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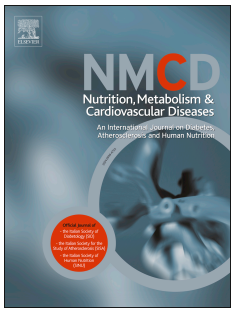

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Fermented dairy products, diet quality and cardio-metabolic profile in a Mediterranean cohort at high cardiovascular risk

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Supplemental Table 1, supplemental table 2 and list of PREDIMED-PLUS study investigators are available from the "Online Supporting Material" link in the online posting of the article and from the same link in the online table of contents at jn.nutrition.org

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Abbreviation list:

CVD: Cardiovascular diseases
FFQ: Food Frequency Questionnaire
IQR: IQR, interquartile range
MedDiet: Mediterranean Diet
MetS: Metabolic syndrome
PA: Physical activity
PREDIMED-Plus study: Prevención con Dieta Mediterránea-Plus study
TG: Triglycerides
T2D: Type 2 diabetes

CONFLICT OF INTEREST STATEMENT

Mena-Sánchez G – Declares no conflicts of interests.

Babio N - Declares that she received payments from Danone S.A. for the purposes of scientific and technical consulting, but not for the preparation of this study.

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ABSTRACT

Background: Fermented dairy products have been associated with a better diet quality and cardio-metabolic profile. However, in Mediterranean populations, these associations have not been well characterized.

Aims: To assess the diet quality and the associations between the consumption of total fermented dairy products and their subtypes and Metabolic Syndrome (MetS) components prevalence in a Mediterranean population at high cardiovascular risk.

Methods: Baseline cross-sectional analyses were conducted on 6,572 men and woman (mean age 65y) with overweight or obesity and MetS recruited into the PREDIMED-Plus cohort. A 143-item FFQ was used and anthropometrical, biochemical and blood pressure measurements were recorded. Multivariable-adjusted Cox regressions were fitted to analyze the association between quartiles of consumption of fermented dairy products and their subtypes and MetS components to estimate the relative risk (RR) and 95% confidence intervals (95% CIs).

Results: High consumers of fermented dairy products reported a higher consumption of fruit, vegetables, fish, nuts and whole bread, and a lower consumption of white bread, alcohol and cookies. Compared with participants in the lowest quartile of cheese consumption, those in the higher quartile showed a lower prevalence of the low HDL-cholesterol component of the MetS (RR=0.88;95%CI:0.78-0.98). Cheese consumption was inversely associated with the prevalence of the hypertriglyceridemia. Total fermented dairy products, yogurt and its types were not associated with any of the MetS components.

Conclusions: Compared to non-consumers, participants consuming fermented dairy products reported a better diet quality and, particularly, cheese consumers presented a lower prevalence of hypertriglyceridemia and low HDL-cholesterol MetS components.

Keywords: fermented dairy, diet quality, metabolic syndrome components,

INTRODUCTION

Metabolic Syndrome (MetS) is defined as a set of metabolic abnormalities including dyslipidemia, high blood pressure, high glucose levels, abdominal obesity or medication for each of these features, affecting approximately 25% of the total world population. This condition has been directly related with the first cause of death worldwide (i.e. cardiovascular disease [CVD]), but also with diabetes, some types of cancer and other chronic diseases (1), leading to considerable negative impacts on public health and increasing overall health care costs. MetS may be prevented by avoiding unhealthy diets, tobacco and harmful alcohol consumption, all recognized risk factors. Some healthy dietary patterns have been consistently and inversely associated with the risk of MetS incidence (2). Mediterranean Diet (MedDiet) is characterized by a low intake of meat and abundant consumption of plant-based foods, such as olive oil, nuts, vegetables, fruits and legumes, but also moderate consumption of fish and fermented dairy foods, particularly cheese and yogurt. In recent years, fermented dairy products, specially yogurt, have been investigated because of their nutritional properties, including the potential probiotic effect, the high quality protein content and the presence of vitamins and minerals (3). It has also been acknowledged that yogurt may be a marker of diet quality in healthy North American populations, and also in some areas of Europe (4–6). Fermented dairy products have been inversely associated with the prevalence or incidence of some cardiovascular risk factors (7–9). However, few studies have analyzed the association between the consumption of specific types of fermented dairy products and the prevalence of the MetS components. Recently, in different epidemiological studies yogurt consumption has been inversely associated with the prevalence of total and central adiposity (10), and the incidence of abdominal obesity, high fasting plasma glucose, high blood pressure, hypertriglyceridemia and low HDL-cholesterol (11). In a recent cross-sectional study, no association was observed between cheese consumption and blood pressure or lipid profile (12). However, in a previous cross-sectional study, cheese consumption was

related with lower plasma triglycerides (TGs) and higher HDL-cholesterol concentrations (13). In contrast, this association between cheese consumption and MetS components or other cardiovascular-related clinical outcomes was not found in either a prospective study (11) or in a systematic review of prospective studies (14).

Given these mixed results, the aims of the present study were: a) to describe whether the consumption of fermented dairy products is associated with a better diet quality in the context of the Prevención con Dieta Mediterránea-Plus (PREDIMED-Plus) study, and b) to analyze the potential associations between the consumption of total fermented dairy foods, yogurt and cheese and the prevalence of the MetS components in Mediterranean overweight/obese individuals with MetS.

MATERIALS AND METHODS

Design and study population. The present study is a cross-sectional analysis conducted in the framework of the PREDIMED-Plus study, a 6-year parallel group, multi-center, randomized controlled clinical trial for the primary prevention of CVD. Participants are men aged 55-75 years and women 60-75 years, with a body mass index ≥27 to <40 kg/m^2 who meet at least three criteria of the MetS defined in accordance with the updated criteria of the International Diabetes Federation and the AHA/National Heart, Lung and Blood Institute (15): abdominal obesity for European individuals (waist circumference ≥88 cm in women and ≥102 cm in men), hypertriglyceridemia (≥150 g/dL) or drug treatment for high plasma TG concentrations, low HDL-cholesterol (≤50 mg/dL in women and ≤40mg/dL in men), high blood pressure (systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mmHg or antihypertensive drug treatment), or high fasting plasma glucose (≥100 mg/dL) or drug treatment for T2D. Randomized participants were recruited in 22 Spanish centers from various Primary Care Health Facilities belonging to the National Health System, research institutes and universities.

The objective of the PREDIMED-Plus trial is to compare the effect of two lifestyle interventions: a) intensive weight-loss intervention with hypocaloric MedDiet, physical activity (PA) and behavioral therapy, b) non-intensive intervention advising participants to follow an unrestricted energy MedDiet in the context of usual care by medical physicians. The principal end-points are: 1) a composite of major clinical cardiovascular events, and 2) weight loss and weight maintenance in the long term. Other secondary end-points include the incidence of several chronic conditions or diseases secondary to obesity and MetS. The recruitment of participants began in September 2013 and finished in November 2016, with 6,874 participants randomized to the trial. The final results are expected to be available in 2020. The study protocol is published in the PREDIMED-Plus website (16). This study was registered at the International Standard Randomized Controlled Trial (ISRCT; http://www.isrctn.com/ISRCTN89898870) with number 89898870. Registration date: 24 July 2014.

This report was based on a cross-sectional analysis of baseline data from all the PREDIMED-Plus randomized participants. For the present analysis, we excluded 122 participants who have not completed the FFQ and 180 participants who reported total energy intake values beyond the specified limits; 500-3,500 kcal/day in women and 800-4,000 kcal/day in men (17). A final sample of 6,572 participants was analyzed.

Diet quality and lifestyle assessment. To assess diet quality and other lifestyle factors of the participants, different questionnaires were administered at baseline by trained interviewers. In terms of PA, sample was dichotomized into meeting or not the current WHO recommendations (18). Diet quality was assessed with a 143-item semi quantitative FFQ and a 17-item Mediterranean Diet adherence questionnaire (19). The FFQ contained 7 items related to fermented dairy products that have nine possible categories of consumption: never or almost never, 1-3/month, 1/week, 2-4/week, 5-6/week, 1/day, 2-3/day, 4-6/day and >6/day for each item. The information collected was transformed into grams per day, multiplying

serving sizes by consumption frequency and dividing the result by the assessed period. We defined fermented dairy products as: low-fat yogurt, whole-fat yogurt and all types of cheese (petit Swiss, ricotta, fresh cheese, cottage, and semi-cured and cured cheeses such as cheddar, Manchego and Emmental). Food groups and energy intake were estimated using Spanish food composition tables (20,21).

Other Measurements: Lifestyle, smoking habits, personal and family history of illness, and medication were also evaluated. Weight was measured by duplicate with calibrated scales, height with wall stadiometers, and waist circumference with measuring tapes at the mid-point between the last rib and ileac crest. Blood pressure was measured three times with a validated semiautomatic oscillometer (Omron HEM-705CP, Hoofddorp, The Netherlands) and the median measurement of the three readings was used. After an overnight fast, blood samples were collected and stored at -80ºC. Total LDL-cholesterol, HDL-cholesterol, TG and plasma glucose concentrations were determined by standard enzymatic methods in automatic analyzers in local laboratories. All the determinations were performed by trained health care professionals who were blinded to the intervention arms.

Statistical Analyses. Participants were categorized into quartiles of fermented dairy consumption. Chi-square and 1-way ANOVA tests were used to assess differences in the baseline characteristics of participants, including dietary and other lifestyle factors. Results are expressed as mean ± SD or median and (P25, P75) for continuous variables. Cox regression models with constant follow-up time were fitted to estimate RR and 95% (CI) for each component of MetS (high blood pressure, high fasting plasma glucose, abdominal obesity, low HDL-cholesterol and hypertriglyceridemia) in quartiles of consumption of total fermented dairy products and specific types (cheese, total yogurt, low-fat yogurt and whole-fat yogurt). The analysis was adjusted for different potential confounders, based on prior knowledge in potential confounders that could affect the present associations, including sex, age, BMI, education (illiterate/primary education, secondary education and higher education),

smoking status and leisure time PA, total energy intake, the 17-item MedDiet adherence questionnaire (score <8 or ≥8), alcohol (grams per day adding a quadratic term) and medication for each of the MetS components. All models were stratified by the recruiting center.

Interaction with quartiles of fermented dairy products with several potential effect-modifying variables such as sex and abdominal obesity was tested (except when abdominal obesity was the main outcome) by comparing the model with and without the product term using the likelihood ratio test.

To assess the linear trend, the median value of each quartile of total fermented dairy products and specific type was assigned and modeled as a continuous variable in the Cox regression models.

In order to test the robustness of our results we conducted several sensitivity analyses. First, we adjusted for other confounding variables, such as components of MetS (except when the MetS component was considered the outcome) and energy-adjusted food groups (consumption of vegetables, fruits, legumes, cereals, nuts, olive oil meat, fish and cookies). Second, total and specific fermented dairy products were mutually adjusted for each other (e.g. when cheese was the exposure variable, the model was also adjusted for different types of milks and yogurts). Third, all the analyses were stratified by sex because differences in specific types of fermented dairy consumption were observed between men and women. The level of significance was set at $p < 0.05$. All the analyses were performed with Stata (15.0, StataCorp LP, Tx. USA).

RESULTS

Of the total 6,572 participants that were included in the present analysis, 48.5% were women and the mean sample age was 65 years. More than 95% of the total population consumed fermented dairy products. The median (P25, P75) consumptions of total fermented dairy products from the lowest to the highest quartile were 24 (13, 34), 68 (58, 77), 122 (101, 136), 176 (158, 314) grams per day, respectively **(Table1)**.

Those individuals with the highest consumption of fermented dairy products were more likely to be women, were older, and had higher HDL-cholesterol concentrations and lower levels of blood pressure, fasting plasma glucose and TG concentrations (all comparisons p <0.05). In addition, those individuals with a higher consumption of fermented dairy products were more likely to use antihypertensive or insulin medication and less likely to be smokers and to use other hypoglycemic medication. A lower percentage of individuals with high blood pressure and hypertriglyceridemia was observed in high consumers of fermented dairy products.

Diet quality and other lifestyle factors. Compared to individuals in the reference quartile (Q1) of fermented dairy consumption, those in the top quartile had a higher consumption of fruit, vegetables, whole meal bread, fish and nuts, and a lower intake of olive oil, cookies, alcohol and white bread (all comparisons, p <0.05). Compared to those in the lowest quartile, participants in the highest quartile were more likely to have a higher adherence to MedDiet **(Table 2)**. Results were similar when participants were classified as cheese and yogurt consumers or non-consumers **(Supplemental table 1)**. Compared to non-consumers (*n=553*), yogurt consumers (*n=6,019*) had a higher intake of fruit, vegetables, fish and whole meal bread, but a lower intake of white bread, alcohol and cookies. Compared to non-consumers, yogurt consumers had a higher adherence to MedDiet and were less likely to be smokers. Yogurt consumers spent less time doing moderate PA but more time doing vigorous PA than non-consumers. Compared to non-consumers, consumers of a daily portion of

cheese (*n=6,367*) consumed less white bread, alcohol, cookies, were less likely to smoke and engaged in less moderate PA.

Cardio-metabolic risk factors. **Figure 1 and supplemental table 2** show the multivariable-adjusted RRs (95% CIs) for the prevalence of MetS components according to categories of consumption of total fermented dairy products and specific types**.** After adjusting for several potential confounders, the consumption of total fermented dairy products was not significantly associated with the prevalence of any of the MetS components. When analyses were conducted for different fermented dairy types, the intake of total yogurt and types of yogurt was not significantly associated with any of the MetS components (**Table 3**). Compared to the participants in the bottom quartile, those in the top quartile of cheese consumption had a lower prevalence of low HDL-cholesterol plasma levels (RR= 0.88; 95% CI: 0.78-0.98; *p-trend*= 0.02). Moreover, those in the highest quartile of cheese consumption compared to the lowest had an estimated 17% lower prevalence of hypertriglyceridemia. No associations were observed with the high blood pressure, high fasting plasma glucose and abdominal obesity components of the MetS.

Sensitivity analyses

Our results remained robust in several sensitivity analyses. When analyses were adjusted for different MetS components or saturated fatty acids, the magnitude and direction of the association did not change (data not shown). People eating more yogurt and cheese also had a healthier dietary pattern, which could affect the observed results (**supplemental table 1**), therefore, we repeated all the analysis adjusting for dietary variables (vegetables, fruits, legumes, cereals, nuts, fish, meat, olive oil and cookies). Results remained in the same line, showing an inverse association between cheese consumption and the prevalence of low HDL-cholesterol plasma levels and hypertriglyceridemia (RR = 0.88; 95% CI: 0.78-0.98; *p-trend*=0.02 and RR = 0.83; 95% CI: 0.74-0.93; *p-trend* <0.01, respectively, comparing highest versus lowest quartiles). Regarding yogurt consumption, results remained non-

significant. In the analyses stratified by sex, women located in the upper quartile of cheese consumption had a lower prevalence of hypertriglyceridemia (RR = 0.78; 95% CI: 0.66-0.92; *p-trend* <0.01) and borderline significant lower prevalence of low HDL-cholesterol MetS component (RR = 0.87; 95% CI: 0.74-1.02; *p-trend* 0.06). On the other hand, in men, a high consumption of cheese was not associated with the low HDL-cholesterol or hypertriglyceridemia MetS component. (**Supplemental table 3**.)

DISCUSSION

To the best of our knowledge, this is the first cross-sectional study conducted in a Mediterranean population with MetS evaluating the associations between the consumption of fermented dairy products, the quality of the diet, and the prevalence of MetS components. Our results show that, compared to consumers below the median, high consumers of total fermented dairy products had a better quality of diet and a greater adherence to the MedDiet. On the other hand, those individuals located in higher quartiles of cheese consumption had a lower prevalence of low HDL-cholesterol and hypertriglyceridemia MetS components. However, the consumption of total fermented dairy products, yogurt and its different types (low-fat and whole-fat yogurt) was not associated with any of the components of the MetS.

Our results regarding diet quality and fermented dairy products, are in line with those of other studies conducted in different countries (22). In a cross-sectional analysis performed in Canadian adults (*n=664*) from the INFOGENE study, individuals who consumed a median of about half a yogurt per day were more likely than non-yogurt-consumers to follow a prudent dietary pattern, characterized by a higher consumption of vegetables, fruits, non-hydrogenated fats, legumes and seafood and a lower consumption of processed meat, refined grains, snacks, alcohol and other food directly related to a Western dietary pattern (6). Compared to non-consumers, yogurt consumers also adhered better to a healthy diet in cross-sectional studies, one performed in two American cohorts of men and women (the Framingham Heart Study Offspring and the Third Generation cohorts) (23) and another one conducted in an Italian population (the ITRAN SCAI study) (5). In addition to all these results, it should be pointed out that, unlike non-consumers, frequent yogurt consumers were less likely to have an inadequate intake of micronutrients such as riboflavin, thiamin, pantothenic acid, vitamin B6, vitamin C, folate, calcium, iodine, selenium and copper (23).

All these findings have been also reported in children. Data from the National Health and Nutrition Examination Survey (NHANES)(24), the UK Diet and Nutrition Survey of Infants

and Young Children and the National Diet (2011) and Nutrition Survey (2008/2009-2010/2011) (25) showed that yogurt consumption also has a positive impact on diet quality and the intake of several micronutrients.

Our results regarding the type of fermented dairy product consumption and MetS components are partly in line with other prospective studies. In the CARDIA (Coronary Artery Risk Development in Young Adults) study, no association between the consumption of cheese or yogurt and the incidence of MetS components was observed (26). Similarly, in the PREDIMED study, conducted in individuals at high cardiovascular risk (8), no associations between the consumption of cheese and the incidence of MetS components were reported. Nonetheless, in the same study, total yogurt intake was inversely associated with the high fasting plasma glucose MetS component (p= <0.01), whereas low-fat yogurt was inversely associated with hypertriglyceridemia (p=<0.01) and low HDL-cholesterol (p= 0.01), and whole fat-yogurt with all the MetS components (8). These mixed results may be partly explained because of the study design, the differences between populations and the different amounts and types of fermented dairy products consumed.

It is important to remark that in our study, those individuals with frequent consumption of cheese had lower prevalence of the hypertiglyceridemia and low HDL-cholesterol components of the MetS. High TG/low HDL-cholesterol is the phenotype for a common lipoprotein abnormality associated with visceral obesity. We can speculate that high cheese consumption protects from this phenotype. However, this do not occur in case of high yogurt consumers. The reasons explaining these divergent results for two fermented dairy products need to be confirmed and elucidated in the future, although some potential mechanisms have been speculated. The extended cheese food matrix may modify the lipid profile through a variety of mechanisms, due to the synergy between different nutrients and probiotic bacteria. First, although protein and calcium content of cheese could differ depending on specific types (e.g. hard vs soft cheese) in general, cheese in Spain has higher protein (casein) and calcium

content than yogurt (21) which may inhibit fatty acids absorption and, therefore, reduce plasma TG concentrations. On the one hand, the casein matrix, made up of aggregated micelles, may trap fat globules(27). On the other hand, calcium could interact with fatty acids to form insoluble calcium-fatty acids soaps (28,29), increasing fecal fat excretion. Second, fermented dairy products, including cheese which could contain different bacterial strains (30), may modulate gut microbiota, reducing the abundance of pathogenic bacteria and stimulating the production of metabolites, such as short-chain fatty acids (31) that modulate lipid metabolism (32), through the fermentation of indigestible carbohydrates from other food sources (e.g. fiber from fruits, vegetables, legumes, nuts etc.), and the fermentation of lactose in individuals with lactose intolerance. Importantly, although cheese is a saturated fatty acid food source, the consumption of 50 g per day has not been associated with the risk of CVD, and even an inverse association with coronary heart disease have been reported in a recent meta-analysis of prospective cohort studies (33,34).

It is important to highlight that future mechanistic studies should be focused on inflammatory biomarkers rather than serum cholesterol levels to explain the potential cardio-metabolic beneficial effects of fermented dairy products consumption (35). For instance, it has been suggested that polar lipids (phospholipids and sphingolipids) located in the membrane of milk fat globules may have anti-inflammatory properties (36), which could partially explain the cardioprotection associated with fermented dairy consumption.

The present study has various limitations that should be borne in mind. Firstly, the inherent nature of cross-sectional studies means that causal relationships cannot be established and possible reverse causality bias could directly affect to our results. Secondly, the results cannot be extrapolated to other populations, since our population comprised elderly Spanish individuals with obesity and MetS. Thirdly, diet was assessed by a validated FFQ, but potential measurement errors are unavoidable. However, the present study also has some

strengths: the large study sample, the analysis of fermented dairy types with different fat contents and the adjustment for a large number of potential confounders.

In conclusion, fermented dairy products consumption, which are part of the MedDiet, seems to be a marker of diet quality. Moreover, cheese consumption is inversely associated with some components of MetS. However, given the mixed results reported in the literature, clinical trials and large prospective epidemiological studies are required to confirm the present results. With the rapid increase in the prevalence of MetS, urgent preventive lifestyle strategies are needed. The present data will be useful for setting nutritional recommendations for the elderly population with obesity and MetS.

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Contribution statement

G.M-S, N.B, and J.S-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. Study concept and design: N.B and J.S-S. Statistical analyses: G.M-S and N.B. Drafting the manuscript: G.M-S, N.B and J.S-S. All authors critically revised the manuscript for important intellectual content and approved the final version of the manuscript.

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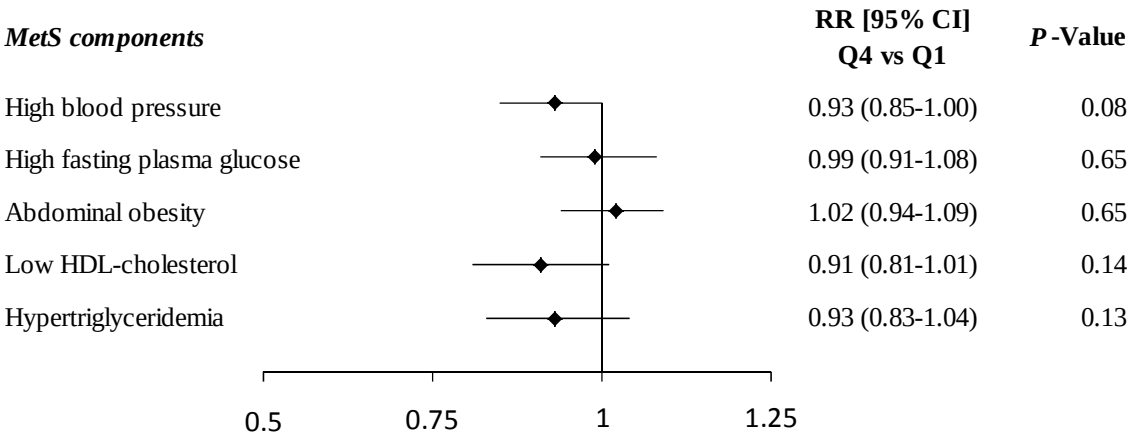

Figure 1. Cross-sectional analysis. Cox regression of components of MetS [high blood pressure (n=6,558), high fasting plasma glucose (n=6,546), abdominal obesity (n=6,125), low HDL-cholesterol (n=6,260), hypertriglyceridemia (n=6,260)] comparing quartile 4 and quartile 1 of total fermented dairy consumption at baseline. Quartiles cut-offs are based in energy-adjusted fermented dairy consumption. Model is adjusted for sex, age (years), education level (illiterate /primary education, secondary education and academic/graduate, physical activity (MET-min/day), BMI (kg/m2), abdominal obesity (unless when abdominal obesity was the main outcome) smoking habit, total energy intake, Mediterranean 17 points questionnaire and use of hypoglycemic, hypolipidemic, antihypertensive, and insulin treatment. The MetS components were defined according to updated harmonizing criteria. Abbreviations: CI, confidence interval, IQR, interquartile range; MetS, metabolic syndrome; HDL, high density lipoprotein; Q, quartile.

Highlights of the core findings within the manuscript titled "Fermented dairy products, diet quality and cardio-metabolic profile in a Mediterranean cohort at high cardiovascular risk".

- The consumption of total fermented dairy products is related with a better quality diet and a higher adherence to the Mediterranean diet pattern.
- Cheese consumption was inversely related with lower risk of low HDL-cholesterol plasma levels and hypertriglyceridemia, components of the metabolic syndrome.