



## Specific nutrient patterns are associated with higher structural brain integrity in dementia-free older adults



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### ABSTRACT

Optimal nutrition may play a beneficial role in maintaining a healthy brain. However, the relationship between nutrient intake and brain integrity is largely unknown. We investigated the association of specific nutrient dietary patterns with structural characteristics of the brain. Within the population-based Swedish National study on Aging and Care-Kungsholmen (SNAC-K), a cross-sectional study of 417 dementia-free participants aged  $\geq 60$  years who underwent structural magnetic resonance imaging (MRI) scans during 2001–2003, was carried-out. Data on dietary intake were collected using a food frequency questionnaire, from which intake of 21 nutrients was estimated. By principal component analysis, five nutrient patterns were extracted: (1) NP1 was characterized by fiber, vitamin C, E,  $\beta$ -carotene, and folate [Fiber&Antioxidants], (2) NP2 by eicosapentaenoic (EPA, 20:5  $\omega$ -3) and docosahexaenoic (DHA, 22:6  $\omega$ -3) polyunsaturated fatty acids (PUFAs), proteins, cholesterol, vitamin B3, B12, and D [long chain (LC)  $\omega$ -3PUFAs&Proteins], (3) NP3 by  $\alpha$ -linoleic (18:2  $\omega$ -6) and  $\alpha$ -linolenic (18:3  $\omega$ -3) PUFAs, monounsaturated fatty acids (MUFAs), and vitamin E [MUFAs& $\omega$ -3,6PUFAs], (4) NP4 by saturated fatty acids (SFAs), trans fats, MUFAs, and cholesterol [SFAs&Trans fats], (5) NP5 by B-vitamins, retinol, and proteins [B-Vitamins&Retinol]. Nutrient patterns scores were tertiled with the lowest tertile as reference, and were related to total brain volume (TBV) and white matter hyperintensities volume (WMHV) using linear regression models adjusting for potential confounders. In the multi-adjusted model, compared to the lowest intake for each pattern, the highest intake of NP1 ( $\beta = 11.11$ ,  $P = 0.009$ ), NP2 ( $\beta = 7.47$ ,  $P = 0.052$ ), and NP3 ( $\beta = 10.54$ ,  $P = 0.005$ ) was associated with larger TBV whereas NP5 was related to smaller TBV ( $\beta = -12.82$ ,  $P = 0.001$ ). The highest intake of NP1 was associated with lower WMHV ( $\beta = -0.32$ ,  $P = 0.049$ ), whereas NP4 was associated with greater WMHV ( $\beta = 0.31$ ,  $P = 0.036$ ). In sum, our results suggest that the identified brain-health specific nutrient combinations characterized by higher intake of fruit, vegetables, legumes, olive and seed oils, fish, lean red meat, poultry and low in milk and dairy products, cream, butter, processed meat and offal, were strongly associated with greater brain integrity among older adults.

### 1. Introduction

A growing body of epidemiological evidence suggests that optimal nutrition may play a beneficial role in preserving cognitive function

and brain health, reducing the burden of age-related diseases (Vauzour et al., 2017). Brain ageing is a heterogeneous process characterized by extensive structural, molecular and functional changes resulting in a reduction in brain volume (both grey and white matter) (Resnick et al., 2003), or an accumulation of periventricular and subcortical white

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**List of abbreviation**

PUFAs	Polyunsaturated fatty acids	WMV	White Matter Volume
MeDi	Mediterranean Diet	TBV	Total Brain Volume
SNAC-K	Swedish National study on Aging and Care-Kungsholmen	WMHV	White Matter Hyperintensities Volume
MRI	Magnetic Resonance Imaging	SFFQ	Semi-Quantitative Food Frequency Questionnaire
BMI	Body Mass Index	SFAs	Saturated fatty acids
MMSE	Mini Mental State Examination	MUFAs	Monounsaturated fatty acids
ATC	Anatomical Therapeutic Chemical classification system	EPA	Eicosapentaenoic fatty acids
APOE $\epsilon$ 4	Apo-lipoprotein E $\epsilon$ 4 carriers	DHA	Docosahexaenoic fatty acids
TIV	Total Intracranial Volume	LC $\omega$ -3PUFAs	Long chain $\omega$ -3 Polyunsaturated fatty acids
GMV	Grey Matter Volume	PCA	Principal Components Analysis
		SEs	Standard Errors

matter hyperintensities reflecting vascular damage in the white matter (Peters, 2006). In the latest years, neuroimaging techniques have been proposed as a precise and sensitive tool to characterize the relationship between diet and age-related brain changes although the number of studies in this pioneering field of research is limited (Pistollato et al., 2015; Zamroziewicz et al., 2016; Monti et al., 2015). Specific individual nutrients have been reported to be deeply implicated in decreasing oxidative stress, neuroinflammation, and vascular dysfunction (Lam et al., 2016; Morris et al., 2012) thus preserving brain integrity. Such nutrients include fiber, proteins,  $\omega$ -3 polyunsaturated fatty acids (PUFAs), antioxidants and B-vitamins that can be found mainly in fruit and vegetables, fish and foods from marine origin, nuts, whole grains, and vegetable oils (Vauzour et al., 2017; Pistollato et al., 2015; Tangney et al., 2011; Moore et al., 2018). Considering the complex interactions between foods and nutrients and that single nutrients taken in isolation may not be sufficiently powerful to protect the brain of older adults, several dietary patterns have been developed and investigated in relation to brain aging. Among them, the widely studied Mediterranean Diet (MeDi)-type was found cross-sectionally or longitudinally associated with less brain atrophy (Titova et al., 2013a,b; Gu et al., 2015; Mosconi et al., 2014b; Luciano et al., 2017; Gardener et al., 2012; Pelletier et al., 2015), larger cortical thickness (Gu et al., 2015; Staubo et al., 2017; Mosconi L. et al., 2018), less white matter hyperintensities (Gardener et al., 2012), preserved structural connectivity (Pelletier et al., 2015), and with Alzheimer's Disease (AD) biomarkers (Walters et al., 2018; Matthews DC et al., 2014; Berti et al., 2018). However, very few studies explored the relationship of nutrient based patterns with brain measures in non-demented older people. They mainly showed a positive association between PUFAs&Vitamin E-nutrient pattern and white matter integrity (Bowman et al., 2010; Gu et al., 2016) and markers of neuronal activity (Berti et al., 2015). Markers of neuronal activity were also positively associated with vitamin B12&D and Antioxidants&Fiber nutrient patterns and negatively with the Fats pattern (Berti et al., 2015). A high trans fats nutrient pattern was reported positively associated with less total cerebral volume (Bowman et al., 2010) and an inflammation-related nutrient pattern with smaller total brain volume (Gu et al., 2018). Furthermore, three nutrient biomarker patterns high in plasma  $\omega$ -3 and  $\omega$ -6 PUFAs and carotene were found associated with enhanced functional brain network efficiency (Zwilling et al., 2019). Except for these cross-sectional studies mostly performed in small samples, which nutrient-based dietary patterns are related to brain health is poorly explored and understood. In the current study we hypothesized that specific nutrient' combinations are associated with structural brain integrity. We aimed to verify this hypothesis by examining the cross-sectional associations between nutrient patterns and measures of total brain volume and white matter hyperintensities volume in a population of dementia-free older adults.

## 2. Methods

### 2.1. Study design and study population

The study population was derived from the Swedish National Study on Aging and Care in Kungsholmen (SNAC-K) (Lagergren et al., 2004), an ongoing population-based longitudinal study on people aged 60 years and older living at home or in institution in Kungsholmen, Stockholm (Sweden). A total of 3363 older adults were examined (response rate, 73.3%) at baseline (2001–2003). Of them, a sub-sample of 555 non-institutionalized, non-disabled, and non-demented participants agreed to undergo a structural brain magnetic resonance imaging (MRI) scan. In this study, we excluded participants with sub-optimal MRI quality ( $n = 47$ ), Parkinson's disease, transient ischemic attack, brain tumours, and other neurological disorders ( $n = 47$ ) that might interfere with MRI data interpretation. We additionally excluded people with missing values on dietary information ( $n = 44$ ) leading to a final sample of 417 participants for the current analysis. Compared with the rest of the SNAC-K sample, participants with MRI scans were younger (mean [SD] age, 70.0 [8.6] vs 75.4 [11.4] years;  $P < 0.001$ ), less likely to be females (59.0% vs 65.7,  $P < 0.001$ ), had higher educational level (42.5% vs 31.3%;  $P < 0.001$ ), were more physically active (28.3% vs 18.5%;  $P < 0.001$ ), never smokers (41.5% vs 48.5%;  $P = 0.023$ ), non-alcohol drinkers (23.7% vs 39.5%;  $P < 0.001$ ), non-users of vitamin supplements (20.9% vs 29.0%;  $P = 0.001$ ), had higher Mini-Mental State Examination (MMSE) total score (mean [SD], 29.2 [1.0] vs 28.2 [2.9];  $P < 0.001$ ), and had higher BMI (mean [SD], 25.9 [1.0] vs 25.5 [2.9];  $P < 0.044$ ). No differences in terms of APOE  $\epsilon$ 4 genotype and presence of cardio-metabolic factors (hypertension, diabetes, and dyslipidaemia) were observed.

SNAC-K and SNAC-K MRI received ethical permissions from the Ethics Committee at Karolinska Institutet, Stockholm, Sweden. Written informed consents were collected from all participants in this study.

### 2.2. Data collection

At baseline, demographic data (such as age, sex, and education), medical history, current use of medications and lifestyle habits (physical activity, alcohol consumption, and smoking status), were collected following a structured protocol. Educational achievement was categorized in a 3-class variable (elementary school, high school, and university). Height and weight were measured using standard protocols and body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Alcohol consumption was assessed as number of drinks per week and categorized as no/occasional, light-to-moderate drinkers (1–7 drinks/week for women and 1–14 drinks/week for men), and heavy drinkers ( $\geq 8$  drinks/week for women and  $\geq 15$  drinks/week for men). Smoking status was classified as never/occasional, former, or current. Physical activity was categorized on the basis of both frequency

and intensity of physical exercise during the past 12 months and divided into inactive (never or less than 2–3 times/month); health-enhancing (light exercise several times per week or every day); and fitness-enhancing (moderate-to-intense exercise several times per week or every day) (Rydwik et al., 2013). Chronic medical conditions (hypertension, diabetes, and dyslipidemia) were ascertained combining data from physician and nurse's examinations, medical records from the Swedish National Patient Register, and laboratory tests (Calderon-Larranaga et al., 2016). Global cognitive function was assessed with the MMSE test (Folstein et al., 1975) following standardized procedures for administration and scoring. Current use of vitamin supplements was categorized according to the Anatomical Therapeutic Chemical (ATC) classification system (ATC codes). 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  $\epsilon 4$  allele carriers vs  $\epsilon 4$  non-carriers.

### 2.3. Dietary assessment

A self-administered country-specific 98-item semi-quantitative food frequency questionnaire (SFFQ) was used to collect dietary habits over the prior year (Johansson et al., 2002). Participants were asked about the frequency of consumption of each food item on a 9-level scale ranging from “never” to “four or more times per day”. Four colour pictures illustrating a plate containing increasing amounts of staple foods, potatoes/rice/pasta, meat/fish, and vegetables, were used to indicate the portion size. For other food items, natural portion sizes such as an apple, or average portion sizes for sex and age were used (Johansson et al., 2002). Frequencies were converted into daily consumption, and the national food composition database (<https://www.livsmedelsverket.se/en/food-and-content/naringsamnen/livsmedelsdatabasen>) was used to calculate energy and nutrient intake by multiplying frequencies of consumption of each portion by the nutrient content of the specified portion. Estimated daily energy and non-energy adjusted nutrients intakes are reported as Supplemental data (Table S1).

### 2.4. MRI data acquisition and preprocessing

Participants were scanned with a 1.5 T MRI scanner (Philips Intera, The Netherlands). The protocol included an axial 3D T1-weighted fast field echo (repetition time [TR] 15 ms, echo time [TE] 7 ms, flip angle (28) 15°, field of view [FOV] 240, 128 slices with slice thickness 1.5 mm and in-plane resolution 0.94 × 0.94 mm, no gap, matrix 256 × 256), and an axial turbo fluid-attenuated inversion recovery (FLAIR; TR 6000 ms, TE 100 ms, inversion time 1900 ms, FA 90°, echo train length 21, FOV 230, 22 slices with slice thickness 5 mm and in-plane resolution 0.90 × 0.90 mm, gap 1 mm, matrix 256 × 256). Volumes of grey matter (GMV), white matter (WMV), and cerebrospinal fluid (CSFV) were computed after segmentation of the T1-weighted images in SMP12 (Statistical Parametric Mapping, <http://www.fil.ion.ucl.ac.uk/spm/>, Wellcome Trust Centre for Neuroimaging, FIL, London, UK), implemented in Matlab 10 (The Mathworks Inc., MA, US), using the improved unified segmentation algorithm. GMV and WMV were summed up to obtain total brain tissue volume (TBV). Total intracranial volume (TIV) was calculated by adding the GMV, WMV and CSFV volumes. All segmentations were inspected by a neuroimaging expert (G.K). White matter hyperintensities volume (WMHV) were manually drawn on FLAIR images by G.K. and further interpolated on the corresponding T1 images to compensate for the gap between slices in FLAIR (the intra-rater reliability was high [ICC >0.987]) (32).

### 2.5. Statistical analysis

Twenty-one nutrients were selected on the basis of their biological functions (Vauzour et al., 2017; Zamroziewicz et al., 2016; Monti et al., 2015; Lam et al., 2016; Morris et al., 2012; Moore et al., 2018;

Lopez-Garcia et al., 2005) and considered for the analysis: proteins, fiber, cholesterol, saturated fatty acids (SFAs), monounsaturated fatty acids (MUFAs), polyunsaturated fatty acids (as  $\alpha$ -linoleic 18:2  $\omega$ -6,  $\alpha$ -linolenic 18:3  $\omega$ -3, eicosapentaenoic [EPA, 20:5  $\omega$ -3] and docosahexaenoic [DHA, 22:6  $\omega$ -3]), trans fatty acids, B-vitamins (B1, B2, B3, B6, folate, B12), vitamin C, D, E, retinol, and  $\beta$ -carotene. Independence scaling of the variances and co-variances was obtained by taking the natural log of the input variables. Nutrient intake was adjusted for total energy intake using the residual method (Willett et al., 1997) and then standardized to make comparable units of measurement. Nutrient patterns were derived by principal component analysis (PCA) using the correlation matrix. The number of factors to retain was chosen based on the interpretability of the patterns, the percentage of total variance explained, and the scree-plots of eigenvalues (eigenvalues > 1.0). The factors were rotated by an orthogonal transformation (varimax rotation). Data suitability for factor analysis were determined using both visual inspection and statistical procedures, including scree plot construction, the Bartlett's Test of Sphericity ( $P$ -value < 0.001), and the Kaiser–Meyer–Olkin (0.6897) measure of sampling adequacy.

Given the skewed distribution of WMHV volume, natural log-transformation was performed. Linear regression models were used to calculate unstandardized  $\beta$  coefficients and standard errors (SEs) from the associations between nutrient patterns (independent variable) and TBV and WMHV (dependent variables). To correct for head size, TBV and WMHV were regressed by TIV to generate TIV-adjusted residuals using the formula:  $\text{Volume}_{\text{adj}} = \text{Volume}_{\text{raw}} - \beta(\text{TIV}_i - \text{TIV}_{\text{mean}})$  (Jack et al., 1989). TBV and WMHV residuals were used in the analyses.

Nutrient pattern scores were tertiled considering the lowest tertile as reference category. The basic-adjusted model (model 1) included age, sex, education, and log-transformed energy intake (Kcal). In the multi-adjusted models, we further controlled for lifestyles factors (smoking status, alcohol consumption, and physical activity), vitamin supplements, and APOE  $\epsilon 4$  genotype (model 2). Finally, we included cardio-metabolic factors (hypertension, diabetes, dyslipidaemia) and BMI (model 3) as they can be considered either confounders or mediators of the hypothesized association. We examined whether the associations between nutrient patterns and brain volumes were modified by sex, age, and APOE  $\epsilon 4$  genotype by performing stratified analyses. In sensitivity analysis, we assessed the robustness of our findings by excluding participants with MMSE score < 27 (Lin et al., 2013), to control for potential reverse causation (which occurs when cognitive impairment modifies dietary intake). We also restricted the analysis to non-users of vitamin supplements ( $n = 330$ ). All statistical analyses were performed using Stata 15.0 version (StataCorp LP, College station, Texas, USA), and a two-sided  $P$ -value  $\leq 0.05$  was considered statistically significant.

#### 2.5.1. Data and code availability statement

The data and code used in this study will be made available upon direct request.

## 3. Results

The characteristics of the participants are reported in Table 1.

### 3.1. Nutrient patterns extraction

Five nutrient patterns were identified explaining about 90% of the total nutrient variability in the data (Table S2). Factor loadings represented how much a variable contributed to that specific pattern. Fig. 1 displays the identified nutrient patterns and their rotated factor loadings as a spider diagram. Nutrients with rotated factor loadings greater than or equal to 0.40 in a given factor were used to characterize each component. NP1, green colour, had the largest positive loadings on fiber, vitamin C, E,  $\beta$ -carotene, and folate, and the largest negative loadings on MUFAs and SFAs, accounting for 24% of variance in nutrient intakes [Fiber&Antioxidant]. NP2, red colour, had the greatest positive loadings

**Table 1**  
Characteristics of study participants (n = 417).

Characteristics	Total (N = 417)
Age categories	
60–69	228 (54.7)
70–79	121 (29.0)
80–89	63 (15.1)
90–96	5 (1.2)
Females	246 (59.0)
Educational level	
Elementary	45 (10.79)
High school	195 (46.76)
University	177 (42.45)
Physical activity	
Inadequate	74 (17.75)
Health-enhancing	225 (53.96)
Fitness-enhancing	118 (28.30)
Smoking status	
Never	173 (41.49)
Former	181 (43.41)
Current smoker	63 (15.11)
Alcohol consumption	
No/occasional	99 (23.74)
Light-to-moderate	271 (64.99)
Heavy drinking	47 (11.27)
Vitamins supplements	87 (20.86)
Energy intake (mean ± SD), Kcal/d	1706.17 ± 544.59
MMSE (mean ± SD)	29 ± 1
BMI (mean ± SD), Kg/m <sup>2</sup>	25.94 ± 3.92
Cardio-metabolic factors*	351 (84.17)
APOE ε4 genotype	110 (26.38)
TBV (mean ± SD), ml	1063.75 ± 130.76
WMHV (mean ± SD), ml	5.08 ± 8.01
TIV (mean ± SD), ml	1498.70 ± 159.21

Abbreviation: MMSE, Mini Mental State Examination; BMI = body mass index; TBV = total brain volume; WMHV = white matter hyperintensities volume; APOE ε4 genotype, apolipoprotein E ε4 allele carriers; TIV = total intracranial volume. \*Hypertension, diabetes, and dyslipidaemia. Data are presented as numbers (percentages) of participants unless otherwise indicated. Missing data: MMSE = 22, BMI = 1, and WMHV = 3.

on EPA and DHA (long-chain [LC] ω-3PUFAs), proteins, cholesterol, vitamin B3, B12, and vitamin D, accounting for 22% of the variance [LC ω-3PUFAs&Proteins]. NP3, yellow colour, accounted for 14% of the

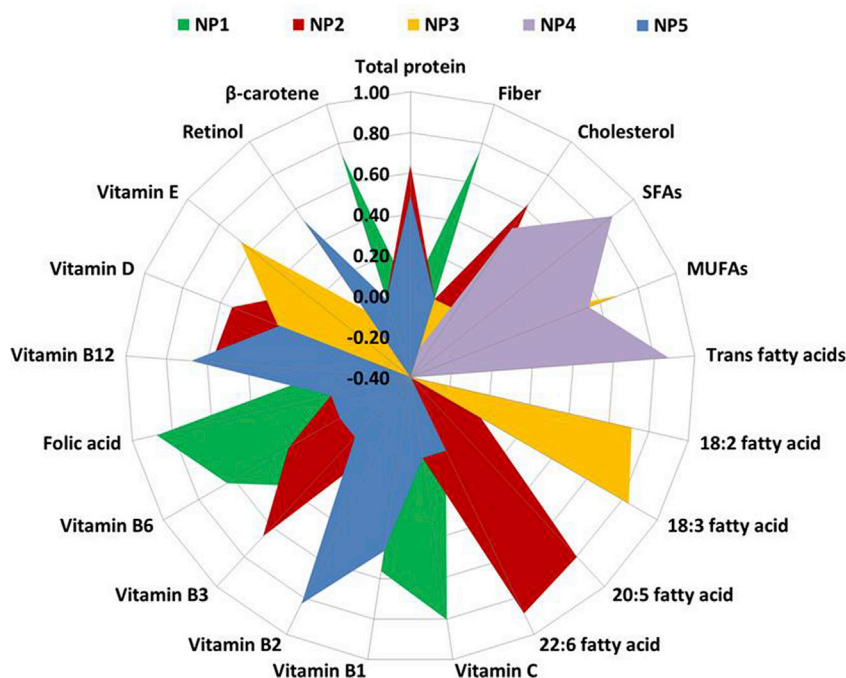
variance and had the greatest loadings on MUFAs, ω-3 and ω-6 PUFAs, and vitamin E [MUFAs, ω-3,6-PUFAs&Proteins]. SFAs, trans fatty acids, MUFAs, and cholesterol loaded positively whereas fiber loaded negatively on the NP4 [SFAs&Trans fats], purple colour, and accounted for the 15% of the total variability. Finally, proteins, vitamin B1, B2, B12 and retinol contributed to the NP5 [B-Vitamins&Retinol], blue colour, and accounted for 13% of variance (Table S2 and Fig. 1). Individual principal component scores were computed by summing up intakes of each nutrient weighted by its factor loading, which represents the relative contribution of that nutrient. Each subject received a factor score for each component extracted, with higher score indicating greater levels of consumption of that pattern. The NP1 standardized individual score varied from -3.01 to 3.97; the NP2 score from -4.02 to 3.00; the NP3 score from -5.58 to 3.30; the NP4 fats score from -3.77 to 2.54; and the NP5 score from -2.40 to 3.68.

### 3.2. Nutrient patterns' food sources

To confirm the interpretability of the identified nutrient patterns, we calculated the Pearson correlation coefficient between the continuous factors and the daily frequency of 19 food groups obtained on the same data (Table S3). NP1 [Fiber&Antioxidants] had the highest values of the correlation coefficient with vegetables and legumes (r = 0.70), fruit (r = 0.56), and vegetables oils (r = 0.20), whereas it was inversely correlated with sweets and sugars (r = -0.26) and margarine (-0.22). NP2 [LC ω-3PUFAs&Proteins] was highly correlated with fish (r = 0.61), poultry (r = 0.32), and lean red meat (r = 0.26). NP3 [MUFAs&ω-3,6PUFAs] was characterized by high intake of vegetables oils (r = 0.45) and margarine (r = 0.39). NP4 [SFAs&Trans fats] was positively correlated with butter (0.58), cheese (r = 0.33), and cream (r = 0.27), and inversely correlated with whole cereals. NP5 [B-Vitamins&Retinol] correlated positively with milk products (r = 0.62), cured and processed meat, offal (r = 0.35), and yogurt (r = 0.20).

### 3.3. Nutrient patterns and demographic-clinical characteristics and other lifestyle factors

Participant's characteristics according to nutrient patterns are presented in Table S4. Compared with people with lower score, participants



**Fig. 1.** Nutrient patterns derived by Principal Component Analysis and rotated factor loadings in 417 participants. Abbreviation SFAs, saturated fatty acids; MUFAs, mono-unsaturated fatty acids. The NP1 [Fiber&Antioxidant], green colour, has the largest positive loadings on fiber, vitamin C, E, β-carotene, and folate, and the largest negative loadings on MUFAs and SFAs. The NP2 [LC ω-3PUFAs&Proteins], red colour, has the greatest positive loadings on EPA and DHA, proteins, cholesterol, vitamin B3, B12, and vitamin D. The NP3 [MUFAs, ω-3,6-PUFAs], yellow colour, has the greatest loadings on MUFAs, ω-3 and ω-6 PUFAs, and vitamin E. The NP4 [SFAs&Trans fats], purple colour, has the greatest positive loadings on SFAs, trans fatty acids, MUFAs, and cholesterol and the largest negative loading on fiber. The NP5 [B-Vitamins&Retinol], blue colour, has the largest loadings on proteins, vitamin B1, B2, B12 and retinol.

with high scores for NP1 [Fiber&Antioxidants] were more likely to be females, more physically active, less likely to be drinkers, and showed smaller TIV. People with high scores for NP2 [LC ω-3PUFAs&Proteins] were more frequently younger, females, and less affected by cardio-metabolic conditions. Those with high scores for NP3 [MUFAs&ω-3,6PUFAs] showed a larger TBV. Individuals with high score for NP5 [B-Vitamins&Retinol] presented a smaller TBV and TIV (*P*-value<0.05).

### 3.4. Associations of nutrient patterns with brain measures

In the basic-adjusted model, participants in the highest tertile of NP1 [Fiber&Antioxidants] had statistically significant larger TBV ( $\beta = 11.13$ , *P* = 0.007) and smaller WMHV ( $\beta = -0.33$ , *P* = 0.037) than participants in the lowest tertile group. Larger TBV was observed among participants with the highest intake of the NP2 [LC ω-3PUFAs&Proteins] ( $\beta = 8.18$ , *P* = 0.035) and NP3 [MUFAs&ω-3,6PUFAs] ( $\beta = 10.38$ , *P* = 0.006). Smaller TBV ( $\beta = -13.40$ , *P* < 0.001) was found in those with higher intake of the NP5 [B-Vitamins&Retinol] (model 1, Table 2).

In the multi-adjusted model (Model 2) the association between NP2 and TBV was slightly attenuated ( $\beta = 7.47$ , *P* = 0.052) whereas the relationship between NP4 and WMHV became statistically significant ( $\beta = 0.31$ , *P* = 0.036). Inclusion of cardio-metabolic factors and BMI in the model further attenuated the associations between NP2 and TBV ( $\beta = 7.12$ , *P* = 0.072); between NP1 and WMHV ( $\beta = -0.31$ , *P* = 0.059); and between NP4 and TBV (although was not significant), and WMHV ( $\beta = 0.28$ , *P* = 0.064) (Model 3). In stratified analyses, we did not find significant differences on the associations between nutrient patterns and MRI measures among different age (younger-old [*<*78 years of age] vs older-old [*≥*78 years of age]), males and females, and *APOE* ε4 allele carriers vs non-carriers. There were no statistically significant interactions between nutrient patterns and age, sex, or *APOE* ε4 genotype. In sensitivity analysis, after excluding participants with MMSE score <27 (*n* = 7), all results remained unchanged (data not shown). However,

some of the associations were attenuated after excluding those who did take vitamin supplements becoming non-significant (Table S5).

## 4. Discussion

In this cross-sectional study of dementia-free older adults, we identified five different nutrient patterns that are associated with brain integrity: NP1 [Fiber&Antioxidant], NP2 [LC ω-3PUFAs&Proteins], NP3 [MUFAs&ω-3,6PUFAs], NP4 [SFAs&Trans fats], and NP5 [B-Vitamins&Retinol]. We found that high intake of NP1, NP2 and NP3 were associated with larger TBV; instead NP5 was associated with smaller TBV. Moreover, high intake of NP1 was related to lower white matter damage whereas high NP4 was associated with greater WMHV.

So far, only a few cross-sectional studies have investigated nutrient patterns in relation to brain structural measures. Within the WHICAP Imaging Study, Gu et al. (2016) observed increased white matter integrity with high consumption of ω-3 and ω-6 PUFAs and vitamin E (Gu et al., 2016); and smaller total brain volume with high adherence to an inflammation-related nutrient pattern characterized by low intake of calcium, vitamins, PUFAs and high intake of cholesterol (Gu et al., 2018). A nutrient pattern high in plasma vitamins B, C, E, and D or high intake of marine n-3 PUFAs was associated with higher total brain tissue volume and white matter integrity (Bowman et al., 2010). Other studies focused on Alzheimer's disease brain biomarkers seem to support these findings. High intake of vitamin B12, vitamin D and ω-3 PUFAs was related with lower Alzheimer's disease brain biomarker and higher β-carotene and folate intake correlated to higher neuronal metabolism (Mosconi et al., 2014a). An Alzheimer's disease "protective" nutrient pattern characterized by vitamin B12, vitamin D, zinc, vitamin E, MUFAs, and ω-3 and ω-6 PUFAs, carotenoids, retinol, vitamin C and fiber, was found to be positively associated with higher neuronal metabolism and low brain atrophy (Berti et al., 2015). Nutrient biomarkers patterns high in plasma ω-3 and ω-6 PUFAs and carotene were also found associated with enhanced

**Table 2**  
Association between nutrient patterns scores (tertiles group) and total brain volume and white matter hyperintensities volume (*n* = 417).

Nutrients patterns	No	TBV						WMHV						
		Model 1		Model 2		Model 3		No	Model 1		Model 2		Model 3	
		β (SEs)	<i>P</i>	β (SEs)	<i>P</i>	β (SEs)	<i>P</i>		β (SEs)	<i>P</i>	β (SEs)	<i>P</i>	β (SEs)	<i>P</i>
<b>NP1</b>														
Middle	139	4.26 (4.08)	0.297	4.12 (4.17)	0.324	3.72 (4.24)	0.382	139	-0.28 (0.15)	0.064	-0.28 (0.15)	0.065	-0.25 (0.15)	0.102
High	139	11.13 (4.11)	0.007	11.11 (4.24)	0.009	10.88 (4.26)	0.011	137	-0.33 (0.16)	0.037	-0.32 (0.16)	0.049	-0.31 (0.16)	0.059
<b>NP2</b>														
Middle	139	2.51 (3.61)	0.488	1.86 (3.63)	0.608	1.96 (3.62)	0.589	138	0.17 (0.15)	0.258	0.16 (0.15)	0.300	0.15 (0.15)	0.322
High	139	8.18 (3.86)	0.035	7.47 (3.84)	0.052	7.12 (3.94)	0.072	137	0.14 (0.15)	0.336	0.19 (0.15)	0.208	0.21 (0.15)	0.152
<b>NP3</b>														
Middle	139	7.37 (3.87)	0.057	7.61 (3.82)	0.047	7.43 (3.83)	0.053	136	-0.13 (0.14)	0.366	-0.08 (0.14)	0.570	-0.07 (0.14)	0.618
High	139	10.38 (3.78)	0.006	10.54 (3.75)	0.005	10.02 (3.73)	0.008	137	0.01 (0.15)	0.960	-0.01 (0.15)	0.978	-0.03 (0.15)	0.824
<b>NP4</b>														
Middle	139	-0.90 (3.80)	0.813	-0.57 (3.86)	0.883	-0.27 (3.83)	0.944	136	0.02 (0.14)	0.908	0.04 (0.14)	0.762	0.03 (0.15)	0.827
High	139	-2.22 (3.79)	0.558	-1.23 (3.71)	0.740	-0.52 (3.68)	0.888	137	0.27 (0.14)	0.060	0.31 (0.15)	0.036	0.28 (0.15)	0.064
<b>NP5</b>														
Middle	139	-7.89 (3.68)	0.032	-7.49 (3.82)	0.050	-7.61 (3.84)	0.048	138	0.01 (0.14)	0.985	0.03 (0.15)	0.812	0.03 (0.15)	0.817
High	139	-13.40 (3.66)	<0.001	-12.82 (3.66)	0.001	-13.73 (3.74)	<0.001	136	-0.07 (0.14)	0.636	-0.07 (0.14)	0.633	-0.03 (0.14)	0.834

Abbreviation: TBV = total brain volume; WMHV = white matter hyperintensities volume; β (SEs) = β-coefficient (standard errors); NP: Nutrient patterns. NP1: Fiber&Antioxidants; NP2: LC-ω-3PUFAs&Proteins; NP3: MUFAs&ω-3,6PUFAs; NP4: SFAs&Trans fats; NP5: B-Vitamins&Retinol. Lowest tertile was used as reference category. Model 1 included age, sex, education, and log-transformed energy intake. Model 2 is model 1 with further inclusion of physical activity, smoking status, alcohol consumption, vitamin supplements, and *APOE* ε4 genotype. Model 3 is model 2 with further inclusion of cardio-metabolic factors and BMI. Nutrient patterns were entered simultaneously into regression models.

functional brain network efficiency (Zwilling et al., 2019).

In accordance with previous results, we found that a pattern high in dietary fiber, vitamin C, B1, B6, folate, and carotenoids (NP1) mainly from fruit, vegetables and legumes, and vegetables oil was associated with larger total brain tissue volume and less white matter damage. People with high consumption of proteins, EPA and DHA, cholesterol, vitamin D, and B12 (NP2) from lean red meat, poultry, and fish, and high intake of MUFAs,  $\omega$ -3 and  $\omega$ -6 PUFAs, and vitamin E (NP3) derived from vegetables oils and margarine, have also a larger total brain tissue. These nutrients have been individually found associated with brain protection possibly through different biological pathways. Carotenoids, vitamins C and E have potent antioxidant properties (Fiedor et al., 2014; Frei et al., 2004). B-vitamins are co-enzymes involved in the regulation of energy-providing nutrients and homocysteine metabolism (Morris et al., 2006). Vitamin D serves to regulate neurotransmitters and neurotrophin and has anti-inflammatory and antioxidant neuroprotective functions (Soni et al., 2012). Fiber may have an impact in regulating the gut microbiota and glucose metabolism and consequently improving insulin-sensitivity at the brain level (Bosco et al., 2011). High protein intake has been related with lower brain Amiloid  $\beta$  burden possibly by reducing blood pressure or adiposity (Fernando et al., 2018). DHA and EPA, apart from their neuronal antioxidant and anti-inflammatory properties, are the major structural lipid components of neuronal membranes and promote plasticity, fluidity, and functionality (Cole et al., 2009). Additionally, the combination of all of these bioactive components may act in synergy. For examples, PUFAs (NP2 and NP3) are particularly vulnerable to lipid peroxidation because of their chemical structures. Thus, antioxidant nutrients, as vitamins and carotenoids (NP1), might be necessary to lower peroxidation in neuronal membranes (Alles et al., 2012; Amadiou et al., 2017).

In line with other studies (Bowman et al., 2010; Berti et al., 2015; Mosconi et al., 2014a), we showed that the NP4 [SFAs&Trans fats] from cheese, cream, and butter was associated with higher volume of white matter damage (WMHV). WMHV are signals that are thought to reflect demyelination and axonal loss, and have been linked to neurodegenerative diseases, such as Alzheimer's and Parkinson's disease (Provenzano et al., 2013). A diet high in SFAs and trans fatty acids (core features of Western Diet) is suspected to be associated with increased incidence of cognitive decline (Morris et al., 2004), dementia (Morris et al., 2014), and Alzheimer's disease (Gu et al., 2010). SFAs might promote chronic-diseases as diabetes, obesity, hypertension, and hyperlipidemia resulting in metabolic, inflammatory, and microvascular changes that induce injury to the white matter of the brain (Lopez-Garcia et al., 2005; Wang et al., 2016). It is noteworthy that after adjustment for cardio-metabolic factors and BMI the associations were slightly attenuated, suggesting that these conditions can be potential mediators in the development of white matter lesions, which have an impact on cognitive decline and dementia (Wang et al., 2016). Future investigations are needed to confirm this hypothesis and to explore the biological mechanistic linking SFAs to cell functions.

Interestingly, we found that MUFAs contributes to two nutrient patterns with different association with brain measures as the "Healthy" NP3 and the "Unhealthy" NP4. One possible explanation of these different effects might reside in the food sources of MUFAs: plant-derived (vegetable fats) vs animal-derived (dairy products), respectively. However, due to the fact that we focused on the nutrient combination instead of the single nutrient effect, our study could not conclude the exact role of MUFAs on MRI measures.

Further, high consumption of NP5 [B-Vitamins&Retinol] was significantly related with less total brain volume. This finding can be counterintuitive since several studies reported that nutrients as vitamin B12 and retinol could be key molecules for maintaining brain integrity (Tangney et al., 2011; Ono et al., 2012). However, an examination of the food sources indicates that this pattern was highly correlated with cured and processed meat, offal, and dairy products, which contain other components exerting adverse effect for the brain. Milk contains lactose (a

components used in animal models to induce neurodegeneration), dairy products are rich of SFAs, and processed meat and offal are usually high in sodium, SFAs, and N-nitroso compounds that were found associated with markers of brain damage and neurodegeneration (Morris et al., 2014; Cui et al., 2006; de la Monte et al., 2009).

The study has some limitations. Because of the cross-sectional design, we cannot infer any causal relationship between nutrient patterns and brain volumes. However, all participants were dementia-free, or even with MMSE  $\geq 27$ , which minimize the probability that alterations in brain structures due to poor cognitive abilities may have induced changes on dietary habits. Dietary information was self-reported and imprecision in dietary recall may have led to misclassify the exposure attenuating the association between the nutrient patterns and brain volumes. Additionally, although we controlled for several potential confounders, we cannot completely rule out the possibility of residual confounding due to unmeasured factors. There might be a concern for selection bias as our MRI study sample was restricted to relatively younger and healthier participants with a better cognitive performance. Accordingly, the strength of the associations might have been underestimated, and generalization to other populations should be done with caution. Limitations of PCA may arise from the arbitrary decisions involved in the definition of nutrient patterns, including the interpretation and the names of each factor. We also acknowledge that examine the combined effect of mixed nutrient patterns in relation to brain integrity would be very interesting. However, due to limited sample size, we could not carry out this analysis in the current study. In this study we did not considered any cognitive measures. How the brain measures are involved in the relationship between nutrient patterns and specific cognitive domains, measured through a comprehensive neuropsychological test battery, should be addressed in future investigations. Finally, we explored the association between nutrient patterns and other brain areas, such as hippocampus, but no significant results were found. One possible reason might be that the impact of nutrient patterns on this specific brain measure is not substantial and/or the study has not sufficient power to detect it. Our study has also several strengths. Firstly, it includes a relatively large sample of older adults with MRI scan and a comprehensive data collection on demographic, clinical, and lifestyle factors. Secondly, the exclusion of people with dementia and of those with MMSE  $< 27$  has reduced possible recall bias in reporting dietary intake due to memory impairment. Thirdly, the use of a data-driven approach to generate patterns at nutrients level is advantageous because it enables to capture the interactive effect of nutrients providing a physiological interpretation of their effects on brain integrity.

In summary, our findings suggest that optimal brain-health combinations of nutrients mainly from high intake of fruit, vegetables, legumes, olive and seed oils, fish, lean red meat, poultry and low in milk and dairy products, cream, butter, processed meat and offal, may help to maintain brain integrity (larger total brain volume and less white matter damage). Further longitudinal studies are needed to confirm our results and to explore whether these nutrient patterns are associated with structural brain changes over time. A better understanding of the precise mechanisms through which diet may impact brain health, is a first step to plan successful nutrition-focused interventions to counteract brain aging and promote human health.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.neuroimage.2019.05.066>.

## Author contributions

FP conceptualized and designed the study, performed the analysis, interpreted the results, and drafted the manuscript. LF contributed to the study concept and design, and to acquire the original data. GK processed the neuroimaging data. IJ contributed to nutrients data calculation. WX contributed to the study concept and design, and supervised the study. LF, GK, MM, FA, IJ, AM, and WL contributed to the interpretations of the results and critically revised the manuscript for important intellectual content.

## Ethics approval

SNAC-K and SNAC-K MRI received ethical permissions from the Ethics Committee at Karolinska Institutet, Stockholm, Sweden. Written informed consents were collected from all participants.

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## Conflicts of interest

The authors have declared that no conflict of interests exist.

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