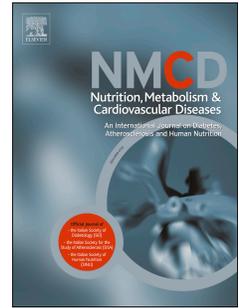


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Yogurt consumption and abdominal obesity reversion in the PREDIMED study

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## Title: Yogurt consumption and abdominal obesity reversion in the PREDIMED study

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**ABSTRACT**

**Background and aims:** Evidence on the association yogurt consumption and obesity is not conclusive. The aim of this study was to prospectively evaluate the association between yogurt consumption, reversion of abdominal obesity status and waist circumference change in elderly.

**Methods and results:** 4,545 individuals at high cardiovascular risk were prospectively followed. Total, whole-fat and low-fat yogurt consumption were assessed using food frequency questionnaires. Generalized estimating equations were used to analyze the association between yogurt consumption and waist circumference change (measured at baseline and yearly during the follow-up). Logistic regression models were used to evaluate the odds ratios (ORs) and 95% CIs of the reversion rate of abdominal obesity for each quintile of yogurt consumption compared with the lowest quintile. After multivariable adjustment, the average yearly waist circumference change in the quintiles of whole-fat yogurt consumption was: Q1: 0.00, Q2: 0.00 (-0.23 to 0.23), Q3: -0.15 (-0.42 to 0.13), Q4: 0.10 (-0.21 to 0.42), and Q5: -0.23 (-0.46 to -0.00) cm; p for trend =0.05. The ORs for the reversion of abdominal obesity for whole-fat yogurt consumption were Q1: 1.00, Q2: 1.40 (1.40-1.90), Q3: 1.33 (0.94-1.89), Q4: 1.21 (0.83-1.77), and Q5: 1.43 (1.06-1.93); p for trend =0.26.

**Conclusion:** Total yogurt consumption was not significantly associated with reversion of abdominal obesity status and a lower waist circumference. However, consumption of whole-fat yogurt was associated with changes in waist circumference and higher probability for reversion of abdominal obesity. Therefore, it seems that whole-fat yogurt has more beneficial effects in

management of abdominal obesity in elderly population at high cardiovascular risk.

**Key words:** yogurt; abdominal obesity; waist circumference; older adults; PREDIMED study.

PREDIMED Registration number: <http://www.controlled-trials.com/ISRCTN35739639>

## INTRODUCTION

Dairy products provide high-quality proteins and diverse essential nutrients, whose consumption is considered marker of diet quality[1]. Thus, most dietary guidelines recommend consumption dairy food, typically 2-3 servings per day and it is frequent to advise preferring low-fat dairy[2].

Yogurt is a nutrient-dense probiotic food and could play a role in improving the nutritional status and health in older adults[3]. Besides, yogurt consumption may be associated with a more beneficial cardio-metabolic risk profile in overweight/obese individuals[4]. Overweight and obesity are the fifth leading risk factor for deaths globally, being the burden of obesity particularly relevant in old age, due to accumulating co-morbidities and changes in body composition[5]. Worldwide, obesity has more than doubled since 1980, and in 2014, 11% of men and 15% of women aged 18 years and older were obese[6]. In Spain, according to the ENRICA Study[7] and EXERNET multicentre study[8] prevalence of abdominal obesity affected, respectively, 62% and 56% of persons aged 65 and over. Evidence suggests that abdominal obesity measures, such as waist circumference, show information independent to measures of general obesity and should be used in clinical practice[9].

The relationship between dairy consumption and obesity parameters has been investigated with controversial results. Evidence from prospective cohort studies suggests a protective, but limited, effect of dairy consumption on risk of overweight and obesity [10-12]. In 2008, a review of 49 clinical trials found no effect of dairy consumption in weight lost [13]. Results from randomized control trials have been recently summarized in three meta- analyses. Abargouei et

al[14], concluded that increased dairy intake without energy restriction, might not lead to a significant change in weight, or body composition, whereas when combined with energy restriction, inclusion of dairy products modestly reduced weight (-0.61kg), fat mass (- 0.72 kg) and waist circumference (-2 cm). Furthermore, Chen et al[15] concluded, that dairy products may have modest benefits in facilitating weight loss but in short term or energy-restricted studies. In contrast, Benatar et al [16] found that increasing in both whole and low fat dairy products, without other dietary intervention, was associated with a modest weight gain.

These controversial results may be partially related with the lack of agreement in defining dairy products in relation to total fat[17]. Among dairy products, yogurt has received more attention, but yogurt, and even other dairy foods, may be allocated into the low or whole/high-fat categories or both. Besides, definition of yogurt consumption levels and bacterial cultures included, also varied across studies[18-20]. A recent systematic review concerning the role of yogurt in weigh management, has concluded that there is association with lower BMI, lower body weight/weight gain, smaller waist circumference and lower body fat in epidemiological studies. Although RCTs suggest weight reduction effects, do not permit determination of a cause/effect relationship [21].

In this context, few studies have prospectively assessed the specific associations between whole-fat versus low-fat yogurt consumption and waist circumference change and abdominal obesity in adults[4, 22, 23]. In this context, we aimed to prospectively examine the relationship between yogurt consumption (total, whole-fat or low-fat) and average yearly waist circumference

change and the reversion of abdominal obesity in an older population of the PREDIMED Study.

## **METHODS**

### ***Study population***

The PREDIMED (PREvención con Dieta MEDiterránea) Study is a large, parallel-group, multicenter, randomized, controlled, clinical trial designed to assess the effects of the Mediterranean diet (MedDiet) on the primary prevention of cardiovascular disease (CVD). The main outcome was cardiovascular events (cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke). The trial was ongoing with 7447 participants at high risk of CVD assigned randomly to three intervention groups: MedDiet supplemented with virgin olive oil (MedDiet +VOO), Mediterranean diet supplemented with mixed nuts (MedDiet +nuts), or low-fat diet (Control). Eligible participants for the PREDIMED Study were men, aged 55 to 80 years, and women, aged 60 to 80 years, who met at least one of the two following criteria: diagnosis of type 2 diabetes or presence of three or more CVD risk factors: smoking, hypertension, dyslipidemia, overweight (BMI  $\geq 25$  kg/m<sup>2</sup>) or obesity (BMI  $\geq 30$  kg/m<sup>2</sup>), and family history of premature coronary heart disease (CHD)[24]. This sub study was devised to evaluate the association between the yogurt (total, whole-fat and low-fat) consumption and the reversion of abdominal obesity. Also the yearly change in waist circumference was analyzed. In the current report, the data were analyzed assuming the design of an observational prospective cohort whose members were selected from all the PREDIMED recruiting centers. We excluded those participants without information about waist circumference at

baseline (n=242), and those without abdominal obesity (waist circumference <102 cm and < 88 cm in men and women respectively) at baseline (n=1938). Further exclusions were: those participants who did not have information about waist circumference during the follow-up (n=589); those who reported implausibly low or high values for total energy intake (less than 800 kcal/d in men and 500 kcal/d in women or more than 4,000 kcal/d in men and 3,500 kcal/d in women; (n=91); those who have missing information about dietary habits (n=18). Among remaining participants, 24 were lost to follow-up, leaving a total of 4,545 for the final analysis.

### ***Dietary and non-dietary assessments***

At baseline participants were requested to answer several self-administrated questionnaires[25] including a validated 137-item food frequency questionnaire (FFQ)[26], a 14-item questionnaire assessing the degree of adherence to the MedDiet[27], a 47-item questionnaire about lifestyles, education, medical conditions, and medication use and a Leisure-Time Physical Activity Questionnaire[28]. Body Mass Index (BMI) was calculated from weight and height measured. Additionally directly measured anthropometric, blood pressure measurements and fasting blood samples were collected. Every year, a follow-up questionnaire and all the measurements were repeated.

### **Ethics approval**

The protocol was written in accordance with the principles of the Declaration of Helsinki, was approved by the Institutional Review Boards at all study sites and was registered at <http://www.controlled-trials.com/> ISRCTN35739639. Written informed consent was provided by all study participants.

### ***Assessment of yogurt consumption***

Participants reported frequency of whole-fat and low-fat yogurt consumption in the previous year. The frequency of total yogurt consumption using the sum of whole-fat and low-fat yogurt consumption was estimated. The consumption of yogurt was adjusted for total energy intake using the nutrient residual method[29] and, then, participants were classified into quintiles of energy-adjusted yogurt consumption (total, whole-fat and low-fat). The lowest quintile of consumption (Q1) was considered as the reference category.

### ***Outcome Ascertainment***

Participants' waist circumference was recorded at baseline and yearly during follow-up. The outcomes were: 1) the average yearly change in waist circumference during follow-up, defined as change in waist circumference by year; and 2) incidence of non- abdominal obesity (those who had abdominal obesity at baseline, and during the follow-up a reversion of this condition happened). Abdominal obesity at baseline was defined as having waist circumference  $\geq 102$ cm in men and  $\geq 88$  cm in women.

### ***Statistical Analyses***

We longitudinally assessed the waist change in all time points (every year) using generalized estimating equations (GEE). We updated waist circumference with all available longitudinal data (every year), and analyzed the association between total yogurt consumption, whole-fat, low-fat yogurt consumption, and waist circumference at all time-points simultaneously. We

assumed a Gaussian distribution with regression models and unstructured matrix as the working correlation structure.

As a secondary analysis, we calculated the total waist circumference change during the first 5 years of follow-up. Linear regression models were used to assess the association between quintiles of yogurt consumption and the total waist change during follow-up, using the lower quintile of yogurt consumption as the reference group. We estimated  $\beta$  regression coefficients (and their 95% confidence interval (CI)) for the other four categories.

In both cases, (GEE analysis and linear regression models), these same analyses were conducted including those participants who did not present abdominal obesity at the beginning of the study. Therefore, 6,244 participants encompassed these secondary analyses.

To assess the relationship between yogurt consumption at baseline and the subsequent risk of reversion of abdominal obesity during the follow-up, logistic regression models were fitted. Tests of linear trend were conducted assigning the median value of each quintile of yogurt, and then using it as a continuous variable. Multiplicative interactions between intervention group [control diet, MedDiet +VOO, and MedDiet +nuts] and yogurt consumption were tested using likelihood ratio tests comparing the fully adjusted model and the same model with the interaction product-term.

For all analyses, we fitted a crude univariate model, an age- and sex-adjusted model, and a multivariable model after additional adjustment for the following potential confounders: leisure-time physical activity as metabolic equivalent (MET) min/d, total energy intake (kcal/day), adherence to the MedDiet pattern (4 categories), smoking status (former, current and never

smokers), baseline body mass index ( $\text{kg}/\text{m}^2$ ), intervention group (control, nut supplemented, olive oil supplemented), and centre. All  $p$  values presented are two-tailed;  $p < 0.05$  was considered statistically significant. Analyses were performed using STATA/SE version 12.1 (StataCorp, College Station, TX, USA).

## Results

Baseline characteristics of participants according to the quintiles of total yogurt consumption are showed in **Table 1**. The mean age of the participants at baseline was 67.4 years old (SD: 6.0). The mean BMI was  $31.1 \text{ kg}/\text{m}^2$  (SD:3.5), with no statistical differences among stratification groups. Those who consumed large amounts of total yogurt (Q5) in comparison with the lowest quintile of consumption (Q1) at baseline was represented by a higher proportion of women and also showed better adherence to the MedDiet, and were more physically active. On average total energy intake was lower in the highest quintile of consumption.

Average annual waist change as continuous outcome is shown in **Table 2**. Participants in the highest quintile (Q5) of total, whole-fat or low-fat yogurt decreased more their waist circumference than those in the lowest quintile (Q1). The average waist change for the Q5 vs Q1 was  $-0.21\text{cm}$  (95% CI:  $-0.46$  to  $0.05$ )  $p$  for trend = 0.25;  $-0.23\text{cm}$  (95% CI:  $-0.46$  to  $-0.00$ )  $p$  for trend = 0.05 and  $-0.15\text{cm}$  (95% CI:  $-0.47$  to  $0.17$ )  $p$  for trend 0.43 for total, whole-fat and low-fat yogurt consumption, respectively.

When we carried out the analysis including those participants, not having abdominal obesity at baseline, the results are the following for the highest

quintile of consumption (Q5) vs the lowest (Q1): 0.12 cm (95% CI: -0.09 to 0.34); -0.07 cm (95% CI: -0.26 to 0.12); and -0.07 cm (95% CI: -0.32 to 0.18) for total, whole-fat and low-fat yogurt consumption, respectively.

The total waist change during the 4.9 years of follow-up was only statistically significant for the whole-fat yogurt consumers. The total waist circumference change during the follow-up in the quintiles of whole-fat yogurt consumption was Q1: 0.00 cm (ref.); Q2: -0.56 cm (95% CI:-1.32 to 0.20); Q3: -0.93 cm (95% CI:-1.84 to -0.09); Q4: -0.73 cm (95% CI:-1.67 to 0.22) and Q5: -0.79 cm (95% CI: -1.55 to -0.02) p for trend= 0.17 (data not shown).

When we analyzed participants without abdominal obesity at baseline we observed only statistically significant results for whole-fat yogurt consumers. We observed that those in the highest quintile of consumption reduced 0.78 cm (95% CI: -1.43 to -0.13) in comparison to the lowest quintile. (data not shown)

We observed 867 incident cases that reversed their abdominal obesity status after a median follow-up of 4.9 years. The multiple adjusted odds ratio (OR) observed between participants in the highest quintile of consumption (Q5) of total, whole-fat and low-fat yogurt consumption versus those in the lowest quintile of yogurt consumption were 1.29 (95% CI: 0.96-1.73); p for trend=0.36; 1.43 (95% CI: 1.06-1.93); p for trend=0.14 and 1.02 (0.73-1.44); p for trend=0.79, for total yogurt, whole-fat yogurt and low-fat yogurt consumption, respectively (**Table 3**).

We did not observed significant interactions between intervention groups (control diet, MedDiet + VOO, and MedDiet + nuts) and yogurt consumption (p

for interaction 0.926, 0.624 and 0.962 for total, whole-fat and low-fat yogurt respectively).

## DISCUSSION

To the best of our knowledge, this is the first epidemiologic study that specifically assessed the association between types of yogurt (total, whole-fat and low-fat) and abdominal obesity and waist circumference in elderly. We found that the probability of reversion of abdominal obesity was 43% higher in participants with a highest consumption of whole-fat yogurt. Moreover, a higher daily intake of whole yogurt was associated with a decrease in the yearly waist circumference change, after controlling for known confounding factors. The percentage of whole fat yogurt consumption in the total yogurt consumption in the present study was 29.4%.

Our results are in line with previous studies suggesting that whole-fat yogurt consumption is associated with a reduced risk of general obesity[23] and also abdominal obesity[22, 30]. An inverse association between yogurt consumption and waist circumference changes has been observed in French middle-aged men[31, 32]. Recently, the Framingham Heart Study reported no association between high-fat or low-fat dairy intake and prevention of waist circumference gain among American adults[11].

The influence of dairy intake in weight management has been previously investigated, but the specific properties and underlying mechanism of the role yogurt are not fully understood[19, 21]. Several mechanisms have been proposed to explain this association.

Firstly, the intake of yogurt is often associated with a healthy dietary pattern[4, 33], and specifically yogurt is considered a good marker of diet quality[2]. In fact, in our sample, high yogurt consumers showed a higher adherence to the MedDiet, which may also, counteracted the harmful effect of abdominal adiposity[34]. Previous research supported that adherence to a healthy eating pattern was strongly associated with the reversion of metabolic syndrome, especially in middle-aged population with abdominal obesity.[35] However, we still found an association between whole-fat yogurt and higher reversion rate of abdominal obesity after controlling for adherence to Mediterranean diet.

Interestingly, we found association with whole-fat yogurt, but not for low-fat yogurt. In this line, Cormier et al[4] observed that normal-weight individuals consumed significantly more high-fat yogurts, while overweight/obese individuals consumed more fat-free yogurts, which may be part of their strategies to manage their body weight, and recommended that yogurt consumption should therefore be encouraged irrespective to their fat content. People compensate or overcompensate for the lower calorie content of reduced-fat milk by eating more of other foods[36] .

Yogurt has been reported to be more satiating than other dairy products, drinks or high-fat snacks[19, 37]. In line with this hypothesis, some authors have stated that the recommendation to replace whole milk with reduced-fat milk lacks an evidence basis for weight management or CVD prevention and may cause harm if sugar or other high glycemic index carbohydrates are substituted for fat[36].

Thus, although whole-fat yogurt contains saturated fatty acids, it also supplies calcium content, which can reduce lipogenesis and stimulate lipolysis and lipid oxidation[38]. Available evidence suggests that the high calcium and protein contents of yogurt influence appetite and energy intake[20, 39]. With respect to calcium, it has been proposed the existence of a calcium-specific appetite control mechanism [40] and human studies have shown that yogurt intake increase the circulation concentration of the anorectic peptides glucagon-like peptide (GLP)-1 and peptide YY (PYY) [41]. Besides, dietary calcium seems to increase fecal fat excretion and modulates circulating calcitriol levels, which affects fat metabolism in human adipocytes [42].

There is a growing-up evidence on the potential health effects of dairy fat. The observational evidence suggests that high-fat dairy consumption within typical dietary patterns is inversely associated with obesity risk[43]. Besides, relation between dairy fat and glucose tolerance may be largely mediated by greater insulin sensitivity because of reduced liver fat content in individuals consuming more dairy fat[44]. Fermented dairy, has been inversely associated with measures of glycemia and insulinemia[45].

Probiotics may have positive influences in prevention of weight gain or even weight loss[19]. Obesity is often accompanied by chronic, low-grade inflammation perpetuated by adipose tissue and the gut, thus yogurt consumption may be beneficial in obese individuals, improving gut health and reducing inflammation [20]. Nestel et al, has observed that the intake of the fermented dairy diet did appear to provide a more favourable cardiovascular biomarkers in overweight adults, than that of the non-fermented dairy diet [46]. A recent meta-analysis has examined the effects of probiotics consumption on

lowering lipids and CVD risk factors, and found significant reduction of body mass index (BMI), waist circumference and inflammatory markers. [47].

Apart from fat, calcium and probiotics, the role of dairy protein has been also investigated in relation to promote weight management[48, 49] and could have a beneficial impact in persons with abdominal obesity[50]. Furthermore, nutrients from dairy products may act synergistically on metabolic pathways [51].

The present study has several strengths, including the prospective design, which limits the possibility of reverse causality bias, the large sample size, the use of a comprehensive and validated FFQ, the adjustment of all possible confounders in the multivariate analysis, and the directly measured anthropometric measures.

However, this analysis has some limitations. First, definition of low-fat and whole-fat dairy products varies in the literature and, particularly, yogurt may be classified in the low or whole-fat categories or in both. This study was conducted only in an elderly population at high cardiovascular risk, which may reduce the generalizability of our findings and they need to be interpreted with caution if these findings will be extrapolated to the general population. Additionally, a measurement error, related to the use of FFQ, could bias our results (more likely towards the null value), and also might lead to find larger confidence intervals. However, because of the relatively high number of participants included in our cohort, the 95% CI were narrow, and we had enough statistical power to detect relevant differences.

To conclude, the present study suggests that total yogurt consumption was not significantly associated with reversion of abdominal obesity status and a lower

waist circumference. However, consumption of whole-fat yogurt was associated with changes in waist circumference and higher probability for reversion of abdominal obesity. Therefore, it seems that whole-fat yogurt has more beneficial effects than low-fat yogurt in management of abdominal obesity in elderly population at high cardiovascular risk..

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**Table 1. Baseline characteristics of participants according to the quintiles of total yogurt consumption. The PREDIMED Study**

	Quintiles of total yogurt consumption					p value*
	Q1	Q2	Q3	Q4	Q5	
n	909	909	909	909	909	
Yogurt consumption (g/d)	3.4 (6.4)	23.2 (22.2)	63.6 (22.3)	119.2 (10.7)	213.5 (113.5)	
Whole-fat yogurt consumption (g/d)	1.7 (4.7)	9.8 (18.7)	21.9 (32.3)	38.3 (54.6)	52.5 (104.1)	
Low-fat yogurt consumption (g/d)	1.7 (4.7)	13.4 (19.8)	41.7 (32.5)	80.9 (54.5)	161.1 (122.2)	
Age (years)	67.4 (0.22)	67.2 (0.20)	67.2 (0.20)	67.7 (0.20)	67.4 (0.20)	0.42
Women (%)	27.1	66.9	80.3	73.5	88.9	<0.001
BMI (kg/m <sup>2</sup> )	31.0 (0.13)	31.2 (0.12)	31.2 (0.12)	31.1 (0.12)	31.2 (0.12)	0.77
Waist circumference (cm)	103.5 (0.30)	104.1 (0.27)	104.0 (0.28)	104.0 (0.27)	103.5 (0.28)	0.35
Waist-to height-ratio	0.65 (0.002)	0.65 (0.002)	0.65 (0.002)	0.65 (0.002)	0.65 (0.002)	0.39
Physical activity (METs/day)	191 (7.5)	203 (6.9)	214 (7.0)	217 (7.0)	224 (7.1)	0.02 <sup>a</sup>
Smoking status (%)						0.05
Current smokers	13.5	11.3	11.8	8.8	10.8	
Former smokers	22.9	20.7	20.1	21.1	22.1	
Total energy intake (kcal/day)	2308 (18.2)	2079 (16.7)	2220 (16.9)	2350 (16.7)	2083 (17.1)	<0.001 <sup>b</sup>
Adherence to the Mediterranean diet (0 to 14 score)	8.4 (0.7)	8.5 (0.6)	8.5 (0.6)	8.8 (0.6)	8.6 (0.6)	0.001 <sup>c</sup>

Values are expressed as means (SE), unless otherwise stated. All values are sex-adjusted (except yogurt consumption which is presented as unadjusted mean and SD). BMI, Body mass index

\*Values determined using  $\chi^2$  test for categorical variables and ANCOVA for continuous variables

<sup>a</sup> Differences observed between Q1 vs Q5

<sup>b</sup> Differences observed between Q1 vs Q2, Q3, Q5; Q2 vs Q1, Q3, Q4; Q3 vs Q1, Q2, Q4, Q5; Q4 vs Q2, Q3, Q5; Q5 vs Q1, Q3, Q4

<sup>c</sup> Differences observed between Q1 vs Q4, Q5

Table 2. Estimates ( $\beta$ -regression coefficients and 95% CIs) for average yearly waist change (cm/year) according to the previous year total, whole-fat, and low-fat yogurt consumption: The PREDIMED Study.

	Q1	Q2	Q3	Q4	Q5	P for trend
<b>Total yogurt</b>						
Absolute yearly waist change (cm), mean (95% CI)	-0.24 (-0.40 to -0.06)	-0.26 (-0.42 to -0.09)	-0.27 (-0.43 to -0.10)	-0.20 (-0.37 to -0.03)	-0.30 (-0.49 to -0.12)	
Crude	0 (Ref.)	-0.03 (-0.24 to 0.18)	-0.16 (-0.38 to 0.07)	0.05 (-0.16 to 0.26)	-0.15 (-0.36 to 0.06)	0.32
Age and sex adjusted	0 (Ref.)	-0.10 (-0.32 to 0.13)	-0.25 (-0.51 to 0.00)	-0.02 (-0.24 to 0.21)	-0.26 (-0.51 to 0.00)	0.17
Multivariable adjusted <sup>a</sup>	0 (Ref.)	-0.06 (-0.29 to 0.16)	-0.19 (-0.44 to 0.07)	-0.01 (-0.22 to 0.21)	-0.21 (-0.46 to 0.05)	0.25
<b>Whole-fat yogurt</b>						
Absolute yearly waist change (cm), mean (95% CI)	-0.15 (-0.31 to 0.00)	-0.30 (-0.46 to -0.14)	-0.31 (-0.49 to -0.12)	-0.24 (-0.42 to -0.06)	-0.27 (-0.42 to -0.12)	
Crude	0 (Ref.)	-0.04 (-0.23 to 0.16)	-0.16 (-0.36 to 0.03)	0.10 (-0.11 to 0.31)	-0.23 (-0.43 to -0.03)	0.19
Age and sex adjusted	0 (Ref.)	-0.04 (-0.24 to 0.16)	-0.17 (-0.37 to 0.04)	0.10 (-0.12 to 0.31)	-0.23 (-0.43 to -0.03)	0.19
Multivariable adjusted <sup>a</sup>	0 (Ref.)	0.00 (-0.23 to 0.23)	-0.15 (-0.42 to 0.13)	0.10 (-0.21 to 0.42)	<b>-0.23 (-0.46 to -0.00)</b>	<b>0.05</b>
<b>Low-fat yogurt</b>						
Absolute yearly waist change (cm), mean (95% CI)	-0.23 (-0.38 to -0.08)	-0.29 (-0.46 to -0.12)	-0.24 (-0.42 to -0.06)	-0.22 (-0.38 to -0.05)	-0.29 (-0.47 to -0.11)	
Crude	0 (Ref.)	0.28 (0.05 to 0.52)	0.07 (-0.18 to 0.32)	0.26 (0.01 to 0.51)	0.01 (0.22 to 0.23)	0.94
Age and sex adjusted	0 (Ref.)	0.08 (-0.25 to 0.41)	-0.10 (-0.40 to 0.19)	0.11 (0.17 to 0.40)	-0.20 (-0.52 to 0.11)	0.21
Multivariable adjusted <sup>a</sup>	0 (Ref.)	0.08 (-0.25 to 0.41)	-0.06 (-0.36 to 0.24)	0.14 (-0.15 to 0.43)	-0.15 (-0.47 to 0.17)	0.43

<sup>a</sup> Adjusted for: Age, sex, physical activity, Mediterranean Diet adherence, total energy intake, smoking status, baseline BMI, intervention group and center.

**Table 3. Odds Ratio (OR) and 95% confidence intervals (CI) of reversion of abdominal obesity according to baseline quintiles of total, whole-fat, and low-fat yogurt consumption in 4,545 participants of the PREDIMED Study.**

	Q1	Q2	Q3	Q4	Q5	P for trend
<b>Total yogurt</b>						
<b>Incident cases/n</b>	209/909	180/909	160/909	156/909	162/909	
<b>Crude</b>	1 (Ref.)	0.83 (0.66-1.04)	0.72 (0.57-0.90)	0.69 (0.55-0.87)	0.73 (0.58-0.91)	<b>0.02</b>
<b>Age and sex-adjusted</b>	1 (Ref.)	1.14 (0.90-1.44)	1.11 (0.87-1.43)	1.01 (0.79-1.30)	1.23 (0.95-1.59)	<b>0.50</b>
<b>Multivariable adjusted<sup>a</sup></b>	1 (Ref.)	1.19 (0.91-1.55)	1.20 (0.91-1.60)	1.01 (0.76-1.33)	1.29 (0.96-1.73)	<b>0.36</b>
<b>Whole-fat yogurt</b>						
<b>Incident cases/n</b>	158/909	194/909	180/909	153/909	182/909	
<b>Crude</b>	1 (Ref.)	1.29 (1.02-1.63)	1.17 (0.93-1.49)	0.96 (0.75-1.23)	1.19 (0.94-1.51)	<b>0.82</b>
<b>Age and sex-adjusted</b>	1 (Ref.)	1.44 (1.14-1.83)	1.36 (1.07-1.73)	1.11 (0.86-1.42)	1.33 (1.04-1.69)	<b>0.63</b>
<b>Multivariable adjusted<sup>a</sup></b>	1 (Ref.)	1.40 (1.04-1.90)	1.33 (0.94-1.89)	1.21 (0.83-1.77)	1.43 (1.06-1.93)	<b>0.26</b>
<b>Low-fat yogurt</b>						
<b>Incident cases/n</b>	251/909	145/909	155/909	168/909	148/909	
<b>Crude</b>	1 (Ref.)	0.50 (0.40-0.63)	0.54 (0.43-0.68)	0.59 (0.48-0.74)	0.51 (0.41-0.62)	<b>0.01</b>
<b>Age and sex-adjusted</b>	1 (Ref.)	1.02 (0.75-1.38)	0.95 (0.72-1.24)	1.02 (0.78-1.33)	1.05 (0.77-1.41)	<b>0.71</b>
<b>Multivariable adjusted<sup>a</sup></b>	1 (Ref.)	1.07 (0.76-1.50)	0.94 (0.69-1.27)	0.97 (0.72-1.31)	1.02 (0.73-1.44)	<b>0.85</b>

<sup>a</sup> Adjusted for: Age, sex, physical activity, Mediterranean Diet adherence, total energy intake, smoking status, baseline BMI, intervention group and center

## REFERENCES

1. Webb D, Donovan SM, Meydani SN: The role of yogurt in improving the quality of the American diet and meeting dietary guidelines. *Nutr Rev* 2014, 72:180-189.
2. Weaver CM: How sound is the science behind the dietary recommendations for dairy? *Am J Clin Nutr* 2014, 99:1217S-1222S.
3. El-Abbadi NH, Dao MC, Meydani SN: Yogurt: role in healthy and active aging. *Am J Clin Nutr* 2014, 99:1263S-1270S.
4. Cormier H, Thifault E, Garneau V, Tremblay A, Drapeau V, Perusse L, Vohl MC: Association between yogurt consumption, dietary patterns, and cardio-metabolic risk factors. *Eur J Nutr* 2015.
5. Corica F, Bianchi G, Corsonello A, Mazzella N, Lattanzio F, Marchesini G: Obesity in the Context of Aging: Quality of Life Considerations. *Pharmacoeconomics* 2014, 33:655-72
6. World Health Organization: Global status report on noncommunicable diseases, 2014.
7. Gutierrez-Fisac JL, Guallar-Castillon P, Leon-Munoz LM, Graciani A, Banegas JR, Rodriguez-Artalejo F: Prevalence of general and abdominal obesity in the adult population of Spain, 2008-2010: the ENRICA study. *Obes Rev* 2012, 13:388-392.
8. Gomez-Cabello A, Pedrero-Chamizo R, Olivares PR, Luzardo L, Juez-Bengochea A, Mata E, Albers U, Aznar S, Villa G, Espino L, et al: Prevalence of overweight and obesity in non-institutionalized people aged 65 or over from Spain: the elderly EXERNET multi-centre study. *Obes Rev* 2011, 12:583-592.
9. Carmienke S, Freitag MH, Pischon T, Schlattmann P, Fankhaenel T, Goebel H, Gensichen J: General and abdominal obesity parameters and their combination in relation to mortality: a systematic review and meta-regression analysis. *Eur J Clin Nutr* 2013, 67:573-585.
10. Louie JC, Flood VM, Hector DJ, Rangan AM, Gill TP: Dairy consumption and overweight and obesity: a systematic review of prospective cohort studies. *Obes Rev* 2011, 12:e582-592.
11. Wang H, Troy LM, Rogers GT, Fox CS, McKeown NM, Meigs JB, Jacques PF: Longitudinal association between dairy consumption and changes of body weight and waist circumference: the Framingham Heart Study. *Int J Obes (Lond)* 2014, 38:299-305.
12. Astrup A: Yogurt and dairy product consumption to prevent cardiometabolic diseases: epidemiologic and experimental studies. *Am J Clin Nutr* 2014, 99:1235S-1242S.

13. Lanou AJ, Barnard ND: Dairy and weight loss hypothesis: an evaluation of the clinical trials. *Nutr Rev* 2008, 66:272-279.
14. Abargouei AS, Janghorbani M, Salehi-Marzijarani M, Esmailzadeh A: Effect of dairy consumption on weight and body composition in adults: a systematic review and meta-analysis of randomized controlled clinical trials. *Int J Obes (Lond)* 2012, 36:1485-1493.
15. Chen M, Pan A, Malik VS, Hu FB: Effects of dairy intake on body weight and fat: a meta-analysis of randomized controlled trials. *Am J Clin Nutr* 2012, 96:735-747.
16. Benatar JR, Sidhu K, Stewart RA: Effects of high and low fat dairy food on cardio-metabolic risk factors: a meta-analysis of randomized studies. *PLoS One* 2013, 8:e76480.
17. Ralston RA, Lee JH, Truby H, Palermo CE, Walker KZ: A systematic review and meta-analysis of elevated blood pressure and consumption of dairy foods. *J Hum Hypertens* 2012, 26:3-13.
18. Wang H, Livingston KA, Fox CS, Meigs JB, Jacques PF: Yogurt consumption is associated with better diet quality and metabolic profile in American men and women. *Nutr Res* 2013, 33:18-26.
19. Jacques PF, Wang H: Yogurt and weight management. *Am J Clin Nutr* 2014, 99:1229S-1234S.
20. Pei R, Martin DA, DiMarco DM, Bolling BW: Evidence for the Effects of Yogurt on Gut Health and Obesity. *Crit Rev Food Sci Nutr* 2015:0.
21. Eales J, Lenoir-Wijnkoop I, King S, Wood H, Kok FJ, Shamir R, Prentice A, Edwards M, Glanville J, Atkinson RL: Is consuming yoghurt associated with weight management outcomes? Results from a systematic review. *Int J Obes (Lond)* 2015.
22. Crichton GE, Alkerwi A: Whole-fat dairy food intake is inversely associated with obesity prevalence: findings from the Observation of Cardiovascular Risk Factors in Luxembourg study. *Nutr Res* 2014, 34:936-943.
23. Martinez-Gonzalez MA, Sayon-Orea C, Ruiz-Canela M, de la Fuente C, Gea A, Bes-Rastrollo M: Yogurt consumption, weight change and risk of overweight/obesity: the SUN cohort study. *Nutr Metab Cardiovasc Dis* 2014, 24:1189-1196.
24. Estruch R, Ros E, Salas-Salvado J, Covas MI, Corella D, Aros F, Gomez-Gracia E, Ruiz-Gutierrez V, Fiol M, Lapetra J, et al: Primary prevention of cardiovascular disease with a Mediterranean diet. *N Engl J Med* 2013, 368:1279-1290.
25. Martinez-Gonzalez MA, Corella D, Salas-Salvado J, Ros E, Covas MI, Fiol M, Warnberg J, Aros F, Ruiz-Gutierrez V, Lamuela-Raventos RM, et al: Cohort profile: design and methods of the PREDIMED study. *Int J Epidemiol* 2012, 41:377-385.

26. Fernandez-Ballart JD, Pinol JL, Zazpe I, Corella D, Carrasco P, Toledo E, Perez-Bauer M, Martinez-Gonzalez MA, Salas-Salvado J, Martin-Moreno JM: Relative validity of a semi-quantitative food-frequency questionnaire in an elderly Mediterranean population of Spain. *Br J Nutr* 2010, 103:1808-1816.
27. Schroder H, Fito M, Estruch R, Martinez-Gonzalez MA, Corella D, Salas-Salvado J, Lamuela-Raventos R, Ros E, Salaverria I, Fiol M, et al: A short screener is valid for assessing Mediterranean diet adherence among older Spanish men and women. *J Nutr* 2011, 141:1140-1145.
28. Elosua R, Marrugat J, Molina L, Pons S, Pujol E: Validation of the Minnesota Leisure Time Physical Activity Questionnaire in Spanish men. The MARATHOM Investigators. *Am J Epidemiol* 1994, 139:1197-1209.
29. Willet W. *Nutritional Epidemiology* 2nd ed. . New York.: Oxford University Press; 1998.
30. Sayon-Orea C, Bes-Rastrollo M, Marti A, Pimenta AM, Martin-Calvo N, Martinez-Gonzalez MA: Association between yogurt consumption and the risk of Metabolic Syndrome over 6 years in the SUN study. *BMC Public Health* 2015, 15:1518.
31. Vergnaud AC, Peneau S, Chat-Yung S, Kesse E, Czernichow S, Galan P, Hercberg S, Bertrais S: Dairy consumption and 6-y changes in body weight and waist circumference in middle-aged French adults. *Am J Clin Nutr* 2008, 88:1248-1255.
32. Samara A, Herbeth B, Ndiaye NC, Fumeron F, Billod S, Siest G, Visvikis-Siest S: Dairy product consumption, calcium intakes, and metabolic syndrome-related factors over 5 years in the STANISLAS study. *Nutrition* 2013, 29:519-524.
33. Bach-Faig A, Berry EM, Lairon D, Reguant J, Trichopoulou A, Dernini S, Medina FX, Battino M, Belahsen R, Miranda G, Serra-Majem L: Mediterranean diet pyramid today. Science and cultural updates. *Public Health Nutr* 2011, 14:2274-2284.
34. Eguaras S, Toledo E, Buil-Cosiales P, Salas-Salvado J, Corella D, Gutierrez-Bedmar M, Santos-Lozano JM, Aros F, Fiol M, Fito M, et al: Does the Mediterranean diet counteract the adverse effects of abdominal adiposity? *Nutr Metab Cardiovasc Dis* 2015, 25:569-574.
35. Akbaraly TN, Singh-Manoux A, Tabak AG, Jokela M, Virtanen M, Ferrie JE, Marmot MG, Shipley MJ, Kivimaki M: Overall diet history and reversibility of the metabolic syndrome over 5 years: the Whitehall II prospective cohort study. *Diabetes Care* 2010, 33:2339-2341.
36. Ludwig DS, Willett WC: Three daily servings of reduced-fat milk: an evidence-based recommendation? *JAMA Pediatr* 2013, 167:788-789.
37. Ortinau LC, Hoertel HA, Douglas SM, Leidy HJ: Effects of high-protein vs. high-fat snacks on appetite control, satiety, and eating initiation in healthy women. *Nutr J* 2014, 13:97.

38. Zemel MB, Richards J, Mathis S, Milstead A, Gebhardt L, Silva E: Dairy augmentation of total and central fat loss in obese subjects. *Int J Obes (Lond)* 2005, 29:391-397.
39. Tremblay A, Doyon C, Sanchez M: Impact of yogurt on appetite control, energy balance, and body composition. *Nutr Rev* 2015, 73 Suppl 1:23-27.
40. Tordoff MG: Calcium: taste, intake, and appetite. *Physiol Rev* 2001, 81:1567-1597.
41. Veldhorst M, Smeets A, Soenen S, Hochstenbach-Waelen A, Hursel R, Diepvens K, Lejeune M, Luscombe-Marsh N, Westerterp-Plantenga M: Protein-induced satiety: effects and mechanisms of different proteins. *Physiol Behav* 2008, 94:300-307.
42. Zemel MB: The role of dairy foods in weight management. *J Am Coll Nutr* 2005, 24:537S-546S.
43. Kratz M, Baars T, Guyenet S: The relationship between high-fat dairy consumption and obesity, cardiovascular, and metabolic disease. *Eur J Nutr* 2013, 52:1-24.
44. Kratz M, Marcovina S, Nelson JE, Yeh MM, Kowdley KV, Callahan HS, Song X, Di C, Utzschneider KM: Dairy fat intake is associated with glucose tolerance, hepatic and systemic insulin sensitivity, and liver fat but not beta-cell function in humans. *Am J Clin Nutr* 2014, 99:1385-1396.
45. Drehmer M, Pereira MA, Schmidt MI, Del Carmen BMM, Alvim S, Lotufo PA, Duncan BB: Associations of dairy intake with glycemia and insulinemia, independent of obesity, in Brazilian adults: the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil). *Am J Clin Nutr* 2015, 101:775-782.
46. Nestel PJ, Mellett N, Pally S, Wong G, Barlow CK, Croft K, Mori TA, Meikle PJ: Effects of low-fat or full-fat fermented and non-fermented dairy foods on selected cardiovascular biomarkers in overweight adults. *Br J Nutr* 2013, 110:2242-2249.
47. Sun J, Buys N: Effects of probiotics consumption on lowering lipids and CVD risk factors: A systematic review and meta-analysis of randomized controlled trials. *Ann Med* 2015, 47:430-440.
48. Murphy KJ, Crichton GE, Dyer KA, Coates AM, Pettman TL, Milte C, Thorp AA, Berry NM, Buckley JD, Noakes M, Howe PR: Dairy foods and dairy protein consumption is inversely related to markers of adiposity in obese men and women. *Nutrients* 2013, 5:4665-4684.
49. Bendtsen LQ, Lorenzen JK, Larsen TM, van Baak M, Papadaki A, Martinez JA, Handjieva-Darlenska T, Jebb SA, Kunesova M, Pfeiffer AF, et al: Associations between dairy protein intake and body weight and risk markers of diabetes and CVD during weight maintenance. *Br J Nutr* 2014, 111:944-953.
50. Bohl M, Bjornshave A, Rasmussen KV, Schioldan AG, Amer B, Larsen MK, Dalsgaard TK, Holst JJ, Herrmann A, O'Neill S, et al: Dairy proteins, dairy

lipids, and postprandial lipemia in persons with abdominal obesity (DairyHealth): a 12-wk, randomized, parallel-controlled, double-blinded, diet intervention study. *Am J Clin Nutr* 2015, 101:870-878.

51. Babio N, Becerra-Tomas N, Martinez-Gonzalez MA, Corella D, Estruch R, Ros E, Sayon-Orea C, Fito M, Serra-Majem L, Aros F, et al: Consumption of Yogurt, Low-Fat Milk, and Other Low-Fat Dairy Products Is Associated with Lower Risk of Metabolic Syndrome Incidence in an Elderly Mediterranean Population. *J Nutr* 2015, 145:2308-2316.

Specific role of yogurt on obesity is not fully understood

Consumption of whole-fat yogurt was associated with changes in waist circumference

Whole-fat yogurt consumption was associated with higher probability of reversion of central obesity

Low-fat yogurt showed no beneficial effects in management of abdominal obesity in elderly population at high cardiovascular risk.