

## Mediterranean diet habits in older individuals: Associations with cognitive functioning and brain volumes

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### ARTICLE INFO

#### Article history:

Received 18 May 2013

Received in revised form 4 September 2013

Accepted 4 October 2013

Available online 11 October 2013

Section Editor: Andrzej Bartke

#### Keywords:

Mediterranean diet

Meat intake

Brain morphometry

Cognitive function

Elderly

### ABSTRACT

To examine the association between dietary habits, cognitive functioning and brain volumes in older individuals, data from 194 cognitively healthy individuals who participated in the Prospective Investigation of the Vasculature in Uppsala Seniors cohort were used. At age 70, participants kept diaries of their food intake for 1 week. These records were used to calculate a Mediterranean diet (MeDi) score (comprising dietary habits traditionally found in Mediterranean countries, e.g. high intake of fruits and low intake of meat), with higher scores indicating more pronounced MeDi-like dietary habits. Five years later, participants' cognitive capabilities were examined by the seven minute screening (7MS) (a cognitive test battery used by clinicians to screen for dementia), and their brain volumes were measured by volumetric magnetic resonance imaging. Multivariate linear regression analyses were constructed to examine the association between the total MeDi score and cognitive functioning and brain volumes. In addition, possible associations between MeDi's eight dietary features and cognitive functioning and brain volumes were investigated. From the eight dietary features included in the MeDi score, pertaining to a low consumption of meat and meat products was linked to a better performance on the 7MS test ( $P = 0.001$ ) and greater total brain volume (i.e. the sum of white and gray matter,  $P = 0.03$ ) when controlling for potential confounders (e.g. BMI) in the analysis. Integrating all dietary features into the total MeDi score explained less variance in cognitive functioning and brain volumes than its single dietary component meat intake. These observational findings suggest that keeping to a low meat intake could prove to be an impact-driven public health policy to support healthy cognitive aging, when confirmed by longitudinal studies. Further, they suggest that the MeDi score is a construct that may mask possible associations of single MeDi features with brain health domains in elderly populations.

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### 1. Introduction

Dietary habits may play a role in cognitive aging, and the Mediterranean diet (MeDi) might help slow aging effects on cognition (Barak and Aizenberg, 2010). High intake of fish and a regular but moderate intake of alcohol are components of a MeDi and these factors have been linked to slower cognitive decline and reduced Alzheimer's Disease (AD) risk (Aberg et al., 2009; Stampfer et al., 2005). Moreover, higher adherence to MeDi may not only reduce the risk for AD (Scarmeas et al., 2006, 2009) but also lower mortality rates and speed of disease progression in those already afflicted (Scarmeas et al., 2007). Conversely, in a prospective cohort study of 1410 older adults, a higher adherence to MeDi did not lower the risk for incident dementia (Féart et al., 2009). In another study, a higher adherence to MeDi failed to delay the transition from a cognitively healthy status to mild cognitive impairment (Cherbuin and Anstey, 2012). One possible reason for these contrasting

**Abbreviations:** AD, Alzheimer's Disease; CI, Confidence interval; EPN, Ethics Committee of Uppsala; FWE, Family Wise Error; MRI, Magnetic resonance imaging; MeDi, Mediterranean diet; MCI, Mild cognitive impairment; MMSE, Mini-mental state examination; PIVUS, Prospective Investigation of the Vasculature in Uppsala Seniors; 7MS, Seven minute screening; SEM, Standard error of mean; SPM, Statistical parametric mapping; TFE, Turbo Field Echo; VBM, Voxel Based Morphometry.

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findings might be that the MeDi score, which is commonly used to explore correlations between MeDi and health outcomes in elderly cohorts, may mask health related effects of certain dietary components by including others that are not relevant for the health domain of interest.

Thus, in the present community-based study involving elderly men and women who were all first examined at age 70, possible associations between MeDi and cognitive functioning were studied. In addition, the relation between MeDi and brain volume was examined in an exploratory manner. Potential associations between single MeDi components and target measures were also separately explored.

## 2. Methods and materials

### 2.1. Study population and design

Data were obtained from the 'Prospective Investigation of the Vasculature in Uppsala Seniors' (PIVUS). This study initially included 1016 (50% females) individuals aged 70 living in the community of Uppsala, Sweden. The primary aim of PIVUS was to identify determinants of endothelial function and arterial compliance in a random sample of elderly individuals (Lind et al., 2005). At the time of the inclusion (between 2001 and 2003), a 7-day food diary was obtained for each 70-year-old individual (for description, please see below). Out of the initial cohort, 827 individuals agreed to participate in a follow-up investigation 5 years later (81.4% response rate), i.e. when they were 75 years old. Among the individuals who were re-investigated at the age of 75 years, a subsample of 409 elderly agreed to participate in a magnetic resonance imaging (MRI) scan of their brains (i.e. 49.5% of the re-investigated individuals), and their global cognitive function was assessed by means of the seven minute screening test (for description, please see Section 2.3). Of this number, 194 elderly men and women satisfied all criteria for this study, including cognitively normal clinical status (identified by a mini-mental state examination (MMSE) score greater than 26) (Folstein et al., 1975), absence of stroke or neurologic disease (e.g., tumors) at ages 70 and 75, valid measures from the magnetic resonance imaging (MRI) brain scan, and reliable food records at the age of 70 (flow-chart, see Fig. 1). Exclusions were administered to minimize the confounding effects of variables related to our main question: does adherence to the MeDi at the age of 70 years relate to cognitive function and brain structure 5 years later among cognitively healthy older adult? Importantly, patients who suffered from mild cognitive impairment and dementia were not considered for a separate analysis because sample size was severely underpowered ( $n = 8$ ). Exclusions were administered because diseases such as diabetes, stroke, and cognitive impairment can induce changes in diet and lifestyle.

The study was approved by the Ethics Committee of Uppsala (EPN) and the participants gave informed consent to participate.

### 2.2. Assessment of adherence to MeDi

Dietary habits were recorded at the age of 70 years. They were not re-assessed at the age of 75 years, the time point at which our dependent variables (brain volume, global cognitive function) were measured. A detailed description of the dietary recall procedure can be found elsewhere (Sjögren et al., 2010). Briefly, each participant was instructed by a dietitian on how to perform the 7-day dietary registration, and the amounts consumed were self-reported in household measurements or specified as portion sizes. Non-adequate reports of energy intake were determined by means of the Goldberg cutoff (as modified by Black, 2000). In this procedure, an acceptable range of energy intake is identified for each subject in relation to estimated energy expenditure – i.e., producing a 95% confidence interval (CI) for energy intake that is required for weight maintenance. Energy expenditure was calculated by adding basal metabolic rate (according to the age adjusted Schofield formula) and exercise-dependent metabolic rate (derived from

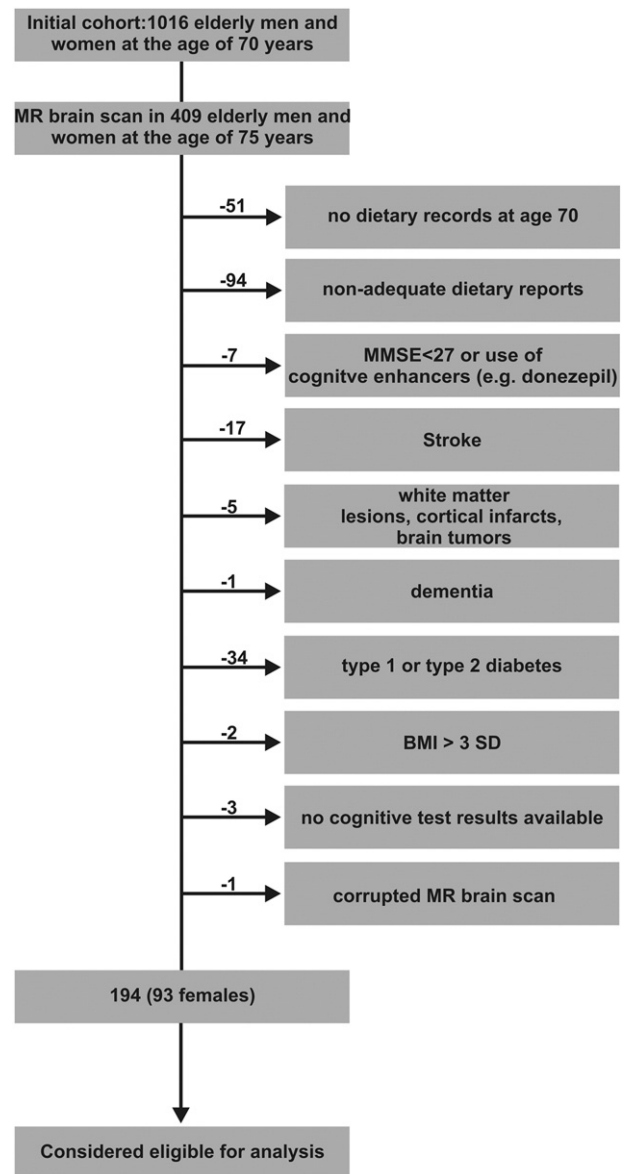


Fig. 1. Subject exclusion criteria and sample size.

questionnaires). Individuals with a reported energy intake outside the 95% CI were regarded as non-adequate reporters.

Based on the 7-day dietary registration, the adherence to MeDi was defined as a scale ranging from 0 (not adherent at all to MeDi) to 8 points (very adherent to MeDi). The median intake in the population served as the cutoff for each dietary variable; hence cutoffs are population specific moreover men and women were scored separately. For instance, those whose weekly fish consumption was below the population median were assigned a value of 0, whereas those whose fish intake was above the median a value of 1 was assigned. Reverse scoring was applied for intakes not considered a part of the Mediterranean diet (e.g. high intake of meat- and milk-products). In terms of alcohol intake, a value of 1 was assigned for moderate alcohol consumption, which was defined as an intake of 10–50 g/day for males and 5–25 g/day for females, respectively. Compared with the original score (Trichopoulou et al., 2003), polyunsaturated fatty acids replaced monounsaturated fatty acids when estimating dietary fat quality since in a traditional Swedish diet saturated and monounsaturated fats have similar food origins. In addition, because of their very low intake, nuts and seeds were excluded, and dietary leguminous plants were pooled with vegetables in our score. The reported intake of potatoes was added to cereals, because potato

consumption contributes considerably to carbohydrate intake in a Swedish population of older adults. All intakes were energy adjusted with the *residual adjusted method* prior to scoring (Willett et al., 1997).

### 2.3. Cognitive assessments

At the age of 75 years, a Swedish translation of the seven minute screening (7MS) test was administered to the participants (Solomon et al., 1998). This test is clinically used to screen for dementia and cognitive decline, and it consists of four brief cognitive tests: Benton temporal orientation (Benton, 1983), enhanced cued recall (Grober et al., 1988), clock drawing (Freedman et al., 1994), and categorical verbal fluency. The raw scores for the four subtests of the 7MS were summed with the logistic regression formula described previously by Solomon (Solomon et al., 1998). Solomon and coworkers estimated the formula by using the scores of the four tests from the screening battery as predictor variables. The lower the total raw score on the 7MS test, the lower the probability of having dementia (Solomon et al., 1998). For purposes of presentation, scores were inverted such that the higher the score the better the performance on the 7MS test.

### 2.4. MRI acquisition and processing

At the age of 75 years, a high resolution 3D T1-weighted “Turbo Field Echo” (TFE) scan was acquired using a Philips 1.5 T scanner (Gyrosan NT, Philips Medical Systems, Best, The Netherlands). Images were processed using Voxel Based Morphometry (VBM), a technique using statistical parametric mapping (SPM) to determine local concentrations of gray matter volumes on a voxel-by-voxel basis (Ashburner and Friston, 2000). For more details about the scanning procedure, please see the supplemental material.

## 3. Calculations

SPSS version 19.0 (SPSS Inc., Chicago, IL) was used. All results are presented as means  $\pm$  SEMs. Gray matter, white matter, and total brain volumes are expressed as relative to the total intracranial volume (defined as the sum of gray matter, white matter and cerebrospinal fluid). Two linear regression models were constructed to examine the association between the MeDi and our target measures, covarying for factors that have been previously associated with brain health outcomes (model A: adjusting for gender; model B: model A + energy intake, education (Foubert-Samier and Catheline, 2012), self-reported physical activity (Benedict et al., 2013), serum concentration of low-density cholesterol (Ward et al., 2010), BMI (Brooks et al., 2013), systolic blood pressure (Muller et al., 2010), and HOMA-IR (Benedict et al., 2012).

In order to examine potential associations between single MeDi components and cognitive functioning and brain volumes respectively, in a separate analysis, all eight MeDi components were entered simultaneously as continuous variables into the constructed regression models. The dietary variables were entered simultaneously as continuous variables into regression models in order to prevent overlapping variance, e.g. to examine the possible association of a single MeDi component with brain volume, while controlling for the remaining dietary variables. Alcohol is commonly supposed to exert protective effects on cognitive functions when consumed in moderate amounts (Stampfer et al., 2005). Thus, alcohol intake was entered as squared term to capture possible non-linear relationships with our dependent variables. Skewed dietary variables were log-transformed to approach normality.

In case of significant findings for global brain measures (i.e. gray matter, white matter, and total brain tissue volume), additional regression analyses of regional brain volume were performed by means of VBM. These models were controlled for total intracranial volume and gender, as well as non-significant MeDi score components. All clusters and peak voxels of gray matter T statistic brain maps were

thresholded at a P-value  $<0.05$  by using Family Wise Error (FWE). In order to avoid possible edge effects between different tissue types, we excluded from our analyses all voxels with gray matter probabilities of less than 0.1 (absolute threshold masking). Overall, a two-sided P-value less than 0.05 was considered significant.

## 4. Results

### 4.1. Descriptive data

Descriptive data of the study population including variables such as educational status, gender distribution, self-reported physical activity per week, and cardiometabolic measures are shown in Table 1.

### 4.2. Cognitive performance

The basic linear regression model A (i.e., covarying for gender) revealed a positive association between the MeDi score and the 7MS score ( $P = 0.02$ ; Table 2). However, this association did not reach significance in regression model B (model A + energy intake, education, self-reported physical activity, serum concentration of low-density cholesterol, BMI, systolic blood pressure, and HOMA-IR; Table 2).

Entering all eight MeDi components as continuous variables into the same regression analysis (i.e. not as a MeDi score) yielded a negative association between self-reported consumption of meat and meat products and the 7MS score ( $P \leq 0.001$  for all regression models; Table 2). No other MeDi component was significantly linked to the 7MS score in the cumulative regression model C (Table 2).

**Table 1**  
Cohort characteristics.

Characteristics	Mean $\pm$ SEM
No. of individuals	194
No. of females	93
Educational level	
Primary school (no.)	109
Secondary school (no.)	34
University (no.)	51
At 70 yrs	
Exact age, years	70.1 $\pm$ 0.01
Energy intake, MJ	8.6 $\pm$ 0.1
BMI, kg/m <sup>2</sup>	25.9 $\pm$ 0.3
Plasma glucose levels, mmol/L (A)	4.9 $\pm$ 0.03
Serum insulin levels, $\mu$ g/dL (B)	7.9 $\pm$ 0.4
HOMA-IR (A * B / 22.5)	1.7 $\pm$ 0.1
Serum LDL cholesterol, mmol/L	3.5 $\pm$ 0.1
Systolic blood pressure, mm Hg	146 $\pm$ 1.7
Self-reported PA	
Very low (no.)	15
Low (no.)	122
Medium (no.)	43
High (no.)	14
At 75 yrs	
Exact age, years	75.3 $\pm$ 0.01
Gray matter volume, ml	577 $\pm$ 5
White matter volume, ml	447 $\pm$ 4
TIV, ml	1746 $\pm$ 11
MMSE, max score 30	29.0 $\pm$ 0.1
Benton temporal orientation, max error score 113	0.5 $\pm$ 0.1
Enhanced cued recall, max score 16	15.8 $\pm$ 0.1
Clock drawing, max score 7	6.4 $\pm$ 0.1
Verbal fluency, words per min	20.8 $\pm$ 0.4
Seven minute screening score	17.5 $\pm$ 0.6

If not otherwise stated, raw data are mean  $\pm$  SEM. Physical activity was divided into light and hard exercise and classified as number of activities for at least 30 min per week. The participant were asked how many times per week he/she performed light (e.g. walking, gardening) respectively hard exercise (e.g. running, swimming) for at least 30 min. Based on the responses to these questions, four PA categories were constructed: very low, low, medium, and very high. Abbreviations: BMI, body mass index; HOMA-IR, homeostasis model assessment; LDL, low-density lipoprotein cholesterol; MMSE, mini-mental state examination; no., number of individuals; PA, physical activity; TIV, total intracranial volume (i.e., the sum of gray matter, white matter, and cerebrospinal fluid).

**Table 2**  
Association of the Mediterranean diet (MeDi) score and its components with cognitive performance and brain volumes.

Dep. variable	Regression model	$\beta$ -value (P-value)								
		MeDi score <sup>a</sup>	Alcohol <sup>b</sup>	Meat and meat products <sup>b</sup>	Milk and milk products <sup>b</sup>	PUFAs/SFAs <sup>b</sup>	Vegetables and legumes <sup>b</sup>	Fruits <sup>b</sup>	Cereals and potatoes <sup>b</sup>	Fish <sup>b</sup>
TBV	A	0.08 (0.26)	−0.07 (0.40)	−0.16 ( <b>0.03</b> )	−0.05 (0.47)	0.04 (0.59)	0.04 (0.60)	−0.01 (0.91)	0.11 (0.18)	−0.06 (0.40)
	B	0.07 (0.32)	−0.09 (0.28)	−0.16 ( <b>0.04</b> )	−0.05 (0.53)	0.06 (0.45)	0.01 (0.92)	0.05 (0.55)	0.12 (0.19)	−0.10 (0.18)
GM	A	0.10 (0.15)	−0.03 (0.72)	−0.13 (0.08)	−0.08 (0.29)	0.08 (0.33)	0.00 (0.99)	0.04 (0.61)	0.09 (0.29)	−0.07 (0.34)
	B	0.10 (0.19)	−0.04 (0.67)	−0.14 (0.07)	−0.06 (0.42)	0.09 (0.29)	−0.01 (0.88)	0.07 (0.39)	0.07 (0.46)	−0.09 (0.25)
WM	A	0.01 (0.89)	−0.08 (0.34)	−0.12 (0.13)	0.01 (0.92)	−0.03 (0.77)	0.07 (0.37)	−0.07 (0.40)	0.08 (0.35)	−0.02 (0.80)
	B	0.00 (0.97)	−0.11 (0.19)	−0.10 (0.20)	0.00 (0.97)	−0.01 (0.93)	0.03 (0.71)	−0.01 (0.94)	0.12 (0.19)	−0.06 (0.44)
7MS	A	0.17 ( <b>0.02</b> )	0.15 (0.07)	−0.28 (< <b>0.0001</b> )	−0.06 (0.39)	−0.13 (0.12)	0.15 (< <b>0.05</b> )	−0.05 (0.57)	0.01 (0.92)	0.08 (0.28)
	B	0.11 (0.13)	0.07 (0.36)	−0.26 (< <b>0.001</b> )	−0.10 (0.17)	−0.11 (0.17)	0.10 (0.21)	−0.03 (0.72)	0.03 (0.73)	0.04 (0.54)

Regression model A: adjusting for gender; regression model B: adjusting for gender, energy intake, education, self-reported physical activity, serum concentration of low-density cholesterol, BMI, systolic blood pressure, and HOMA-IR. Overall, a P-value less than 0.05 was considered significant (significances are indicated in bold).

<sup>a</sup> MeDi was defined as scale ranging from 0 (not adherent at all to MeDi) to 8 points (very adherent to MeDi). Note that the cutoffs of each dietary feature used to calculate the Mediterranean diet score are specific for the examined population, and are different for males and females.

<sup>b</sup> These variables were entered simultaneously into regression models.

### 4.3. Brain volume

No associations were found between the MeDi score and volumes of gray matter, white matter, or their sum (Table 2). However, separate regression models revealed a negative association between the self-reported intake of meat and meat products and total brain volume, i.e. the sum of white and gray matter (Table 2). Using whole-brain correction for multiple comparisons, voxel-based morphometry did not show any association between the self-reported intake of meat and meat products and gray matter volume at specific central sites.

For all analyses presented above, the interaction term of meat intake by gender did not reach significance ( $P > 0.05$ ).

## 5. Discussion

Using data from a community-based cohort of elderly Swedish men and women, we show an association between a MeDi feature, cognitive functioning and brain volumes. Specifically, the lower the self-reported intake of meat and meat products was, the higher the score obtained on the seven minute screening test, and the greater the total brain volume (i.e. the sum of white and gray matter). Importantly, integrating MeDi components into a 9-point scale did not explain additional variance in cognitive functioning and brain volumes. Our study findings add to preliminary findings from the *Adventist Health Study* in which individuals who ate meat were more than twice as likely to become demented as their vegetarian counterparts (Giem et al., 1993). However, the authors would like to point out that as we age, there is a slow and inevitable decline in skeletal muscle mass, referred to as sarcopenia. As age-related sarcopenia increases mortality and morbidity in the elderly (Cederholm et al., 2013; Landi et al., 2013), caution is warranted before recommending a low intake of protein-rich meat to elderly populations. This is an important issue, particularly in light of the correlational nature of our analysis.

In a multi-ethnic community study that initially included 1393 cognitively healthy participants, a higher adherence to the MeDi was associated with a trend for a reduced risk of developing mild cognitive impairment (MCI), and with reduced risk of MCI conversion to AD in a 4-year follow-up investigation (Scarmeas et al., 2009). In another study, a higher adherence to MeDi was significantly associated with a lower risk for AD, in that those individuals who were in the highest tertile had 34% less risk of developing AD, compared to those in the lowest tertile of MeDi (Gu et al., 2010). Cross-sectional study of S. Gardener et al. showed also that AD and MCI patients had a lower adherence to the MeDi in comparison with HC participants (Gardener et al., 2012). However, there are also negative findings. For instance, a

higher adherence to MeDi did not lower the risk for incident dementia (Féart et al., 2009), and failed to delay the transition from a cognitively healthy status to mild cognitive impairment (Cherbuin and Anstey, 2012). Based on our study's findings, one explanation for these opposing results could be that, under certain circumstances, integrating healthy dietary choices into MeDi scores does not predict inherent variance in measures of brain health, than its single components do. Thus, when analyzing the influence of MeDi on measures related to brain health, based on our observations it appears essential to consider both the MeDi scale as well as its individual components.

The mechanisms by which a low intake of meat and meat products support cognitive functioning and brain volumes in the elderly cannot be derived from our data. However, there are findings from other studies that suggest potential mechanisms. For instance, meat and meat products are major sources of saturated fatty acids, trans-fatty acids, and conjugated linoleic acid. Previous studies in rats have shown that diets rich in these nutrients adversely impact central nervous system pathways involved in brain plasticity and neuroprotection, as well as cognitive functioning (Granholm et al., 2008; Sartorius et al., 2012). Finally, large prospective cohort studies have found a direct association of saturated fat intake with cognitive decline (Morris et al., 2004), and vascular dementia (Kalmijn et al., 1997) in elderly people.

In line with others (Kalmijn et al., 2004; van Gelder et al., 2007), in a previous study using data from the same cohort, we have shown a positive association between omega-3 fatty acids intake and cognitive functioning, as well as brain volumes (Titova et al., 2013). Considering that fish is considered as the main dietary source supplying these nutrients, at first glance it appears surprising that the present analysis did not show such associations. However, it should be taken into account that there are important differences between the previous analysis and the one presented herein. In the present analysis, all MeDi components were simultaneously entered into the regression analysis, thereby controlling for overlapping variance among the dietary features. Finally, it should be borne in mind that the amount of omega-3 fatty acids in fish varies greatly depending on the type of fish, and that fish is not the only source of omega-3 fatty acids (e.g. eggs).

## 6. Strengths and limitations

The strengths of our study include the fact that the obtained association was found in a homogeneously aged sample, and that only those with reliable 7-day dietary information were considered for analysis. The major limitation of our study is that a high MeDi score does not, per se, reflect a true MeDi, especially when it is recorded in a non-Mediterranean population and environment. With this in mind,

caution is needed before drawing firm conclusions regarding the generalizability of our findings. Another limitation is that there was an interval of 5 years between the assessment of the dietary pattern (underlying the calculation of the MeDi score) and our dependent variables (cognitive function and brain volume). As a result, no definite conclusions can be drawn as to whether the participants followed a similar dietary pattern between the ages of 70 and 75, although habitual eating behavior, particularly in the elderly is highly likely. An important factor that warrants deeper discussion is the population based approach of the MeDi score. Actual intake of MeDi components may vary substantially between populations and so might therefore also the association of the MeDi score with outcome and the contribution of separate factors (variables in the score) to the association with the outcome. Another issue that requires the readers' attention is that the brain size of an elderly person does not necessarily predict his/her cognitive performance. Supporting this view, entering the total brain volume as a covariate into our regression models did not change the observed inverse association between the performance on the 7MS and self-reported meat consumption (data not shown). Our study is of correlative nature. Thus, the inverse association between self-reported meat consumption and cognitive performance on the 7MS observed in our study could also indicate that elderly persons with superior cognitive function tend to avoid eating meat in amounts that do not comply with general dietary recommendations. Finally, confounds by other factors, such as genetic background, that were not considered in the present analysis cannot be excluded.

## 7. Conclusions

The question of whether or not adherence to a certain dietary pattern benefits our cognitive ability in late life is particularly pertinent, in light of the growth of aging populations in Western societies. Here we report in a Swedish elderly population that a low intake of meat and meat products is linked to greater brain volume and better performance on a cognitive test battery used by clinicians to screen for dementia (Solomon et al., 1998). However, if keeping to a low meat intake during late life could prove to be an impact-driven public health policy to support healthy cognitive aging, it requires additional longitudinal research, particularly in light of the correlational nature of our analysis.

## Disclosure statement

All authors had full access to all data in the study and take responsibility for the integrity and accuracy of the data analysis.

## Conflict of interest

The authors have no conflicts of interests.

## Acknowledgments

Work from the authors was funded by the Swedish Research Council, the Swedish Brain Research Foundation (Sweden), the Novo Nordisk (Denmark), the Tore Nilsons Foundation (Sweden), the Gunvor och Josef Anérs Foundation (Sweden), the Åke Wibergs Foundation (Sweden), the Åhlens Foundation (Sweden), AstraZeneca (Sweden), and Uppsala University (Sweden). The funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript.

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