Age and Ageing 2022; **51:** 1–7
https://doi.org/10.1093/ageing/afab246

SHORT REPORT

Vitamin K dietary intake is associated with cognitive function in an older adult Mediterranean population

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Abstract

Background: In the last years, evidence that dietary vitamin K could have a role in the cognitive domain has increased. However, data from large trials are limited. The objective of this study was to assess the association of 2 year changes in the dietary intake of vitamin K with cognitive function measured through neuropsychological performance tests.
Methods: In 5,533 participants of the multicentre PREDIMED-Plus study (48.1% women, age 65.1 ± 4.9 years with overweight/obesity and metabolic syndrome), we assessed the adjusted odds ratios of cognitive function decline according to 2 year changes in vitamin K intake. Participants answered a battery of cognitive function tests and Food Frequency Questionnaires (FFQs) in order to estimate the vitamin K dietary intake.
Results: After adjusting for potential cofounders, the highest tertile of change of dietary vitamin K intake (median [IQR]; 194.4 μg/d [120.9, 373.1]) was inversely associated with a Mini-Mental State Examination (MMSE) score ≤24 (OR [95% CI]; 0.53 [0.35, 0.79] P for trend = 0.002) compared with a decrease in the intake of vitamin K (median [IQR]; −97.8 μg/d [−292.8, −51.5]). A significant positive association between changes in dietary vitamin K intake and the semantic verbal fluency test scores (OR [95% CI]; 0.69 [0.51, 0.94] P for trend = 0.019) was found.
Conclusions: An increase of the intake of dietary vitamin K was associated with better cognitive function scores, independently of recognised risk factors for cognitive decline, in an older adult Mediterranean population with high cardiovascular risk.

Keywords: Vitamin K, phylloquinone, cognitive impairment, cognitive-neuropsychological tests, older people

Key Points

- Increased dietary intake of vitamin K may be associated with a better cognitive function.
- Increased dietary intake of vitamin K is associated with higher scores in the Mini Mental State-Examination (MMSE) cognitive impairment assessment test.
- Increased dietary intake of vitamin K is associated with better performance in verbal fluency tests.

Introduction

Mild cognitive impairment (MCI) is a result of impaired cognitive function beyond the normal decline observed during the ageing process. It is characterised by a progressive decline in memory, concentration and the depletion of the ability to learn new things. Up to a third of cases of MCI progress to dementia [1].

The progress of MCI is determined by multiple metabolic factors, including the presence of cardiovascular diseases, hypertension, hypercholesterolaemia, overweight or obesity [2] and type 2 diabetes [3, 4]. Other potential contributing processes related to these metabolic derangements are insulin resistance, inflammation and oxidative stress [2, 4].

Modifiable risk factors, such as nutrition, might also play a crucial role [5]. In the last years, evidence that vitamin K could play a role in cognitive function has increased. Among other actions in the brain, vitamin K is involved in sphingolipid metabolism [6]. Alterations in sphingolipid metabolism have been associated with neurodegenerative disorders, including Alzheimer's and Parkinson's diseases [7]. Likewise, vitamin K anti-inflammatory [8, 9] and antioxidant properties [10] could also play an important role in decreasing the risk of MCI, as well as having beneficial effects on insulin sensitivity and glucose metabolism [11–13].

A cross-sectional analysis, examining specifically vitamin K and cognitive function, has found that a higher dietary intake was associated with better cognition and behaviour among older adults [14], and with better verbal episodic memory performance [15].

The present analysis aimed to assess whether an increased dietary intake of vitamin K was associated with a better cognitive functioning measured through scores of cognitive–neuropsychological tests.

Methods

The PREDIMED-plus study design and subjects

The present observational longitudinal analysis was conducted in the context of the PREDIMED-PLUS study, an ongoing randomised multicentre clinical trial conducted in Spain. The study protocol is available at http://predimedplus.com. Participants were men aged 55–75 years and women aged 60–75 years, with overweight or obesity (body mass index (BMI) 27–40 kg/m [2]), who at baseline met at least three components of the metabolic syndrome. The final sample included in this analysis was $n = 5{,}533$ participants. A flowchart of the study population is represented in Appendix 1.

Dietary phylloquinone intake

Total energy, and macro- and micronutrient intake were assessed at baseline and at the 2 year follow-up by a validated 143 item Food Frequency Questionnaire (FFQ) [16] and estimated using Spanish food composition tables [17, 18]. To estimate the dietary intake of vitamin K, we used the United States Department of Agriculture (USDA) nutrient database, as this information is not available in the Spanish food composition tables.

Assessment of cognitive functioning

In order to evaluate changes in cognitive function, a battery of different tests, standardised for the Spanish population, was administered at baseline and at the 2 year follow-up visit. The battery of test included: Mini-Mental State Examination (MMSE), Clock Drawing Test (CDT), Wechsler Adult Intelligence Scale III—Digit Span (WAIS III—DS), Verbal Fluency Test (VF) and Trail Making Test (TMT). A detailed description of the variables can be found in Appendix 2.

Statistical analysis

Multivariate logistic regression models were applied to evaluate the relationship between tertiles of 2 year changes in vitamin K dietary intake and each of the cognitive function tests measured at 2 years of follow-up. Models were adjusted for potential confounding variables. A detailed description of the statistical analysis is presented in Appendix 3.

Results

Participants

Table 1 shows baseline characteristics of the study participants by tertiles of 2 year changes in vitamin K dietary intake. No significant differences were observed, except in sex and high-density lipoprotein cholesterol values. Regarding the assessment of cognitive function, we observed significant differences in the MMSE scores, though the mean differences between groups were not clinically relevant.

Cognitive decline and vitamin K association

After adjusting for potential cofounders, our results show a positive association between the normal cognition prevalence (MMSE $\geq$24) and a higher increase of vitamin K dietary intake (OR [95% CI]; 0.53 [0.35, 0.79] P for trend = 0.002) (Figure 1).

No significant associations were found for the other cognitive function tests, except for the semantic verbal fluency test (Table 2 in Appendix 4). Participants located in the highest tertile of change in dietary vitamin K had a significant lower likelihood of having a worse performance in the test, compared with those who decreased their intake (OR [95% CI]; 0.69 [0.51, 0.94] P for trend = 0.019).

Since the presence of diabetes is associated with cognitive decline, we explored the differential risks among those individuals with or without type 2 diabetes (Table 3 in Appendix 5). After segregation into two groups, our results show that participants in the highest tertile of change in vitamin K dietary intake had a better cognitive function in the case

TABLE 1. Baseline characteristics of the subjects by tertiles of 2-year changes in dietary vitamin K1 intake

	Vitamin K1 intake (μg/d)			
Variable[a]	T1 (*n* = 1,844)	T2 (*n* = 1,844)	T3 (*n* = 1,845)	*P*[b]
2 year changes in vitamin K1 intake (μg/d), median (IQR) [2]	−171.5 (−292.8, −51.5)	27.3 (2.6, 51.5)	256.4 (120.9, 373.1)	
Women, *n* (%)	934 (50.7)	871 (47.2)	855 (46.4)	0.023
Age, years	65.2 ± 4.8	65.0 ± 4.9	65.0 ± 4.9	0.206
BMI, kg/m^2	32.5 ± 3.4	32.5 ± 3.5	32.4 ± 3.4	0.548
Waist circumference, cm	107.4 ± 9.9	107.3 ± 9.5	107.2 ± 9.5	0.749
Leisure-time physical activity, MET-min/d	373.7 ± 354.5	358.0 ± 314.5	354.8 ± 328.6	0.183
Glucose, mg/dl	113.5 ± 28.7	113.3 ± 28.2	113.5 ± 28.8	0.963
Total cholesterol, mg/dl	195.8 ± 37.2	197.3 ± 37.0	196.9 ± 39.2	0.473
Triglycerides, mg/dl	149.3 ± 76.6	153.1 ± 80.4	151.3 ± 76.2	0.332
HDL-cholesterol, mg/dl	48.7 ± 11.7	47.7 ± 11.6	48.0 ± 12.2	0.030
Diabetes, *n* (%)	589 (31.9)	553 (30.0)	546 (29.6)	0.256
Hypertension, *n* (%)	1,546 (83.8)	1,549 (84.0)	1,573 (85.3)	0.406
Hypercholesterolaemia, *n* (%)	1,291 (70.0)	1,257 (68.2)	1,286 (68.8)	0.244
Use of anticoagulant medication, *n* (%)	25 (1.4)	29 (1.6)	39 (2.1)	0.182
Smoking status, *n* (%)				0.661
Never	836 (45.3)	819 (44.4)	822 (44.6)	
Current	225 (12.2)	232 (12.6)	208 (11.3)	
Former	783 (42.5)	793 (43.0)	814 (44.1)	
Education, *n* (%)				0.377
Primary education	951 (51.6)	901 (48.9)	902 (48.9)	
Secondary education	497 (27.0)	548 (29.7)	550 (29.8)	
Higher education	396 (21.4)	395 (21.4)	392 (21.3)	
Cognitive functioning assessment, raw scores				
Mini-Mental State Examination Score	28.1 ± 1.9	28.3 ± 1.9	28.3 ± 1.8	0.002
Clock Drawing Test	5.9 ± 1.2	5.9 ± 1.3	6.0 ± 1.2	0.139
WAIS III—Digit Span—Forward Recall	8.8 ± 2.4	8.8 ± 2.6	8.8 ± 2.4	0.948
WAIS III—Digit Span—Backward Recall	5.0 ± 2.2	5.1 ± 2.2	5.2 ± 2.2	0.072
Phonology Verbal Fluency Test	12.2 ± 4.6	12.1 ± 4.5	12.0 ± 4.4	0.530
Semantic Verbal Fluency Test	16.0 ± 4.9	16.1 ± 5.0	16.0 ± 4.8	0.922
Trail Making Test—A	53.1 ± 28.5	52.5 ± 28.6	52.1 ± 26.2	0.559
Trail Making Test—B	131.4 ± 71.2	130.4 ± 73.2	129.3 ± 71.4	0.684
Beck Depression Inventory-II, raw scores	8.7 ± 7.6	8.3 ± 7.4	8.2 ± 7.2	0.103

[a]Means ± SDs or n (%), unless otherwise indicated. BMI, body mass index; HDL, high-density lipoprotein; IQR, interquartile range; MET, metabolic equivalent of task; T, tertile. [b]*P*-values are based on the difference between tertiles of 2 year changes in dietary vitamin K1 intake (ANOVA for the continuous variables and χ^2 test for categorical variables).

of those participants without diabetes (OR [95% CI]; 0.45 [0.27, 0.76] P for trend = 0.003), but this association was non-significant in the case of subjects with diabetes (OR [95% CI]; 0.79 [0.40, 1.54] P for trend = 0.464).

Discussion

In this prospective analysis of the PREDIMED-Plus trial we showed that a higher increase of vitamin K dietary intake was associated with a better cognitive function assessed by MMSE test in an adult high cardiovascular risk population followed for 2 years. This association was not found in the other considered cognitive function tests, with the exception of the semantic verbal fluency test. Even though it has been observed that semantic fluency is reduced in patients with MCI [19], this is the first study showing a positive association between vitamin K intake and the score provided by this test.

There are previous studies linking the dietary intake or serum concentrations of vitamin K with cognitive decline. In the CLIP Study Geriatric Population, the authors observed a positive significant association between dietary phylloquinone intake and the MMSE score, as well as an inverse association with the Frontotemporal Behavioural Rating Scale (FBRS) score [14]. Along the same lines but considering performances in the Rey Complex-Figure recalls, higher levels of serum phylloquinone were associated with better performances in this non-verbal episodic memory test. In a cross-sectional study, those participants with serious subjective memory complaints had a lower mean dietary vitamin K intake compared with participants without memory complaints [20]. Our results not only reaffirm the previous evidence in a larger sample, but also extend these associations to a longitudinal perspective assessment.

Vitamin K may affect cognitive functioning through several interconnected mechanisms. It is not fully understood how insulin acts on the brain, and how it can influence cognitive functions, but it has been linked to being a risk factor for neurodegenerative diseases, including Alzheimer's disease

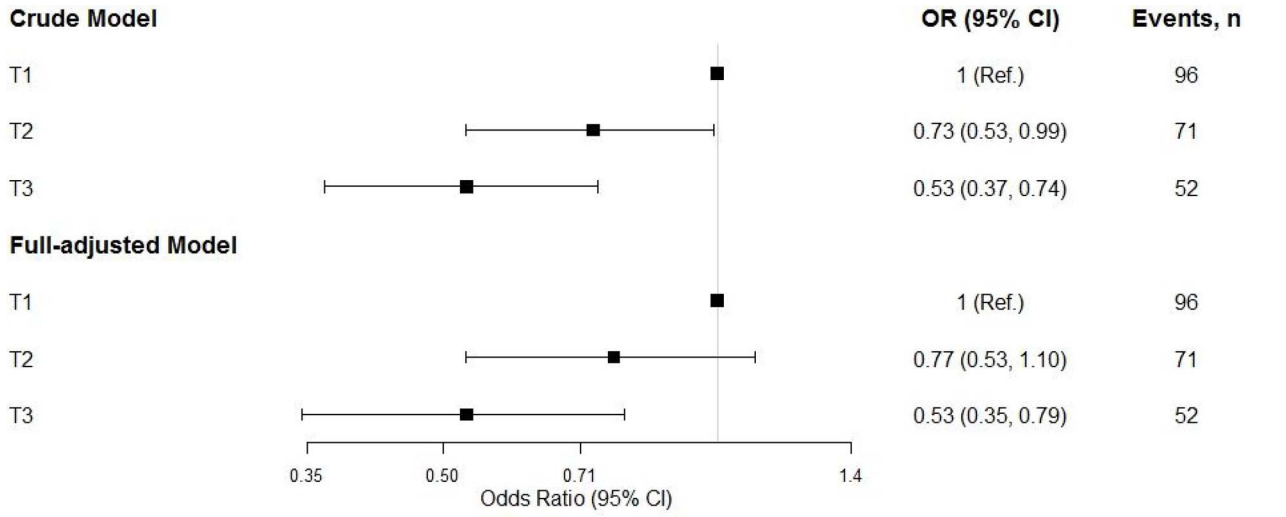

Figure 1. Odds ratios of cognitive impairment assessed by MMSE scores (MMSE score ≤24) according to tertiles of 2 year changes of vitamin K1. Logistic regression analysis comparing the presence of cognitive impairment by tertiles of 2 year changes of vitamin K1 intake. *n* = 1844 in T1 and T2, *n* = 1845 in T3. Median (IQR) of 2 year changes in vitamin K1 intake (μg/d), T1 = −97.8 (−292.8, −51.5), T2 = 23.9 (2.6, 23.9) and T3 = 194.4 (120.9, 373.1). The model was adjusted for sex, age, body mass index, smoking habit, leisure time activity and education, baseline score of MMSE, prevalence of hypertension and hypercholesterolaemia, use of medication (anticoagulant medicines, oral diabetes medicines and insulin), baseline food intake (dairy, meat, fish, fruit, nuts, legumes and cereals), alcohol and alcohol squared in grams per day, and moderate to high risk of depression assessed by the Beck Depression Inventory-II. In addition the model was adjusted for intervention group and stratified by centre.

[21]. There is an important amount of evidence suggesting that this vitamin regulates insulin sensitivity and glucose tolerance, having a direct effect on insulin metabolism [8, 12, 13, 22].

Likewise, the anti-inflammatory effect of vitamin K can influence the inflammatory processes associated with cognitive impairment [23]. A study aiming to associate vitamin K status, inflammation and cognition found that higher levels of inflammatory markers correlate with cognitive decline. This study reported significantly higher levels of dietary phylloquinone in those individuals with better cognition compared with those with the poorest function. Additionally, after controlling for other confounding variables, both dietary and serum phylloquinone levels were significant independent predictors of normal scores in the MMSE, indicating better cognitive function [24].

The strengths of our study include a large sample size, a longitudinal analysis based on 2 year changes in the dietary vitamin K intake and the use of different tests to assess various dimensions of the cognitive decline. In addition, all analyses were controlled for potential confounders that were carefully recorded by trained professional personnel. However, there are several factors influencing our results that cannot be addressed in large sample sizes such as hidden malnutrition and endothelial dysfunction that might influence cognitive performance. On the other hand, our study also has limitations. First, due to the design of the study, our sample only included adult Mediterranean participants with overweight/obesity and metabolic syndrome; therefore, these results cannot be extended to the general population. Second, the vitamin K intake was estimated using FFQs and was not assessed by levels of a plasma circulating marker that takes into consideration the levels of absorption. Either way, previous reports showed a significant association between dietary phylloquinone intake and plasma phylloquinone [25, 26]. Third, we did not include an educational level standardisation for the cognitive decline cut-off values and decided on the standard deviation from the mean of our study population. However, to minimise its effect on the results, each model was adjusted for the educational level variable defined in three different categories: primary, secondary and higher education. The last limitation that we must acknowledge is the preliminary nature of these results, with a short incitement time and a partial sample of the total study population.

In conclusion, our findings demonstrated that increased intake of dietary vitamin K is associated with better cognitive function scores, independently of traditional risk factors for cognitive decline, in an older adult Mediterranean population.

Supplementary Data: Supplementary data mentioned in the text are available to subscribers in Age and Ageing online.

Acknowledgements: We thank all the volunteers for their participation, and the personnel for their contribution to the PREDIMED-Plus trial. CIBEROBN, CIBERESP and CIBERDEM are initiatives of Instituto de Salud Carlos III (ISCIII), Madrid, Spain. The authors also thank the PREDIMED-Plus Biobank Network as a part of the

National Biobank Platform of the ISCIII for storing and managing the PREDIMED-Plus biological samples.

Declaration of Conflicts of Interest: None.

Declaration of Sources of Funding: The PREDIMED-Plus trial was supported by the official Spanish Institutions for funding scientific biomedical research, CIBER Fisiopatología de la Obesidad y Nutrición (CIBERobn) and Instituto de Salud Carlos III (ISCIII), through the Fondo de Investigación para la Salud (FIS), which is co-funded by the European Regional Development Fund (four coordinated FIS projects led by J.S.-S. and J.Vi., including the following projects: PI13/00673, PI13/00492, PI13/00272, PI13/01123, PI13/00462, PI13/00233, PI13/02184, PI13/00728, PI13/01090, PI13/01056, PI14/01722, PI14/00636, PI14/00618, PI14/00696, PI14/01206, PI14/01919, PI14/00853, PI14/01374, PI14/00972, PI14/00728, PI14/01471, PI16/00473, PI16/00662, PI16/01873, PI16/01094, PI16/00501, PI16/00533, PI16/00381, PI16/00366, PI16/01522, PI16/01120, PI17/00764, PI17/01183, PI17/00855, PI17/01347, PI17/00525, PI17/01827, PI17/00532, PI17/00215, PI17/01441, PI17/00508, PI17/01732 and PI17/00926), the Special Action Project entitled: Implementación y evaluación de una intervención intensiva sobre la actividad física Cohorte PREDIMED-Plus grant to J.S.-S., the European Research Council (Advanced Research Grant 2013–2018, 340, 918) to M.Á.M.-G., the Recercaixa grant to J.S.-S. (2013ACUP00194), grants from the Consejería de Salud de la Junta de Andalucía (PI0458/2013, PS0358/2016 and PI0137/2018), a grant from the Generalitat Valenciana (PROMETEO/2017/017) and a SEMERGEN grant and funds from the European Regional Development Fund (CB06/03). This research was also partially funded by EU-H2020 Grant (Eat2beNICE/H2020-SFS-2016-2; Ref 728,018) and PERIS (Generalitat de Catalunya, SLT006/17/00077). L.C.-B. is the recipient of a pre-doctoral fellowship from the Generalitat de Catalunya's Department of Universities (FI-DGR 2017). J.G.-G. has received a pre-doctoral grant "Contratos Predoctorales de Formación en Investigación en Salud" (PFIS FI17/00255) of Acción Estratégica en Salud (AES) programme from the Institue of Health Carlos III (ISCIII). J. Salas-Salvadó, the senior author of this article, gratefully acknowledges financial support by ICREA under the ICREA Academia programme. S.G. was supported by a pre-doctoral fellowship from AGAUR (2018FI_B_00444). C.B. was supported by a pre-doctoral fellowship from Fernando Tarongí Bauzà Grant. J.K. is contracted by the "FOLIUM" programme within the FUTURMed project; talent for the medicine within the future from the Fundació Institut d'Investigació Sanitària Illes Balears. The food companies Hojiblanca (Lucena, Spain) and Patrimonio Comunal Olivarero (Madrid, Spain) donated extra virgin olive oil, and the Almond Board of California (Modesto, CA, USA), American Pistachio Growers (Fresno, CA, USA) and Paramount Farms (Wonderful Company, LLC, Los Angeles, CA, USA) donated nuts for the PREDIMED-Plus pilot study.

None of the funding sources took part in the design, collection, analysis or interpretation of the data or in the decision to submit the manuscript for publication.

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Received 25 January 2021; editorial decision 6 October 2021