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MILK AND DAIRY PRODUCTS INTAKE IS RELATED TO COGNITIVE IMPAIRMENT AT BASELINE IN PREDIMED PLUS TRIAL

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ABSTRACT

Introduction: The worldwide prevalence of dementia is increased in ageing populations. Recent evidence indicates that nutrition may play an important role in the causation and prevention of age-related cognitive decline and dementia. A limited number of studies have conducted in-depth assessments of the relationship between consumption of milk and dairy products and cognitive impairment or dementia. Our objective was to examine the association between milk and dairy product intake and the prevalence of cognitive impairment and cognitive test performance among Spanish individuals at high cardiovascular risk.

Materials and methods: Cross-sectional analyses were performed on baseline data from 6744 adults (men aged 55-75 years; women aged 60-75 years) who were overweight or obese and had the metabolic syndrome included in the PREDIMED-PLUS trial from October 2013 to October 2016. Intake of milk and dairy products was estimated using a 143-item semi-quantitative food frequency questionnaire grouped into quartiles. The risk of developing cognitive impairment was based on the Mini-Mental State Examination (MMSE). We also administered the Beck Depression Inventory.

Results: We found a higher prevalence of cognitive decline in subjects who consumed more grams of milk and dairy products. Patients with a worse MMSE score (10-24) consumed a mean of 395.14 ± 12.21 g of milk and dairy products, while patients with a better MMSE score (27-30) consumed a mean of 341.23 ± 2.73 g of milk and dairy products ($p<0.05$). Those subjects with the lower milk consumption (<220 g/day) had a higher MMSE score (28.35 ± 0.045), while higher milk consumers (≥500 g/day) had a lower MMSE score (28.01 ± 0.053). Higher intake of fermented dairy products was also observed in participants with a lower MMSE score (OR 1.612, $p<0.000$). A positive correlation was found between the consumption of whole milk and dairy products and the MMSE score ($r = 0.066$, $p <0.000$). Those participants who consumed semi-skimmed and skimmed milk and dairy products presented a lower MMSE score ($r = -0.031$, $p = 0.013$ and $r = -0.027$, $p = 0.033$, respectively).

Conclusions: These findings suggest that greater consumption of milk and dairy products could be related to a worse MMSE score. Higher intake of fermented dairy products could also be associated with greater cognitive decline according to MMSE. Conversely, consumption of whole-fat milk and dairy products could be linked with less cognitive impairment in our cross-sectional study. Consumers of low-fat milk and dairy products had a higher prevalence of cognitive decline.

KEY WORDS: cognition, cognitive decline, consumption, cheese, dairy products, milk, yoghurt.

INTRODUCTION:

The worldwide prevalence of dementia is increasing and is predicted to affect 81.1 million people by 2040 (1,2). This will place a considerable burden on health care resources, and will substantially impact quality of life in the individuals affected. As the populations of developed countries around the world age (3), cognitive decline and dementia are emerging as major health problems. Cognitive decline may range from the very minimal decline associated with normal ageing, to mild cognitive impairment (MCI), or very severe dementia, with the latter regarded as the clinical endpoint of cognitive impairment (4). Recent evidence indicates that nutrition may play an important role in the causation and prevention of age-related cognitive decline and dementia (5,6).

While positive associations have been shown between a number of nutrients and cognitive performance (antioxidants, folate, omega-3 and omega-6 fatty acids) (7, 8, 9), little attention has been paid to the potential role of milk and dairy foods in modulating neurological and psychological parameters. Consumption of milk and dairy products may reduce the likelihood of cognitive decline either directly or via mediating effects on cardiometabolic health. A growing body of literature describes this association, but the results of different studies are not conclusive.

The first cross-sectional studies evaluated this relationship and found that higher milk and dairy product intake was likely to have a protective effect against cognitive impairment (10,11,12). Later, two cohort studies (13,14) reported contradictory results. Almeida et al. in their cohort of men aged 80 and over, observed the influence of fat in milk; regular full-cream milk consumption was inversely related to good mental health at follow-up compared with rare consumption (13). The study by Vercambre et al. found no significant associations between milk and dairy product consumption and cognitive decline in French elderly women (14).

Subsequently, the meta-analysis by Wu et al. supported the idea that high milk consumption was associated with a lower likelihood of cognitive impairment in Asian populations. However, high intakes of full-fat milk and dairy products may be associated with declines in cognitive performance (15). These concepts were not validated in two contemporary prospective cohort studies among older male and female adults after a long-term follow-up. Kesse-Guyot et al. observed that milk intake was negatively associated with verbal memory performance (16), and Petruski-Ivleva et al. found that milk intake greater than one glass per day during midlife was associated with a higher rate of cognitive decline over a 20-year period (17). Previous epidemiological and clinical studies have concluded that fermented dairy products can help to prevent cognitive decline (18,19). A systematic review in 2017 compiled information from 7 cohort studies and one randomized controlled trial. This review revealed that the current evidence was inadequate to draw a conclusion for the causal relationship between milk or dairy intake and cognitive decline or disorders in older adults as the majority of studies were observational (20).

On the other hand, type 2 diabetes (T2D) and obesity are well recognized risk factors for poor cognitive outcomes, including cognitive decline, MCI, and dementia (21, 22). It has been estimated that 175 000 Alzheimer's disease cases in the United States could be attributable to T2D (23). Approximately one-quarter of older adults are diabetic, and an additional 50% are prediabetic. Given the high prevalence of T2D and obesity, it is becoming increasingly important to better understand the association between T2D and cognitive outcomes. These medical conditions are risk factors for cardiovascular disease and are suggested to also increase the likelihood of reduced cognitive function in later life. Observational, epidemiological and intervention trials indicate that milk and dairy consumption may have positive effects on metabolic parameters (24-28). If milk and dairy product consumption can improve cardiometabolic health, a beneficial consequence of this may contribute to reducing the risk of cognitive decline. Recent reviews, however, have suggested that milk and dairy product intake, although associated with better cardiometabolic health, may also be associated with cognitive impairment (17). Given the mixed results and the potential global impact that milk and dairy product consumption may have on cognitive decline and cardiovascular diseases outcomes, understanding these relationships is crucial for informing dietary guidelines. Therefore, the objective of this study was to examine the relationship between milk and dairy product intake and the prevalence of cognitive impairment and cognitive test performance among Spanish individuals at high cardiovascular risk.

MATERIAL AND METHODS:

We investigated the cross-sectional associations between baseline milk and dairy product consumption and cognitive outcomes among patients enrolled in this population-based study. We compared patient consumption from the lowest to highest quantities of milk and dairy products. Thus, we reviewed 6744 Spanish women and men who were free from cardiovascular disease and cancer and who completed a 143-item food frequency questionnaire (FFQ; presenting data on milk and dairy product consumption) between the years 2013 to 2016. The cases of cognitive disorders were recorded after assessing the MMSE as a cognitive function test. We also evaluated scores from the Beck Depression Inventory (BDI-II).

Study design and participants

The present study is a cross-sectional analysis of baseline data within the framework of the PREDIMED-PLUS study, a 6-year multicentre, randomised, parallel-group, primary prevention clinical trial conducted in Spain to assess the effect on cardiovascular disease morbidity and mortality of an intensive weight-loss intervention program based on an energy-restricted traditional Mediterranean diet with promotion of physical activity and behavioural support compared to a usual care intervention with an energy-unrestricted Mediterranean diet only (control group) and no goals for weight loss. A more detailed description of the PREDIMED-PLUS study is available at http://predimedplus.com/(29). (Data Base: 201706131354_PREDIMEDplus_2017-06-13). This study was registered at the International Standard Randomized Controlled Trial (ISRCT; http://www. isrctn.com/ISRCTN89898870) with the registration number 89898870. Registration date: 24 July 2014.

From September 2013 to December 2016, a total of 6874 participants were recruited and randomised in 23 centres from different universities, hospitals and research institutes in Spain. 130 participants did not complete a 146-item food frequency questionnaire with data on milk and dairy products consumption and were excluded. 6744 participants were evaluated by their data on milk and dairy products consumption but 318 patients did not completed MMSE questionnaire or presented a score of 10 or less also, were excluded from the analysis. Finally, 6426 participants were included (those who have completed the MMSE questionnaire validated for the Spanish population and the food frequency questionnaire) (Figure 1).

Each of these centres recruited participants from several primary health care facilities pertaining to the National Health System. The eligible participants were community-dwelling adults (men aged 55-75; women aged 60-75), who were overweight or obese (body mass index [BMI] >27 and <40 kg/m^2), met at least three criteria for the metabolic syndrome according to the updated harmonised criteria of the International Diabetes Federation, the American Heart Association, and the National Heart, Lung and Blood Institute (30), and were without cardiovascular disease at enrolment.

All participants provided written informed consent, and the study protocol and procedures were approved according to the ethical standards of the Declaration of Helsinki by all the research ethics committees (RECs) or clinical research ethics committees (CRECs) of the participating institutions: REC Malaga, REC Virgen Macarena and Virgen del Rocío University Hospitals, REC University of Navarra, REC Balearic Islands, CREC Clinical Hospital of Barcelona, CREC Barcelona MAR Health Park, CREC Sant Joan de Reus University Hospital, REC San Cecilio University Hospital, CREC Jiménez Díaz Foundation, CREC Basque Country, REC University of Valencia, CREC Doctor Negrón University Hospital of Gran Canaria, CREC Bellvitge University Hospital, REC Córdoba, REC Madrid Institute for Advanced Studies, CREC San Carlos Clinical Hospital, REC for Biomedical Research of Andalusia, and CREC León.

At the first visit, the examination by the physician or dietitian-nutritionist included a review of the medical history and administration of the MMSE. For analysis, we included all participants who completed the MMSE questionnaire validated for the Spanish population (31). The MMSE measures five cognitive domains: serial subtraction, language, memory, orientation, and visuospatial. We also performed a 143-item FFQ. In total, information on 6426 participants who completed both questionnaires was included.

Dietary Assessment:

Intake of milk and dairy foods was assessed using a self-administered FFQ on which participants reported their average frequency and quantity consumed (in grams) of 143 food and beverage items during the previous week. This FFQ requests information relating to food choices, preparation, portion size, quantity and consumption of milk and dairy products, and of different food and beverage items.

Total daily milk intake from all sources was calculated, and the fat content of each item categorised into whole fat, semi-skimmed and skimmed from the FFQ. We categorised milk and dairy intake into quartiles. Detailed information on fermented dairy products (all types of cheese, cottage cheese and yoghurt but no dairy desserts) was analysed.

Assessment of Cognitive Functioning:

Currently, the MMSE is the most commonly used brief cognitive screening test. It is a 30-point questionnaire which examines functions including registration (repeating named prompts), attention and calculation, recall, language, ability to follow simple commands, and orientation). The MMSE is scored from 0 to 30, with higher scores indicating absence of cognitive decline. It was developed in 1975 as a global assessment of cognitive status. A perfect score is 30 points; those patients with a score of 10 or less were excluded from the analysis. An MMSE score between 10-24 was considered mild to moderate dementia, a score between 25-26 was considered uncertain/questionable dementia and an MMSE score between 27-30 was considered a normal cognitive range.

Individuals who performed in the normal cognitive range and did not meet criteria for MCI or dementia, which was diagnosed using DSM-IV criteria, (32) were deemed clinically unimpaired. The ease of administering the MMSE and its utility in detecting Alzheimer's disease has made it a popular neuropsychological tool (33).

Assessment of depressive symptoms was undertaken using the BDI-II in addition to cognitive state. A total score ranging from 0 to 63 was calculated, with higher scores indicating more frequent depressive mood. Suggested score ranges for mild depression, moderate to severe depression and severe depression were 10-19, 20-30, and 31 or higher, respectively (34).

Covariate assessment

The covariates were evaluated using self-reported general questionnaires about socio-demographic factors (gender, age, educational level, and employment status), smoking habits, personal history of illness, medical conditions, and medication use. These were collected prior to randomisation. Anthropometric variables and blood pressure were determined by trained staff and in accordance with the PREDIMED-PLUS operations protocol. Obesity was defined as a BMI ≥30 kg/m^2. T2D was defined as having a previous clinical diagnosis of diabetes, or HbA1c levels ≥6.5% or use of antidiabetic medication at baseline. Individual components of the metabolic syndrome were defined as follows: abdominal obesity (waist circumference ≥102 cm in men; ≥88 cm in women), high blood pressure (systolic and/or diastolic ≥130/85 mmHg or using antihypertensive drugs), hyperglycaemia (glucose ≥100 mg/dl or taking medication for elevated glucose), hypertriglyceridaemia (triglycerides ≥150 mg/dl or taking triglyceride-lowering medication), low HDL-cholesterol (HDL-c <40 mg/dl in men and <50 mg/dl in women or taking HDL-c raising medication). Physical activity was self-reported by the Minnesota test.

Statistical Analysis

Statistical analyses of the data were performed primarily using the SPSS program (version 22.0.0 for Windows, SPSS Iberica, Spain). Statistical significance was set at $p<0.05$. Baseline characteristics were described as means and dispersion (standard deviation, SD) for quantitative variables and as proportions for qualitative variables. We categorised baseline consumption of milk and dairy products into approximate quartiles, defining the four groups as “Very low” Q1 (<220 g/day), “Low” Q2 (221-307 g/day), “Low to Moderate” Q3 (308-499 g/day) and “Moderate to High” Q4 (≥500 g/day). We compared the total score on the MMSE across the four levels of milk and dairy product consumption.

We also analysed the differences according to MMSE score. We divided subjects according to MMSE score in three groups to differentiate those with mild to moderate risk of dementia (MMSE score 10-24) from those with uncertain/questionable risk of dementia (MMSE score 25-26) and no dementia risk (MMSE ≥27). We compared quartiles of milk and dairy intake with ANOVA. We also analysed the relationship using Pearson correlations models and linear regression models. We used four different models to study the link between milk and dairy products consumption and dementia, measured with the score provided by the MMSE questionnaire. In the first model, we analysed the global mean intake of milk and dairy products; in the second, we analysed fermented dairy product intake; in the third model we analysed whole-fat milk and dairy products consumption and in fourth model we analysed skimmed milk and dairy products consumption.

Binary logistic regression models were fitted to assess the relationship between dementia (by MMSE score) and milk and dairy product intake based on consumption of 100g and categorised by quartiles. Odds ratios and their 95% confidence intervals were calculated considering the lowest quartile as the reference category. To control for potential confounding factors, the results were adjusted for ten covariates that were known as potential risk or protective factors for cognitive decline and : age (years, continuous); gender (male or female); BMI (kg/m2, continuous); smoking habits (smoker and non-smoker); educational level (years of school, continuous); history of diabetes mellitus; history of high blood pressure, depression diagnosis, BDI-II score (absence-mild depression risk [score 0-19] or moderate-severe depression risk [score 20-63]), physical activity (measured by total caloric expenditure); and nutritional information adjusted by food groups (consumption of meat, fish, vegetables, fruits, dried fruits, alcohol). We constructed three adjusted models: Model 1: adjusted for gender, age and BMI. Model 2: adjusted for gender, age, BMI, smoking habit, years of school. Model 3: adjusted for gender, age, BMI, smoking habit, years of school, diagnosis of T2D, diagnosis of high blood pressure, diagnosis of depression, and moderate-high risk of depression assessed by the BDI-II. Model 4: adjusted for gender, age, BMI, smoking habit, years of school, diagnosis of T2D, diagnosis of high blood pressure, diagnosis of depression, and moderate-high risk of depression assessed by the BDI-II, physical activity (measured by total caloric expenditure). Model 5: adjusted for gender, age, BMI, smoking habit, years of school, diagnosis of T2D, diagnosis of high blood pressure, diagnosis of depression, and moderate-high risk of depression assessed by the BDI-II, physical activity, food groups (consumption of meat, fish, vegetables, fruits, dried fruits, alcohol).

RESULTS:

The mean age of the participants was 65 ± 4.9 years, 48.5% of whom were women. Of the total, 27.2% of the patients were diabetic, 69.3% had dyslipidaemia, 83.1% had high blood pressure, and 12.5% were smokers. Concerning the level of education attained, 47.7% had primary school studies or less, 28.9% had secondary studies and 22.1% were college graduates. Retirees accounted for 55.9%, and 20.8% were active workers. Prior to inclusion, 20.8% had a diagnosis of depression; 91% had a BDI-II score under 20, and 9% had a moderate to severe risk of depression (score 20-30). Regular physical activity was undertaken by 43.3% of the patients, while 52.6% had sedentary behaviour.

We calculated the percentage of patients according to their MMSE score to assess the degree of dementia: 5% scored between 10-24, 9% between 25-26, and 79.5% had no dementia (MMSE score 27-30). The baseline characteristics of the PREDIMED-Plus participants are shown in Table 1 according to quartiles of milk and dairy product intake. Those patients with a lower intake of milk and dairy products (<220 g/day: Q1) had a mean MMSE of 28.4 ±1.8 while subjects consuming more than ≥500 g/day (Q4) of milk and dairy products had a mean MMSE score of 28.0 ±2.1 $p<0.001$. Participants included in Q2 and Q3 had an MMSE score of 28.2 ±1.9. Supplementary Table 1 shows additional information regarding the fat content of the milk and dairy products, intake of fermented products and MMSE score according to quartiles of milk and dairy product consumption.

We studied the relationship between analytical parameters and the MMSE score; higher glucose levels were presented in those subjects with a lower MMSE score ($r = -0.042$, $p = 0.001$). When we analysed lipid profiles, a higher MMSE score was observed in subjects with higher triglycerides, total cholesterol and LDL cholesterol values ($r=0.039$, $p = 0.002$; $r = 0.025$, $p = 0.049$; $r = 0.026$, $p = 0.044$). Unexpectedly, HDL cholesterol showed an inverse relationship ($r = -0.055$, $p < 0.001$) with the MMSE score.

The relationship between overall milk and dairy product consumption and cognitive decline evaluated by the MMSE was analysed (Table 2). We found higher total milk and dairy product intake in subjects with lower MMSE scores. Those subjects who consumed more fermented dairy products had a lower MMSE score. Conversely, those who consumed a higher quantity of whole-fat milk and dairy products had a higher MMSE score. No statistically significant differences were found in the percentage of semi-skimmed and skimmed milk and dairy products between groups according to MMSE score (Table 2).

Total milk and dairy product intake showed a negative correlation with the MMSE score (r = -0.07, p < 0.000). We analysed our results dividing the participants according to the type of dairy products consumed. Correlation was found in the same way; fermented (r = -0.027, p = 0.032) vs non-fermented (r = -0.067, p < 0.001).

We divided subjects according to the fat content of the milk and dairy products. Intake of semi-skimmed and skimmed milk was higher in those participants with lower MMSE score (r = -0.031, p = 0.013 and r =- 0.027, p = 0.033, respectively), whereas intake of whole milk was more frequent in those subject with a higher MMSE score (r = 0.066, p < 0.001). Therefore, it may be postulated the fat provided by milk and dairy products could be related with higher cognitive function.

When we evaluated the possible implication of the overall consumption of milk and dairy products in the diet, we found that this was associated with a 10.5% increase in the odds of presenting dementia in the crude model (OR 1.105 [1.071-1.141), p < 0.001). This trend was also maintained in the adjusted models by the confounding variables (Table 3). Likewise, the consumption of fermented dairy products was also associated with an increase of 12.1% in the odds of presenting dementia in the crude model (OR 1.121 [1.042-1.205], p = 0.002), with this relationship being maintained in the adjusted models (Table 3). However, we found that whole-fat milk did not influence cognitive decline in either the crude model (OR 0.966 [0.935-1.062], p = 0.913) or the adjusted models (Table 3).

Multiple logistic regression analysis of the quartiles of total milk and dairy consumption revealed an increase in the odds of cognitive decline (evaluated by abnormal MMSE scores ≤26) in those patients with a higher intake (≥500 g/day: Q4) in the crude model (OR 1.612 [1.326-1.959], p<0.001), as well as in the models adjusted for the confounding variables (Table 4), versus subjects whose overall milk and dairy product intake was lower than <220 g/day: Q1 (Table 4).

We also performed a multiple logistic regression analysis of the quartiles of fermented dairy product consumption which showed that a higher consumption of fermented dairy products (Q4) was related to an increase of 34% in the odds of worse cognitive function in the crude model (OR 1.340 [1.106-1.625], p = 0.003). However, this possible association was not significant in the adjusted models (Table 5).

Multiple logistic regression analysis were also calculated dividing our population into quartiles according to their consumption of whole milk and dairy products (Table 6). A higher proportion of whole-fat milk and dairy products consumed (≥103 g/day: Q4) was significantly associated with a 24.9% decrease in the odds of cognitive impairment according to the MMSE in the crude model (OR 0.751 [0.623-0.906], p = 0.003), compared to subjects with a lower whole-fat milk and dairy product intake (≤18 g/day: Q1). However, this association was not significant in the adjusted models (Table 6). The moderate consumption of whole-fat milk and dairy (Q2 and Q3) gave higher protection against cognitive decline according to our results which were 31.1% and 33.7%, respectively (OR 0.689

[0.569-0.834], p<0.001 and OR 0.663 [0.547-0.804], p<0.001, respectively). This association continued in the adjusted models for Q2 moderate consumption. However, at higher doses this protection was lost due to other variables.

In addition, we examined the possible association between milk and dairy product intake and diagnosis of depression, according to the BDI-II. A higher proportion of diagnosis of depression was found with higher total milk and dairy intake ($p<0.001$, $r = 0.06$), and higher whole-fat milk and dairy product consumption was found in those participants with better scores on the BDI-II ($p = 0.042$, $r = -0.025$).

DISCUSSION:

This cross-sectional study showed a significant relationship between the intake of milk and dairy products and the prevalence of cognitive decline measured by the MMSE score. Our results indicated that those subjects that consumed higher milk and dairy product had the poorer cognitive function and an increase in the diagnosis of depression according to the BDI-II. Furthermore, the total consumption of fermented dairy products was also higher in those with worse MMSE scores indicating a higher prevalence of cognitive impairment. By contrast, those individuals who consumed whole-fat milk and dairy products had a lower prevalence of cognitive decline in our middle-aged Mediterranean population.

Our results regarding cognitive function and milk and dairy product intake are in line with recent studies conducted in other countries. Two prospective cohort studies (16, 17) investigating the associations between milk or dairy intake and cognitive functions among older male and female adults after 5 to 20 years of follow-up in France and in the U.S showed mixed results. One cohort study assessed milk intake using a FFQ (16), and the other evaluated total dairy and milk intake using a 24-h recall (17). They utilized different tools to assess cognitive function. The SU.VI.MAX 2 study (16) included a cohort of 3076 participants, 65.5 years of age at the time of neurocognitive evaluation, in which milk consumption was negatively associated with verbal and working memory performance. These results are consistent with results from the ARIC study (17) that suggested that greater milk intake during midlife may be associated with a greater rate of cognitive decline over a 20-year period.

Previous studies tried to explain the relationship between milk and dairy product constituents or specific ingredients and cognitive health and found contradictory results (11, 13, 14, 35, 36). They were grouped in the first meta-analysis by Wu et al. (15) which concluded that milk consumption (with or without other dairy products) was significantly associated with a lower risk of cognitive disorders but recognised several limitations due to heterogeneity in the characteristics of the subjects, categories and types of milk intake, and different dietary questionnaires and tools to diagnose age-related cognitive disorders.

The role of milk and dairy products in Asian populations deserves further investigation. Consumption patterns in Asian countries differ from those in Western countries, and Asian populations are known to consume less milk and dairy (35). The Hisayama study (36) concluded that milk and fermented dairy products reduce the risk of dementia in the general Japanese population, and the clinical trial by Ogata et al. (37) found that intake of dairy products was highly associated with better short-term memory. However, their results cannot be extrapolated to Caucasian subjects.

The most recent systematic review compiled information from previous studies. Results revealed that the current evidence was inadequate to draw a conclusion for the causal relationship between milk or dairy intake and cognitive decline or disorders in older adults (20). Our results could be in line with these studies. That systematic review conclusions were made based on included cohort studies that showed large clinical and methodological heterogeneity, hampering the comparability of the study findings, and adjusted for different sets of confounding factors in the statistical analyses.

Our comparison of the consumption of fermented dairy products with the prevalence of cognitive decline showed a higher prevalence of cognitive impairment in those subjects who consumed more fermented dairy products. Several epidemiological and clinical studies have concluded that fermented dairy products can help to prevent cognitive decline (35, 38). Camfield et al. (38) suggested, as a possible explanation, that certain bioactive peptides might be beneficial for promoting healthy brain function during ageing. Furthermore, intake of Camembert cheese prevents Alzheimer’s disease in a mouse model (19), and novel lactopeptides from digested fermented dairy products have been investigated (18). Although these studies suggest that a diet that includes fermented dairy products is beneficial in the prevention of the age-related cognitive decline, their observations were based on peptides whose active compounds responsible for the effect remain to be completely elucidated.

Finally, we found that subjects who consumed whole-fat milk and dairy products had a lower prevalence of cognitive decline according to their MMSE score. Our results are consistent with recent studies that propose certain dairy fatty products may be beneficial for diabetes, metabolic syndrome and cardiovascular diseases (30, 39-42). Interestingly, several recent larger prospective cohort studies including the Nurses’ Health Study (39, 40), Health Professionals Follow-Up Study (40), Multi Ethnic Study of Atherosclerosis (41, 42) and the Cardiovascular Health Study (42) have reported substantial beneficial effects of dairy fat products on diabetes prevention. Consequently, the effects of dairy fat and fatty acids found in dairy products on cardiovascular risk need to be further investigated. The findings from our study do not support an adverse association between dairy fat consumption and prevalent cognitive decline. Unexpectedly, low-fat dairy products, but not whole-fat milk and dairy, were found in those participants with greater cognitive decline. The description of dairy intake, including specific dairy products, average intakes, serving sizes, and fat content were widely reported in our study.

In relation to this theory, it has been postulated that phospholipids in the milk fat globule membrane (MFGM) might affect cognitive function (43). There are several possible reasons why the intake of MFGM could benefit cognitive function (44). First, MFGM contains high levels of choline derivatives (i.e., phosphocholine, glycerophosphocholine, phosphatidylcholine and sphingomyelin) (45). These compounds may play an important role in the development of the nervous system. Second, sphingomyelin metabolites are essential elements of the myelin sheath that covers the axons of neurons. Therefore, sphingomyelin metabolites support the myelination and production of neurotransmitters in the brain. Additionally, previous studies have suggested that dietary phospholipids are effective transporters of essential fatty acids that could improve brain health by lowering endoplasmic reticulum stress (46), which is known to increase the risk of neurodegenerative disorders such as Alzheimer's disease. Lastly, the solubility of phospholipids in brain cell membranes may enhance the neuroplasticity of the hippocampus and support dopamine and glutamate transmission (45).

A cohort study by Almeida et al. found that the regular full-cream milk consumption group demonstrated a significant decrease in successful mental health ageing compared with the rare consumption group (adjusted hazard ratio = 0.63; 95% CI: 0.45, 0.89) (13). A review by Crichton et al. (47) reported that individuals who consumed low-fat dairy products, including yoghurt and cheese, once a week had a higher cognitive function than those who did not. Subsequently, a survey-based study of self-reported health information undertaken in 2013 found that consumption of low-fat dairy products was associated with increased memory recall, increased social functioning, and decreased stress (35, 36).

High dietary intakes of saturated fat have been associated with an increased risk of impaired cognitive function in middle-aged people in elderly populations in both cross-sectional and prospective studies (48, 49). Saturated fat may provide the link between stress and depression, intake of high-fat dairy products, and risk of cognitive decline in the CAIDE study (50). Nevertheless, these studies were conducted taking into account total dietary fat intake, and no results centred on whole-fat milk and dairy products were analysed.

Our findings could be related to the modification in the proportion of energy substrates of the diet (fat / carbohydrates) and its possible repercussion at the level of the nervous system. However, these are controversial aspects in the literature, and more research is required in this regard.

Methodological Considerations/Limitations

Given that our study was cross-sectional it was not possible to determine the cause and effect of milk and dairy product consumption on cognitive function. We cannot be sure of the causal direction of these relationships; however, the findings warrant further research exploring milk and dairy products and cognition.

Our study has some considerations that should be taken into account. Self-reported nutritional intake can lead to underestimation or overestimation of true associations, and measurement at only one point may not reflect long-term consumption patterns. Mild cognitive impairment has been shown to attenuate the validity of FFQs when comparing to biomarkers of nutrient intake (51). Poor cognitive ability was associated with suspected recall errors on the FFQ. These limitations are likely to have introduced some misclassification of food intake. We attempted to control for potential confounding variables, adjusted for gender, age, BMI and other related variables.
In light of the limitations in this study, we propose that future research should use biomarkers in order to overcome the limitations of self-reported dietary assessments and standardized assessment tools for cognitive function to identify causal inferences.

As with any health research, often people who are more health conscious are those who are interested in volunteering to participate. In addition, it was not possible to delineate the exact mechanism behind the associations or to exclude a more beneficial lifestyle pattern in whole-fat milk consumers.

Concerning the test administered, the MMSE, the extent of its usefulness has been questioned, especially for milder forms of cognitive impairment. It has also been found that age and education account for 12% of the variance in MMSE scores. Moreover, we do not know whether milk and dairy intake is associated with established dementia, since patients who had dementia at baseline were excluded from the study. To date, however, the number of studies evaluating cognitive function and milk consumption has been too small to allow a conclusive evaluation of the effect, and thus further investigations are needed.

CONCLUSIONS:

We concluded that extensive consumption of milk and dairy products was found in those subjects with worse cognitive function. Higher milk and dairy intake were found in participants with lower MMSE scores. Conversely, whole-fat milk and dairy product intake may play a protective role in cognitive impairment, as higher consumers had better results in MMSE.

Examining the potential biological mechanisms linking dietary consumption and cognitive outcomes in large cohort studies will be critical to understanding the link between milk and dairy intake and multiple outcomes. These results can generate new hypotheses to guide future research. Diet is a modifiable factor that could be considered an appropriate intervention area to optimise cognitive health and well-being throughout life.

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A.M-G and F.J.T designed research, A.M-G, I.C.P, and F.J.T wrote the manuscript. A.M-G, JC.F-G and MR.B-L conducted research; JC.F-G and I.C-P analyzed data; A.M-G had primary responsibility for final content.

Conflicts of Interest

The authors declare no conflict of interest.

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Figure.

Figure 1. Flow chart diagram of the selection patients in our analysis.

6874 possible participants (in 23 Spanish centres) between the years 2013 to 2016.

130 participants did not completed a 146-item food frequency questionnaire with data on milk and dairy product consumption and were excluded

6744 participants were evaluated by their data on milk and dairy product consumption

318 patients more that did not completed MMSE questionnaire or those patients with a score of 10 or less were excluded from the analysis.

6426 participants included (those who have completed the MMSE questionnaire validated for the Spanish population and food frequency questionnaire).

The diagram shows the selection patients process for our study.

TABLES

Table 1. Baseline Characteristics of the participants from the PREDIMED-PLUS trial according to Quartiles of Milk and Dairy product intake.

VARIABLES	Milk and dairy product intake <220 g/day (Q1) (n = 1669)		Milk and dairy product intake 221-307 g/day (Q2) (n = 1688)		Milk and dairy product intake 308-499 g/day (Q3) (n = 1688)		Milk and dairy product intake ≥500 g/day (Q4) (n = 1699)		p
	MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD	
Age (years)	64.6	5.0	64.7	4.9	65.1	4.9	65.4	4.9	<0.001
Female gender (%)	40.9		44.5		51.3		57.0		<0.001
Weight (Kg)	87.7	13.0	86.7	12.9	86.4	13.0	85.7	12.8	<0.001
Waist circumference (cm)	108.2	9.7	107.7	9.6	107.2	9.7	107.2	9.7	0.010
Hip circumference (cm)	109.7	8.1	109.6	8.3	110.1	8.8	110.7	8.7	0.001
BMI (Kg/m2)	32.6	3.4	32.5	3.4	32.6	3.5	32.6	3.5	0.839
Educational level (years)	11.8	5.6	11.2	5.2	11.3	5.3	11.0	5.4	<0.001
Smokers (%)	14.6		13.7		10.9		10.6		<0.001
Former Smokers (%)	48.0		44.3		43.6		38.3		<0.001
Time smoking (years)	37.1	12.9	36.6	12.8	37.4	11.7	38.2	12.4	0.643
Cigarette smoking (pack-years)	23.9	20.1	25.1	21.2	19.3	18.8	26.1	21.8	0.016
Total energy intake (Kcal/day)	2227.9	572.0	2336.1	585.3	2461.3	607.1	2606.4	680.3	<0.001

Vegetables (g/day)	316.9	135.0	316.5	139.6	332.6	136.1	338.9	147.1	<0.001
Fruits (g/day)	333.2	210.8	349.7	205.8	366.4	197.3	387.6	219.6	<0.001
Legumes (g/day)	19.9	11.3	20.1	10.2	21.2	11.4	21.6	11.7	<0.001
Grains (g/day)	146.3	83.7	151.9	81.0	151.0	80.2	164.6	87.1	<0.001
Meats and subproducts (g/day)	142.8	60.9	148.7	58.3	151.2	58.0	148.6	63.7	0.001
Fish (g/day)	99.3	47.0	99.2	46.0	106.1	47.2	101.4	49.3	<0.001
Dried fruits (g/day)	15.2	18.2	14.2	16.8	16.1	18.7	15.5	18.1	0.017
Olive oil (g/day)	41.0	17.4	40.6	17.0	40.1	16.7	39.1	17.5	0.009
Alcohol (g pure alcohol)	13.7	17.5	12.5	16.7	10.6	13.8	7.9	12.0	<0.001
Vitamin D (mcg/day)	5.9	3.4	6.0	3.3	6.5	3.5	6.2	3.5	<0.001
Calcium (mg/day)	712.2	202.8	913.0	184.9	1101.2	246.6	1446.0	321.0	0.891
Carbohydrates (%)	39.5	7.3	40.4	6.7	40.6	6.5	43.2	6.3	<0.001
Proteins (%)	15.7	2.8	16.3	2.6	16.8	2.6	17.3	2.8	<0.001
Total fat (%)	40.7	7.0	39.9	6.5	39.7	6.1	37.5	6.2	<0.001
MMSE score	28.4	1.8	28.2	1.9	28.2	1.9	28.0	2.1	<0.001

Glucose (mg/dL)	113.4	28.7	113.4	27.6	111.4	27.6	115.3	32.2	0.002
Triglycerides (mg/dL)	157.7	87.6	153.1	78.4	148.7	74.6	150.3	75.0	0.006
Total cholesterol (mg/dl)	197.9	38.7	196.4	37.5	197.6	37.9	196.8	37.1	0.644
HbA1c (%)	6.08	0.9	6.09	0.8	6.06	0.8	6.22	1.0	<0.001

Data are presented as mean ± SD unless otherwise indicated.

Abbreviations: BMI, Body mass index; HDL-c, High-density lipoprotein cholesterol; MMSE, Mini-Mental State Examination; SD, standard deviation

Table 2. Milk and dairy product consumption according to MMSE score.

VARIABLES	MMSE 10-24 n = 343		MMSE 25-26 n = 616		MMSE 27-30 n = 5467		P
	MEAN	SD	MEAN	SD	MEAN	SD	
MMSE score	22.5	1.8	25.6	0.5	28.8	1.0	<0.001
Total milk and dairy products (g)	395.1	225.4	380.5	215.4	341.2	201.0	<0.001
Fermented dairy products (g)	123.0	102.6	114.5	91.3	107.7	88.4	0.003
Non-fermented dairy products (g)	272.2	190.9	266.0	188.4	233.4	176.4	<0.001
Whole-milk and dairy products (%)	23.8	29.5	25.0	29.2	29.7	31.4	<0.001
Semi-skimmed milk and dairy products (%)	33.0	34.6	31.4	34.3	30.0	33.7	0.189
Skimmed milk and dairy products (%)	43.3	37.6	43.6	38.1	40.3	37.9	0.060

Abbreviations: MMSE, Mini-Mental State Examination; SD, standard deviation

Table 3. Adjusted models for cognitive decline screening (abnormal MMSE test)

	Cognitive decline screening (MMSE)							
	Milk and dairy products global consumption /100 g		Fermented dairy products /100 g		Whole fat milk and dairy products/100 g		Skimmed milk and dairy products/100 g	
	OR (CI)	p	OR (CI)	p	OR (CI)	p	OR (CI)	p
Crude model	1.105 (1.071-1.141)	<0.001	1,121 (1.042-1.205)	0.002	0.966 (0.935-1.062)	0.913	1.244 (1.038-1.491)	0.018
Model 1	1.086 (1.051-1.123)	<0.001	1.085 (1.006-1.171)	0.034	1.052 (0.987-1.120)	0.118	1.078 (0.894-1.299)	0.432
Model 2	1.085 (1.047-1.124)	<0.001	1.107 (1.021-1.201)	0.014	1.038 (0.970-1.110)	0.281	1.175 (0.963-1.434)	0.112
Model 3	1.085 (1.046-1.125)	<0.001	1.108 (1.020-1.204)	0.015	1.042 (0.973-1.116)	0.234	1.167 (0.953-1.429)	0.136
Model 4	1.086 (1.047-1.126)	<0.001	1.103 (1.015-1.198)	0.021	1.045 (0.976-1.119)	0.203	1.157 (0.945-1.418)	0.159
Model 5	1.084 (1.045-1.124)	<0.001	1.099 (1.010-1.195)	0.029	1.047 (0.978-1.122)	0.186	1.142 (0.931-1.401)	0.204

Binary logistic regression analysis: Odds ratio (OR) and 95% confidence interval (CI) for the association between cognitive impairment associated with overall consumption 100 gr of milk and dairy products, fermented dairy products, whole-fat milk and dairy products and skimmed milk and dairy products in the PREDIMED-PLUS trial. An abnormal MMSE questionnaire was defined as a score ≤26 points. Dependent variable: cognitive decline screening - MMSE score between 27-30 points (0) vs. MMSE score ≤26 points (1).

Model 1: adjusted for gender, age and BMI.

Model 2: additionally adjusted for smoking habit, years of school.

Model 3: additionally adjusted for diagnosis of T2D, diagnosis of high blood pressure, diagnosis of depression and moderate to high risk of depression assessed by the BDI-II.

Model 4: additionally adjusted for physical activity (measured by total caloric expenditure)

Model 5: additionally adjusted for food groups (consumption of meat, fish, vegetables, fruits, dried fruits, alcohol).

Abbreviations: MMSE, Mini-Mental State Examination; OR, odds ratio; CI: confidence interval.

Table 4. Adjusted models for cognitive decline screening (abnormal MMSE test) – Milk and dairy product intake in quartiles

	Cognitive decline screening (MMSE)						
	Q1	Q2		Q3		Q4	
	Milk and dairy intake <220 g/day	Milk and dairy intake 221-307 g/day		Milk and dairy intake 308-499 g/day		Milk and dairy intake ≥500 g/day	
		OR (CI)	p	OR (CI)	p	OR (CI)	p
Crude model	1.0 (ref)	1.119 (0.911-1.376)	0.285	1.216 (0.992-1.490)	0.059	1.612 (1.326-1.959)	<0.001
Model 1	1.0 (ref)	1.099 (0.891-1.356)	0.379	1,106 (0.899-1.361)	0.342	1.399 (1.145-1.709)	0.001
Model 2	1.0 (ref)	0.994 (0.796-1.240)	0.956	1.093 (0.878-1.360)	0.427	1.305 (1.055-1.614)	0.014
Model 3	1.0 (ref)	1.010 (0.806-1.266)	0.929	1.121 (0.897-1.402)	0.314	1.316 (1.059-1.635)	0.013
Model 4	1.0 (ref)	1.010 (0.806-1.265)	0.932	1.109 (0.887-1.386)	0.366	1.321 (1.062-1.642)	0.012
Model 5	1.0 (ref)	1.011 (0.807-1.268)	0.921	1.104 (0.882-1.382)	0.386	1.308 (1.051-1.628)	0.016

Binary logistic regression analysis: Odds ratio (OR) and 95% confidence interval (CI) for the association between cognitive impairment and overall consumption of milk and dairy products (categorised by quartiles) in the PREDIMED-PLUS trial. An abnormal MMSE questionnaire was defined as a score ≤26 points. Dependent variable: cognitive decline screening - MMSE score between 27-30 points (0) vs. MMSE score ≤26 points (1).

Model 1: adjusted for gender, age and BMI.

Model 2: additionally adjusted for smoking habit, years of school.

Model 3: additionally adjusted for diagnosis of T2D, diagnosis of high blood pressure, diagnosis of depression and moderate to high risk of depression assessed by the BDI-II.

Model 4: additionally adjusted for physical activity (measured by total caloric expenditure)

Model 5: additionally adjusted for food groups (consumption of meat, fish, vegetables, fruits, dried fruits, alcohol).

Abbreviations: MMSE, Mini-Mental State Examination; OR, odds ratio; CI: confidence interval.

Table 5. Adjusted models for cognitive decline screening (abnormal MMSE test) - Fermented product intake in quartiles.

	Cognitive decline screening (MMSE)						
	Q1	Q2		Q3		Q4	
	Fermented ≤46 g/day	Fermented 47-86 g/day		Fermented 87-145 g/day		Fermented ≥146 g/day	
		OR (CI)	p	OR (CI)	p	OR (CI)	P
Crude model	1.0 (ref)	1.167 (0.955-1.425)	0.131	1.107 (0.902-1.359)	0.330	1.340 (1.106-1.625)	0.003
Model 1	1.0 (ref)	1.157 (0.943-1.419)	0.162	1,006 (0.815-1.240)	0.959	1.205 (0.989-1.468)	0.064
Model 2	1.0 (ref)	1.133 (0.913-1.407)	0.256	1.021 (0.818-1.274)	0.853	1.241 (1.007-1.529)	0.043
Model 3	1.0 (ref)	1.115 (0.896-1.389)	0.330	1.020 (0.814-1.278)	0.865	1.228 (0.992-1.519)	0.059
Model 4	1.0 (ref)	1.112 (0.893-1.385)	0.344	1.010 (0.805-1.266)	0.933	1.215 (0.982-1.504)	0.073
Model 5	1.0 (ref)	1.106 (0.887-1.378)	0.371	1.003 (0.799-1.259)	0.977	1.200 (0.967-1.489)	0.099

Binary logistic regression analysis: Odds ratio (OR) and 95% confidence interval (CI) for the association between cognitive impairment associated with fermented dairy product consumption (categorised by quartiles) in the PREDIMED-PLUS trial. An abnormal MMSE questionnaire was defined as a score ≤26 points. Dependent variable: cognitive decline screening - MMSE score between 27-30 points (0) vs. MMSE score ≤26 points (1).

Model 1: adjusted for gender, age and BMI.

Model 2: additionally adjusted smoking habit, years of school.

Model 3: additionally adjusted for diagnosis of T2D, diagnosis of high blood pressure, diagnosis of depression and moderate to high risk of depression assessed by the BDI-II.

Model 4: additionally adjusted for physical activity (measured by total caloric expenditure)

Model 5: additionally adjusted for food groups (consumption of meat, fish, vegetables, fruits, dried fruits, alcohol).

Abbreviations: MMSE, Mini-Mental State Examination; OR, odds ratio; CI: confidence interval.

Table 6. Adjusted models for cognitive decline screening (abnormal MMSE test) – Whole-fat milk and dairy products in quartiles.

Cognitive decline screening (MMSE)							
	Q1	Q2		Q3		Q4	
	Whole-fat milk and dairy products ≤18 g/day	Whole-fat milk and dairy products 19-39 g/day		Whole fat-milk and dairy products 40-102 g/day		Whole-fat milk and dairy products ≥103 g/day	
		OR (CI)	p	OR (CI)	p	OR (CI)	P
Crude model	1.0 (ref)	0.689 (0.569-0.834)	<0.001	0.663 (0.547-0.804)	<0.001	0.751 (0.623-0.906)	0.003
Model 1	1.0 (ref)	0.725 (0.597-0.882)	0.001	0.739 (0.607-0.900)	0.003	0.905 (0.746-1.098)	0.313
Model 2	1.0 (ref)	0.757 (0.616-0.931)	0.008	0.811 (0.657-1.000)	0.050	0.911 (0.741-1.120)	0.376
Model 3	1.0 (ref)	0.748 (0.605-0.925)	0.007	0.837 (0.676-1.036)	0.101	0.919 (0.745-1.134)	0.431
Model 4	1.0 (ref)	0.756 (0.612-0.934)	0.010	0.843 (0.681-1.044)	0.118	0.932 (0.755-1.150)	0.511
Model 5	1.0 (ref)	0.753 (0.608-0.932)	0.009	0.841 (0.678-1.044)	0.117	0.934 (0.756-1.155)	0.530

Binary logistic regression analysis: risk (odds ratio (OR) of cognitive decline associated with whole-fat milk and dairy product consumption categorised by quartiles. An abnormal MMSE questionnaire was defined as a score ≤ 26 points. Dependent variable: cognitive decline screening - MMSE score between 27-30 points (0) vs. MMSE score ≤26 points (1).

Model 1: adjusted for gender, age and BMI.

Model 2: additionally adjusted for smoking habit, years of school.

Model 3: additionally adjusted for diagnosis of T2D, diagnosis of high blood pressure, diagnosis of depression and moderate to high risk of depression assessed by the BDI-II.

Model 4: additionally adjusted for physical activity (measured by total caloric expenditure)

Model 5: additionally adjusted for food groups (consumption of meat, fish, vegetables, fruits, dried fruits, alcohol).

Abbreviations: MMSE, Mini-Mental State Examination; OR, odds ratio; CI: confidence interval.

SUPPLEMENTARY MATERIAL

Supplementary Table 1. Fat content of milk and dairy products, fermented product intake and MMSE score according to Quartiles of milk and dairy product consumption.

Data are presented as mean ± SD unless otherwise indicated.

VARIABLES	Q1		Q2		Q3		Q4		p
	Milk and dairy intake <220 g/day		Milk and dairy intake 221-307 g/day		Milk and dairy intake 307-499 g/day		Milk and dairy intake ≥500 g/day		
	MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD	
Total milk and dairy products (g)	125.9	64.5	263.4	24.4	364.6	40.3	641.8	143.4	<0.001
Fermented milk products (g)	62.5	50.7	71.4	44.4	152.9	69.3	149.8	124.1	<0.001
Non-fermented milk products (g)	63.4	65.6	192.1	42.4	211.7	65.7	492.0	152.6	<0.001
Whole dairy proportion (%)	44.8	36.1	25.6	28.6	27.9	27.1	17.1	25.3	<0.001
Semi-skimmed dairy proportion (%)	23.6	30.4	35.5	36.2	26.6	26.9	34.8	38.8	<0.001
Skimmed dairy proportion (%)	31.6	35.3	28.9	38.2	45.5	34.6	48.1	41.2	<0.001
MMSE score	28.4	1.8	28.2	1.9	28.2	1.9	28.0	2.1	<0.001

Abbreviations: MMSE, Mini-Mental State Examination; SD, standard deviation.