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

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ABSTRACT

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

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

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

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

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

INTRODUCTION

Type 2 diabetes (T2D) incidence is increasing at an alarming rate worldwide and especially in elderly population [1]. Compelling evidence shows that dietary and lifestyle changes are a key element in the prevention of T2D and obesity-associated metabolic disturbances [2, 3]. Of the many food groups that may offer protection against T2D, dairy products are one of the most frequently investigated. Largely owing to their saturated fat content, dairy products are conventionally perceived as having an adverse impact on health [4]. However, they are nutrient-dense food, and contain high-quality protein, vitamins (A, D, B_2, B_{12} and menaquinones), and minerals (calcium, magnesium and potassium), which have been shown to have beneficial effects on T2D risk [5].

Limited evidence suggests that insulin sensitivity can be improved when dairy consumption is promoted [6, 7]. In addition, four meta-analyses of prospective studies have recently reported an overall reduced risk of T2D incidence in subjects with higher dairy consumption, particularly the low-fat variety [8–11]. Nonetheless, the results of studies from these meta-analyses have shown mixed results: some have reported inverse associations for low-fat dairy [12–16], milk [17, 18], low-fat or skim milk [12, 13, 19], cheese [13], and yogurt [12, 13, 16], whereas other failed to find associations between dairy-subtype consumption and T2D [20–26]. The largest studies in all these meta-analyses were from the USA [12–15, 21] and Asia [22], and European studies have provided limited evidence on this issue [26, 27]. Recent studies conducted on European population that have focused on specific dairy subtypes and T2D risk have found inconsistent results. In two large prospective studies using data from the European Prospective Investigation into Cancer and Nutrition (EPIC) cohorts [EPIC-InterAct study [27] including eight European countries, and the EPIC-Norfolk study [28] including a UK population-based cohort)], only the consumption of fermented dairy, specifically yogurt and low-fat unripened cheese, were associated with decreased risks of incident T2D. Nevertheless, consumption of total and whole-fat dairy, milk, cheese and whole-fat fermented dairy were not associated with T2D [27, 28]. Conversely, in the EPIC-Potsdam study [26], and two other prospective studies conducted in English and Danish populations [23, 24] no association between dairy and T2D was found.

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

MATERIALS AND METHODS

Study design and participants

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

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

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

Ascertainment of incident T2D

T2D was a prespecified secondary outcome of the PREDIMED-trial. It was considered to be present at baseline by clinical diagnosis or use of antidiabetic medication. Incident (new-onset) cases of T2D during the follow-up were diagnosed using the American Diabetes Association criteria: namely, fasting plasma glucose ≥126 mg/dL (7 mmol/L) or 2-hour plasma glucose ≥200 mg/dL (11.1 mmol/L) after a 75-g oral glucose load. All participants' medical records were reviewed yearly in each center by physicians-investigators. When cases of new-onset T2D were identified on the basis of a medical diagnosis reported in the medical charts or a glucose test during routine biochemical analyses, these reports and all medical documentation of the participant were sent to the PREDIMED Clinical Events Committee, whose members were blinded to treatment allocation. Only when a second test had been done using the same criteria within the following 3 months and the new case of T2D confirmed was the end point definitively confirmed by the adjudication committee. Only T2D events that were confirmed between 1 October 2003 and 1 December 2010 were included in the analyses.

Assessment of dairy consumption

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

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

Assessment of covariates

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

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

Statistical analysis

Person-time of follow-up was calculated as the interval between the randomization date and the earliest date of the follow-up contact at which a new diagnosis of T2D was ascertained, death from any cause, or date of the last contact visit, whichever came first. To better represent long-term consumption of dairy products and to minimize within-person variation, we used the cumulative average of energy-adjusted dairy consumption for all analyses based on assessments from items of all FFQs administered at baseline and yearly during the follow-up. Given that after developing T2D participants may alter their dietary pattern, we only used data from all the available FFQs until a year before the last date of T2D diagnoses was ascertained. Participants were categorized into dairy consumption tertiles. Two upper tertiles were compared with the lowest tertile (reference). Multivariate time-dependent Cox proportional hazard regression models were fitted to estimate the hazard ratios (HRs) and 95%CIs of T2D for dairy consumption. Modelo1 was adjusted for baseline age, sex and BMI. Model 2 was additionally adjusted for intervention group, baseline smoking status, physical activity, educational level, hypertension or antihypertensive drug use, fasting glucose, HDL-cholesterol and triglycerides concentrations. To minimize confounding by other dietary factors, a third model (model 3) was additionally adjusted for the cumulative average consumption of vegetables, legumes, fruits, meat, fish, olive oil and nuts (all in energy-adjusted quintiles), and alcohol.

We conducted subsequent multivariate analyses to examine the HRs for T2D of substituting one-serving/day of alternative foods for one serving/day of dairy products (only those dairy products that were associated with T2D). These dietary variables were included as continuous variables in the same multivariate model (model 2). The differences in their β-coefficients, variances and covariance were used to estimate the β-coefficient ±SE for the substitution effect, and the HRs and 95%CIs were calculated from these parameters.

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

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

RESULTS

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

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

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, respectively) were inversely associated with T2D risk (model 2), but only low-fat milk consumption remained significantly associated with lower T2D risk after adjustment for additional confounders (Table 3). Similarly, subjects with higher total yogurt consumption exhibited a 40% lower risk of T2D (P-trend=.002).

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

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

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

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

0.96), respectively (Table 4).

DISCUSSION

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

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

In terms of milk consumption, we found that only low-fat milk consumption was significantly inversely associated with T2D when we assessed both baseline and cumulative average consumption. Surprisingly, we found no associations between low-fat milk consumption changes during the follow-up and T2D risk. Therefore, these findings should be taken with caution. The apparent discrepancy between our findings might be explained by a high consumption of low-fat milk at baseline (median consumption 198 g/day), making it difficult to find an additional protective effect against T2D with an increment of their consumption during follow-up period. For milk consumption, previous findings are inconsistent: they show inverse associations with total and low-fat milk [12, 19, 31], positive associations with whole-fat milk [12, 17], or no association with total, low-fat [12, 18, 21–24, 27, 28], or whole-fat milk [13, 20]. In our cohort, the major dairy sources were low-fat dairy products, which were consumed more frequently than whole-fat dairy food. Overall, milk was the largest contributor to total dairy product consumption, and more than two-thirds of milk consumption was from low-fat milk. The amount and type of fat contained in these dairy products could mitigate their potential benefits on T2D, thus explaining the null relationship found in the present study in whole-fat dairy. However, in the present study, the non-significant association observed between whole-fat dairy consumption and T2D could be due to the lack of power to detect associations, because of the low consumption of these dairy products. In addition, observational evidence does not support the hypothesis that dairy fat or whole-fat dairy foods may contribute to T2D risk. A recent systematic review of observational studies on the consumption of regular/high-fat dairy products suggests no association with or beneficial impact on T2D [32]. Thus, it is difficult, then, to draw any conclusions about whether the consumption of whole-fat or low-fat dairy products can be more beneficial.

Regarding other dairy-subtypes, many observational studies, but not all [23, 26], suggest that a high consumption of fermented dairy products tends to be associated with lower T2D risk, either significantly [12, 13, 16, 27, 28] or non-significantly [19, 21, 22, 24]. As in other large prospective studies [12, 13, 16, 28, 33], in our study, individuals in the top tertile of total yogurt consumption had a 40% lower risk of T2D than those in the reference tertile. A non-significant positive association between cheese consumption (including all types of cheese), and T2D risk was demonstrated in the present study. In agreement with our results, after a 5-year follow-up, in the recent prospective EPIC-Norfolk study [28], individuals in the top tertile of yogurt consumption had a 28% lower risk of T2D than those in the reference tertile. In the same cohort an increased low-fat fermented dairy consumption (all yogurt and low-fat unripened cheeses) was associated with a 24% reduction in the risk of T2D, whereas total fermented dairy and cheese showed no associations [28]. Interestingly, in another large prospective study, the EPIC-InterAct study [27], a reduction in the T2D risk was only observed in individuals in the highest versus the lowest quintile of consumption of total fermented dairy products and cheeses. Although there was a trend toward lower risk, the authors did not find a significant association with total yogurt consumption. In a recent analysis of three large cohort studies, a high consumption of yogurt was also associated with a reduced risk of T2D, whereas other dairy foods and consumption of total dairy were not appreciably associated with incidence of T2D [33]. In contrast, other studies do not support a protective role for fermented dairy consumption and T2D risk [23, 24]. In our study we also found that the consumption of combined fermented dairy products (all yogurt and types of cheese) had a non-significant protective association with T2D, which was significant for subjects in the second tertile compared to the reference tertile. Regarding cheese consumption, unlike our results, previous prospective studies suggested a trend but not a statistically significant inverse association with T2D [12, 13, 19, 21–24]. Differences in the design, population studied, dietary assessment tools used, disparities in the combination of different types of cheese and/or the inability to distinguish between them, may explain the conflicting results. Thus, future intervention studies are warranted to demonstrate whether consumption of cheese or fermented dairy have any beneficial effect on T2D.

In our study, both yogurt and low-fat milk consumption were strongly associated with a lower risk of T2D. However, only yogurt consumption was associated with a reduction in risk when one serving of a combination of biscuits and chocolate confectionary or whole-grain biscuits and homemade pastries was replaced with one serving of yogurt. The reason for the reduction in the risk of T2D associated with yogurt but not with milk consumption remains unclear. Although nutritionally yogurt is comparable to milk, processing, added ingredients and fermentation improve the nutritional value of yogurt and provide it with unique properties that enhance the bioavailability of some nutrients (e.g. riboflavin, vitamin B_{12}, calcium, magnesium, and zinc) [34, 35]. Therefore, yogurt consumption may help ameliorate some of the most common nutritional deficits, and related complications in older adults.

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

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

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

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

The present study has strengths that distinguish it from previous studies. The incidence of T2D was not self-reported and was verified by a second analytical test, thus making the identification of new incident cases more reliable. In addition, cases were ascertained and confirmed by an independent Clinical Event Adjudication committee. Other strengths of our study include the use of yearly repeated measurements of diet, a relatively long follow-up period, control for many potential confounding factors, and a relatively high consumption of low-fat dairy products and yogurt , which allows a better assessment of the associations between dairy consumption and T2D.

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

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

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Authors' contributions

MAM-G, DC, RE, MF, EG-G, MFiol, ER, LS-M, XP, MAM and JS-S designed the research. AD-L, MB, MAM-G, DC, RE, MF, EG-G, MFiol, FJG, ER, NB, LS-M, XP, MAM, FF, PB-C and JS-S conducted the research. AD-L and JS-S analyzed the data. AD-L and JS-S wrote the paper. MAM-G, DC, RE, MF, EG-G, MFiol, ER, LS-M, XP, MAM and JS-S were the coordinators of subject recruitment at the outpatient clinics. AD-L and JS-S had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors revised the manuscript for important intellectual content, read and approved the final manuscript.

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Dr. Serra-Majem reports serving on the boards of the Mediterranean Diet Foundation and the Beer and Health Foundation. Dr. Pintó reports serving on the board of and receiving grant support through his institution from the Residual Risk Reduction Initiative (R3i) Foundation; serving on the board of Omegafort; serving on the board of and receiving payment for the development of educational presentations, as well as grant support through his institution, from Ferrer; receiving consulting fees from Abbott Laboratories; receiving lecture fees, as well as grant support through his institution, from Merck and Roche; receiving lecture fees from Danone and Esteve; receiving payment for the development of educational presentations from Menarini; and receiving grant support through his institution from Sanofi-Aventis, Kowa, Unilever, Boehringer Ingelheim, and Karo Bio. Dr. Salas-Salvadó reports serving on the board of and receiving grant support through his institution from the International Nut and Dried Fruit Council; serving on the scientific board of the Institute Danone, Spain; receiving consulting fees from Danone; and receiving grant support through his institution from Eroski and Nestlé. No other potential conflict of interest relevant to this article was reported.

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

	Total dairy consumption[a]			
	Tertile 1 (n=1151)	Tertile 2 (n=1152)	Tertile 3 (n=1151)	P value[b]
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
Biochemistry, mg/dL				
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
Dietary variables				
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 ± 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.

[a]Tertile cut-offs are based on energy-adjusted cumulative average dairy consumption.

[b]P value for differences between tertiles by ANOVA.

[c]Total 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] Tertile 1	Tertile 2	Tertile 3	P for trend
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

[a]Tertile cut-offs are based on energy-adjusted cumulative average dairy consumption and values are medians and interquartile range (IQR). [b]Includes all dairy products: all types of milk, yogurt and cheeses, custard, whipped cream, butter and ice cream. [c]Includes semi-skim/skim milk and skim yogurt. [d]Includes 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

	Dairy consumption [a]			
Variable	Tertile 1	Tertile 2	Tertile 3	P for trend
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)[i]	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)[j]	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

[a]Tertile cut-offs are based on energy-adjusted cumulative average dairy consumption and values are medians and interquartile range (IQR). [b]Includes all milk: semi-skim/skim and whole-fat milk. [c]Includes semi-skim/skim milk. [d]Includes whole-fat milk. [e]Includes all yogurt: low-fat and whole-fat yogurt. [f]Includes low-fat yogurt. [g]Includes whole-fat yogurt. [h]Includes all cheese: petit Suisse, ricotta, cottage, spreadable, semi-cured/cured cheeses. [i]Includes all fermented dairy: all types of yogurt, and cheeses. [j]Includes butter, whipped cream, and all types of cheeses. [k]Includes 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)

[a]Petit 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]				Whole-fat dairy consumption[a]			
	Tertile 1 (n=1151)	Tertile 2 (n=1152)	Tertile 3 (n=1151)	P value[b]	Tertile 1 (n=1151)	Tertile 2 (n=1152)	Tertile 3 (n=1151)	P value[b]
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
Biochemistry, mg/dL								
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.

[a]Tertile 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.

[b]P value for differences between tertiles by ANOVA.

[c]Total 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]				Total yogurt consumption[a]			
	Tertile 1 (n=1151)	Tertile 2 (n=1152)	Tertile 3 (n=1151)	P value[b]	Tertile 1 (n=1151)	Tertile 2 (n=1152)	Tertile 3 (n=1151)	P value[b]
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
Biochemistry, mg/dL								
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.

[a]Tertile 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.

[b]P value for differences between tertiles by ANOVA.

[c]Total 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 ≥ median at follow-up	No change at follow-up	Decreased to ≤ 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 yogurt [i]				
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)

[a]At 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. [b]Includes all dairy products: all types of milk, yogurt and cheeses, custard, whipped cream, butter and ice cream. [c]Includes semi-skim/skim milk and skim yogurt. [d]Includes whole-fat milk and whole-fat yogurt. [e]Includes all milk: semi-skim/skim and whole-fat milk. [f]Includes semi-skim/skim milk. [g]Includes whole-fat milk. [h]Includes all yogurt: low-fat and whole-fat yogurt. [i]Includes low-fat yogurt. [j]Includes whole-fat yogurt. [k]Includes all cheese: petit Suisse, ricotta, cottage, spreadable, semi-cured/cured cheeses. [l]Includes all fermented dairy: all types of yogurt, and cheeses. [m]Includes butter, whipped cream, and all types of cheeses. [n]Includes 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.