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The impact of nutrient-based dietary patterns on cognitive decline in older adults

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SUMMARY

Background & aims: The impact of nutrient patterns on cognitive decline is complex and findings are still inconclusive. We aimed to identify major nutrient patterns and to explore their association with cognitive decline over time among older adults.

Methods: In a population-based cohort, 2250 cognitively healthy people aged ≥60 years were identified at baseline (2001–2004), and followed-up to 9 years. Global cognitive function was tested with the Mini-Mental State Examination (MMSE) at baseline and follow-ups. Nutrients intake was assessed on the basis of food intake using a 98-semi-quantitative food frequency questionnaire at baseline, and nutrient-based patterns were identified by principal components analysis based on 30 nutrients. Mixed-effects linear regression models were used to determine their association with change in cognitive function taking into account potential confounders.

Results: Four major patterns (the plant-, animal-, dairy-derived nutrients and animal/plants-derived fats) were identified. Over the follow-up time, each one unit increment in plant- ($\beta = 0.081$, $P = 0.002$) and animal-derived nutrients pattern scores ($\beta = 0.098$, $P < 0.001$) was associated with slower decline in MMSE score. On the other hand, one-unit higher in dairy-derived nutrients pattern was related to a faster decline in global cognitive function ($\beta = -0.064$, $P = 0.014$). No significant association between animal/plants fats pattern and cognitive decline was observed. In stratified analyses, the association of high scores of plants- and animal-derived nutrient pattern with slower cognitive decline was stronger in *APOE* ε4 carriers than in ε4 non-carriers.

Conclusions: Plant- and animal -derived nutrients are associated with preserved cognitive function, especially among the *APOE* ε4 carriers, whereas nutrients derived from dairy products may accelerate cognitive decline in older adults.

1. Introduction

With global aging of population, number of older adults with cognitive decline and dementia has increased dramatically becoming a pressing public health concern [1]. The current absence of effective pharmacological treatment opens new avenues in identifying strategies able to prevent or delay the onset and the disease progression [2]. Among them, adoption of healthy lifestyle and intervention on dietary habits, seem to be particularly feasible and cost effective [3].

Despite considerable research efforts over the last two decades, the role of nutrients in influencing age-related cognitive decline is

Abbreviations: Swedish National study on Aging and Care-Kungsholmen, SNAC-K; Mini-Mental State Examination, MMSE; Semi-Quantitative Food Frequency Questionnaire, SFFQ; Body Mass Index, BMI; Apolipoprotein epsilon 4, APOE ε4; Principal Component Analysis, PCA; 95% confidence intervals, 95% CI.

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still open to discussion. Epidemiological evidence suggests that the intake of single nutrients including antioxidants (carotenoids, C, and E), B vitamins group (B9, B6, B12), and long chain n-3 fatty acids from dietary sources, is associated with lower cognitive decline in most observational studies [4]. However, results from intervention trials on individual nutrients supplementation are inconclusive [5]. Since people consume a complex combination of dietary components interacting with each other rather than isolated foods or nutrients, recently a growing body of research has focused on dietary patterns (DPs) to assess usual diet in relation to cognitive decline [6]. The majority of these studies derived DPs based on *a* priori assumptions (hypothesis-driven approaches) about healthy dietary components, such as Mediterranean Diet [7,8], or using *a* posteriori approaches, that have the advantage of reflecting the actual dietary intakes observed in a given population by capturing all the complexity of the food 'matrix' [9–17]. Most of the prospective studies that applied data-driven methods have focused on food patterns, reporting that adherence to Healthy/Prudent dietary patterns characterized by high consumption of fruit, vegetables, legumes, nuts, poultry, fish, and vegetables oils are associated with better cognitive function. At the same time, the high content of red and processed meat, animal and trans fats, and sweets of the modern Western diet, may accelerate cognitive decline [9–12,14,15,17]. Although foods-based DPs offer a more immediate interpretation of the results and an easily translation into public health recommendations, they do not provide information about the bioactive components of the food with biological function, beyond various dietary habits, independently from the specific food sources they derive from [18].

As far we know, no prospective studies have investigated the impact of nutrients-based dietary patterns on cognitive decline. Within the Swedish National Study on Aging and Care in Kungsholmen (SNAC-K), we have previously shown that high adherence to the Prudent dietary pattern, based on food groups, was associated with less cognitive decline over 6 years of follow-up, whereas a high adherence to the Western dietary pattern was related to a faster decline in cognitive function [11]. In order to explore the possible biological basis for the observed association, in the present work we aimed to identify major diet-derived nutrient patterns, and to examine their association with cognitive decline using 9-year follow-up data from the SNAC-K study.

2. Methods

2.1. Study design and study population

Participants were derived from the ongoing longitudinal study, SNAC-K [19], which includes individuals aged 60 years and older living in the Kungsholmen district, a central area in Stockholm, Sweden. At baseline (2001–2004), the sample was randomly selected from 11 age groups: 60, 66, 72, 78, 81, 84, 87, 90, 93, 96, and 99 or older. The follow-up assessment is performed at 6-year intervals for younger age cohorts (60, 66, and 72 years) and at 3-year intervals for older age cohorts (78, 81, 84, 87, 90, 93, 96, and 99 years). The first follow-up for the older cohorts was conducted from 2004 through 2007 (3-years follow-up), the second follow-up for the older cohorts and the first follow-up for the younger cohorts were carried out form 2007 through 2010 (6-year follow-up), and the third follow-up for the older cohorts was performed from 2010 through 2013 (9-year follow-up). Among the 5111 persons initially invited to participate, 3363 were examined (response rate, 73.3%). Of them, 2250 participants were left for the current study after exclusion of 322 people with dementia at baseline, 164 subjects with missing Mini-Mental State Examination (MMSE) score, 33 persons with MMSE score $\leq$ 24, and 594 people with incomplete dietary data at baseline (Fig. 1).

The Regional Ethical Review Board in Stockholm, Sweden approved the SNAC-K project. Written informed consent was obtained from each participant, or from a proxy (i.e. a close family member) for cognitively impaired participants.

2.2. Dietary intake assessment

Dietary intake at baseline was collected using a country-specific SFFQ with 98 food and beverage items [20]. Participants were inquired about how often on average over the past 12 months they consumed each food item on a fixed 9-level scale ranging from never to four or more times per day. The respondents indicated their average portion with the support of four colour pictures illustrating a plate containing increasing amounts of staple foods: [1] potatoes/rice/pasta, [2] meat/fish, and [3] vegetables. For other food items, natural portion sizes such as an apple, or average portion sizes for sex and age were used [20]. Frequencies were converted into daily consumption, and total energy and nutrients intake was derived from the food composition database of the National Food administration [21]. Because intake of most nutrients was not normally distributed, variables were log transformed. Nutrients intake was adjusted for total energy intake using the residual method [22] and then standardized to make comparable different units of measurement. The 98-food items were collapsed into 32 food groups, according to their nutrient composition and food similarities.

2.3. Cognitive function assessment

The global cognitive functioning was assessed with the MMSE [23] administered by trained neuropsychologist at baseline and at the 3-, 6- and 9-year follow-ups. The assessment followed a standardized procedure for administration and scoring.

2.4. Covariates assessment

At enrolment, nurses and physicians collected data on sociodemographics including age, sex, and education, medical history, current use of medications and lifestyle habits, through face-to-face interviews by trained staff following a structured protocol. Participants also underwent a general clinical assessment including anthropometrics and arterial blood pressure measurements. Educational level was divided into elementary school, high school, and university. Civil status was classified as married (including cohabitants), widow (er)/divorced, and single. Height and weight were measured using standard protocols and body mass index

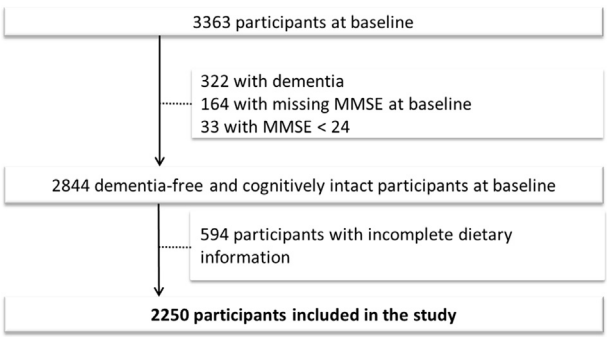

Fig. 1. Flow chart of SNAC-K study participants.

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(BMI) was calculated as weight (kg) divided by height (m^2). Alcohol consumption was categorized into three categories: no/occasional, light-to-moderate drinkers (1–7 drinks/week for women and 1–14 drinks/week for men), and heavy (≥8 drinks/week for women and ≥15 drinks/week for men). Smoking status was grouped as never- or occasional smokers, former, and current smokers. Physical activity was categorized on the basis of both frequency and intensity during the past 12 months, as: i) physically inactive (never or less than 2–3 times/month; ii) health enhancing (light exercise several times per week or every day); and iii) fitness-enhancing (moderate-to-intense exercise several times per week or every day) [24]. Chronic diseases at baseline as vascular (hypertension, stroke, coronary heart disease, atrial fibrillation, cerebrovascular diseases, and heart failure), metabolic (diabetes and dyslipidaemia), cancer, and depression were defined using a combination of clinical examinations, patient medical histories, and medical records [25]. Peripheral blood samples were collected from all participants and genotyping was performed to determine Apo-lipoprotein E (*APOE*) allelic status that was dichotomized into any ε4 carriers or ε4 non–carriers. Information about the participants' vital status was ascertained through the Swedish Cause of Death Register during the entire follow-up period.

2.5. Data analysis

2.5.1. Identification of nutrient-based dietary patterns

A panel of 30 macro- and micronutrients providing a comprehensive and non-redundant picture of the traditional Swedish diet was set to identify nutrient patterns. Exploratory principal component analysis (PCA) was performed on the correlation matrix of the nutrients (Table 1). To determine the number of components to retain, we considered a combination of the following criteria: the interpretability of the factors, the proportion of total explained variance, and the visual inflections in the scree-plot of eigenvalues. Varimax (orthogonal) rotation was applied to the factor loadings matrix in order to facilitate the factors interpretability. Nutrients with rotated factor loadings greater or equal 0.40 in a given factor were used to label the factor. Each subject received a factor score for each component extracted, with higher score indicating relatively higher adherence to that nutrient pattern. Nutrient-based patterns were modelled both continuously by assessing the linear effect for every unit increase in nutrients patterns score, and categorically as low and high score (the value below the 50^{th} percentile was considered as reference category).

2.5.2. Statistical analysis

Characteristics of the participants by nutrient-based patterns intake were compared using Chi-square tests for categorical variables and t-test for continuous variables. To test the hypothesis that nutrients-based patterns would affect the rate of change in MMSE scores over time, we used linear mixed-effects model using follow-up time (years), as the time variable. Random effects included intercept and slope for time. Fixed effects included the interaction term between time and each nutrients score. Specifically, positive β-coefficients indicated a decreased rate of cognitive function decline over time attributable to increase in nutrients-based

Table 1
Factor loading matrix for the four nutrient-based patterns identified by Principal Component Analysis carried out on 30 nutrients (n = 2250).

Nutrients[a]	Nutrients-based patterns			
	Plant-derived nutrients	Animal-derived nutrients	Dairy-derived nutrients	Animal/plant fats
Total protein	-	0.77	0.54	-
Fibre	0.82	-	-	-
Disaccharides	-	−0.43	0.51	-
Monosaccharides	0.72	−0.37	-	-
Starch	0.31	-	-	−0.30
Cholesterol	–	0.50	-	0.61
SFAs	−0.63	-	-	0.48
MUFAs	−0.56	-	-	0.65
PUFAs	-	-	−0.37	0.48
Iodine	-	0.69	-	-
Phosphate	-	0.42	0.82	-
Iron	0.28	0.40	-	-
Calcium	-	-	0.89	-
Potassium	0.81	-	0.36	-
Sodium	-	0.79	-	-
Magnesium	0.73	-	0.32	−0.34
Selenium	-	0.70	0.43	0.35
Vitamin C	0.85	-	-	-
Vitamin B1	0.57	0.34	0.33	-
Vitamin B2	–	-	0.90	-
Vitamin B3	0.34	0.79	-	–
Vitamin B6	0.72	0.29	-	-
Folic acid	0.86	-	0.30	-
Vitamin B12	–	0.49	0.54	0.26
Vitamin K	-	0.26	-	0.45
Vitamin D	-	0.51	-	0.33
Vitamin E	0.44	-	-	0.67
Zinc	-	0.72	0.45	-
Retinol	−0.39	-	0.28	0.30
β-carotene equivalents	0.70	-	-	-
% Variance explained by each factor	28.16	21.67	17.93	10.96
Cumulative % of variance explained	28.16	49.83	67.75	78.72

Abbreviation: SFAs, saturated fatty acids; MUFAs, monounsaturated fatty acids; PUFAs, polyunsaturated fatty acids. The importance of the corresponding nutrient to the factor was measured by the magnitude of each loading measures. A positive loading indicates an increased intake of the nutrients Loadings ≥0.40 in absolute value define the main nutrients for each factor and were shown in bold typeface; loadings <0.25 in absolute value were suppressed.

[a] Energy-adjusted nutrients.

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patterns scores. The basic model was adjusted for age, sex, education, and included simultaneously each retained nutrients pattern score. Then, in the multiple-adjusted model, we further controlled for civil status, physical activity, smoking, total energy intake (Kcal), and alcohol intake. We ran separate analysis by adding *APOE* ε4 status to the model. We also adjusted for vascular and metabolic disorders, cancer, depression, and body mass index in a separate model as they can be considered either confounders or mediator of the hypothesized association. We explored our data for potential effect modification by covariates on the association between nutrients patterns and cognitive decline by adding interaction terms to the model. When heterogeneity was present, stratum-specific estimates were evaluated.

We also performed sensitivity analyses comparing characteristics of the participants included and excluded from this study according to the completion of the SFFQ at baseline. We ran the analysis after excluding participants with prevalent diabetes at baseline to be confident that the degree of adherence to nutrients patterns was not affected by this condition. Moreover, we controlled for the confounding effect of any potential pre-existing undiagnosed chronic diseases at baseline, by excluding from the analysis those subjects who had died within the first 3 years of follow-up. Finally, due to the high education level of the study population, we also performed the analysis restricted to participants with MMSE > 27 at baseline [26] to avoid reverse causation on dietary habits due to under diagnosed pre-dementia stage.

All statistical analyses were performed using Stata 15.0 version (StataCorp LP., College station, Texas, USA), and a two-sided *P*-value ≤ 0.05 was considered statistically significant.

3. Results

Table 1 shows the factor-loading matrix and total cumulative explained variance for the four main nutrients-based dietary patterns extracted, which explained 78.7% of the total variance (total nutrient variability). The first factor retained labelled 'Plant-derived nutrients' had the greatest positive loading on fibre, monosaccharide, potassium, magnesium, Vitamin C, Vitamin B1, B6, folic acid, Vitamin E, and β-carotene, and the largest negative loadings on monounsaturated and saturated fatty acids, and accounted for 28.2% of the total variance. The pattern 'Animal-derived nutrients' was characterized by the greatest loadings on total proteins, cholesterol, phosphate, sodium, selenium, vitamin B3, B12, vitamin D, and zinc, and negative loading on disaccharides, and explained 21.7% of the variability. The third pattern named 'Dairy-derived nutrient' with 17.9% of the explained variance had the greatest loading on proteins disaccharides, phosphate, calcium, selenium, vitamin B2 and B12. The last pattern called 'Animal/plant fats' explained 11.0% of the variance and was related to the greatest loading on cholesterol, saturated fatty acids (SFAs), monounsaturated fatty acids (MUFAs), polyunsaturated fatty acids (PUFAs), Vitamin K, and Vitamin E.

3.1. Food sources of each nutrients pattern

To improve the interpretability of the identified patterns, we calculated the Pearson's correlation coefficient between the continuous factors and the daily frequency of 32 food groups obtained on the same data. For the 'Plant-derived nutrients' pattern the highest values of the correlation coefficient were with all types of fruit (r = 0.66), vegetables (r = 0.62), and vegetables oils (r = 0.23), but it was inversely correlated with refined cereals (r = -0.26), butter (r = -0.24), and alcoholic beverages (r = -0.22). The 'Animal-derived nutrients' pattern was highly correlated with fresh meat (r = 0.35), poultry (r = 0.29), and fish (0.30) and inversely related to total fruit (r = -0.25), sweet/sugars (r = -0.26), and sweet beverages (r = -0.25). The 'Dairy-derived nutrients' pattern was characterized by high intake of milk (r = 0.70), yogurt (r = 0.37) and cheese (r = 0.23), and was inversely correlated with alcoholic beverages (r = -0.21). The 'Animal/plant-derived fats' pattern positively correlated with eggs (r = 0.47), butter (r = 0.27), and vegetable oils (r = 0.26) and negatively with whole bread (r = -0.25), grains and cereals (r = -0.27).

3.2. Nutrients-based dietary patterns and demographic-clinical characteristics and other lifestyle factors

Participants' characteristics according to nutrient-based dietary patterns are presented in Table 2. Participants with low scores for "Plant-derived nutrients" pattern were more likely to be older, males, less educated, married, less physically active, former or current smokers, and heavier drinkers. People with lower intake of "Animal-derived nutrients" pattern were more likely to be older, widower or divorced, and had lower BMI. Participants with high scores for "Dairy-derived nutrient" pattern were more likely to be older, females, widower or divorced, and abstainers or occasionally drinkers. Individuals with high intake of "Animal/plant fats" pattern were more frequently current smokers. There were no differences in their baseline MMSE score.

3.3. Association between nutrient-based dietary patterns and cognitive decline

The three years rate of change in global cognitive function was a decline of 0.612 units in MMSE score (β = -0.612). Table 3 reports the β-coefficients with 95% Confidence Intervals (CI) and *P*-values representing the change in mean MMSE score comparing the high versus the low intake of each pattern and for 1-unit increment in nutrients pattern score. After adjusting for age, sex, education, and total energy intake (model 1), compared to the low intake (below the median values) of plant- and animal-derived nutrient pattern those with high intake experienced slower decline on global cognitive function. However, higher intake of dairy-derived nutrients pattern was associated with faster decline. There was no significant association between the animal/plants fats pattern and cognitive function. Adjusting additionally for civil status, smoking, alcohol consumption, and physical activity only slightly affected these associations (model 2). The estimated effects were slightly attenuated with further adjustment for *APOE* ε4 status, vascular and metabolic disorders, depression, cancer, and BMI (data not shown). We found that APOE ε4 status modified the relationship of plant- (*P* for interaction = 0.001) and animal-derived nutrients patterns (*P* for interaction = 0.062) with cognitive function. In stratified analysis, higher intake of plant-derived and animal-derived nutrients patterns showed significantly slower cognitive decline in APOE ε4 carriers than in ε4 non-carriers (Table 4).

In sensitivity analyses, we compared people excluded from the study (n = 594) with the analytical sample (n = 2250). Persons excluded were likely to be older, females, widow (er)/divorced, with lower BMI, less physically active, never smokers, non-alcohol drinkers, more affected by chronic diseases at baseline, and exhibited lower global cognitive function at baseline. No differences in terms of APOE ε4 status were observed (Supplemental Table 1). The exclusion of participants, who reported a diagnosis of diabetes at baseline and those who had died within the first 3 years of follow-up, did not change the associations between nutrients patterns and cognitive decline. Further, the results remained largely unchanged after restricting the analysis among participants with MMSE > 27 at baseline (Supplemental Table 2).

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Table 2
Baseline characteristics of participants by nutrient-based dietary pattern (n = 2250).

Characteristics	Plant-derived nutrients (−4.33; 3.41)		Animal-derived nutrients (−4.08; 3.56)		Dairy-derived nutrients (−3.58; 4.68)		Animal/plant fats (−5.81, 3.23)	
	Low intake	High intake	Low intake	High intake	Low intake	High intake	Low intake	High intake
Age, mean ± SD	71.7 ± 9.3	70.0 ± 9.0	72.2 ± 9.4	69.4 ± 8.6	69.9 ± 9.1	71.7 ± 9.1	70.6 ± 9.0	71.0 9.3
Sex								
Males	626 (55.6)	247 (22.0)	436 (38.8)	437 (38.8)	498 (44.3)	375 (33.3)	445 (39.6)	428 (38.0)
Females	499 (44.4)	878 (78.0)	689 (61.2)	688 (61.2)	627 (55.7)	750 (66.7)	680 (60.4)	697 (62.0)
Educational level								
Elementary	147 (13.1)	118 (10.5)	132 (11.7)	133 (11.8)	133 (11.8)	132 (11.7)	143 (12.7)	122 (10.9)
High school	560 (49.8)	542 (48.2)	554 (49.2)	548 (48.8)	538 (47.8)	564 (50.2)	548 (48.7)	554 (49.3)
University	418 (37.2)	464 (41.3)	439 (39.0)	443 (39.4)	454 (40.4)	428 (38.1)	434 (38.6)	448 (39.9)
Civil status								
Married	605 (53.8)	534 (47.6)	546 (48.5)	593 (52.9)	619 (55.1)	520 (46.3)	548 (48.8)	591 (52.6)
Widow (er)/divorced	336 (29.9)	413 (36.8)	416 (37.0)	333 (29.7)	325 (28.9)	424 (37.8)	377 (33.5)	372 (33.1)
Unmarried	184 (16.4)	175 (15.6)	163 (14.5)	196 (17.5)	180 (16.0)	179 (15.9)	199 (17.7)	160 (14.3)
BMI, mean ±SD	25.91 ± 4.1	25.91 ± 3.9	25.44 ± 3.9	26.38 ± 4.1	25.87 ± 3.9	25.95 ± 4.1	25.75 3.9	26.08 ± 4.1
Physical activity								
Inadequate	296 (26.3)	183 (16.3)	252 (22.4)	227 (20.2)	227 (20.2)	252 (22.4)	234 (20.8)	245 (21.8)
Health-enhancing	603 (53.6)	592 (52.6)	598 (53.2)	597 (53.1)	596 (53.0)	599 (53.2)	580 (51.6)	615 (54.7)
Fitness-enhancing	226 (20.1)	350 (31.1)	275 (24.4)	301 (26.8)	302 (26.8)	274 (24.4)	311 (27.6)	265 (23.6)
Smoking status								
Never	444 (39.6)	538 (48.3)	498 (44.5)	484 (43.3)	477 (42.8)	505 (45.1)	489 (43.7)	493 (44.2)
Former	473 (42.2)	439 (39.4)	450 (40.3)	462 (41.4)	479 (43.0)	433 (38.7)	479 (42.8)	433 (38.8)
Current smoker	204 (18.2)	137 (12.3)	170 (15.2)	171 (15.3)	159 (14.3)	182 (16.3)	152 (13.6)	189 (17.0)
Alcohol consumption								
No/occasional	293 (26.1)	319 (28.4)	324 (28.9)	288 (25.7)	261 (23.2)	351 (31.3)	302 (26.9)	310 (27.6)
Light-to-moderate	637 (56.7)	740 (70.0)	676 (60.2)	701 (62.5)	702 (62.5)	675 (60.2)	682 (60.7)	695 (61.9)
Heavy drinking	193 (17.2)	63 (5.6)	123 (11.0)	133 (11.9)	160 (14.3)	96 (8.6)	139 (12.4)	117 (10.4)
Vascular disorders	858 (76.3)	837 (74.4)	837 (74.4)	858 (76.3)	843 (74.9)	852 (75.7)	837 (74.4)	858 (76.3)
Metabolic disorders	630 (56.0)	648 (57.6)	625 (55.6)	653 (58.0)	637 (56.6)	641 (57.0)	643 (57.2)	635 (56.4)
Cancer	96 (8.5)	83 (7.4)	91 (8.1)	88 (7.8)	83 (7.4)	96 (8.5)	97 (8.6)	82 (7.3)
Depression symptoms	79 (7.0)	90 (8.0)	94 (8.4)	75 (6.7)	80 (7.1)	89 (7.9)	83 (7.4)	86 (7.6)
APOE ε4	311 (29.2)	320 (29.7)	329 (30.8)	302 (28.2)	325 (30.1)	306 (28.8)	311 (29.2)	320 (29.7)
MMSE baseline, median (range)	29 (24–30)	29 (24–30)	29 (24–30)	29 (24–30)	29 (24–30)	29 [24–30]	29 [24–30]	29 [24–30]

Data are presented as numbers and proportions, means ± standard deviations (SD), or median and range. Abbreviations: BMI, body mass index; APOE ε4, apolipoprotein ε4 allele; MMSE, Mini-Mental State Examination; Nutrient-based patterns were categorized in low and high intake using the median of each component as cut-off point (the value below the 50th percentile was considered the reference category).

Table 3
Association between nutrients-based patterns and three years mean change in MMSE scores. Positive β-coefficients indicate that an increase in the nutrient-based pattern intake was associated with a decreased rate of decline in cognitive function during follow-up.

Nutrients-derived patterns	Model[1]		Model[2]	
	β-coefficient (95% CIs)	*P– value*	β-coefficient (95% CIs)	*P– value*
Plant- derived nutrients x time[a]				
High intake vs. low intake	0.207 (0.107, 0.307)	<0.001	0.202 (0.102, 0.302)	<0.001
One unit increase	0.085 (0.033, 0.137)	0.001	0.081 (0.029, 0.133)	0.002
Animal- derived nutrients x time[a]				
High intake vs. low intake	0.150 (0.050, 0.249)	0.003	0.148 (0.048, 0.247)	0.004
One unit increase	0.098 (0.047, 0.150)	<0.001	0.098 (0.046, 0.149)	<0.001
Dairy- derived nutrients x time[a]				
High intake vs. low intake	−0.124 (−0.224, −0.024)	0.015	−0.125 (−0.225, −0.025)	0.014
One unit increase	−0.064 (−0.116, −0.013)	0.014	−0.064 (−0.116, −0.013)	0.014
Animal/plant fats x time[a]				
High intake vs. low intake	−0.023 (−0.123, 0.078)	0.653	−0.015 (−0.115, 0.085)	0.767
One unit increase	−0.021 (−0.073, 0.032)	0.437	−0.019 (−0.071, 0.033)	0.467

Abbreviation: MMSE, Mini Mental State Examination. β-coefficients (95% confidence intervals) and P-values represent three years change in mean MMSE score comparing the high versus the low intake of that pattern and per 1-unit increase in nutrients pattern score.

[a] Change in MMSE score over time attributable to nutrients patterns. Model[1] included terms for age, sex, and education. Model[2] included also civil status, physical activity, smoking, alcohol consumption, and total energy intake (Kcal). Four nutrients patterns were mutually adjusted.

4. Discussion

In this large population-based longitudinal cohort study of older adults, we found that i) the major nutrients patterns based on food intake included plant-, animal-, and dairy-derived nutrients patterns and animal/plant fats pattern; ii) higher intake of the plant- and animal -derived nutrients were associated to decreased decline in cognitive function over 9 years, whereas a diet high in nutrients derived from dairy products may accelerate cognitive decline over time; and iii) the relation between the first two nutrient patterns and change in cognitive decline appeared to be more pronounced among persons who are *APOE ε4* carriers. The association of animal/plant fats patterns with cognitive decline was not evident.

So far, no prospective cohort studies explored dietary patterns at nutrients level in relation to cognitive decline, but a few cross-sectional studies on this topic are available. One study derived

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Table 4
Association between nutrients-based patterns and three years mean change in MMSE scores according to APOE ε4 status. Positive β-coefficients indicate that an increase in the nutrient-based pattern intake was associated with a decreased rate of decline in cognitive function during follow-up.

Nutrients-derived patterns	*APOE ε4* non-carriers (n = 1499)		*APOE ε4* carriers (n = 624)	
	β-coefficient (95% CIs)	*P– value*	β-coefficient (95% CIs)	*P– value*
Plant- derived nutrients x time[a]				
High intake vs. low intake	0.176 (0.057, 0.295)	0.004	0.254 (0.069, 0.439)	0.007
One unit increase	0.040 (−0.023, 0.102)	0.212	0.178 (0.084, 0.273)	<0.001
Animal- derived nutrients x time[a]				
High intake vs. low intake	0.033 (−0.085, 0.152)	0.583	0.364 (0.180, 0.550)	<0.001
One unit increase	0.053 (−0.007, 0.114)	0.085	0.161 (0.066, 0.256)	0.001
Dairy- derived nutrients x time[a]				
High intake vs. low intake	−0.142 (−0.261, −0.024)	0.019	−0.067 (−0.253, 0.117)	0.474
One unit increase	−0.059 (−0.120, 0.002)	0.060	−0.073 (−0.168, 0.021)	0.129
Animal/plant fats x time[a]				
High intake vs. low intake	−0.038 (−0.157, 0.081)	0.531	0.004 (−0.181, 0.190)	0.962
One unit increase	−0.037 (−0.098, 0.024)	0.230	0.017 (−0.087, 0.121)	0.751

AbbreviationsMMSE, Mini Mental State Examination. β-coefficients (95% confidence intervals) and P-values represent three years change in mean MMSE score comparing the high versus the low intake of that pattern and per 1-unit increase in nutrients pattern score.

[a] Change in MMSE score over time attributable to nutrients patterns. Model adjusted for age, sex, education, civil status, physical activity, smoking, alcohol consumption, and total energy intake (Kcal). Four nutrients patterns were mutually adjusted.

nutrient patterns based on plasma biomarkers and reported that a pattern high in plasma vitamins B (B1, B2, B6, B9, and B12), C, D, and E was associated with better cognitive function among older adults [16]. In another study, Gu et al. found that an inflammation-related nutrients pattern characterized by low intake of calcium, vitamins (D, E, A, A, B1, B2, B5, B6, B9), n3-PUFAs, and high intake of cholesterol was associated with worse cognitive function in non-demented older people [27]. Since current evidence on the role of *a* posteriori dietary patterns and cognitive decline is mainly based on food groups, we discuss the identified associations also in terms of food items. A previous cross-sectional study reported that a dietary pattern dominated by frequent intake of vegetables, fruits, and legumes, and highly correlated with fibre, vitamins A, C, magnesium and potassium, was associated with lower cognitive impairment in older Chinese women [13]. Similar results were observed in a US cohort aged 45 and older, in whom a pattern consisting of plant-based foods, was associated with higher cognitive performance over time and a pattern including fried food and processed meat was associated with lower cognitive performance [15]. Furthermore, adherence to “Healthy/Prudent” dietary patterns characterized by vegetables, fruits, legumes, fish and/or poultry, were found associated with lower cognitive deficit in other prospective cohort studies of older adults, whereas “Western” patterns were related with high cognitive decline [11,17,28]. Other cross-sectional studies report that food patterns rich in plant-based foods and fish were associated with lower whereas pattern characterized by higher intake of red and processed meat, and fried food was related with greater cognitive deficit [9,10,14]. In addition, a recent study showed that low intake of poultry, fish, animal fats, dietary fibre and vitamins B2, B6, and B12 was associated with increased cognitive and functional impairment among older women [29]. In agreement with these studies, we found that nutrient's combinations of fibre, vitamins B, C, E, minerals, and β-carotene (Plant-derived nutrients pattern) and of proteins, cholesterol, phosphate, sodium, selenium, vitamin B3, B12, vitamin D, and zinc (Animal-derived nutrients patterns), were associated with lower cognitive impairment. Possible biological explanations for this protective effect may come from beneficial properties of the nutrients with high loadings on these two nutrient patterns. Vitamin C, B1, E, β-carotene [30,31], niacin, and selenium [32,33] may exert an effect via their antioxidant capability of reducing brain damage due to reactive oxygen species (ROS), or by regulating the methylation of homocysteine cycle (Vitamin B6, B12, and B9), which in turn impact on neurotoxicity [34]. Adequate protein intake is associated with less cognitive impairment in particular among older people possibly through its pivotal role in maintaining brain integrity and function, and for their contents of tryptophan and tyrosine, precursors of serotonin and catecholamines (e.g. dopamine), respectively [35]. Vitamin D has potential effect on neurotrophic factor production, neurotransmitter release, oxidative stress mechanisms and modulation of inflammatory processes [36]. In our study, we found that the nutrient pattern characterized by high intake of proteins, disaccharides, selenium, Vitamin B2, and B12 (Dairy-derived nutrients pattern) was related with faster cognitive decline. This finding could be counterintuitive since some of these nutrients have been considered key protective molecules for cognition (32, 33. 35). However, the interpretation of the effect of each single nutrient is little informative without taking into account the food sources (dairy products) and those nutrients that are highly correlated to them (i.e. SFAs) [37]. Examining the food sources, results from previous epidemiological studies are contradictory. A recent meta-analysis reported that the inverse association between milk consumption and the risk of cognitive disorders was limited to Asian and African populations, characterized by lower intake of milk and dairy products [38]. It has been suggested that high intake of fermented dairy foods (e.g. yogurt and cheese) is inversely related with cognitive disorders [39], on the contrary milk consumption is associated with greater decline over time [40]. One of the possible biological explanations for this detrimental effect can be attributable to the high lactose and D-galactose (sugars) content in non-fermented dairy products, as liquid milk, which induces neurodegeneration in animals [41]. This observation is particularly considerable in Scandinavian countries that are characterized by high milk consumption together with a high lactase enzyme activity, raising the concentration of glucose and D-galactose in blood [42]. However, further studies are needed to confirm this finding, especially considering that very few studies on nutrient-based dietary pattern are available. The null association between global cognitive function and Animal/plant fats pattern, which was mainly based on eggs, butter, fish, and vegetable oils, might be due to the fact that this nutrient pattern correlates positively with nutrients, which might have different biological effect on our outcome. For examples, previous studies reported that higher SFAs consumption, particularly from milk products and spread, is related with worse global cognitive decline trajectories, whereas higher intake of MUFAs and long-chain n-3 PUFAs, from vegetables oils and fish, is related to better trajectories [43,44]. In the present study, higher adherence to Animal/plant fats pattern

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might result in consumption of nutrients with opposite effect related to cognitive outcome such as PUFAs (a considered protective factor) vs SFAs (a believed risk factor), particularly considering the different food sources they come from (butter and cream vs vegetables oils and fish). Thus, the reduction of these nutrients into a single pattern might hinder detection of these effects resulting in attenuating the association [37]. Further longitudinal studies aimed to disentangle the effects of different types of fats and also their food sources should be performed.

The findings on the identified nutrients patterns are generally supporting our previous study on dietary patterns [11] and proved possible biological explanations for previous results. The Plant-derived and the Animal-derived nutrient patterns mostly reflect the Prudent pattern and the Dairy-derived pattern and the Animal/plant pattern are generally reflecting the Western pattern. However, food items and nutrients estimated might reflect not exactly the same concept. People consume a diet that consists of a combination of nutrients with cumulative and interactive effect [18,37]. For example, the differences between meat intake in previous study and Animal-derived nutrient pattern in this study could be interpreted with the fact that meat contains bioactive components (i.e. proteins, selenium, zinc, etc.), which are protective for cognitive function, while others (i.e. SFAs) are considered harmful. Dietary patterns were identified according to the correlation between food items, while nutrients patterns were extracted on the basis of the correlation between individual nutrients. Thus, Animal-related nutrient pattern does not only reflect meat intake [18].

Interestingly, our findings suggest that *APOE* ε4 status, the well-established genetic risk factor of sporadic Alzheimer Disease [45], significantly modified the effect of the Plant- and Animal-derived nutrient patterns on cognitive decline revealing a stronger protective effect in ε4 carriers as compared with ε4 non-carriers. In agreement with this finding, it has been reported a protective effect of seafood/dietary Ω-3 fatty acids on cognitive function only in the ε4 carriers [46]. The exact mechanisms behind these observations need to be clarified. One hypothesis is that *APOE* ε4 carriers might have compromised neuroanatomical reserves, poor brain protection and repair mechanisms than ε4 non-carriers, making them more vulnerable to environmental risk conditions that could affect the brain [45]. On the other hand, this also means that ε4 carriers might be also more susceptible to such factors that can be considered protective amplifying their effects [45,46].

When interpreting the results, some shortcomings should be acknowledged. In our study, a selection bias cannot be rule out as the exclusion of people with incomplete dietary data resulted in overrepresentation of younger and healthier participants, underestimating the true association between nutrients patterns and cognitive function. Dietary information was self-reported and imprecision in dietary recall may have affected the observed association. In addition, diet was assessed once at baseline and data on possible dietary changes thereafter were not available although we expect that dietary patterns remain quite stable over time, particularly among older adults [47]. Limitations of PCA may arise from the arbitrary decisions involved in the definition of nutrient patterns, including the interpretation and labelling of the factors [48]. However, as there is no standard procedure and terminology for the names of the pattern, we labelled each pattern based on the possible effect on health and easy interpretation as well possible intervention at population level. Although the MMSE is the most often used screening instrument for providing a global measure of cognitive function in clinical and research settings, is less sensitive than other screening tools in detecting slight cognitive deterioration, therefore the observed associations might be underestimated [49]. Future investigations should focus on specific cognitive domains measured through comprehensive neuropsychological test battery. Moreover, we cannot exclude the possible residual or unmeasured confounding, although we adjusted for all the most known risk factors. Finally, SNAC-K population sample included urban and well-educated people limiting the generalizability of our findings. Major strengths of this study include its community-based longitudinal design with comprehensive data collection, and the long follow-up period. Further, we generated nutrients patterns using PCA, an exploratory data reduction technique able to provide an overall picture of the dietary behaviours of the population under examination taking into account for the complex interactions among nutrients and their cumulative effect. This approach is particularly useful when researches are interested in exploring whether there are underlying patterns that explain variability on people' nutrients intake [50]. Another strength of the study is the use of nutrients that, compared to foods, are universal, not exchangeable, and less country-specific. Besides, dietary patterns at nutrient level, reflecting a combination of bioactive components largely implicated in the pathophysiology, can be easily interpreted in a biological framework [18, 51].

In conclusion, our study provides evidence that an optimal combination of nutrients mainly from fruit, vegetables, whole cereals, fish, fresh meat, and poultry are associated with preserved cognitive function especially among the *APOE* ε4 carriers, whereas higher consumption of certain foods, as dairy products, may accelerate cognitive decline in older adults. These findings might have public health implication encouraging the importance of food choices in usual diet, and promoting tailored nutritional interventions targeted to older adults at high risk of developing cognitive impairment and dementia.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnu.2018.12.012.

Authorship

Federica Prinelli study concept and design, dietary and statistical data analysis, interpretation of data, and writing the manuscript. Laura Fratiglioni is the study coordinator, contributed to the study concept and design, interpretation of data, and revision of the manuscript for intellectual content. Massimo Musicco and Fulvio Adorni contributed to the interpretation of data and revision of the manuscript for intellectual content. Ingegerd Johansson and Behnaz Shakersain contributed to the dietary data analysis and interpretation of data. Debora Rizzuto contributed to the study concept and design, statistical data analysis, interpretation of data, and revision of the manuscript for intellectual content. Weili Xu contributed to the study concept and design, interpretation of data, and revision of the manuscript for intellectual content. All the authors revised and approved the last version to be published.

Conflicts of interest

The authors have declared that no conflict of interests exists.

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