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Dairy Product Consumption and Changes in Cognitive Performance: Two-Year Analysis of the PREDIMED-Plus Cohort

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Scope: Dairy consumption has been suggested to impact cognition; however, evidence is limited and inconsistent. This study aims to longitudinally assess the association between dairy consumption with cognitive changes in an older Spanish population at high cardiovascular disease risk.

Methods and results: Four thousand six hundred sixty eight participants aged 55–75 years, completed a validated food frequency questionnaire at baseline and a neuropsychological battery of tests at baseline and 2-year follow-up. Multivariable linear regression models are used, scaled by 100 (i.e., the units of β correspond to 1 SD/100), to assess associations between baseline tertile daily consumption and 2-year changes in cognitive performance. Participants in the highest tertile of total milk and whole-fat milk consumption have a greater decline in global cognitive function (β: –4.71, 95% CI: –8.74 to –0.69, *p*-trend = 0.020 and β: –6.64, 95% CI: –10.81 to –2.47, *p*-trend = 0.002, respectively) compared to those in the lowest tertile. No associations are observed between low fat milk, yogurt, cheese or fermented dairy consumption, and changes in cognitive performance.

Conclusion: Results suggest there are no clear prospective associations between consumption of most commonly consumed dairy products and cognition, although there may be an association with a greater rate of cognitive decline over a 2-year period in older adults at high cardiovascular disease risk for whole-fat milk.

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1. Introduction

As the population ages, the rise in the global prevalence of cognitive impairment, including dementia, is an increasingly major public health concern.[1] Cognitive decline refers to the attenuation in cognitive function which encompasses the mental processes such as attention, short-term and long-term memory, reasoning, coordination of movement and planning of tasks, that are crucial for the conduct of daily living activities.[1,2] The concept of cognitive decline ranges from minimal age-related cognitive decline to mild cognitive impairment to dementia, which is the most severe cognitive impairment, as the final stage of this dysfunction.[3,4] Worldwide, at least 55 million people are living with dementia, and it is predicted that by 2050 over 139 million people will be affected.[5] In Spain, more than 800 000 people are living with Alzheimer's disease, which is the most frequent cause of dementia.[6]

Faster rates of cognitive decline may lead to earlier onset of cognitive impairment and dementia.[2] This is concerning as there is a diverse etiology and, mainly due to limited long-term evidence, factors affecting cognitive function are poorly understood.[1,2] Furthermore, effective treatments to cure cognitive disorders or to slow the rate of cognitive decline are still not available.[1] For that reason, prevention strategies targeting modifiable risk factors, such as nutritional intake and dietary habits, remain a promising approach.[3,4]

Milk and other dairy product consumption may play an important role in the prevention of age-related cognitive decline and dementia.[7–9] Previous studies have suggested that phospholipids in the milk fat globule membrane (MFGM) may explain the possible biological mechanisms linking milk and other types of dairy consumption to cognitive function.[4] Additionally, various researchers have demonstrated that nutrients found in dairy products may exert beneficial effects directly or indirectly on cognitive function, including whey protein, bioactive peptides, α-lactalbumin, vitamin B12, and calcium.[9] The actions of probiotics contained in fermented dairy products modulating gut microbiota may also impact cognitive function.[7,9,10]

However, findings from a limited number of epidemiological studies investigating the association between dairy product

consumption and cognitive function remain inconsistent with high heterogeneity, and most are cross-sectional in design.[11–16] Therefore, to investigate the association between dairy consumption and cognitive function, longitudinal studies exploring the associations between milk and specific types of dairy products with cognitive performance are needed.[13]

Based on the aforementioned potential mechanisms and evidence to date, in the present study we hypothesized that milk and dairy product consumption may help in delaying cognitive decline and maintaining cognitive functioning during aging. Thus, to test this hypothesis, the aim was to assess the short-term longitudinal associations between milk and dairy product consumption overall and by subcategories (e.g., fat content, fermented, or nonfermented), with subsequent changes over a 2-year follow-up in cognitive performance in an older Spanish population at high cardiovascular disease risk.

2. Experimental Section

2.1. Study Design and Participants

The present study was conducted within the framework of the PREDIMED-Plus study, a randomized, parallel-group, 6-year multicenter, controlled clinical trial designed to assess the effect of lifestyle interventions on the primary prevention of cardiovascular disease (n = 6874). A more detailed description and the study protocol was available at https://www.predimedplus.com/ and elsewhere.[17] The study was registered with the International Standard Randomized Controlled Trial registry in 2014 (ISRCT; http://www.isrctn.com/ISRCTN89898870). Eligible participants were community-dwelling adults (55–75 years) with overweight or obesity (BMI: 27–40 kg m^{-2}) who met at least three criteria for metabolic syndrome,[18] without cardiovascular or neurodegenerative diseases at baseline. From October 2013 to December 2016, participant recruitment was conducted in 23 Spanish health centers. A total of 6874 participants who met eligibility criteria were randomly allocated in a 1:1 ratio to the intensive diet and lifestyle intervention group or to the usual care control group, using a centrally controlled, computer-generated random-number internet-based system with stratification by center, sex, and age. Couples sharing the same household were randomized together, using the couple as a unit of randomization. The randomization procedure was blinded to all staff and principal investigators of each recruitment center. The participant recruitment and randomization procedures have been previously described elsewhere.[17] All participants provided written informed consent and institutional review boards of each participating center approved the final protocol and procedures.

In the present study, baseline and 2-year follow-up data from the PREDIMED-Plus trial participants was analyzed as an observational prospective cohort. Participants without completed cognitive tests at baseline (n = 1163) and 2-year follow-up (n = 816), or without a completed Food Frequency Questionnaire (FFQ) which included the dairy product items at baseline (n = 36), or who had energy intake levels outside of prespecified limits (daily energy intakes for men <800 kcal or >4000 kcal and women <500 kcal or >3500 kcal) (n = 191) were excluded.[19]

Table 1. Description of the dairy product groups utilized.

Dairy product group	Included dairy products
Total dairy	All types of milk
	– Whole-fat milk
	– Semi-skimmed milk
	– Skimmed milk
	All types of yogurt
	– Whole-fat yogurt
	– Skimmed yogurt
	All types of cheese
	– Petit-suisse
	– Ricotta and cottage cheese
	– Cream cheese
	– Semi-cured and cured cheese, such as Cheddar, Manchego, and Emmental
	– Fresh cheese
Classified by fat content	
Low-fat dairy	Semi-skimmed, skimmed milk, and skimmed yogurt
Whole-fat dairy	Whole-fat milk, whole-fat yogurt, and all types of cheese
Fermented versus Non-fermented	
Fermented dairy	All types of yogurt and cheese
Non-fermented dairy	All types of milk

2.2. Dietary Assessment

At baseline, a validated 17-item energy-restricted Mediterranean Adherence Screener,[20] and a 143-item validated semiquantitative FFQ[21] specifying usual portion sizes, were administered by trained dietitians to assess habitual dietary intake. The FFQ contained 16 items related to dairy products with nine possible frequency categories, which ranged from "never or almost never" to ">6 portions/day." However, based on the dietary guidelines for the Spanish population[22] and dairy-related recommendations, dairy products such as condensed milk, cream, milkshakes, custard, ice-cream, and butter were not included in the analysis. In the present study, total dairy products included all types of milk, yogurt, and cheese. Dairy food consumption was further categorized into dairy subtypes: low-fat dairy, whole-fat dairy, fermented, and nonfermented dairy (**Table 1**). The information collected was converted into grams per day, multiplying portion sizes by consumption frequency and dividing the result by the period assessed. Food groups and energy intake were estimated using Spanish food composition tables.[23,24]

2.3. Assessment of Cognitive Performance

An extensive neuropsychological battery of tests assessing different cognitive domains was administered at baseline and 2-year follow-up by trained staff to assess cognitive performance, which included the following tests: the Mini–Mental State Examination (MMSE), Verbal Fluency Tests (VFTs), Digit Span Tests (DSTs) of the Wechsler Adult Intelligence Scale-III (WAIS-III), the Clock Drawing Test (CDT), and Trail Making Tests (TMTs).

Briefly, a Spanish validated version of the MMSE questionnaire, a commonly used cognitive screening test, was used in the present analysis. A higher MMSE score indicated better cognitive performance.[25,26] Verbal ability and executive function were evaluated using the VFTs, which consisted of two parts: the semantic verbal fluency task-animal category version (VFT-a), and the phonemic verbal fluency task-letter "p" version (VFT-p).[27] The DST of the WAIS-III Spanish version assessed attention and memory. The DST forward recall (DST-f), being representative of attention and short-term memory capacity, and the DST backward recall (DST-b), considered as a test of working memory capacity.[28,29] The CDT validated Spanish version was mainly used to evaluate visuospatial and visuo-constructive capacity.[30–32] Lastly, the TMT, another tool often used to assess executive function, consists of two parts. Part A (TMT-A) assessed attention and processing speed capacities, and part B (TMT-B) further examined cognitive flexibility.[33] All instruments included in the cognitive battery had been standardized for the Spanish population in the age range of the study population.

2.4. Covariate Assessment

Socio-demographic (sex, age, education level, and civil status) and lifestyle (physical activity, smoking habits, and consumption of specific food groups) related variables, as well as information about medication use, were collected at baseline by trained staff in face-to-face interviews using self-reported general questionnaires. Personal history of illness (type 2 diabetes, hypertension, and hypercholesterolemia) was self-reported or collected from patient medical records. Weight and height were measured by trained staff using calibrated scales and wall-mounted stadiometers, respectively. BMI was calculated as weight in kilograms divided by height in meters squared. Waist circumference was measured at the midway point between the lowest rib and the iliac crest. Leisure-time physical activity was estimated using the validated short Spanish version of the Minnesota Leisure Time Physical Activity Questionnaire.[35] Intake of dietary factors, including vegetables, fruits, legumes, cereals, nuts, olive oil, meat, and fish, were determined via a validated 143-item semiquantitative FFQ.[21] Depressive symptomatology was evaluated using the Beck Depression Inventory-II (BDI-II), where depressive symptomatology risk was established as a score ≥14.[36]

2.5. Statistical Analyses

For the present analyses, the PREDIMED-Plus database updated to December 22, 2020, was used. Participants were categorized into tertiles according to total dairy and different subtypes of dairy product consumption, adjusted for baseline total energy intake using the residual method.[19,37,38] Baseline characteristics of participants for each tertile of energy-adjusted total dairy product consumption were presented as numbers and percentages using the Pearson's chi-square test for categorical variables and means ± standard deviations (SD) or median (interquartile range [P25–P75]) using one-way ANOVA or Kruskal–Wallis test for continuous variables, as appropriate.

To assess cognitive function a global cognitive function (GCF) score was determined as the main outcome measure, in addition to evaluating the individual neuropsychological tests (supplementary analyses). Cognitive change was presented as the 2-year changes in GCF *z*-score, as well as 2-year changes in individual test *z*-scores, which were calculated by subtracting each participant's test score at year 2 from the mean score at baseline and dividing by the SD of the baseline mean value.[39,40] GCF was calculated as a composite *z*-score of all eight assessments, adding or subtracting each individual test value based on whether a higher score indicated higher or lower cognitive performance, respectively, using the formula: GCF = (zMMSE + zCDT + zVFT-a + zVFT-p + (–zTMT-A) + (–zTMT-B) + zDST-f + zDST-b)/8.[41] Following this, GCF was further restandardized to baseline using the mean and SD of the global *z*-score at baseline. In this way, a *z*-score of −1 would describe cognitive performance at year 2 that was 01 SD below the mean score at the baseline visit.[39]

Multivariable linear regression models were fitted, to assess longitudinal associations comparing 2-year changes in cognitive function across tertiles of baseline per 100 g of dairy product consumption. AMultivariable linear regression models were adjusted for several potential confounders. Model 1 adjusted for age (years), sex, intervention group, participating center size (<100, 100 to <200, 200 to <300, ≥300 participants), and respective baseline cognitive function score. Model 2 was additionally adjusted for BMI (kg m^{-2}), educational level (primary, secondary, or college), civil status (single, divorced or separated, married, widower), physical activity (METs min^{-1} day^{-1}), smoking habit (current, former, or never), alcohol consumption in g day^{-1} (and adding the quadratic term), depressive symptomatology (yes/no), diabetes prevalence (yes/no), hypertension (yes/no), hypercholesterolemia (yes/no). Finally, Model 3 was further adjusted for dietary factors (consumption of vegetables, fruits, legumes, cereals, nuts, oils and fats, biscuits, meat, fish [g day^{-1}], coffee, and tea [mL day^{-1}]). To assess the linear trend, the median value of each tertile of exposure variables (total dairy and different subtypes of dairy product consumption) was assigned to each participant and was modeled as continuous variables in linear regression models. All analyses were conducted with robust estimates of the variance to correct for intracluster correlation.

In addition, sex-stratified regression approaches were employed to examine relationships between these dairy products consumption categories and 2-year changes in global cognitive function. Several sensitivity analyses were additionally performed to test the robustness of the findings. First, removal of participants with baseline MMSE <24 (mild dementia and poorer).[42] Second, removal of participants with extreme GCF *z*-scores at baseline (<5% and >95%).

The data were analyzed using the Stata 14 software program (StataCorp LP, TX, USA) and statistical significance was set at a two-tailed p value <0.05.

3. Results

A total of 4668 participants (mean age 65.0 ± 4.9 years and 48.1% women) were included in the final sample for the analysis of GCF (**Figure 1**). **Table 2** presents the baseline characteristics of the study population according to energy-adjusted tertiles of total dairy product consumption. The median (interquartile range, [IQR]) consumption of total dairy products from the lowest to the highest tertile was 148 (78, 213), 282 (253, 325), and 546 (408,

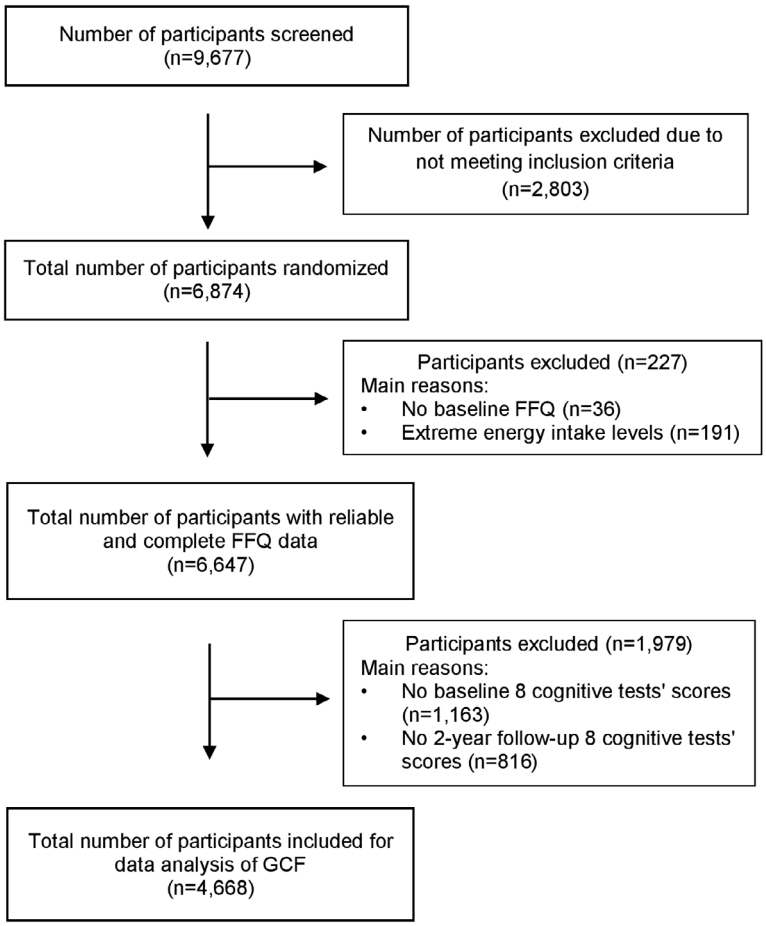

Figure 1. Flow of the participants for the analysis of the association between dairy product consumption and global cognitive function in the PREDIMED-Plus study. FFQ indicates food frequency questionnaire; GCF, global cognitive function.

617) g per day. Compared with the participants in the lowest tertile of total dairy product consumption, those in the highest tertile were more likely to be older and women, with higher prevalence of type 2 diabetes, hypercholesterolemia, and respective medication use, as well as with greater depressive symptomatology. Additionally, they had lower educational attainment with a lower GCF z-score at baseline, and they were less likely to partake in physical activity in their leisure time, compared with participants in the lowest tertile. However, participants with the highest consumption of total dairy products were less likely to smoke and showed better adherence to the Mediterranean diet with higher intake of fruits, coffee and tea, greater consumption of protein and carbohydrates, and less intake of meat, alcohol, total oil, and fats. We observed no relevant differences in body mass index or waist circumference according to energy-adjusted consumption of total dairy products.

Table 3 shows the unadjusted and multiadjusted β-coefficients (95% CIs) per 100 g of dairy products for the changes in GCF *z*-score over the 2-year follow-up across tertiles of total dairy consumption and intake of specific subtypes of dairy products. Results of the linear regression analyses suggest the presence of an association between milk consumption, in particular whole-fat milk intake, with cognitive decline over a 2-year period. The response was graded across tertiles of total milk and whole-fat milk consumption. Participants with the highest total milk consumption presented with a 4.71-point decline (β: –4.71; 95% CI: –8.74 to –0.69; p for trend = 0.020) in GCF per 100 g of milk intake over a 2-year period compared with those who in the tertile reporting the lowest milk consumption. Of the subtypes of milk, we observed that higher whole-fat milk consumption was significantly associated with greater cognitive decline, as assessed by GCF *z*-score. The difference in the 2-year change in GCF *z*-score between those who had the highest whole-fat milk consumption and those in the lowest tertile of intake was –6.64 (95% CI: –10.81 to –2.47; p for trend = 0.002), equivalent to a decline of 6.64 points per 100 g of whole-fat milk intake. When each neuropsychological test was investigated separately, participants in the highest tertile of total milk consumption were observed to have a greater decline in cognition than those in the lowest tertile when evaluated by MMSE (β: –5.76; 95% CI: –11.13 to –0.40; p for trend = 0.041) and VFT-a (β: –7.06; 95% CI: –12.26 to –1.86; p for trend = 0.006) (Table S1, Supporting Information). Similarly, participants in the highest compared to lowest tertiles of whole-fat milk consumption showed greater cognitive decline when assessed by CDT (β: –6.76; 95% CI: –13.26 to –0.25; p for trend = 0.033), VFT-a (β: –5.84; 95% CI: –11.46 to –0.23; p for trend = 0.035), TMT-A

Table 2. Baseline characteristics of the PREDIMED-Plus participants according to energy-adjusted categories of total dairy product consumption.

	Total dairy product consumption				
	Total population	T1 (lowest)	T2	T3 (highest)	*p* value[a)]
Total dairy consumption, [g day^{-1}], median [IQR]	284 (207, 413)	148 (78, 213)	282 (253, 325)	546 (408, 617)	
Frequency, n	4668	1556	1556	1556	
Total energy intake [kcal day^{-1}]	2380.7 ± 546.3	2452.5 ± 584.6	2299.8 ± 498.2	2389.7 ± 542.4	**<0.001**
Socio-demographic variables					
Age [years]	65.0 ± 4.9	64.4 ± 4.9	65.0 ± 4.7	65.5 ± 4.9	**<0.001**
Women, *n* [%]	2243 (48.1)	553 (35.5)	778 (50.0)	912 (58.6)	**<0.001**
Education level, *n* [%]					
Primary or less	2280 (48.8)	703 (45.2)	770 (49.5)	807 (51.9)	**0.003**
Secondary	1360 (29.1)	471 (30.3)	455 (29.2)	434 (27.9)	
College	1028 (22.0)	382 (24.6)	331 (21.3)	315 (20.2)	
Civil status, *n* [%]					
Single, divorced, or separated	592 (12.7)	202 (13.0)	182 (11.7)	208 (13.4)	**<0.001**
Married	3596 (77.0)	1237 (79.5)	1216 (78.2)	1143 (73.5)	
Widower	480 (10.3)	117 (7.5)	158 (10.2)	205 (13.2)	
Anthropometric variables					
BMI [kg m^{-2}]	32.5 ± 3.4	32.5 ± 3.4	32.4 ± 3.4	32.4 ± 3.5	0.387
Waist circumference [cm]					
Women	103.7 ± 9.3	104.0 ± 9.3	103.2 ± 9.1	103.9 ± 9.3	0.232
Men	110.7 ± 8.8	111.0 ± 8.9	110.6 ± 8.7	110.4 ± 8.6	0.320
Lifestyle variables					
MedDiet score (17-points)	8.5 ± 2.7	8.3 ± 2.7	8.5 ± 2.7	8.6 ± 2.7	**0.004**
Physical activity [METs min^{-1} day^{-1}]	360.9 ± 333.2	377.7 ± 335.2	366.6 ± 344.6	338.4 ± 318.2	**0.003**
Smoking habit, *n* [%]					
Current smoker	605 (13.0)	243 (15.6)	194 (12.5)	168 (10.8)	<0.001
Former smoker	1994 (42.7)	750 (48.2)	658 (42.3)	586 (37.7)	
Never smoked	2069 (44.3)	563 (36.2)	704 (45.2)	802 (51.5)	
Disease present at recruitment					
Type 2 diabetes, *n* [%]	1329 (28.5)	405 (26.0)	436 (28.0)	488 (31.4)	**0.004**
Hypertension, *n* [%]	3921 (84.0)	1311 (84.3)	1319 (84.8)	1291 (83.0)	0.370
Hypercholesterolemia, *n* [%]	3246 (69.5)	1039 (66.8)	1093 (70.2)	1114 (71.6)	**0.011**
Depressive symptomatology, *n* [%]	906 (19.4)	268 (17.2)	309 (19.9)	329 (21.1)	**0.019**
Medication use, n [%]					
Antihypertensive agents	3691 (79.1)	1225 (78.7)	1227 (78.9)	1239 (79.6)	0.800
Insulin or other antidiabetic drugs	1151 (24.7)	338 (21.7)	389 (25.0)	424 (27.3)	**0.002**
Statins or other hypolipidemic drugs	2409 (51.6)	761 (48.9)	808 (51.9)	840 (54.0)	**0.017**
Dietary variables					
Protein [En%]	16.7 ± 2.8	15.6 ± 2.7	16.7 ± 2.4	17.8 ± 2.8	**<0.001**
Carbohydrates [En%]	40.6 ± 6.7	39.7 ± 7.0	40.2 ± 6.6	41.8 ± 6.4	**<0.001**
Total fat [En%]	39.6 ± 6.5	40.4 ± 6.6	40.0 ± 6.4	38.4 ± 6.2	**<0.001**
Fiber [g day^{-1}]	26.2 ± 8.7	26.3 ± 9.1	25.7 ± 8.3	26.5 ± 8.6	**0.049**
Vegetables [g day^{-1}]	329.1 ± 137.8	324.8 ± 137.2	328.0 ± 136.7	334.6 ± 139.4	0.128
Fruits [g day^{-1}]	360.1 ± 198.5	350.5 ± 206.7	357.2 ± 187.8	372.5 ± 200.1	**0.007**
Legumes [g day^{-1}]	20.4 ± 10.6	20.8 ± 11.5	19.8 ± 9.7	20.5 ± 10.4	**0.021**
Cereals [g day^{-1}]	153.2 ± 78.9	162.6 ± 85.6	146.8 ± 73.2	150.2 ± 76.5	**<0.001**
Nuts [g day^{-1}]	14.9 ± 16.6	15.9 ± 17.6	14.3 ± 15.7	14.4 ± 16.3	**0.009**
Oils and fats [g day^{-1}]	43.5 ± 17.2	45.9 ± 17.7	43.2 ± 16.6	41.3 ± 17.1	**<0.001**
Total meat [g day^{-1}]	147.9 ± 56.9	153.9 ± 61.0	145.9 ± 53.4	143.9 ± 55.4	**<0.001**
Total fish [g day^{-1}]	102.4 ± 47.6	104.1 ± 48.9	102.4 ± 47.1	100.7 ± 46.9	0.144

(*Continued*)

Table 2. (Continued).

	Total dairy product consumption				
	Total population	T1 (lowest)	T2	T3 (highest)	*p* value[a)]
Biscuits [g day^{-1}]	26.7 ± 29.1	26.7 ± 29.5	25.4 ± 26.0	28.0 ± 31.4	**0.045**
Coffee and tea [mL day^{-1}]	88.6 ± 60.1	82.7 ± 60.6	83.9 ± 55.4	99.2 ± 62.8	**<0.001**
Total alcohol [g day^{-1}]	11.4 ± 15.4	16.1 ± 19.0	10.7 ± 13.9	7.5 ± 11.0	**<0.001**
Cognitive function tests					
GCF z-score, median [IQR][b)]	0.06 (–0.60, 0.69)	0.17 (–0.44, 0.78)	0.05 (–0.66, 0.68)	–0.02 (–0.73, 0.60)	**<0.001**
MMSE score	28.31 ± 1.80	28.48 ± 1.66	28.29 ± 1.76	28.16 ± 1.95	**<0.001**
CDT score	5.95 ± 1.20	6.01 ± 1.15	5.95 ± 1.20	5.89 ± 1.24	**0.018**
VFT-a score	16.31 ± 4.90	16.75 ± 4.81	16.23 ± 4.95	15.94 ± 4.91	**<0.001**
VFT-p score	12.35 ± 4.52	12.71 ± 4.46	12.20 ± 4.54	12.15 ± 4.54	**0.001**
TMT-A score[c)]	51.85 ± 26.52	48.60 ± 23.03	53.26 ± 27.81	53.67 ± 28.11	**<0.001**
TMT-B score[c)]	128.24 ± 70.68	118.84 ± 64.72	129.45 ± 70.81	136.43 ± 75.08	**<0.001**
DST-f score	8.80 ± 2.45	8.94 ± 2.46	8.75 ± 2.44	8.71 ± 2.44	**0.016**
DST-b score	5.11 ± 2.20	5.26 ± 2.24	5.12 ± 2.21	4.95 ± 2.13	**<0.001**

Data are presented as *n* (%) and mean ± SD or median [IQR] for categorical and continuous variables, respectively. BMI indicates body mass index; CDT, Clock Drawing Test; DST-b, Digit Span test backward; DST-f, Digit Span test forward; En, energy; GCF, global cognitive function; IQR, interquartile range; MedDiet, Mediterranean diet; METs, metabolic equivalent; MMSE, Mini-Mental State Examination; T, tertile; TMT-A, Trail Making Test Part A; TMT-B, Trail Making Test Part B; VFT-a, Verbal Fluency tasks semantical; VFT-p, Verbal Fluency tasks phonological. [a)] *p*-value for differences between tertiles of total dairy product consumption was calculated by Pearson's Chi-square test and one-way ANOVA or Kruskal-Wallis as appropriate; [b)] GCF was calculated using the formula GCF = $(Z_{MMSE} + Z_{CDT} + Z_{VFT\text{-}a} + Z_{VFT\text{-}p} + (-Z_{TMT\text{-}A}) + (-Z_{TMT\text{-}B}) + Z_{DST\text{-}f} + Z_{DST\text{-}b})/8$; [c)] Inverse neuropsychological assessment score.

(β: 5.37; 95% CI: 0.02–10.73; Inverse neuropsychological assessment score; *p* for trend = 0.039), and TMT-B (β: 6.72; 95% CI: 1.31–12.14; Inverse neuropsychological assessment score; *p* for trend = 0.021) (Table S1, Supporting Information).

No significant inverse association was observed between semiskimmed or skimmed milk consumption and changes in GCF in the multiadjusted models (Table 3). However, significantly greater declines in cognitive performance were observed in participants in the higher tertile of skimmed milk consumption when evaluated by VFT-a (β: –4.69; 95% CI: –9.94–0.55; *p* for trend = 0.027) and TMT-B (β: 6.22; 95% CI: 1.01–11.43; Inverse neuropsychological assessment score; *p* for trend = 0.020) (Table S1, Supporting Information).

Regarding fermented dairy (yogurt, cheese, total), their associations with GCF were not significant after multivariable adjustment (Table 3), although higher yogurt intake was significantly associated with greater decline in the cognitive test VFT-a (β: –6.57; 95% CI: –11.67 to –1.46; *p* for trend = 0.009) (Table S1, Supporting Information).

In the analysis stratified by sex, a significant association between total milk consumption and changes in GCF over a 2-year period in the fully adjusted model was observed in men, but not women (Table S2, Supporting Information). Regarding the sensitivity analyses, the main results did not substantially change after removal of extreme GCF baseline *z*-scores (<5% and >95%) as well as with the removal of participants with a baseline MMSE score <24 (data not shown).

4. Discussion

This short-term longitudinal study is one of the few prospective studies evaluating the association of milk and other dairy product consumption with cognitive performance. In this large sample of an older Spanish population at high cardiovascular disease risk, we found no clear associations between the most commonly consumed dairy products; however, higher total milk intake, likely related specifically to higher whole-fat milk intake, was shown to be associated with greater global cognitive decline over a 2-year period. Our results align with previous prospective studies' findings.[2,14,43,44] A 20-year follow-up study of 13 751 American adults reported that milk intake greater than one glass (8 ounces) per day was associated with a greater decline in global cognitive *z*-score relative to the group reporting the lowest intake of milk.[2] Another study in a French adult population ($n = 3076$) found that milk intake was negatively associated with verbal memory and phonological performance, assessed by VFT-a and VFT-p tests, respectively.[14] The present study found similar associations between total milk and whole-fat milk intake in relation to GCF and VFT-a. Investigators of the Cardiovascular Risk Factors, Aging and Dementia (CAIDE) study demonstrated that high saturated fat intake from dairy products was associated with poor cognitive function and increased risk of mild cognitive impairment.[43] Likewise, whole-fat milk intake was inversely associated with successful cognitive and mental health aging, assessed by MMSE and 15-item Geriatric Depression Scale, among older Australian men.[44] In our subanalysis stratified by sex, the impact of total milk and whole-fat milk consumption on cognitive decline showed greater significance in men than women. Conversely, results from prospective studies in a Japanese population showed higher consumption of dairy products was associated with better cognitive performance.[45,46] This discrepancy might be related to differences in the participants' ethnicity, age, and dietary habits. For instance, the amount of dairy consumed in Japan (≥198 g d^{-1} for women and ≥174 g d^{-1} for men)[46] is relatively low compared to that in European countries (e.g., ≥418 g d^{-1} in our Spanish population). A recent cross-sectional study

Table 3. Multivariable adjusted mean 2-year change (β-coefficients and 95% CIs) in cognitive performance (GCF *z*-score) according to tertiles of energy-adjusted total dairy and different subtypes of dairy product consumption in the PREDIMED-Plus cohort.

	Dairy product consumption[a-c)]			
	T1 (lowest)[d)]	T2	T3 (highest)	*p* trend
Total dairy [g day^{-1}], median [IQR][e)]	154 (89, 199)	291 (264, 321)	540 (418, 611)	
Crude model	0 (Ref.)	−15.82 (−22.69 to −8.95)	−27.11 (−34.05 to −20.17)	**<0.001**
Model 1	0 (Ref.)	−0.74 (−4.52–3.03)	−4.35 (−8.30 to −0.39)	**0.024**
Model 2	0 (Ref.)	−0.71 (−4.45–3.02)	−4.25 (−8.20 to −0.30)	**0.028**
Model 3	0 (Ref.)	0.11 (−3.65–3.86)	−3.45 (−7.49–0.60)	0.069
Low-fat dairy [g day^{-1}], median [IQR][f)]	42 (2, 107)	215 (198, 244)	495 (332, 549)	
Crude model	0 (Ref.)	−10.88 (−17.77 to −3.99)	−22.66 (−29.76 to −15.56)	**<0.001**
Model 1	0 (Ref.)	-3.03×10^{-5} (−3.83–3.83)	−3.19 (−7.17–0.78)	0.093
Model 2	0 (Ref.)	−0.20 (−3.99–3.60)	−2.73 (−6.71–1.24)	0.156
Model 3	0 (Ref.)	0.66 (−3.15–4.46)	−1.71 (−5.73–2.31)	0.352
Whole-fat dairy [g day^{-1}], median [IQR][g)]	15 (1, 23)	46 (38, 55)	129 (87, 205)	
Crude model	0 (Ref.)	−14.58 (−21.66 to −7.51)	−6.73 (−13.70–0.25)	0.363
Model 1	0 (Ref.)	−2.47 (−6.43–1.49)	0.02 (−3.85–3.90)	0.707
Model 2	0 (Ref.)	−2.47 (−6.38–1.43)	−0.47 (−4.32–3.39)	0.912
Model 3	0 (Ref.)	−1.26 (−5.26–2.74)	−0.44 (−4.44–3.56)	0.956
Total milk [g day^{-1}], median [IQR][h)]	50 (9, 109)	195 (180, 209)	465 (240, 502)	
Crude model	0 (Ref.)	−16.83 (−23.60 to −10.06)	−30.36 (−37.47 to −23.26)	**<0.001**
Model 1	0 (Ref.)	−2.13 (−5.94–1.68)	−6.15 (−10.06 to −2.24)	**0.002**
Model 2	0 (Ref.)	−1.50 (−5.27–2.27)	−5.58 (−9.48 to −1.68)	**0.004**
Model 3	0 (Ref.)	−1.43 (−5.22–2.36)	−4.71 (−8.74 to −0.69)	**0.020**
Whole-fat milk, [g day^{-1}], median [IQR]	0 (0, 0)	3 (1, 6)	17 (12, 97)	
Crude model	0 (Ref.)	−17.69 (−24.64 to −10.74)	−25.18 (−32.08 to −18.28)	**<0.001**
Model 1	0 (Ref.)	−4.25 (−8.16 to −0.34)	−7.46 (−11.27 to −3.66)	**<0.001**
Model 2	0 (Ref.)	−4.12 (−8.03 to −0.21)	−7.66 (−11.55 to −3.77)	**<0.001**
Model 3	0 (Ref.)	−2.84 (−6.92–1.24)	−6.64 (−10.81 to −2.47)	**0.002**
Semi-skimmed milk [g day^{-1}], median [IQR]	0 (0, 0)	16 (9, 26)	206 (189, 471)	
Crude model	0 (Ref.)	−21.45 (−28.53 to −14.37)	−18.34 (−25.36 to −11.32)	**0.002**
Model 1	0 (Ref.)	−3.62 (−7.55–0.30)	−2.19 (−6.00–1.62)	0.689
Model 2	0 (Ref.)	−4.14 (−8.07 to −0.22)	−1.43 (−5.19–2.33)	0.866
Model 3	0 (Ref.)	−2.05 (−6.29–2.18)	−0.06 (−3.91–3.79)	0.634
Skimmed milk [g day^{-1}], median [IQR]	0 (0, 0)	3 (2, 5)	202 (198, 496)	
Crude model	0 (Ref.)	−22.08 (−28.97 to −15.18)	−20.10 (−27.14 to −13.06)	**0.003**
Model 1	0 (Ref.)	−5.01 (−8.88 to −1.14)	−3.87 (−7.73 to -6.61×10^{-4})	0.435
Model 2	0 (Ref.)	−5.29 (−9.14 to −1.44)	−4.48 (−8.33 to −0.63)	0.288
Model 3	0 (Ref.)	−3.34 (−7.44–0.76)	−2.98 (−6.88–0.92)	0.450
Total yogurt, [g day^{-1}], median [IQR][i)]	5 (0, 13)	55 (51, 59)	127 (122, 133)	
Crude model	0 (Ref.)	−6.26 (−13.27–0.75)	−12.48 (−19.46 to −5.50)	**0.001**
Model 1	0 (Ref.)	−0.56 (−4.34 to 3.22)	−1.14 (−5.05–2.77)	0.571
Model 2	0 (Ref.)	−0.50 (−4.21–3.22)	−1.39 (−5.27–2.49)	0.481
Model 3	0 (Ref.)	−0.19 (−3.92–3.53)	−0.84 (−4.72–3.03)	0.662
Total cheese [g day^{-1}], median [IQR][j)]	10 (5, 14)	26 (23, 31)	48 (42, 59)	
Crude model	0 (Ref.)	−4.02 (−11.20–3.15)	0.76 (−6.20–7.73)	0.743
Model 1	0 (Ref.)	0.86 (−3.06–4.79)	3.48 (−0.38–7.34)	0.072
Model 2	0 (Ref.)	0.60 (−3.25–4.46)	2.22 (−1.57–6.01)	0.242
Model 3	0 (Ref.)	0.96 (−2.90–4.81)	2.31 (−1.51–6.13)	0.234

(*Continued*)

Table 3. (Continued).

	Dairy product consumption[a-c]			
	T1 (lowest)[d]	T2	T3 (highest)	*p* trend
Total fermented dairy products [g day^{-1}], median [IQR][k]	31 (18, 46)	87 (75, 105)	161 (146, 206)	
Crude model	0 (Ref.)	−8.69 (−15.65 to −1.72)	−12.55 (−19.58 to −5.52)	**0.001**
Model 1	0 (Ref.)	0.46 (−3.32–4.23)	0.65 (−3.30–4.60)	0.755
Model 2	0 (Ref.)	0.55 (−3.16–4.26)	− 0.11 (−4.02–3.79)	0.932
Model 3	0 (Ref.)	1.13 (−2.62–4.87)	0.61 (−3.30–4.53)	0.794

Multivariable linear regression was used to assess longitudinal association to compare the 2-year changes in cognitive function across tertiles of diary product intake. Multivariable model 1: adjusted for baseline global cognitive function *z*-score, age (years), sex, intervention PREDIMED-Plus randomized group, and participating center (<100, 100 to <200, 200 to <300, ≥300 participants). Multivariable model 2: additionally adjusted for body mass index (kg m^{-2}), educational level (primary, secondary, or college), civil status (single, divorced or separated, married, widower), physical activity (METs min^{-1} day^{-1}), smoking habit (current, former, or never), alcohol consumption in g day^{-1} (and adding the quadratic term), depressive symptomatology (yes/no), diabetes prevalence (yes/no), hypertension (yes/no), and hypercholesterolemia (yes/no). Multivariable model 3: additionally adjusted for dietary factors (consumption of vegetables, fruits, legumes, cereals, nuts, oils and fats, biscuits, meat, fish [g day^{-1}], coffee, and tea [mL day^{-1}]). β-coefficients were estimated using linear regression models with robust standard errors to account for intracluster correlations. CI indicates confidence interval; GCF, global cognitive function; IQR, interquartile range; T, tertile. [a] β-coefficients and 95% CI are presented as 100× original data; [b] GCF was calculated using the formula GCF = $(Z_{MMSE} + Z_{CDT} + Z_{VFT\text{-}a} + Z_{VFT\text{-}p} + (-Z_{TMT\text{-}A}) + (-Z_{TMT\text{-}B}) + Z_{DST\text{-}f} + Z_{DST\text{-}b})/8$; [c] Dairy product consumption was adjusted for baseline total energy intake using the residual method; [d] Negative values of dairy consumption resulting from the energy adjustment were set to 0 for interpretability;[38,39] [e] Includes all dairy products: all types of milk, yogurt, and cheese; [f] Includes semi-skimmed/skimmed milk and skimmed yogurt; [g] Includes whole-fat milk, whole-fat yogurt, and all types of cheese; [h] Includes all types of milk: whole-fat milk, semi-skimmed, and skimmed milk; [i] Includes all types of yogurt: whole-fat and skimmed yogurt; [j] Includes all types of cheese: petit-suisse, ricotta, cottage cheese, cream cheese, semi-cured and cured cheese, fresh cheese; [k] Includes all types of yogurt and cheese.

conducted within the PREDIMED-Plus cohort reported that participants who consumed a higher amount of dairy products had lower cognitive function based on MMSE score.[15] Other studies conducted in different countries have reported either no or positive associations of dairy consumption with cognitive function; however, most of these studies were cross-sectional in design, therefore subject to potential reverse causation, and had high heterogeneity which may also partly explain the discrepancy.[12,13,16,47]

Evidence examining the association between total fermented dairy consumption and cognitive performance is limited. In older Spanish and Dutch adults, positive associations between the intake of fermented dairy with cognitive function assessments have been shown.[13,15] One small randomized, double-blind, controlled trial, which assessed the effects of fermented milk with a mixture of probiotics for 12 weeks on cognitive function among 60 patients with Alzheimer's disease, showed a significant improvement in MMSE score among the probiotic treated patients compared with the control group receiving milk.[48] We did not observe significant associations between specific fermented dairy product consumption and changes in cognitive performance over a 2-year period. A few studies have previously reported that consumption of cheese, despite its relatively high proportion of saturated fat, may have a protective effect on cognitive function.[11,13–16,49] In the present study, cheese consumption showed a nonsignificant positive trend with GCF. Furthermore, yogurt intake was found to be inversely associated with VFT-a, suggesting a negative impact on verbal ability/executive function.

The present analysis detected no significant associations in the fully adjusted models for total dairy, nor low-fat or whole-fat total dairy in regard to GCF. However, when assessing the individual neuropsychological tests, a higher intake of total dairy, specifically low-fat dairy was associated with worse verbal ability/executive function as measured by VFT-a. Findings from other observational studies are inconsistent in relation to the association of the fat content of total daily consumption with cognitive performance.[11,13,15,50] The aforementioned cross-sectional analysis of the PREDIMED-Plus cohort reported that participants who consumed whole-fat dairy products had higher cognitive performance measured by MMSE.[15] In contrast, Crichton et al.,[11] concluded in their cross-sectional study that individuals who consumed low-fat dairy had better cognitive (i.e., perception, memory, and motor) function than those who did not, while intakes of whole-fat dairy products, including ice cream and cream, were associated with poorer cognitive performance. Another cross-sectional study of 619 Dutch community-dwelling adults aged ≥65 years found that higher consumption of low-fat dairy was associated with better executive function in cognition evaluated using TMT-B, the Stroop Color–Word Test part-III, and the Letter Fluency test.[13] Among 4809 older French women, higher intakes of dairy desserts and ice cream were positively associated with cognitive decline over a 13-year follow-up.[50] The comparison of findings across studies is challenging due to the notable disparity in the dairy consumption assessment, not only in the subtypes included in the analyses but also in the amounts analyzed. Moreover, there are a large variety of cognitive measurements, as well as diverse study populations among the few existing studies.

The underlying biological mechanism explaining possible associations between daily consumption and cognitive performance is still unclear. One possibility is that dairy consumption may influence cognitive status via its effect on cardiovascular risk factors, such as obesity, type 2 diabetes, hypertension, and dyslipidemia, which have been frequently associated with increased risk of cognitive dysfunction related to vascular pathological changes.[8] Whole-fat milk is high in saturated fat (about 58% of whole-cows cow's milk is saturated fat),[51] and saturated fat has been suggested to increase low-density lipoprotein (LDL) cholesterol adversely affecting blood lipids and increasing risk

for arteriosclerosis and other cardiovascular diseases.[51] While saturated fat is one nutrient in dairy products proposed to affect cognition, it has been suggested that the effects of saturated fat should be considered within the context of the source of calories (beverage or food source) and within the context of the dietary pattern.[51] For example, findings can differ if dairy products are replaced or compared with a refined carbohydrate versus an unsaturated fat source, such as nuts which in themselves have been considered as possibly protective against cognitive decline.[52] In the present study population, people with a high intake of whole-fat milk consumed less nuts and more carbohydrates, particularly refined grains and sugar, which may be other potential risk factors for cognitive impairment.[53] Nonetheless, this potential dietary confounding has been accounted for in our statistical analyses. Just as dairy products contribute to an overall dietary pattern and may synergistically interact with or replace other food groups or items, the potential biological mechanism by which whole fat milk or total dairy intake may influence cognitive function is likely dependent on more than a single risk biomarker (i.e., more than just the impact of the saturated fat content on LDL cholesterol). In our results, the associations between total milk, whole-fat milk consumption, and cognitive decline remained significant after adjustment for several cardiovascular risk factors, suggesting that physiobiological mechanisms may relate to the effect of dairy constituents other than fat content. As mentioned, it has been postulated that various dairy components, such as MFGM, lactose, calcium, magnesium, vitamin B12, probiotics, and whey protein content, may affect dementia development.[2,4,7,9,13,45,46] However, given the current findings, it is unknown whether these nutrients possibly mitigated the observed associations, and hence more research is warranted to clarify which compounds might modulate cognitive function and to provide more insight into the potential link between dairy product consumption, individually and as part of a dietary pattern, and cognitive performance.

Based on previous research, our hypothesis was that dairy product consumption may help in delaying cognitive decline and maintaining cognitive function during aging. Our findings argue for a more complex association depending on the type of dairy product and quantity consumed, along with considering the whole diet context, with a potential negative association observed for a higher amount of dairy consumption with cognitive performance. There are several considerations that should be made when interpreting the main findings of the current study for practical use. In particular, the amount of whole-fat milk consumed by participants. The median amount of whole-fat milk intake in the highest tertile was shown to be relatively low at 17.0 g day^{-1}, which may be considered to have little clinical meaning, though the mean value was 76.3 g day^{-1} (data not shown); however, this data was energy adjusted. When the amount was calculated not adjusting for overall energy intake (crude whole fat milk consumption by tertiles of energy adjusted whole fat consumption), the mean value of the highest tertile was observed to be 70 g day^{-1}. For context, in the Spanish population as a whole, total milk consumption has been estimated at 200 mL per person per day, of which 24% consisted of whole-fat milk.[22]

This study is not without limitations. First, the results may not be generalizable to other populations since the participants are older Spanish individuals with high cardiovascular disease risk. Second, the use of a FFQ to estimate daily consumption, although it has been determined as a reliable method of assessing long-term intake,[21] is subject to possible measurement error and recall bias as it relies heavily on responders' memory.[19,21] In addition, despite its longitudinal design, the dairy consumption was considered only once, at baseline. However, as the FFQ measures habitual food intake and older adults are considered to have reasonably stable dietary habits,[19,21] we do not expect a substantial impact on the results. As well, there is less probability of FFQ responses being affected by any potential decline in cognition given they were assessed at baseline. While the possibility of reverse causality also cannot be disregarded, as individuals with mild cognitive impairment may modify their dietary intake in response, those with cognitive impairment at baseline were not eligible to participate and sensitivity analyses also did not observe any difference in those with MMSE scores indicative of possible mild cognitive impairment. The clinical significance of the main results of the present study should be considered with caution, as the impact of total milk and whole-fat milk consumption on changes in GCF *z*-score, as well as on the individual test *z*-scores, over the 2-year period are small and while statistical significance was observed, the effect size of the findings may not result in clinically relevant outcomes. As well, the findings related to total milk consumption and cognition could possibly be driven by those of whole-fat milk intake. The strengths of the study include its longitudinal, prospective design, the large sample size, the use of an extensive cognitive test battery, the information given in relation to a broad variety of dairy subgroups recorded, the robustness of our results by the adjustment of relevant covariates, and performance of sensitivity and stratified analyses.

5. Conclusion

Our results suggest that there are no clear associations between the intake of the most commonly consumed dairy products (most milks, cheese, yogurt) with cognitive performance, although whole-fat milk intake in older adults at high cardiovascular disease risk may be associated with greater decline in cognitive function. Further prospective cohort studies and randomized clinical trials are required to confirm our results and to better understand the link between dairy product consumption and changes in cognitive performance, ultimately to provide specific nutritional recommendations to promote healthy cognitive aging.

Supporting Information

Supporting Information is available from the Wiley Online Library or from the author.

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Conflict of Interest

S.K.N. is a volunteer member of the not-for profit group Plant–Based Canada. D.C. reported receiving grants from Instituto de Salud Carlos III. R.E. reported receiving grants from Instituto de Salud Carlos III, Uriach Laboratories and Grand–Fountain Laboratories for clinical trial, and personal fees from Brewers of Europe, Fundación Cerveza y Salud, Instituto Cervantes in Albuquerque, Milano and Tokyo, Fundación Bosch y Gimpera; nonfinancial support from Wine and Culinary International Forum, ERAB (Belgium), and Sociedad Española de Nutrición; and fees of educational conferences from Pernaud Richart (Mexico) and Fundación Dieta Mediterránea (Spain). R.C. reported receiving fees of educational conferences from Fundación para la investigación del Vino y la Nutrición (Spain). J.S.-S. reported receiving research support from the Instituto de Salud Carlos III, Ministerio de Educación y Ciencia, the European Commission, the USA National Institutes of Health; receiving consulting fees or travel expenses from Eroski Foundation, Instituto Danone, Nestle, and Abbott Laboratories, receiving nonfinancial support from Hojiblanca, Patrimonio Comunal Olivarero, the California Walnut Commission, Almond Board of California, La Morella Nuts, Pistachio Growers and Borges S.A.; serving on the board of and receiving grant support through his institution from the International Nut and Dried Foundation and the Eroski Foundation; and personal fees from Instituto Danone; Serving in the Board of Danone Institute International. The rest of the authors have declared that no competing interests exist. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results.

Author Contributions

All the principal PREDIMED-Plus investigators contributed to study concept and design and to data extraction from the participants. J.N. and S.K.N. performed the statistical analyses. J.N., S.K.N., N.B., and J.S.-S. drafted the manuscript. All authors reviewed the manuscript for important intellectual content and approved the final version to be published.

Data Availability Statement

Data described in the manuscript, code book, and analytic code will be made available upon request pending application and approval of the PREDIMED-Plus Steering Committee. There are restrictions on the availability of data for the PREDIMED-Plus trial, due to the signed consent agreements around data sharing, which only allow access to external researchers for studies following the project purposes. Requestors wishing to access the PREDIMED-Plus trial data used in this study can make a request to the PREDIMED-Plus trial Steering Committee chair: jordi.salas@urv.cat. The request will then be passed to members of the PREDIMED-Plus Steering Committee for deliberation.

Keywords

cognition, cognitive decline, dairy, milk, PREDIMED-Plus

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