
64 and yogurt [12, 13, 16], whereas other failed to find associations between dairy-subtype consumption and
65 T2D [20–26]. The largest studies in all these meta-analyses were from the USA [12–15, 21] and Asia [22],
66 and European studies have provided limited evidence on this issue [26, 27]. Recent studies conducted on
67 European population that have focused on specific dairy subtypes and T2D risk have found inconsistent
68 results. In two large prospective studies using data from the European Prospective Investigation into Cancer
69 and Nutrition (EPIC) cohorts [EPIC-InterAct study [27] including eight European countries, and the EPIC-
70 Norfolk study [28] including a UK population-based cohort]), only the consumption of fermented dairy,
71 specifically yogurt and low-fat unripened cheese, were associated with decreased risks of incident T2D.
72 Nevertheless, consumption of total and whole-fat dairy, milk, cheese and whole-fat fermented dairy were not
73 associated with T2D [27, 28]. Conversely, in the EPIC-Potsdam study [26], and two other prospective studies
74 conducted in English and Danish populations [23, 24] no association between dairy and T2D was found.

75 The aforementioned studies were conducted in apparently healthy young or middle-aged individuals.
76 However, to our knowledge, no study has examined the association between dairy consumption and T2D risk
77 in elderly individuals at high cardiovascular risk. Therefore, we aimed not only to prospectively explore the
78 associations between total consumption of dairy and specific dairy subgroups and the T2D risk, but also to
79 estimate substitution effects of alternative foods for dairy products on T2D risk in an elderly Mediterranean
80 population at high cardiovascular risk in the frame of the PREDIMED study.

81 **MATERIALS AND METHODS**

82 *Study design and participants*

83 The present study was conducted with data from non-diabetic participants at high risk of coronary heart
84 disease (CHD) from the PREDIMED (PREvención con DIeta MEDiterránea) study. The PREDIMED
85 study is a large, parallel-group, randomized, multicenter, controlled trial designed to assess the effect of
86 the Mediterranean diet on the primary prevention of cardiovascular disease (CVD)
87 (<http://www.predimed.es>). Recruitment took place between October 2003 and January 2009, and 7447
88 participants were randomly assigned to three intervention groups: two Mediterranean diet groups
89 (supplemented with either virgin olive oil or nuts), and a control low-fat diet group. The design of the
90 PREDIMED trial has been reported in detail elsewhere [29]. The study was conducted in agreement with
91 the Declaration of Helsinki. The Institutional Review Board of the recruitment centers approved the study
92 protocol and participants gave their informed consent.

93 The participants were eligible if they were men aged 55-80 years and women aged 60-80 years, who were
94 free of CVD at baseline and fulfilled at least one of the two following criteria: presence of T2D and/or
95 three or more cardiovascular-risk factors, including family history of early-onset CHD, smoking,
96 hypertension, dyslipidemia or overweight.

97 In the present study, we analyzed data as in an observational prospective cohort, and only participants
98 without diagnoses of T2D at baseline were included (n=3833). Individuals who lacked measures of
99 glucose control, who did not have information on the baseline FFQ, or implausible daily energy intake
100 (<500 or >3500 kcal/day for women and <800 or >4000 kcal/day for men) (n=379) were excluded. The
101 final analyses included 3454 individuals.

102 *Ascertainment of incident T2D*

103 T2D was a prespecified secondary outcome of the PREDIMED-trial. It was considered to be present at
104 baseline by clinical diagnosis or use of antidiabetic medication. Incident (new-onset) cases of T2D during
105 the follow-up were diagnosed using the American Diabetes Association criteria: namely, fasting plasma
106 glucose ≥ 126 mg/dL (7 mmol/L) or 2-hour plasma glucose ≥ 200 mg/dL (11.1 mmol/L) after a 75-g oral

107 glucose load. All participants' medical records were reviewed yearly in each center by physicians-
108 investigators. When cases of new-onset T2D were identified on the basis of a medical diagnosis reported
109 in the medical charts or a glucose test during routine biochemical analyses, these reports and all medical
110 documentation of the participant were sent to the PREDIMED Clinical Events Committee, whose
111 members were blinded to treatment allocation. Only when a second test had been done using the same
112 criteria within the following 3 months and the new case of T2D confirmed was the end point definitively
113 confirmed by the adjudication committee. Only T2D events that were confirmed between 1 October 2003
114 and 1 December 2010 were included in the analyses.

115 *Assessment of dairy consumption*

116 At baseline and yearly during follow-up, diet was assessed using a 137-item semi-quantitative food-
117 frequency questionnaire (FFQ) validated for the PREDIMED study [29]. Energy and nutrient intake were
118 calculated from Spanish food composition tables [29]. With regard to dairy product, in the validation
119 study, the intra-class correlation coefficient between dairy product consumption from the FFQ and
120 repeated food records was 0.84.

121 Responses to individual dairy items of the FFQ were converted to average daily consumptions (g/day) and
122 then combined and categorized into total dairy (including all types of milk, yogurt and cheeses, custard,
123 whipped cream, butter and ice cream), low-fat dairy (semi-skim/skim milk and skim yogurt), whole-fat
124 dairy (whole-fat milk and whole-fat yogurt). Dairy consumption was also categorised by subtype into the
125 consumption of milk (total, low-fat and whole-fat milk), yogurt (total, low-fat and whole-fat yogurt), cheese
126 (petit Suisse, ricotta, cottage, spreadable, semi-cured/cured cheeses), fermented dairy (all types of yogurt and
127 cheeses), concentrated full-fat dairy (butter, whipped cream, and all types of cheeses) and processed dairy
128 (condensed milk, milkshakes, ice cream and custard). The dairy consumption at baseline and in every
129 follow-up assessment was adjusted for total energy intake using the residuals method.

130 *Assessment of covariates*

131 At baseline and yearly, all participants completed: a) a 47-item questionnaire about education, lifestyle,
132 history of illnesses and medication use; b) a validated Spanish version of the Minnesota Leisure-Time

133 Physical Activity Questionnaire [29]. In addition, anthropometric variables and blood pressure were
134 determined by trained staff. Blood samples were also collected from all participants after an overnight
135 fast. Plasma fasting glucose and serum levels of total cholesterol, HDL-cholesterol and triglycerides were
136 measured by routine laboratory tests using standard enzymatic methods.

137 *Statistical analysis*

138 Person-time of follow-up was calculated as the interval between the randomization date and the earliest
139 date of the follow-up contact at which a new diagnosis of T2D was ascertained, death from any cause, or
140 date of the last contact visit, whichever came first. To better represent long-term consumption of dairy
141 products and to minimize within-person variation, we used the cumulative average of energy-adjusted
142 dairy consumption for all analyses based on assessments from items of all FFQs administered at baseline
143 and yearly during the follow-up. Given that after developing T2D participants may alter their dietary
144 pattern, we only used data from all the available FFQs until a year before the last date of T2D diagnoses
145 was ascertained. Participants were categorized into dairy consumption tertiles. Two upper tertiles were
146 compared with the lowest tertile (reference). Multivariate time-dependent Cox proportional hazard
147 regression models were fitted to estimate the hazard ratios (HRs) and 95% CIs of T2D for dairy
148 consumption. Model 1 was adjusted for baseline age, sex and BMI. Model 2 was additionally adjusted for
149 intervention group, baseline smoking status, physical activity, educational level, hypertension or
150 antihypertensive drug use, fasting glucose, HDL-cholesterol and triglycerides concentrations. To minimize
151 confounding by other dietary factors, a third model (model 3) was additionally adjusted for the cumulative
152 average consumption of vegetables, legumes, fruits, meat, fish, olive oil and nuts (all in energy-adjusted
153 quintiles), and alcohol.

154 We conducted subsequent multivariate analyses to examine the HRs for T2D of substituting one-
155 serving/day of alternative foods for one serving/day of dairy products (only those dairy products that were
156 associated with T2D). These dietary variables were included as continuous variables in the same
157 multivariate model (model 2). The differences in their β -coefficients, variances and covariance were used

158 to estimate the β -coefficient \pm SE for the substitution effect, and the HRs and 95%CIs were calculated
159 from these parameters.

160 To test the robustness of our primary findings we conducted a series of sensitivity analyses: a) repeating
161 the models with only dairy consumers; b) using the dairy consumption at baseline to assess the predictive
162 power of simple measure of the dairy consumption on T2D risk instead of cumulative average
163 consumption; and c) longitudinal analysis was conducted also to assess the associations between dairy
164 consumption changes during the follow-up and T2D risk. The average dairy consumption changes were
165 calculated as changes from baseline to follow-up divided by the number of years of follow-up. Subjects
166 were categorized into 4 groups according to their dairy consumption changes: a) constant, < median
167 (subjects with dairy consumption below median at baseline and follow-up); b) increased consumption
168 (subjects who increased their dairy consumption from below to above median during follow-up); c)
169 constant, \geq median (subjects with dairy consumption equal or above median at baseline and follow-up)
170 and; d) decreased consumption (subjects who decreased their dairy consumption from equal or above to
171 below median during follow-up); the group with constant low dairy consumption was considered the
172 reference group.

173 Finally, effect modification by sex, BMI, and intervention group was examined also by including the
174 interaction terms in univariate models. We examined linear trend by modelling the median values for dairy
175 consumption categories as a continuous variable. All significance levels were calculated two-sided and the
176 significance level was set at $P < .05$. Analyses were performed with SPSS version 19.0.

177 **RESULTS**

178 During a median follow-up of 4.1 [2.5-5.7] years, we documented 270 incident cases of T2D. The
179 cumulative average consumption of total dairy in the study population was 363 g/d, with low-fat dairy
180 products being the largest contributors (71%). The main dairy products consumed were: milk (63%, of
181 which 85% was semi-skim/skim); yogurt (24%, of which 70% was skim); cheese (11%) and processed
182 dairy (4%). The baseline characteristics of study population according to total dairy consumption tertile
183 are shown in Table 1. Those individuals with higher dairy product consumption were more likely to be
184 older and women, and have higher BMI and lower educational levels. And they were less likely to smoke,
185 be physically active, and have lower plasma concentrations of fasting glucose and triglycerides and
186 increased concentrations of total and HDL-cholesterol. Participants in the highest tertile of dairy also had
187 a lower consumption of total energy, and were more likely to have a healthier dietary pattern. Similar
188 trends were observed for tertile of consumption of other dairy subgroups (low-fat, whole-fat dairy, total
189 milk and yogurt), except for the consumption of vegetable, fruit and protein that were significantly lower
190 in subjects with a high whole-fat dairy consumption than in subjects with a low consumption. Participants
191 in the highest tertile of whole-fat dairy also had a higher consumption of total fat (Online Supplemental
192 Table S1 and Table S2).

193 The HRs of T2D incidence according to dairy products consumption tertiles are shown in Table 2 and
194 Table 3. Total and low-fat dairy consumption was associated with a reduced risk of T2D incidence after
195 adjustment for various confounders (model 1 and model 2; P-trend<.05). Adjustment for other major food
196 groups (model 3) did not materially alter the associations, and the corresponding HRs (95% CIs) for the
197 highest versus the lowest tertile of total and low-fat dairy consumptions were 0.68 (0.47-0.98) and 0.65
198 (0.45-0.94), respectively (Table 2).

199 Both total and low-fat milk consumption [HRs (95%CI): 0.64 (0.45-0.89) and 0.53 (0.37-0.75); P-trend<.05,
200 respectively) were inversely associated with T2D risk (model 2), but only low-fat milk consumption
201 remained significantly associated with lower T2D risk after adjustment for additional confounders (Table 3).
202 Similarly, subjects with higher total yogurt consumption exhibited a 40% lower risk of T2D (P-trend=.002).

203 Furthermore, this risk reduction of T2D was maintained in both low-fat yogurt (HR: 0.68 [95%CI, 0.47-0.97];
204 P-trend<.047) and whole-fat yogurt (HR: 0.66 [95%CI, 0.47-0.92]; P-trend<.020), when they were examined
205 separately. We also analyzed total yogurt and low-fat milk consumptions as continuous variables, in model2,
206 an average increment of one-serving/day of the standard serving of yogurt (125 g) and low-fat milk (200 ml)
207 was associated with a 33% and 23% lower risk of T2D, respectively. After adjustment for other food
208 (model3), only the association of total yogurt with T2D remained statistically significant (HR: 0.74 [95%CI,
209 0.55-0.98]). For fermented dairy, the relative reduction in the risk of T2D was 41% (model 3 HR: 0.59
210 [95%CI, 0.41-0.84]) for the second versus the first tertile (Table 3). No significant association was found for
211 whole-fat dairy products, total and whole-fat milk, cheese, concentrated full-fat dairy and processed dairy
212 products.

213 When we repeated all our analyses including only dairy consumers, the consumption of total and low-fat dairy
214 and total yogurt were associated with a lower risk of T2D. Similarly, after full adjustment for potential
215 confounders (model 3), total, low-fat dairy and subtypes dairy (low-fat milk and total yogurt) were inversely
216 associated with T2D when baseline dairy consumption instead of cumulative average consumption was used
217 as the exposure variable. For the associations between dairy consumption changes during follow-up and T2D
218 risk, results were not substantially different. Compared with subjects who consistently consumed below the
219 median (reference group), subjects who increased their consumption of total, low-fat dairy and total yogurt
220 and yogurt subtypes (low-fat and whole-fat yogurt) during the follow-up period had a lower risk of
221 developing incident T2D in the fully adjusted model (model 3) (Online Supplemental Table S3).

222 We also have considered the possible effect of dairy consumption on BMI over time, but further adjustment of
223 the models for BMI changes during follow-up did not affect the results (data not shown). Furthermore, we
224 found no interaction between total dairy or main dairy subtypes (milk, yogurt, and cheese) and sex, BMI, or
225 intervention group.

226 Lower risks of T2D were also shown when 1-serving/day of a combination of biscuits and chocolate
227 confectionary (50 g), and whole-grain biscuits and homemade pastries (50 g) were replaced with one-
228 serving/day of yogurt (125 g), and the corresponding HRs (95%CIs) were 0.60 (0.38-0.94), and 0.55 (0.32-

229 0.96), respectively (Table 4).

230 **DISCUSSION**

231 In this prospective study conducted on community-dwelling elderly subjects at high cardiovascular risk,
232 we observed that a high consumption of dairy products was associated with decreased risk of T2D. The
233 consumption of low-fat dairy products, mainly low-fat milk and both low-fat and whole-fat yogurt, were
234 the main contributors to this association. Replacing biscuits and chocolate confectionary, or whole-grain
235 biscuits and homemade pastries, typical deserts or snacks in Spain, for yogurt was associated with a
236 significantly lower risk of T2D. These findings highlight the potential role of dairy products in the
237 prevention of T2D in older adults.

238 Our results are supported by a recent meta-analysis of prospective studies conducted in apparently healthy
239 individual showing a relative risk reduction of T2D in subjects who had a high compared to a low
240 consumption of dairy [10]. Similarly, a recent evidence-based review [30] and three previous meta-
241 analyses [8, 9, 11] using similar cohort studies also support the hypothesis that dairy consumption is
242 associated with a reduced risk of T2D, and that this association is dose-dependent. However, it is
243 noteworthy that our population was elderly and had several cardiovascular risk factors. It is not known
244 whether the associations that have been reported in apparently healthy individuals also occur in this
245 population group, highly predisposed to develop T2D.

246 In terms of milk consumption, we found that only low-fat milk consumption was **significantly** inversely
247 associated with T2D when we assessed both baseline and cumulative average consumption. Surprisingly, we
248 found no associations between low-fat milk consumption changes during the follow-up and T2D risk.
249 Therefore, these findings should be taken with **caution**. The apparent discrepancy between our findings might
250 be explained by a high consumption of low-fat milk at baseline (median consumption 198 g/day), making it
251 difficult to find an additional protective effect against T2D with an increment of their consumption during
252 follow-up period. For milk consumption, previous findings are inconsistent: they show inverse associations
253 with total and low-fat milk [12, 19, 31], **positive** associations with whole-fat milk [12, 17], or no association
254 with total, low-fat [12, 18, 21–24, 27, 28], or whole-fat milk [13, 20]. In our cohort, the major dairy sources
255 were low-fat dairy products, which were consumed more frequently than whole-fat dairy food. Overall, milk

256 was the largest contributor to total dairy product consumption, and more than two-thirds of milk consumption
257 was from low-fat milk. The amount and type of fat contained in these dairy products could mitigate their
258 potential benefits on T2D, thus explaining the null relationship found in the present study in whole-fat dairy.
259 However, in the present study, the non-significant association observed between whole-fat dairy consumption
260 and T2D could be due to the lack of power to detect associations, because of the low consumption of these
261 dairy products. In addition, observational evidence does not support the hypothesis that dairy fat or whole-fat
262 dairy foods may contribute to T2D risk. A recent systematic review of observational studies on the
263 consumption of regular/high-fat dairy products suggests no association with or beneficial impact on T2D [32].
264 Thus, it is difficult, then, to draw any conclusions about whether the consumption of whole-fat or low-fat
265 dairy products can be more beneficial.

266 Regarding other dairy-subtypes, many observational studies, but not all [23, 26], suggest that a high
267 consumption of fermented dairy products tends to be associated with lower T2D risk, either significantly [12,
268 13, 16, 27, 28] or non-significantly [19, 21, 22, 24]. As in other large prospective studies [12, 13, 16, 28,
269 33], in our study, individuals in the top tertile of total yogurt consumption had a 40% lower risk of T2D
270 than those in the reference tertile. A non-significant positive association between cheese consumption
271 (including all types of cheese), and T2D risk was demonstrated in the present study. In agreement with our
272 results, after a 5-year follow-up, in the recent prospective EPIC-Norfolk study [28], individuals in the top
273 tertile of yogurt consumption had a 28% lower risk of T2D than those in the reference tertile. In the same
274 cohort an increased low-fat fermented dairy consumption (all yogurt and low-fat unripened cheeses) was
275 associated with a 24% reduction in the risk of T2D, whereas total fermented dairy and cheese showed no
276 associations [28]. Interestingly, in another large prospective study, the EPIC-InterAct study [27], a
277 reduction in the T2D risk was only observed in individuals in the highest versus the lowest quintile of
278 consumption of total fermented dairy products and cheeses. Although there was a trend toward lower risk,
279 the authors did not find a significant association with total yogurt consumption. In a recent analysis of
280 three large cohort studies, a high consumption of yogurt was also associated with a reduced risk of T2D,
281 whereas other dairy foods and consumption of total dairy were not appreciably associated with incidence

282 of T2D [33]. In contrast, other studies do not support a protective role for fermented dairy consumption
283 and T2D risk [23, 24]. In our study we also found that the consumption of combined fermented dairy
284 products (all yogurt and types of cheese) had a non-significant protective association with T2D, which
285 was significant for subjects in the second tertile compared to the reference tertile. Regarding cheese
286 consumption, unlike our results, previous prospective studies suggested a trend but not a statistically
287 significant inverse association with T2D [12, 13, 19, 21–24]. Differences in the design, population
288 studied, dietary assessment tools used, disparities in the combination of different types of cheese and/or
289 the inability to distinguish between them, may explain the conflicting results. Thus, future intervention
290 studies are warranted to demonstrate whether consumption of cheese or fermented dairy have any
291 beneficial effect on T2D.

292 In our study, both yogurt and low-fat milk consumption were strongly associated with a lower risk of T2D.
293 However, only yogurt consumption was associated with a reduction in risk when one serving of a
294 combination of biscuits and chocolate confectionary or whole-grain biscuits and homemade pastries was
295 replaced with one serving of yogurt. The reason for the reduction in the risk of T2D associated with yogurt
296 but not with milk consumption remains unclear. Although nutritionally yogurt is comparable to milk,
297 processing, added ingredients and fermentation improve the nutritional value of yogurt and provide it with
298 unique properties that enhance the bioavailability of some nutrients (e.g. riboflavin, vitamin B₁₂, calcium,
299 magnesium, and zinc) [34, 35]. Therefore, yogurt consumption may help ameliorate some of the most
300 common nutritional deficits, and related complications in older adults.

301 Multiple mechanisms might mediate the relationship between dairy consumption and T2D risk.

302 Such components of dairy products as calcium, magnesium, potassium and vitamin-D have been attributed
303 with having a potential benefit on T2D [36–38]. However, most studies have found that the inverse
304 association between dairy consumption and T2D persisted after adjustment for these micronutrients,
305 suggesting that it is unlikely that these micronutrients mediate such associations. Other postulated
306 mechanisms include the satiating effect of some dairy proteins and fats, which may help in maintaining a
307 lower energy intake, and decreasing weight and obesity risk [32], an important mediator in T2D development

308 [12, 13, 16]. However, the observed associations were not substantially changed when we made further
309 adjustments for BMI changes during follow-up. We found also no significant interaction between BMI and
310 dairy on T2D risk. Therefore, it is unlikely that the BMI might be responsible for the beneficial effect
311 observed in our study. Participants of the PREDIMED trial are at high cardiovascular risk, only very few of
312 them had a normal weight (less than 10%), and therefore our statistical power to perform subgroup analyses
313 regarding overweight status is insufficient.

314 Another potential mechanism is that some dairy proteins are also known to be insulinotropic [39],
315 contributing to the reduction in T2D risk. However, this is merely a speculation, and further research
316 investigating the effects of dairy proteins in particular on the glycemic response and T2D risk is required.
317 Furthermore, it should be taken into account that the beneficial metabolic effects on health of fermented dairy,
318 and particularly yogurt, could be explained by the live microorganisms they contain (probiotic bacteria) [35,
319 40]. Thus, it is plausible that bioactive components present in dairy products may act synergistically or
320 antagonistically to produce a holistic beneficial effect on T2D, such as was observed in our study.

321 In addition to the direct effects of dairy products, we cannot ignore displacement effects [34], as individuals
322 who consumed higher amounts of dairy also consumed higher amounts of other foods, such as fruit, legumes,
323 and lower amounts of total meat, fish, nuts and alcohol, which might also have an impact on associations
324 observed. However, the apparently protective relationship of dairy persisted in multivariate models that
325 accounted for dietary variables. On the other hand, it has also been reported that a dairy-rich diet produces
326 significant and substantial suppression of the oxidative and inflammatory stress associated with overweight
327 and obesity [41], and thus with reduced T2D risk.

328 The present study has strengths that distinguish it from previous studies. The incidence of T2D was not
329 self-reported and was verified by a second analytical test, thus making the identification of new incident
330 cases more reliable. In addition, cases were ascertained and confirmed by an independent Clinical Event
331 Adjudication committee. Other strengths of our study include the use of yearly repeated measurements of
332 diet, a relatively long follow-up period, control for many potential confounding factors, and a relatively

333 high consumption of low-fat dairy products and yogurt , which allows a better assessment of the
334 associations between dairy consumption and T2D.

335 However, some limitations should also be noted. First, the generalizability of our results to other
336 populations may be limited because participants were elderly Mediterranean individuals at high
337 cardiovascular risk. Second, although diet was assessed by a validated FFQ, measurement errors are
338 inevitable. However, to minimize the random measurement error caused by within-person variation and
339 dietary changes during the follow-up, we calculated cumulative average for dietary variables to better
340 represent a long-term habitual dietary consumption. A third limitation of our study is that the low
341 consumption of whole-fat dairy products, such as whole-fat milk and cheese, might limit the ability to
342 detect possible associations.

343 In conclusion, this study suggests that a high consumption of dairy products, and particularly yogurt, may
344 be protective against T2D in elderly individuals at high cardiovascular risk highly predisposed to develop
345 this condition.

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357 **Authors' contributions**

358 MAM-G, DC, RE, MF, EG-G, MFiol, ER, LS-M, XP, MAM and JS-S designed the research. AD-L, MB,
359 MAM-G, DC, RE, MF, EG-G, MFiol, FJG, ER, NB, LS-M, XP, MAM, FF, PB-C and JS-S conducted the
360 research. AD-L and JS-S analyzed the data. AD-L and JS-S wrote the paper. MAM-G, DC, RE, MF, EG-G,
361 MFiol, ER, LS-M, XP, MAM and JS-S were the coordinators of subject recruitment at the outpatient clinics.
362 AD-L and JS-S had full access to all the data in the study and take responsibility for the integrity of the data
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479 inflammatory stress in overweight and obese subjects. *Am J Clin Nutr* 91:16–22

Table 1. Baseline characteristics of the study population by tertile of total dairy consumption

	Total dairy consumption ^a			P value ^b
	Tertile 1 (n=1151)	Tertile 2 (n=1152)	Tertile 3 (n=1151)	
Total dairy consumption (g/day)	182 ± 73	343 ± 39	562 ± 119	
Age (years)	66 ± 6	67 ± 6	67 ± 6	<.001
Women, n (%)	506 (44)	744 (64)	891 (77)	<.001
BMI (kg/m ²)	29.7 ± 3.5	29.9 ± 3.5	30.4 ± 3.7	<.001
Waist circumference (cm)				
Women	96.5 ± 10.6	97.5 ± 10.9	97.4 ± 10.2	.16
Men	104.1 ± 8.8	102.8 ± 9.0	103.2 ± 8.4	.07
Overweight/obesity, n (%)	1080 (94)	1090 (95)	1110 (96)	.014
Hypertension, n (%)	1039 (91)	1056 (92)	1044 (91)	.64
Tobacco use				<.001
Never smoker, n (%)	560 (49)	754 (65)	842 (73)	
Current smoker, n (%)	250 (22)	154 (13)	140 (12)	
Former smoker, n (%)	341 (29)	244 (22)	169 (14)	
Education level, n (%)				<.001
Primary education	789 (68)	895 (77)	932 (81)	
Secondary education	231 (20)	176 (15)	152 (13)	
Academic/graduate	131 (12)	81 (7)	67 (6)	
Leisure-time physical activity, (MET-min/day)	253.9 ± 232.6	222.4 ± 223.5	216.2 ± 206.1	<.001
Medication use, n (%)				
Antihypertensive agents	873 (75)	905 (78)	879 (76)	.20
Statins or other hypolipidemic drugs	580 (50)	591 (51)	574 (50)	.88
<i>Biochemistry, mg/dL</i>				
Fasting glucose	99.7 ± 15.5	97.3 ± 15.4	97.7 ± 16.8	.002
Total cholesterol	218.7 ± 38.2	218.9 ± 37.5	222.7 ± 42.9	.03
HDL-cholesterol	54.5 ± 14.2	56.2 ± 14.3	57.0 ± 13.8	<.001
Triglycerides	136.2 ± 78.9	129.1 ± 69.4	129.9 ± 68.6	.049
MeDiet+VOO / MeDiet+Nuts / Control dietary intervention groups, n	362/426/363	389/395/368	384/381/386	.34
<i>Dietary variables</i>				
Energy intake (kcal/d)	2315 ± 554	2196 ± 502	2287 ± 519	<.001
Total protein intake (g/d) ^c	86.4 ± 13.6	91.1 ± 14.7	95.7 ± 13.3	<.001
Total carbohydrate intake (g/d) ^c	240.2 ± 45.3	245.4 ± 39.9	248.4 ± 40.6	<.001
Total fat intake (g/d) ^c	96.1 ± 16.4	96.6 ± 16.6	95.3 ± 17.2	.17
Vegetable intake (g/d) ^c	323.2 ± 139.3	330.8 ± 132.6	329.0 ± 138.3	.41
Fruit intake (g/d) ^c	355.8 ± 204.4	376.6 ± 190.1	381.7 ± 197.4	.005
Legume intake (g/d) ^c	20.0 ± 13.1	20.0 ± 11.5	21.5 ± 14.1	.003
Cereal intake (g/d) ^c	157.3 ± 77.1	147.4 ± 70.8	130.8 ± 68.4	<.001
Total meat intake (g/d) ^c	135.6 ± 54.1	135.9 ± 55.4	124.8 ± 50.1	<.001
Total fish intake (g/d) ^c	100.9 ± 46.2	96.5 ± 45.2	95.9 ± 43.3	.014
Olive oil intake (g/d) ^c	38.9 ± 15.0	38.7 ± 15.0	37.5 ± 15.4	.05
Nut intake (g/d) ^c	10.2 ± 12.4	10.9 ± 13.0	9.5 ± 12.9	.018
Total alcohol intake (g/d)	14.2 ± 18.6	7.8 ± 12.8	5.4 ± 10.5	<.001

Data are mean \pm SD or number (%). Abbreviations: T=Tertile; BMI=Body mass index; HDL=High-density lipoprotein; MeDiet+VOO: Mediterranean diet supplemented with virgin olive oil; MeDiet+nuts: Mediterranean diet supplemented with nuts.

^aTertile cut-offs are based on energy-adjusted cumulative average dairy consumption.

^bP value for differences between tertiles by ANOVA.

^cTotal energy-adjusted.

Table 2. HRs (95% CI) for type 2 diabetes according to tertiles of consumption of total, low-fat and whole-fat dairy in the PREDIMED cohort

Variable	Dairy consumption ^a			P for trend
	Tertile 1	Tertile 2	Tertile 3	
Total dairy (g/d), median (IQR)^b	200 (136-243)	342 (311-376)	539 (475-617)	
Cases/person-years, n	116/4473	72/4751	82/4612	
Multivariate model 1	1.00 ref.	0.63 (0.47-0.86)	0.70 (0.51-0.95)	.031
Multivariate model 2	1.00 ref.	0.61 (0.44-0.85)	0.58 (0.41-0.81)	.002
Multivariate model 3	1.00 ref.	0.67 (0.47-0.94)	0.68 (0.47-0.98)	.040
Low-fat dairy (g/d), median (IQR)^c	85 (8-145)	256 (220-295)	462 (391-543)	
Cases/person-years, n	116/4595	78/4516	76/4730	
Multivariate model 1	1.00 ref.	0.75 (0.55-1.00)	0.66 (0.48-0.90)	.008
Multivariate model 2	1.00 ref.	0.72 (0.52-1.00)	0.52 (0.37-0.74)	<.001
Multivariate model 3	1.00 ref.	0.86 (0.61-1.22)	0.65 (0.45-0.94)	.017
Whole-fat dairy (g/d), median (IQR)^d	(0)	20 (14-28)	97 (60-173)	
Cases/person-years, n	98/4596	90/4619	82/4626	
Multivariate model 1	1.00 ref.	0.90 (0.67-1.21)	0.83 (0.61-1.12)	.26
Multivariate model 2	1.00 ref.	0.95 (0.68-1.30)	0.77 (0.55-1.06)	.099
Multivariate model 3	1.00 ref.	0.98 (0.70-1.37)	0.73 (0.52-1.02)	.086

^aTertile cut-offs are based on energy-adjusted cumulative average dairy consumption and values are medians and interquartile range (IQR). ^bIncludes all dairy products: all types of milk, yogurt and cheeses, custard, whipped cream, butter and ice cream. ^cIncludes semi-skim/skim milk and skim yogurt. ^dIncludes whole-fat milk and whole-fat yogurt. Multivariate model 1: Adjusted for age, sex and BMI. Multivariate model 2: Additionally adjusted for dietary intervention group (MedDiet supplemented with virgin olive oil, and/or nuts, or control group), leisure time physical activity (MET-min/d), educational level (primary education, secondary education, or academic/graduate), smoking (never, former, or current smoker), hypertension, or antihypertensive use (yes/no), and fasting glucose, HDL-cholesterol and triglyceride concentrations. Multivariate model 3: Additionally adjusted for cumulative average consumption of dietary variables in energy-adjusted quintiles (vegetables, legumes, fruits, cereals, meat, fish, olive oil and nuts), alcohol and alcohol squared in grams/day. All models were stratified by recruitment center.

Table 3. HRs (95% CI) for type 2 diabetes according to tertiles of specific dairy consumption in the PREDIMED cohort

Variable	Dairy consumption ^a			P for trend
	Tertile 1	Tertile 2	Tertile 3	
Total milk (g/d), median (IQR)^b	109 (39-155)	216 (200-237)	400 (335-480)	
Cases/person-years, n	106/4560	81/4609	83/4670	
Multivariate model 1	1.00 ref.	0.82 (0.61-1.10)	0.77 (0.57- 1.05)	.12
Multivariate model 2	1.00 ref.	0.80 (0.58-1.10)	0.64 (0.45-0.89)	.009
Multivariate model 3	1.00 ref.	0.93 (0.66-1.31)	0.80 (0.56-1.14)	.22
Low-fat milk (g/d), median (IQR)^c	32 (1.3-99)	200 (184-210)	370 (304-480)	
Cases/person-years, n	108/4512	88/4508	74/4820	
Multivariate model 1	1.00 ref.	0.86 (0.65-1.15)	0.64 (0.47-0.87)	.005
Multivariate model 2	1.00 ref.	0.85 (0.62-1.17)	0.53 (0.37-0.75)	<.001
Multivariate model 3	1.00 ref.	0.98 (0.71-1.38)	0.67 (0.46-0.95)	.034
Whole-fat milk (g/d), median (IQR)^d	(0)	6 (3-9)	41 (20-136)	
Cases/person-years, n	100/4635	73/4715	97/4490	
Multivariate model 1	1.00 ref.	0.77 (0.56-1.06)	1.00 (0.75-1.34)	.61
Multivariate model 2	1.00 ref.	0.86 (0.61-1.21)	1.03 (0.75-1.43)	.63
Multivariate model 3	1.00 ref.	0.85 (0.61-1.21)	1.00 (0.72-1.40)	.79
Total yogurt (g/d), median (IQR)^e	13 (1.7-29)	71 (56-89)	128 (123-185)	
Cases/person-years, n	126/4554	73/4718	71/4568	
Multivariate model 1	1.00 ref.	0.60 (0.45-0.82)	0.60 (0.44-0.81)	.001
Multivariate model 2	1.00 ref.	0.62 (0.45-0.85)	0.53 (0.37-0.75)	<.001
Multivariate model 3	1.00 ref.	0.61 (0.43-0.85)	0.60 (0.42-0.86)	.002
Low-fat yogurt (g/d), median (IQR)^f	3 (0-7)	44 (30-57)	120 (96-157)	
Cases/person-years, n	129/4377	77/4858	64/4606	
Multivariate model 1	1.00 ref.	0.56 (0.42-0.75)	0.50 (0.36-0.68)	<.001
Multivariate model 2	1.00 ref.	0.64 (0.46-0.88)	0.61 (0.43-0.85)	.005
Multivariate model 3	1.00 ref.	0.69 (0.49-0.97)	0.68 (0.47-0.97)	.047
Whole-fat yogurt (g/d), median (IQR)^g	(0)	7 (5-10)	45 (29-71)	
Cases/person-years, n	106/4533	88/4533	76/4774	
Multivariate model 1	1.00 ref.	0.83 (0.62-1.11)	0.67 (0.49-0.91)	.016
Multivariate model 2	1.00 ref.	0.87 (0.62-1.20)	0.64 (0.46-0.89)	.008
Multivariate model 3	1.00 ref.	0.84 (0.60-1.18)	0.66 (0.47-0.92)	.020
Total cheese (g/d), median (IQR)^h	11(6-15)	25 (22-28)	40 (35-48)	
Cases/person-years, n	95/4760	81/5893	94/4491	

Multivariate model 1	1.00 ref.	0.99 (0.72-1.35)	1.15 (0.85-1.55)	.35
Multivariate model 2	1.00 ref.	1.18 (0.84-1.66)	1.31 (0.94-1.83)	.11
Multivariate model 3	1.00 ref.	1.39 (0.97-1.99)	1.38 (0.97-1.97)	.10
Total fermented dairy (g/d), median (IQR) ^g	39 (22-55)	100 (85-118)	167 (147-213)	
Cases/person-years	127/4553	65/4834	78/4454	
Multivariate model 1	1.00 ref.	0.51 (0.37-0.69)	0.68 (0.50-0.92)	.008
Multivariate model 2	1.00 ref.	0.54 (0.38-0.76)	0.63 (0.45-0.87)	.003
Multivariate model 3	1.00 ref.	0.59 (0.41-0.84)	0.75 (0.52-1.07)	.049
Concentrated full-fat dairy (g/d), median (IQR) ^h	11 (7-15)	25 (22-28)	40 (36-48)	
Cases/person-years	93/4773	81/4571	96/4496	
Multivariate model 1	1.00 ref.	1.01 (0.74-1.38)	1.21 (0.89-1.63)	.21
Multivariate model 2	1.00 ref.	1.22 (0.87-1.73)	1.37 (0.98-1.92)	.061
Multivariate model 3	1.00 ref.	1.36 (0.95-1.94)	1.41 (0.99-2.01)	.081
Processed dairy (g/d), median (IQR) ^k	(0)	5 (3-6)	15 (10-25)	
Cases/person-years	80/4512	94/4654	96/4675	
Multivariate model 1	1.00 ref.	1.07 (0.78-1.46)	0.97 (0.71-1.33)	.72
Multivariate model 2	1.00 ref.	1.26 (0.90-1.78)	0.98 (0.68-1.39)	.58
Multivariate model 3	1.00 ref.	1.33 (0.93-1.89)	0.97 (0.67-1.40)	.46

^aTertile cut-offs are based on energy-adjusted cumulative average dairy consumption and values are medians and interquartile range (IQR). ^bIncludes all milk: semi-skim/skim and whole-fat milk. ^cIncludes semi-skim/skim milk.

^dIncludes whole-fat milk. ^eIncludes all yogurt: low-fat and whole-fat yogurt. ^fIncludes low-fat yogurt. ^gIncludes whole-fat yogurt. ^hIncludes all cheese: petit Suisse, ricotta, cottage, spreadable, semi-cured/cured cheeses. ⁱIncludes all fermented dairy: all types of yogurt, and cheeses. ^jIncludes butter, whipped cream, and all types of cheeses.

^kIncludes processed dairy, such as condensed milk, milkshakes, ice cream and custard. Multivariate model 1: Adjusted for age, sex and BMI. Multivariate model 2: Additionally adjusted for dietary intervention group (MedDiet supplemented with virgin olive oil, and/or nuts, or control group), leisure time physical activity (MET-min/d), educational level (primary education, secondary education, or academic/graduate), smoking (never, former, or current smoker), hypertension, or antihypertensive use (yes/no), and fasting glucose, HDL-cholesterol and triglyceride concentrations. Multivariate model 3: Additionally adjusted for cumulative average consumption of dietary variables in energy-adjusted quintiles (vegetables, legumes, fruits, cereals, meat, fish, olive oil and nuts), alcohol and alcohol squared in grams/day. All models were stratified by recruitment center.

Table 4. HRs (95% CI) for type 2 diabetes of the substitution of one serving per day of alternative foods for one serving per day of yogurt and low-fat milk in the PREDIMED cohort

Substituted foods	Yogurt (125 g)	Low-fat milk (200 mL)
Dairy desserts (100g) ^a	0.58 (0.29-1.18)	0.71 (0.35-1.41)
Biscuits and chocolate confectionary (50g)	0.60 (0.38-0.94)	0.69 (0.47-1.03)
Whole-grain biscuits and homemade pastries (50g)	0.55 (0.32-0.96)	0.63 (0.38-1.05)

^aPetit Suisse cheese or custard or ice cream. The servings are based on energy-adjusted cumulative average food consumption. Values are given as HR (95% CI) from Cox regression models adjusted for age, sex, BMI, dietary intervention group (MedDiet supplemented with virgin olive oil, and/or nuts, or control group), leisure time physical activity (MET-min/d), educational level (primary education, secondary education, or academic/graduate), smoking (never, former, or current smoker), hypertension, or antihypertensive use (yes/no), and fasting glucose, HDL-cholesterol and triglyceride concentrations. All models were stratified by recruitment center.

Online Supplemental material.

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Online Supplemental Table S1. Baseline characteristics of the study population by tertile of low-fat and whole-fat dairy consumption

	Low-fat dairy consumption ^a			P value ^b	Whole-fat dairy consumption ^a			P value ^b
	Tertile 1 (n=1151)	Tertile 2 (n=1152)	Tertile 3 (n=1151)		Tertile 1 (n=1151)	Tertile 2 (n=1152)	Tertile 3 (n=1151)	
Low-fat dairy consumption (g/day)	83 ± 69	258 ± 41	482 ± 119					
Whole-fat dairy consumption (g/day)					< 8.26	21 ± 9	141 ± 121	
Age (years)	66 ± 6	67 ± 6	67 ± 6	<.001	66 ± 6	67 ± 6	67 ± 6	<.001
Women, n (%)	538 (47)	726 (63)	877 (76)	<.001	599 (52)	812 (70)	760 (63)	<.001
BMI (kg/m ²)	29.7 ± 3.6	29.9 ± 3.4	30.3 ± 3.7	.001	29.5 ± 3.5	30.3 ± 3.7	30.2 ± 3.5	<.001
Waist circumference (cm)								
Women	96.9 ± 11.2	97.5 ± 9.8	97.1 ± 10.4	.56	95.5 ± 10.6	97.9 ± 10.2	97.9 ± 10.4	<.001
Men	103.8 ± 8.1	103.5 ± 8.4	103.0 ± 8.7	.42	103.1 ± 8.4	104.4 ± 9.2	103.3 ± 8.9	.10
Overweight/obesity, n (%)	1071 (93)	1102 (95)	1107 (96)	.001	1080 (94)	1105 (96)	1095 (95)	.07
Hypertension, n (%)	1039 (91)	1056 (92)	1044 (91)	.98	1039 (91)	1056 (92)	1044 (91)	.64
Tobacco use				<.001				<.001
Never smoker, n (%)	576 (50)	745 (65)	835 (72)		663 (57)	776 (67)	717 (62)	
Current smoker, n (%)	250 (22)	154 (13)	140 (12)		201 (17)	142 (12)	201 (17)	
Former smoker, n (%)	325 (28)	253 (22)	176 (15)		287 (25)	234 (20)	233 (20)	
Education level, n (%)				<.001				<.001
Primary education	811 (70)	887 (77)	918 (79)		811 (70)	899 (78)	906 (79)	
Secondary education	228 (20)	170 (15)	161 (14)		224 (19)	175 (15)	160 (14)	
Academic/graduate	112 (10)	95 (8)	72 (6)		116 (10)	78 (7)	85 (7)	
Leisure-time physical activity, (MET-min/day)	245.5 ± 229.8	228.6 ± 223.0	218.4 ± 221.5	.013	259.9 ± 246.7	220.9 ± 213.4	211.6 ± 198.9	<.001
Medication use, n (%)								
Antihypertensive agents	870 (76)	893 (77)	894 (78)	.43	871 (76)	894 (78)	892 (78)	.48
Statins or other hypolipidemic drugs	526 (45)	603 (52)	581 (50)	.004	564 (49)	628 (54)	518 (45)	<.001
<i>Biochemistry, mg/dL</i>								
Fasting glucose	99.7 ± 15.7	97.5 ± 15.1	97.4 ± 16.9	.001	98.1 ± 17.1	97.8 ± 14.7	98.8 ± 15.7	.33
Total cholesterol	217.9 ± 36.1	219.8 ± 39.3	222.6 ± 43.1	.021	219.6 ± 43.5	220.4 ± 37.5	220.4 ± 37.6	.89
HDL-cholesterol	55.1 ± 14.5	55.8 ± 14.0	56.8 ± 13.8	.019	55.2 ± 14.1	56.4 ± 13.6	56.2 ± 14.6	.13
Triglycerides	135.5 ± 71.7	130.9 ± 77.4	128.9 ± 68.3	.10	132.1 ± 77.8	130.9 ± 74.4	132.2 ± 64.2	.89
MeDiet+VOO / MeDiet+Nuts / Control	376/419/356	361/393/398	398/390/363	.21	401/467/283	354/365/433	380/370/401	<.001

dietary intervention groups, n

Dietary variables

Energy intake (kcal/d)	2337 ± 562	2191 ± 507	2269 ± 503	<.001	2495 ± 446	2045 ± 456	2258 ± 556	<.001
Total protein intake (g/d) ^c	86.1 ± 13.4	91.0 ± 14.4	96.2 ± 13.6	<.001	92.7 ± 16.3	92.1 ± 13.2	88.4 ± 13.0	<.001
Total carbohydrate intake (g/d) ^c	239.5 ± 45.5	245.2 ± 38.0	249.1 ± 42.0	<.001	243.5 ± 46.6	245.4 ± 37.5	245.0 ± 41.8	.49
Total fat intake (g/d) ^c	97.7 ± 17.1	95.8 ± 15.7	94.5 ± 17.2	<.001	95.2 ± 18.4	95.2 ± 14.9	97.5 ± 16.6	.001
Vegetable intake (g/d) ^c	319.6 ± 138.5	329.4 ± 130.8	333.9 ± 140.5	.038	334.6 ± 141.0	331.3 ± 133.7	316.9 ± 136.7	.004
Fruit intake (g/d) ^c	348.3 ± 193.0	381.1 ± 198.5	384.7 ± 199.5	<.001	378.7 ± 214.8	378.1 ± 189.8	357.2 ± 186.6	.012
Legume intake (g/d) ^c	20.0 ± 10.4	20.3 ± 14.5	21.2 ± 13.6	.052	20.5 ± 14.4	20.3 ± 11.5	20.5 ± 12.7	.92
Cereal intake (g/d) ^c	150.1 ± 76.4	148.9 ± 72.4	136.5 ± 69.4	<.001	147.2 ± 80.1	150.2 ± 66.3	138.2 ± 71.5	<.001
Total meat intake (g/d) ^c	133.2 ± 53.7	136.2 ± 56.5	126.9 ± 49.6	<.001	135.4 ± 59.4	134.8 ± 50.4	126.0 ± 49.4	<.001
Total fish intake (g/d) ^c	96.3 ± 45.2	98.1 ± 45.6	99.0 ± 44.9	.35	103.7 ± 48.6	100.5 ± 42.9	89.1 ± 41.7	<.001
Olive oil intake (g/d) ^c	37.9 ± 15.7	38.8 ± 14.5	38.3 ± 15.1	.42	38.9 ± 15.0	39.2 ± 14.0	36.9 ± 15.7	.001
Nut intake (g/d) ^c	9.9 ± 12.7	10.7 ± 12.0	10.0 ± 13.5	.25	12.0 ± 15.4	10.1 ± 11.1	8.6 ± 11.1	<.001
Total alcohol intake (g/d)	13.3 ± 18.3	8.2 ± 13.1	5.8 ± 11.1	<.001	12.1 ± 17.0	6.7 ± 12.1	8.5 ± 14.5	<.001

Data are mean ± SD or number (%). Abbreviations: T=Tertile; BMI=Body mass index; HDL=High-density lipoprotein; MeDiet+VOO: Mediterranean diet supplemented with virgin olive oil; MeDiet+nuts: Mediterranean diet supplemented with nuts.

^aTertile cut-offs are based on energy-adjusted cumulative average low-fat (includes semi-skim/skim milk and skim yogurt) and whole-fat (includes whole-fat milk and whole-fat yogurt) dairy consumption.

^bP value for differences between tertiles by ANOVA.

^cTotal energy-adjusted.

Online Supplemental Table S2. Baseline characteristics of the study population by tertile of total milk and total yogurt consumption

	Total milk consumption ^a			P value ^b	Total yogurt consumption ^a			P value ^b
	Tertile 1 (n=1151)	Tertile 2 (n=1152)	Tertile 3 (n=1151)		Tertile 1 (n=1151)	Tertile 2 (n=1152)	Tertile 3 (n=1151)	
Total milk consumption (g/day)	96 ± 64	221 ± 26	415 ± 103					
Total yogurt consumption (g/day)					17 ± 15	72 ± 17	160 ± 60	
Age (years)	65 ± 6	67 ± 6	67 ± 6	<.001	66 ± 6	66 ± 6	67 ± 6	.15
Women, n (%)	536 (46)	747 (64)	858 (74)	<.001	526 (45)	775 (67)	840 (73)	<.001
BMI (kg/m ²)	29.6 ± 3.5	30.0 ± 3.5	30.4 ± 3.7	<.001	29.8 ± 3.6	30.1 ± 3.6	30.0 ± 3.5	<.001
Waist circumference (cm)								
Women	96.3 ± 10.4	97.6 ± 10.6	97.5 ± 10.2	.053	96.9 ± 10.8	97.9 ± 10.4	96.8 ± 10.1	.07
Men	103.8 ± 8.9	103.3 ± 9.1	103.3 ± 8.9	.61	103.7 ± 8.8	103.7 ± 8.8	102.8 ± 8.8	.25
Overweight/obesity, n (%)	1082 (94)	1091 (95)	1107 (96)	.053	1082 (94)	1098 (95)	1100 (96)	.07
Hypertension, n (%)	1044 (91)	1040 (90)	1052 (91)	.72	1046 (91)	1056 (91)	1034 (90)	.29
Tobacco use				<.001				<.001
Never smoker, n (%)	581 (50)	752 (65)	823 (71)		580 (50)	763 (66)	813 (70)	
Current smoker, n (%)	229 (20)	162 (14)	153 (13)		257 (22)	157 (13)	130 (11)	
Former smoker, n (%)	341 (29)	238 (21)	175 (15)		314 (27)	232 (20)	208 (18)	
Education level, n (%)				<.001				.012
Primary education	771 (67)	915 (79)	930 (80)		841 (73)	892 (77)	883 (76)	
Secondary education	252 (22)	153 (13)	154 (13)		191 (16)	181 (16)	187 (16)	
Academic/graduate	128 (11)	84 (7)	67 (5)		119 (10)	79 (7)	81 (7)	
Leisure-time physical activity, (MET-min/day)	259.2 ± 242.4	214.7 ± 204.7	218.7 ± 213.2	<.001	245.6 ± 233.4	227.4 ± 223.3	219.5 ± 206.4	.015
Medication use, n (%)								
Antihypertensive agents	859 (75)	903 (78)	895 (78)	.065	886 (77)	891 (77)	880 (76)	.86
Statins or other hypolipidemic drugs	558 (48)	594 (52)	558 (48)	.21	563 (49)	557 (48)	590 (51)	.35
<i>Biochemistry, mg/dL</i>								
Fasting glucose	99.2 ± 15.3	97.5 ± 15.4	97.9 ± 17.0	.06	98.9 ± 15.2	98.4 ± 17.5	97.3 ± 14.9	.065
Total cholesterol	219.6 ± 44.9	218.9 ± 44.9	221.7 ± 37.5	.22	216.6 ± 38.2	220.4 ± 37.5	223.4 ± 42.8	<.001
HDL-cholesterol	55.3 ± 14.5	55.8 ± 14.2	56.7 ± 13.6	.073	53.8 ± 14.1	56.5 ± 13.9	57.5 ± 14.0	<.001
Triglycerides	134.7 ± 70.5	128.9 ± 73.9	131.6 ± 73.2	.18	139.6 ± 83.5	129.4 ± 72.7	126.1 ± 58.3	<.001
MeDiet+VOO / MeDiet+Nuts / Control	366/435/350	382/390/380	387/377/387	.12	356/405/390	404/394/354	375/403/373	.28

dietary intervention groups, n

Dietary variables

Energy intake (kcal/d)	2352 ± 563	2139 ± 478	2306 ± 516	<.001	2288 ± 547	2262 ± 521	2247 ± 515	.17
Total protein intake (g/d) ^c	87.3 ± 13.3	91.5 ± 15.8	94.5 ± 13.0	<.001	87.5 ± 13.9	92.3 ± 15.0	93.4 ± 13.5	<.001
Total carbohydrate intake (g/d) ^c	240.7 ± 43.6	245.2 ± 42.5	248.0 ± 39.9	<.001	241.8 ± 44.9	243.0 ± 42.0	249.0 ± 39.0	<.001
Total fat intake (g/d) ^c	96.0 ± 16.8	96.7 ± 15.8	95.3 ± 17.5	.13	96.2 ± 16.4	97.0 ± 17.3	94.8 ± 16.4	.006
Vegetable intake (g/d) ^c	332.2 ± 140.1	327.2 ± 135.3	323.5 ± 134.8	.30	315.4 ± 138.8	334.9 ± 130.5	332.5 ± 140.0	.001
Fruit intake (g/d) ^c	369.3 ± 212.9	377.6 ± 193.2	367.7 ± 185.9	.48	348.1 ± 200.1	364.5 ± 187.5	401.4 ± 201.5	<.001
Legume intake (g/d) ^c	20.2 ± 13.1	19.3 ± 9.9	22.0 ± 15.1	<.001	20.3 ± 11.1	20.5 ± 15.1	20.5 ± 12.2	.90
Cereal intake (g/d) ^c	153.0 ± 77.4	148.8 ± 70.7	133.7 ± 69.4	<.001	153.9 ± 75.1	142.5 ± 72.5	139.1 ± 70.7	<.001
Total meat intake (g/d) ^c	133.7 ± 51.4	138.5 ± 58.2	124.0 ± 49.3	<.001	134.3 ± 53.4	136.9 ± 58.1	125.0 ± 47.6	<.001
Total fish intake (g/d) ^c	100.2 ± 45.8	98.2 ± 46.0	94.9 ± 42.7	.016	97.7 ± 47.3	97.0 ± 45.5	98.7 ± 41.8	.67
Olive oil intake (g/d) ^c	38.7 ± 15.0	38.8 ± 14.6	37.6 ± 15.7	.090	38.1 ± 15.2	38.4 ± 15.2	38.5 ± 15.1	.83
Nut intake (g/d) ^c	10.6 ± 12.8	10.8 ± 12.1	9.2 ± 13.4	.008	9.7 ± 12.3	10.5 ± 13.0	10.5 ± 13.0	.25
Total alcohol intake (g/d)	13.6 ± 18.0	7.5 ± 12.7	6.2 ± 11.9	<.001	12.6 ± 18.0	8.1 ± 13.1	6.7 ± 11.9	<.001

Data are mean ± SD or number (%). Abbreviations: T=Tertile; BMI=Body mass index; HDL=High-density lipoprotein; MeDiet+VOO: Mediterranean diet supplemented with

virgin olive oil; MeDiet+nuts: Mediterranean diet supplemented with nuts.

^aTertile cut-offs are based on energy-adjusted cumulative average total milk (includes all milk: semi-skim/skim and whole-fat milk) and total yogurt (includes all yogurt: low-fat and whole-fat yogurt) consumption.

^bP value for differences between tertiles by ANOVA.

^cTotal energy-adjusted.

Online Supplemental Table S3. HRs (95% CI) for type 2 diabetes according to dairy consumption changes during follow-up in the PREDIMED cohort

Variable	Dairy products consumption at baseline ^a			
	< median consumption		> median consumption	
	No change at follow-up	Increased to \geq median at follow-up	No change at follow-up	Decreased to \leq median at follow-up
Total dairy^b				
Multivariate model 1	1.00 ref.	0.55 (0.34-0.89)	0.64 (0.50-0.93)	0.80 (0.49-1.29)
Multivariate model 2	1.00 ref.	0.53 (0.32-0.87)	0.60 (0.40-0.89)	0.64 (0.36-1.12)
Multivariate model 3	1.00 ref.	0.50 (0.29-0.85)	0.68 (0.44-1.05)	0.67 (0.37-1.21)
Low-fat dairy^c				
Multivariate model 1	1.00 ref.	0.59 (0.38-0.92)	0.72 (0.50-1.02)	0.88 (0.49-1.57)
Multivariate model 2	1.00 ref.	0.37 (0.22-0.63)	0.67 (0.46-0.98)	0.91 (0.49-1.66)
Multivariate model 3	1.00 ref.	0.44 (0.26-0.75)	0.72 (0.47-1.08)	1.11 (0.59-2.09)
Whole-fat dairy^d				
Multivariate model 1	1.00 ref.	0.75 (0.47-1.20)	0.78 (0.54-1.11)	0.79 (0.51-1.20)
Multivariate model 2	1.00 ref.	0.56 (0.33-0.95)	0.66 (0.45-0.97)	0.78 (0.50-1.22)
Multivariate model 3	1.00 ref.	0.63 (0.37-1.08)	0.70 (0.46-1.03)	0.78 (0.49-1.24)
Total milk^e				
Multivariate model 1	1.00 ref.	0.92 (0.60-1.40)	0.85 (0.59-1.23)	0.86 (0.52-1.43)
Multivariate model 2	1.00 ref.	0.66 (0.41-1.05)	0.79 (0.54-1.17)	0.87 (0.51-1.47)
Multivariate model 3	1.00 ref.	0.75 (0.47-1.22)	0.89 (0.59-1.36)	0.83 (0.48-1.46)
Low-fat milk^f				
Multivariate model 1	1.00 ref.	1.14 (0.74-1.75)	1.00 (0.69-1.43)	0.99 (0.61-1.62)
Multivariate model 2	1.00 ref.	0.84 (0.52-1.36)	0.86 (0.58-1.27)	0.98 (0.59-1.65)
Multivariate model 3	1.00 ref.	0.95 (0.58-1.54)	0.93 (0.62-1.42)	0.94 (0.54-1.60)
Whole-fat milk^g				
Multivariate model 1	1.00 ref.	1.06 (0.66-1.69)	1.11 (0.78-1.59)	0.78 (0.50-1.21)
Multivariate model 2	1.00 ref.	0.99 (0.60-1.64)	1.17 (0.79-1.73)	0.93 (0.58-1.49)
Multivariate model 3	1.00 ref.	1.00 (0.59-1.68)	1.13 (0.75-1.70)	0.97 (0.50-1.58)
Total yogurt^h				
Multivariate model 1	1.00 ref.	0.47 (0.29-0.75)	0.57 (0.40-0.82)	1.26 (0.78-2.04)
Multivariate model 2	1.00 ref.	0.50 (0.30-0.83)	0.53 (0.35-0.79)	1.36 (0.80-2.31)
Multivariate model 3	1.00 ref.	0.55 (0.33-0.93)	0.58 (0.38-0.88)	1.41 (0.80-2.47)
Low-fat yogurtⁱ				
Multivariate model 1	1.00 ref.	0.53 (0.35-0.80)	0.64 (0.45-0.92)	1.10 (0.63-1.91)
Multivariate model 2	1.00 ref.	0.61 (0.39-0.95)	0.82 (0.56-1.21)	1.09 (0.59-2.04)
Multivariate model 3	1.00 ref.	0.63 (0.40-0.99)	0.85 (0.56-1.28)	1.12 (0.59-2.15)
Whole-fat yogurt^j				
Multivariate model 1	1.00 ref.	0.67 (0.42-1.05)	0.73 (0.51-1.06)	1.29 (0.86-1.93)
Multivariate model 2	1.00 ref.	0.56 (0.34-0.93)	0.64 (0.43-0.96)	1.22 (0.79-1.87)

Multivariate model 3	1.00 ref.	0.57 (0.34-0.96)	0.67 (0.44-1.03)	1.30 (0.83-2.04)
Total cheese ^k				
Multivariate model 1	1.00 ref.	1.20 (0.76-1.89)	1.35 (0.93-1.95)	1.27 (0.81-1.99)
Multivariate model 2	1.00 ref.	1.26 (0.77-2.07)	1.35 (0.91-2.00)	1.39 (0.87-2.22)
Multivariate model 3	1.00 ref.	1.39 (0.82-2.36)	1.44 (0.95-2.17)	1.46 (0.89-2.38)
Total fermented dairy ^l				
Multivariate model 1	1.00 ref.	0.46 (0.28-0.78)	0.61 (0.43-0.87)	1.03 (0.64-1.64)
Multivariate model 2	1.00 ref.	0.52 (0.30-0.91)	0.58 (0.39-0.86)	1.06 (0.63-1.79)
Multivariate model 3	1.00 ref.	0.61 (0.35-1.07)	0.66 (0.43-1.00)	1.22 (0.70-2.10)
Concentrated full-fat dairy ^m				
Multivariate model 1	1.00 ref.	1.16 (0.73-1.85)	1.29 (0.89-1.86)	1.23 (0.79-1.91)
Multivariate model 2	1.00 ref.	1.34 (0.80-2.26)	1.62 (1.09-2.39)	1.55 (0.97-2.47)
Multivariate model 3	1.00 ref.	1.28 (0.74-2.21)	1.47 (0.97-2.22)	1.51 (0.94-2.44)
Processed dairy ⁿ				
Multivariate model 1	1.00 ref.	0.85 (0.52-1.38)	0.93 (0.64-1.37)	1.26 (0.85-1.87)
Multivariate model 2	1.00 ref.	0.81 (0.48-1.36)	0.94 (0.62-1.42)	1.47 (0.97-2.24)
Multivariate model 3	1.00 ref.	0.88 (0.52-1.51)	0.92 (0.60-1.41)	1.24 (0.80-1.91)

^aAt baseline, the median consumption for each dairy group were: 321 g/day for total dairy, 209 g/day for low-fat dairy, 19 g/day for whole-fat dairy, 205 g/day for total milk, 198 g/day for low-fat milk, 7 g/day for whole-fat milk, 55 g/day for total yogurt, 14 g/day for low-fat yogurt, 5 g/day for whole-fat yogurt, 24 g/day for total cheese, 89 g/day for fermented dairy, 25 g/day for concentrated full-fat dairy and 5 g/day for processed dairy. ^bIncludes all dairy products: all types of milk, yogurt and cheeses, custard, whipped cream, butter and ice cream. ^cIncludes semi-skim/skim milk and skim yogurt. ^dIncludes whole-fat milk and whole-fat yogurt. ^eIncludes all milk: semi-skim/skim and whole-fat milk. ^fIncludes semi-skim/skim milk. ^gIncludes whole-fat milk. ^hIncludes all yogurt: low-fat and whole-fat yogurt. ⁱIncludes low-fat yogurt. ^jIncludes whole-fat yogurt. ^kIncludes all cheese: petit Suisse, ricotta, cottage, spreadable, semi-cured/cured cheeses. ^lIncludes all fermented dairy: all types of yogurt, and cheeses. ^mIncludes butter, whipped cream, and all types of cheeses. ⁿIncludes processed dairy, such as condensed milk, milkshakes, ice cream and custard. Multivariate model 1: Adjusted for age, sex and BMI. Multivariate model 2: Additionally adjusted for dietary intervention group (MedDiet supplemented with virgin olive oil, and/or nuts, or control group), leisure time physical activity (MET-min/d), educational level (primary education, secondary education, or academic/graduate), smoking (never, former, or current smoker), hypertension, or antihypertensive use (yes/no), and fasting glucose, HDL-cholesterol and triglyceride concentrations. Multivariate model 3: Additionally adjusted for cumulative average consumption of dietary variables in

energy-adjusted quintiles (vegetables, legumes, fruits, cereals, meat, fish, olive oil and nuts), alcohol and alcohol squared in g/day. All models were stratified by recruitment center.