Dietary patterns, cognitive function, and structural neuroimaging measures of brain aging

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Janie Corley PhD[a*] Simon R. Cox PhD[a,b], Adele M. Taylor MA[a], Maria Valdés Hernandez PhD[b,c], Susana Muñoz Maniega PhD[b,c], Lucia Ballerini PhD[b,c,d], Stewart Wiseman PhD[b,c,d], Rozanna Meijboom PhD[b,c,d], Ellen V. Backhouse PhD[b,c], Mark E. Bastin DPhil[b,c], Joanna M. Wardlaw PhD[b,c,d], Ian J. Deary PhD[a]

[a]Lothian Birth Cohorts Group, Department of Psychology, University of Edinburgh, UK

[b]cottish Imaging Network, A Platform for Scientific Excellence (SINAPSE)

[c]Brain Research Imaging Centre, Division of Neuroimaging Sciences, Centre for Clinical Brain Sciences, University of Edinburgh, UK

[d]MRC UK Dementia Research Institute, University of Edinburgh

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Author email addresses: janie.corley@ed.ac.uk; simon.Cox@ed.ac.uk; adele.taylor@ed.ac.uk; m.valdes-hernan@ed.ac.uk; s.m.maniega@ed.ac.uk; lucia.ballerini@ed.ac.uk; stewart.wiseman@ed.ac.uk; rozanna.meijboom@ed.ac.uk; ellen.backhouse@ed.ac.uk; mark.bastin@ed.ac.uk; joanna.wardlaw@ed.ac.uk; i.deary@ed.ac.uk

*Corresponding author: Dr Janie Corley, Lothian Birth Cohorts Group, Department of Psychology, University of Edinburgh, 7 George Square, Edinburgh, EH8 9JZ, Scotland, UK.

Phone: +44-131-651-1683. *Email*: janie.corley@ed.ac.uk

Abstract

Objective: To examine the cross-sectional relationship between dietary patterns and psychometric and imaging indices of brain health concurrently in the same sample of healthy older adults.

Methods: Dietary patterns were derived from a 130-item food frequency questionnaire for 511 individuals in the Lothian Birth Cohort 1936 (mean age 79.3 ± 0.6 years). Composite variables for global cognitive function, visuospatial ability, processing speed, memory, and verbal ability were assessed. Brain volumes and white matter microstructure were assessed in participants (n = 358) who also underwent structural magnetic resonance imaging.

Results: A Mediterranean-style dietary pattern and a processed dietary pattern were identified using principal component analysis of food frequency questionnaire items. In fully-adjusted linear regression models, adherence to the Mediterranean-style pattern was associated with better verbal ability ($\beta = 0.121$, $P = 0.002$). Associations with global cognitive function ($\beta = 0.094$, $P = 0.043$), visuospatial ability ($\beta = 0.113$, $P = 0.019$), and memory ($\beta = 0.105$, $P = 0.029$) did not survive correction for multiple comparisons. Associations between the processed pattern and lower cognitive scores were attenuated by around 50% following adjustment for prior (childhood) cognitive ability; only an association with verbal ability remained ($\beta = -0.130$, $P = 0.001$). Neither dietary pattern was associated with brain volumes or white matter microstructure. Specific Mediterranean diet features—green leafy vegetables and a low intake of red meat—were associated with better cognitive functioning.

Conclusions: These observational findings suggest that adherence to a Mediterranean-style diet is associated with better cognitive functioning, but not better brain structural integrity, in older adults.

Keywords: Mediterranean diet; dietary patterns; cognitive function; neuroimaging; older adults

1. Introduction

Accumulating evidence indicates that diet plays an important role in healthy cognitive and brain aging and is therefore a potential target for interventions (Vauzour et al., 2017; Zamroziewicz & Barbey, 2018). Adherence to the Mediterranean diet (Willett et al., 1995) has been associated with better cognitive function (McEvoy et al., 2017; Ye et al., 2013) and slower cognitive decline (Gardener et al., 2015; Kesse-Guyot et al., 2012; Tangney et al., 2011), though some studies have reported null findings (Cherbuin & Anstey, 2012; Haring et al., 2016; Samieri et al., 2013). Diet has also been implicated in the preservation of brain structural integrity. Previous neuroimaging studies of older individuals suggest that adherence to the Mediterranean diet has global and region-specific benefits for brain structure (Gardener et al., 2012; Gu et al., 2015, 2016; Karstens et al., 2019; Mosconi et al., 2014; Pelletier et al., 2015; Staubo et al., 2017).

Research in this emerging area is limited and only three studies, to our knowledge, have examined diet in relation to cognitive *and* imaging indices of brain health concurrently in the same sample, and with mixed results (Karstens et al., 2019; Pelletier et al., 2015; Titova et al., 2013). Integrating these outcomes is important for our understanding of the potential link between diet, cognitive aging, and aging-related neurodegeneration. However, many studies have used relatively limited cognitive assessment batteries that do not allow for an assessment of particular aging-related cognitive domains. Furthermore, the widespread use of *a priori* Mediterranean diet scores based on adherence to several pre-determined food categories, may under-represent variability in this dietary pattern.

We have previously shown that closer Mediterranean-style diet adherence at age 70 was associated with less brain atrophy at age 73 but did not test associations with cognitive functioning (Luciano et al., 2017). In the current study, we present new data from age 79, and combine dietary pattern analysis, global and domain-specific cognitive functioning scores and multiple indices of brain structural aging, in the same report.

2. Materials and methods

2.1. Study population and design

The study sample was drawn from the Lothian Birth Cohort 1936 (LBC1936) study, an ongoing study of cognitive and brain aging in community-dwelling older adults (Taylor et al., 2018). Participants were born in 1936, and most had previously taken part in the Scottish Mental Survey of 1947 (SMS1947) (SCRE, 1949). The SMS1947 tested the intelligence of 70,805 children in 1947 in Scotland at the age of 11 years. Almost 60 years later, men and women who had taken the survey in childhood, and mostly living in Edinburgh and the Lothians, were recruited to the LBC1936. Since baseline (wave 1: 2004-2007, n = 1091), participants have subsequently attended additional follow-up assessments at ages ~73 (Wave 2, n = 866), age~76 (Wave 3, n = 697), age~79 (Wave 4, n = 550), and age~82 (Wave 5, n = 431). Extensive phenotypic data have been collected, including cognitive, neuroimaging, health, medical, genetic and epigenetic, psychosocial, and lifestyle measures. The present study is a cross-sectional analysis of data from the Wave 4 assessment at ~age 79 years when a food frequency questionnaire (FFQ) was administered. Of the 550 participants tested at wave 4, 16 did not return an FFQ. We excluded 6 participants with >10 missing responses, according to standard FFQ protocol, and 1 participant defined as an outlier (>3.5 times the SD from the mean score) on the Mediterranean-style dietary pattern. We further excluded 16 participants with a history of dementia and/or scores <24 on the Mini-Mental State Examination. The final sample for the current study was n = 511. Of these, 358 participants had MRI data. Reasons for imaging not being performed were: medical exclusion, e.g. cardiac pacemaker, metal in body, or recent surgery (n = 11); death or withdrawal from study in the period between cognitive assessment and scan (n = 7); health reasons, e.g. back pain or other complaint affecting ability to complete the scan (n = 7); claustrophobia (n = 3); no reason given (n = 9); participant unavailable (n = 2). A further 121 participants who attended wave 4 did not complete a scan at the previous wave 3 and therefore were not required to participate or give a reason for continuing non-participation at wave 4. Thus, of the 550 participants tested at wave 4, 160 (29.1%) did not participate in an MRI brain scan. Of the

remaining 390 (70.9%) who attended the scan, two scans were terminated due to technical (scanner) issues, leaving 388 successful scans. For the current study, we examined 358 scans, once we accounted for FFQ and cognitive exclusions.

2.2. Standard protocol approvals, registrations, and patient consents

All participants provided written informed consent before testing. The LBC1936 study was approved by the Multi-Centre Research Ethics Committee for Scotland (MREC/01/0/56) and the Lothian Research Ethics Committee (LREC/2003/2/29) for Wave 1 and the Scotland A Research Ethics Committee (07/MRE00/58) for Waves 2-5.

2.3. Dietary assessment

Dietary intake at wave 4 was assessed using the open-access 130-item EPIC-Norfolk FFQ which has been extensively used and well-validated in previous research, and for use in older people (Bingham et al., 1997). A similar FFQ was administered at the baseline assessment (wave 1, age 70) and the food groupings, individual items, and scoring are broadly similar. A common unit or portion size for each FFQ item was specified and participants were asked how often, on average, they had consumed that amount of each item during the previous year. Responses to all items was on a 9-point scale, ranging from 'Never or less than once a month' to 6+ per day'.

Dietary patterns were derived using principal component analysis (PCA) of FFQ items based on linear correlation and outputs were evaluated on the basis of eigenvalues, scree plots, and interpretation of the derived components. Identified components were rotated with varimax rotation creating orthogonal, uncorrelated factors, with maximum interpretability. Individuals were assigned a score for each retained component. Dietary patterns were labelled based on the types of foods exhibiting the strongest correlations and having the highest factor loadings >0.30.

2.4. Cognitive assessment

Four cognitive domains are represented in the LBC1936 cognitive battery (full details of cognitive testing are available in an open-access protocol article) (Taylor et al., 2018). Visuospatial ability is assessed by scores on tests of Matrix Reasoning and Block Design from the Wechsler Adult Intelligence Scale (WAIS-III^{UK}) (Wechsler, 1998a) and Spatial Span Forward and Backward from the Wechsler Memory Scale (WMS-III^{UK}) (Wechsler, 1998b). Processing speed is assessed using scores on tests of Symbol Search and Digit-Symbol Substitution from the WAIS-III^{UK}, Four-Choice Reaction Time (Deary et al., 2001), and Visual Inspection Time (Deary et al., 2004). Memory is assessed using scores on tests of Verbal Paired Associates (sum of immediate and delayed) and Logical Memory (sum of immediate and delayed) from the WMS-III^{UK,} and Digit Span Backwards from the WAIS-III^{UK}. Verbal ability is assessed using the National Adult Reading Test (NART) (Nelson & Willison, 1991) and the Wechsler Test of Adult Reading (WTAR) (Holdnack, 2001) and a test of phonemic Verbal Fluency (Lezak et al., 2004). The MMSE (Folstein et al., 1975) was used solely to identify participants with likely cognitive impairment or dementia. The criterion for exclusion in the present study was a score of < 24 out of a possible 30.

Categorisation of the individual subtests into cognitive domains was based on a previous confirmatory factor analysis (Ritchie et al., 2016). See **Supplementary Table 1** for details of the individual cognitive tests which contribute to the composite variables and their associations with the dietary patterns. Composite cognitive scores were built for each cognitive domain using PCA of the tests outlined above: visuospatial ability (accounting for 53.0% of the variance); processing speed (60.5%); memory (57.8%); and verbal ability (71.4%). We further extracted a global cognitive factor (accounting for 34.2% of the variance), using PCA of all 14 individual subtests, to account for the variance common to all cognitive tasks.

2.5. MRI acquisition and processing

MRI data were acquired in the Brain Research Imaging Centre, University of Edinburgh using a 1.5T GE Signa Horizon clinical scanner (General Electric, Milwaukee, WI) equipped with a self-shielding

gradient set (33 mT/m maximum gradient strength) and manufacturer supplied eight-channel phased-array head coil. Scans were performed shortly after the clinic assessment (mean lag in days for the present study sample M = 32.4, SD = 28.7). We used an Image Processing pipeline developed in-house that refines the output from the previously published protocol with those obtained from the FSL segmentation tools (Wardlaw et al., 2011). The examination comprised the following whole-brain sequences: T1-, T2-, T2*-, FLAIR- and diffusion-weighted sequences, and took approximately 70 minutes. All segmented images were visually checked for incorrectly classified tissue by the automated pipelines and manually corrected. Manual editing of MRI data was conducted blind to all other participant characteristics prior to any statistical analyses. Brain volumes were then normalised to the subject's ICV and the measures expressed as percentages of ICV. Focal lesions such as cortical infarcts were manually removed from the masks.

Diffusion MRI (dMRI) parameters were also used to generate two measures of general brain white matter microstructure. Fractional anisotropy (FA) is the directional coherence of water molecule diffusion (a higher FA indicates higher directionality of water diffusion and potentially preserved microstructure), and mean diffusivity (MD) is the magnitude of water molecule diffusion (where lower MD indicates lower magnitude of water diffusion and potentially preserved microstructure). FA and MD were measured in twelve major white matter tracts, identified using probabilistic neighborhood tractography (Clayden et al., 2007; Wardlaw et al., 2011). Tracts assessed were the genu and splenium of corpus callosum, and bilateral anterior thalamic radiations, cingulum cingulate gyrus, arcuate, uncinate, and inferior longitudinal fasciculi. PCA was used to extract general factors for FA (gFA) and MD (gMD) separately from across white matter tracts. Scree plots provided evidence for a strong single factor capturing common variance across these tracts. The general factor of FA accounted for 31.75% of the variance and a general factor of MD accounted for 42.18% of the variance among measures.

2.6. Covariates

Other non-dietary variables were acquired at the participants' interview and included: education (years of formal full-time education); smoking status (never, former, current); alcohol intake (units per week); history of cardiovascular disease (CVD), hypertension, diabetes, stroke, or high cholesterol; body mass index (BMI) was calculated as weight (in kilograms)/height (in metres)^2; symptoms of anxiety and depression were assessed using the subscales (HADS-A and HADS-D) of the Hospital Anxiety and Depression Scale (HADS) (Zigmond & Snaith, 1983). Age 11 IQ (childhood cognitive ability) scores were derived from the SMS1947's Moray House Test No. 12. Physical activity level was derived from questionnaire responses and ranged from 'moving only in accordance with household chores' (level 1) to 'keep fit or aerobic exercise several times a week' (level 6). *APOE* e4 carrier status was derived at baseline from whole blood samples. Genomic DNA was isolated from whole blood and the target sequences for two polymorphic sites (rs7412 and rs429358) were genotyped with TaqMan technology by the Wellcome Trust Clinical Research Facility Genetics Core, Western General Hospital, Edinburgh.

2.7. Statistical analysis

Dietary patterns were divided into tertiles, for descriptive purposes only, to examine the characteristics associated with adherence to the identified dietary patterns; the full continua of scores were used in the main analyses. Means and standard deviations are provided for continuous variables and percentages for categorical variables. One-way ANOVA or Chi-Square tests were performed to evaluate group differences as appropriate. We report the P-value for trend. Pearson's correlation coefficient was used to examine correlations between cognitive and neuroimaging variables.

In the main analyses, a series of linear regression models were constructed to examine associations between dietary patterns (as continuous variables) as exposures, and cognitive scores and neuroimaging measures as outcomes. In Model 1 we adjusted for age and sex. In Model 2, the analyses were further adjusted for physical activity, alcohol intake, smoking, diabetes, stroke, hypertension, hypercholesterolaemia, and *APOE* e4 carrier status. In Model 3, we further adjusted for

age 11 IQ; a potential confounder of diet-cognition associations in later life. Finally, we repeated the same models using Mediterranean diet components (fruit, vegetables, green leafy vegetables, legumes, wholegrains, fish, red meat) as exposures rather than the dietary patterns in order to assess the potential contribution of Mediterranean diet food groups to cognitive outcomes. Analyses were conducted in R version 3.6.1. We report standardised beta (β) values and P-values. The false discovery rate (FDR) was applied to adjust for multiple comparisons across the linear regression models given the large number of statistical tests.

Secondary analyses were conducted to examine the degree to which any association between greater adherence to the dietary patterns and global and domain-specific cognitive functioning was accounted for (mediated via) by neuroimaging measures. We used a multiple mediator model in a structural equation model framework in the 'lavaan' R package (Rosseel, 2012). Dietary pattern score was set as the X (independent) variable, composite cognitive score was set as the Y (outcome) variable, with GMV, NAWMV, WMHV, gFA and gMD as covarying mediators (M). The degree to which the association between X and Y (known as the c path) is attenuated by M (the c' path) denotes the mediation effect.

2.8. Data availability

Anonymized data will be shared by request from any qualified investigator.

3. Results

The analyses were performed on 511 (female, 50.3%) participants with dietary, cognitive and covariates data; 358 (female, 46.9%) participants also had structural brain MRI data. Average age was 79.3 ± 0.6 years at time of assessment and 79.4 ± 0.6 at time of MRI assessment. The subsample who underwent MRI did not significantly differ on any of the dietary or cognitive variables, but had

a slightly lower alcohol intake (t = 2.22, P = 0.028, Cohen's d = 0.24) and more years of education (t = -2.14, P = 0.033, Cohen's d = 0.20), than those without MRI data.

3.1. Dietary patterns

Two dietary patterns were identified (as shown in **Table 1**) accounting for 17.0% of the variance. Component (pattern) scores were calculated using food items with factor loadings exceeding 0.30. The first pattern, labelled as the 'Mediterranean-style pattern' (accounting for 9.4% of the variance), was loaded by a high intake of fruits, vegetables, salad dressing, legumes, fish, wholemeal bread, wine, and rice. The second pattern, labelled as the 'processed food' pattern (accounting for 7.6% of the variance), was loaded by a high intake of meat, sweet foods (desserts, cakes, biscuits, sweets, chocolate), fried food, tinned fruit, and potatoes. Participants received a component score for each dietary patterns representing degree of adherence.

3.2. Participant characteristics

Sample characteristics across tertiles of the Mediterranean-style diet and processed diet patterns are presented in **Table 2**. Greater adherence to the Mediterranean diet pattern was associated with a higher proportion of females, more years of education, higher IQ score in youth, less ever- (but not current) smoking, a lower BMI, higher physical activity levels, higher alcohol intake, a lower HADS-D (depression) score, and a higher MMSE score. Greater adherence to the processed pattern was associated with a higher proportion of males, less education, a lower IQ score in youth, a higher BMI, lower physical activity levels, and a lower alcohol intake. Neither dietary pattern was associated with a history of the diseases that were included.

We report the summary statistics (mean, SD, range) for the cognitive tests and imaging measures (**Supplementary Table 2**) and associations between composite cognitive function scores and neuroimaging outcomes are presented as a correlation matrix (**Supplementary Table 3)**. Global cognitive function, processing speed, and memory were significantly correlated (all $P < 0.01$) with all of the brain volume measures. Visuospatial ability was associated with TBV ($P < 0.05$), NAWMV

and WMHV (both $P < 0.01$), but not GMV. Verbal ability was associated with NAWMV ($P < 0.05$) but not with any of the other volumetric variables. The white matter microstructural measure gFA was correlated with visuospatial ability ($P < 0.01$) and processing speed ($P < 0.05$) only, and gMD was not associated with any of the cognitive function scores.

3.3. Dietary patterns and cognitive functioning

The associations between the dietary patterns and cognitive functioning are presented in the upper part of **Table 3**. We present the significant associations before and after FDR correction. In Model 1, adjusting for age and sex, the Mediterranean-style diet pattern was significantly and positively associated with global cognitive function ($\beta = 0.147$, $P = 0.003$), visuospatial ability ($\beta = 0.143$, $P = 0.001$), memory ($\beta = 0.142$, $P = 0.002$), and verbal ability ($\beta = 0.234$, $P < 0.001$), but not processing speed. In Model 2, following further adjustment for a range of covariates (but not including IQ tested at age 11), these associations remained significant and with similar effect sizes. In Model 3, with additional adjustment for age 11 IQ, the Mediterranean-style diet associations were attenuated from the previous model, by on average a third, though they remained significant for better visuospatial ability ($\beta = 0.113$, $P = 0.019$), memory ($\beta = 0.105$, $P = 0.029$), and verbal ability ($\beta = 0.121$, $P = 0.002$), and the association with global cognitive function remained marginally significant ($\beta = 0.094$, $P = 0.043$). The nominal associations with memory, and global cognitive function, did not survive correction for multiple comparisons, and the association with visuospatial ability narrowly missed the corrected threshold for significance (of $P < 0.018$). The strongest association throughout was with verbal ability which was attenuated by 7%, following adjustment for other lifestyle and health factors (model 2), and 48% with the additional adjustment for age 11 IQ (model 3). The association between the Mediterranean-style pattern and global cognitive function was attenuated by 12% in Model 2, and 36% in Model 3.

The processed diet pattern was significantly associated, in model 1, with lower global cognitive function ($\beta = -0.163$, $P = 0.001$) and lower scores across all of the specific cognitive domains tested:

visuospatial ability (β = -0.089, P = 0.045); processing speed (β = -0.118, P = 0.013); memory (β = -0.144, P = 0.001); and verbal ability (β = -0.213, P < 0.001). In Model 2, all of the associations remained significant with slightly larger absolute effect sizes. In Model 3, with the addition of age 11 IQ, these associations were attenuated by over 50% overall, compared with Model 2. All but one of these associations was attenuated to non-significance; only the association with verbal ability remained (β = -0.130, P = 0.001), even before FDR correction, though it was attenuated from the previous model by 42%.

3.4. Dietary patterns and neuroimaging outcomes

The associations between the dietary patterns and neuroimaging outcomes are presented in the lower part of **Table 3**. None of the MRI-derived indices of brain volumes or white matter microstructure we tested were significantly associated with the Mediterranean pattern or the processed diet pattern. A further analysis, suggested during review, tested the individual tractography measures which contributed to gFA and gMD in order to test for associations at the regional level (see **Supplementary Table 4**). We did not observe any significant tract associations with the dietary patterns with the exception of an inverse association between a higher processed diet score and lower FA values in the splenium of the whole corpus callosum, which was significant in the fully adjusted model (β = -0.180, P = 0.008), but not robust to FDR correction.

3.5. Mediation analysis

A multiple-mediator analysis showed that the associations between dietary patterns and global and domain-specific cognitive functioning was not mediated by any of the neuroimaging measures (results not presented). Standardised beta values for the sum of the indirect effects attributable to the brain measures (GMV, NAWMV, WMHV, gFA, and gMD) ranged from -0.024 to 0.001, for the associations between the cognitive scores and Mediterranean pattern, and from -0.026 to 0.005, for the associations between the cognitive scores and the processed pattern. All associations were non-significant.

3.6. Components of the Mediterranean diet and cognitive functioning

We further explored whether there were any associations between Mediterranean food groups—fruits, vegetables, green leafy vegetables, legumes, wholegrains, fish, and red meat—and cognitive functioning (**Table 4**). These groups are consistent with the Mediterranean food pyramid [7] and with the highest food loadings on the PCA-derived Mediterranean component in this sample.

Throughout the models, there was a trend for better cognitive functioning with higher intakes of fruits, vegetables, and fish, and lower intake of red meat. Legumes and wholegrains were not associated with cognitive functioning scores. In the fully-adjusted model (including age 11 IQ), we found associations of: better visuospatial ability and higher fruit ($\beta = 0.108$, $P = 0.024$) and green leafy vegetable intake ($\beta = 0.106$ $P = 0.025$); faster processing speed and lower red meat intake ($\beta = 0.129$, $P = 0.011$); better memory and higher fruit intake ($\beta = 0.104$, $P=0.029$); and better verbal ability and higher vegetable ($\beta = 0.088$, $P = 0.022$) and green leafy vegetable intake ($\beta = 0.110$, $P = 0.004$), higher fish intake ($\beta = 0.072$, $P = 0.049$), and lower red meat ($\beta = 0.119$, $P = 0.001$). The composite measure of global cognitive function was associated with a lower red meat intake only ($\beta = 0.114$, $P = 0.009$). Following FDR correction, several of these food component-cognitive associations fell below the threshold for significance. Robust to this correction were inverse associations of red meat intake with global cognitive function, processing speed, and verbal ability, and a positive associations of green leafy vegetable intake and verbal ability.

3.7. Sensitivity analysis

Finally, we conducted a post-hoc sensitivity analysis to see if the general pattern of results was similar between dietary patterns and cognitive function in the smaller subset of participants (n = 358) that also had imaging (see Supplementary Table 5). The effect sizes of the associations were comparable in magnitude to those in the full sample (n = 511), though the fact that fewer were significant following correction was probably driven by reduced statistical power, due to lower sample size.

4. Discussion

In this cross-sectional study of community-dwelling 79-year-olds, we found that adherence to a Mediterranean-style dietary pattern was related to better global- and domain-specific cognitive functioning, independently of other lifestyle factors, health variables, and childhood IQ. The largest effect sizes were observed for verbal and visuospatial ability. Associations were most likely driven by a high intake of green leafy vegetables, and a low red meat consumption. We did not find that adhering to a Mediterranean-style dietary pattern was associated with better MRI measures of brain structural integrity, even though these latter measures were associated with cognitive test scores. Nor did we find evidence to support a mediating effect of brain structure on the relation between diet and cognitive functioning. Our results are important as they provide evidence that healthy diets such as the Mediterranean diet may not be associated with a beneficial impact on brain health via the preservation of these aspects of brain structure, globally measured. This suggests that markers of brain aging may not be an underlying cause of the well-documented relationship between a Mediterranean-style diet and cognitive functioning.

Our findings extend and refine evidence in this area. Several decades of research have garnered a large volume of research on dietary patterns, cognitive-, and more recently, brain aging, but findings have been conflicting. Our results are in line with a recent systematic review which reports that out of 18 empirical studies, 13 linked closer adherence to the Mediterranean diet with reduced rates of cognitive decline, reduced risk of conversion to Alzheimer's disease, or improved cognitive function (Hardman et al., 2016). However, the assessment of cognitive functioning in many of the studies to date were limited to brief assessments of cognitive status such as the Mini-Mental State Examination (MMSE) or adapted version of the test (e.g. Psaltopoulou et al., 2008; Wengreen et al., 2013; Ye et al., 2013). The MMSE is a useful cognitive screening instrument for measuring the progression of dementia, but is not sensitive to the cognitive changes in a healthy population or to specific domains

of ability. Here, positive associations of Mediterranean diet adherence with sensitive and specific tests of cognitive function, which assess a variety of important aging-related cognitive domains, support previous reports of better visuospatial ability or executive function (Gardener et al., 2015), memory (Anastasiou et al., 2017; Kesse-Guyot et al., 2012; Samieri et al., 2013), and verbal ability (Corley et al., 2013; Tangney et al., 2014), in older adults. In the current study, we observed the strongest associations of a Mediterranean-style diet with verbal ability, otherwise known as crystallised intelligence, which is known to remain relatively intact throughout the adult life course (Deary et al., 2013).

The associations between the PCA-derived Mediterranean pattern and better cognitive performance may potentially be driven by a higher intake of green leafy vegetables, and a lower intake of meat. Further associations with higher intakes of fruits and other vegetables did not survive correction for multiple comparisons. However, our findings are broadly in accordance with studies linking vegetable intake, and fruit intake to a lesser extent, with slower cognitive decline (Kang et al., 2005; Morris et al., 2006; Nooyens et al., 2011). The Nurses' Health Study (n = 13,388) reported that intake of green leafy vegetables was associated with less decline in episodic memory, an MMSE-type test, and a composite global cognitive score of six tests. Consistent with the present findings, these associations were stronger than with overall vegetable intake (Kang et al., 2005). A further study found that specific subgroups of fruit and vegetables (nuts, cabbage and root vegetables) were associated with better cognitive function, whereas total fruit and total vegetable intakes were not (Nooyens et al., 2011). Many antioxidant nutrients, anti-inflammatory agents, and bioactive substances (such as carotenoids, flavonoids, polyphenols) found in vegetables and fruits are hypothesized to reduce brain oxidative stress; animal studies report that antioxidants improve cognitive performance and prevent neuronal damage (Cotman et al., 2002). Though the identification of underlying biological mechanisms is beyond the scope of this study, it is plausible that the particularly high antioxidant content of green leafy vegetables may be one potential avenue for future research.

Here, low red meat consumption was associated with better overall cognitive function, faster processing speed, and higher verbal ability. These findings are in agreement with another study of older people in which meat intake accounted for more of the variance in cognitive functioning than the overall Mediterranean score (Titova et al., 2013). The Mediterranean diet pyramid (Willett et al., 1995) recommends infrequent consumption of red meat (<2 servings a week), considered a detrimental component in the calculation of a 'Medi' score. Red meat is high in saturated fats and trans fatty acids which are known to adversely impact the central nervous system pathways involved in neuroprotection and neuronal plasticity, which may eventually lead to irreversible damage (Haast & Kiliaan, 2015). Studies have found a direct association of saturated fat intake with incidence of cognitive decline (Okereke et al., 2012) and vascular changes leading to white matter damage (Wang et al., 2016).

Despite our findings of better cognitive functioning in those who eat more healthily, our results indicate that the Mediterranean diet pattern does not appear to benefit brain health via preservation of brain structural integrity, using MRI-derived brain volumes and white matter microstructure. Previous MRI investigations of mostly smaller samples than here, show larger total-, grey matter-, and white matter- brain volumes (Gu et al., 2015), better white-matter microstructure (Pelletier et al., 2015), and larger cortical thickness (Mosconi et al., 2014; Staubo et al., 2017), were associated with higher Mediterranean diet adherence. Longitudinal studies reporting slower rates of hippocampal atrophy (by 2.5 years) measured over 5 years (Gu et al., 2016) and less total brain atrophy over 3 years in the LBC1936 (Luciano et al., 2017), indicate that greater Mediterranean diet adherence influences trajectories of brain changes in older adults. The absence of associations between either of the diet patterns and the neuroimaging measures is unexpected, given the strong cognitive-brain measure correlations in the current study, and is not likely due to a lack of variability in the imaging measures, given that they covary with other important and valid health outcomes (Corley et al., 2018). Although our sample was older (at age 79) than in previous studies, as a self-selected sample they may be relatively healthier than those samples which have found higher rates of, for example,

white matter hyperintensities. In more diseased samples there may be a more dynamic range in such features of interest. We also note that Luciano et al. previously reported an association of Mediterranean diet (MeDi score) with total brain atrophy over 3 years (age 73 to 76), but not with baseline brain volumes, in the same cohort (Luciano et al., 2017). Moreover, the nominal longitudinal association (P = 0.044) would likely not have survived correction for multiple comparisons.

Importantly, studies which concurrently examine cognitive functioning and neuroimaging outcomes in the same sample are of value—they have the potential to elucidate specific neural structures upon which diet may act to benefit cognitive function—yet such studies are limited. One reported better cross-sectional learning and memory performance and larger dentate gyri volumes in 82 participants >60 years with higher Mediterranean adherence, but no significant association with information processing, executive functioning, or white matter hyperintensities (Karstens et al., 2019). In contrast, a further study observed no significant association between the Mediterranean diet score and performance on the 7MS test or with brain volumes, in 194 men and women aged 70 from the PIVUS study (Titova et al., 2013). Our results are partly in agreement with Pelletier et al., the only other known study to examine both brain volumes and white matter microstructure, who also reported null findings for grey- and white matter volumes in 146 participants (≥65 years) of the Bordeaux Three City Study. However our results are not consistent with their finding of better white matter microstructure which appeared to relate to cognitive benefits on two brief cognitive screening measures for cognitive impairment, the 7MS and Clock Drawing Test (Pelletier et al., 2015). Discrepancies between the current study and others may be due to various methodologic differences. For instance, several studies had time lags between dietary assessment and assessment of brain volumes, ranging from 3 years to 9 years (Luciano et al., 2017; Pelletier et al., 2015; Titova et al., 2013), compared with the current study which conducted the assessments contemporaneously. Secondly, these previous studies differed from the current, in the use of an *a priori* defined score for measuring adherence to the Mediterranean diet based on several pre-determined food groups. This

approach allows for meaningful comparison between studies but has the disadvantage of limiting the variance captured by the data compared with the whole-diet approach.

Mediation models did not provide any support for an indirect effect of the Mediterranean (or processed-) diet on cognitive functioning, via brain measures. Protection against neurodegeneration is often proposed as the underlying mechanism in those studies which identified better cognitive functioning with closer adherence to the Mediterranean diet, but without MRI data to test this hypothesis. Our results are important because they do ostensibly support the hypothesis that markers of brain aging may not be the common cause underlying the well documented relationship between a Mediterranean-style diet and cognitive functioning. We caution here, however, that while mediation models allow the testing of causal hypotheses with correlational data, our cross-sectional, global brain MRI data are not necessarily optimal for addressing the within-individual dynamics of cognitive and brain aging. Moreover, it is possible that the current study did not have sufficient power to detect relatively smaller effect sizes reliably for diet-MRI associations than were present for diet-cognitive functioning. Smaller effect sizes might be expected, given that the measures included here represent only some facets of brain macrostructure and other plausible brain mediators of diet-cognitive associations, such as those indexed by functional MRI and positron emission tomography, were not assessed. As such, more work is needed to understand the underlying mechanisms for the synergistic effects of a Mediterranean diet on healthy cognitive aging.

4.1. Study strengths and limitations

The strengths of our study include a homogenously–aged sample who have undergone comprehensive cognitive testing with proven validity, structural MRI and dietary assessment in the same time period, careful control of various potential confounders (including a direct measure of IQ obtained in youth), and dietary data based on the previous year rather than shorter-term dietary measures such as 7-day diaries. We applied a stringent correction for multiple comparisons across several iterations (3 models) of the data. One of the limitations of our study is the cross-sectional

design and therefore we are unable to determine whether the diet associations with cognitive function and brain structural integrity are causal or merely markers. Whereas we consider it likely that the dietary patterns observed reflect the sample's longstanding dietary habits, we cannot exclude that current diet preference may be a more recent lifestyle choice. We also acknowledge the potential issue of measurement error inherent in the FFQ: the list of foods is finite; portion sizes are estimates only; and self-reports are subject to social desirability and recall bias. However, FFQs have been demonstrated to be the most appropriate method in assessing habitual diet in large cohorts (Willett, 2013). The FFQ used in this study is age-appropriate; the EPIC-Norfolk FFQ has been validated for use in an older population. In terms of factors potentially influencing bias, we note here that the LBC1936 are a narrow-age cohort (born in the same year) reducing the possibility of bias by chronological age. We have taken further steps to address any bias from demographic factors; in all of the regression models, we adjust for exact age (in days) and gender. In the fully-adjusted models we further adjust for a range of demographic, lifestyle and health factors, including cognitive ability from youth, a substantial predictor of both education and SES in later life (Deary & Gow, 2008). We analysed global volumetric imaging parameters, therefore masking any potential brain-regional-specific effects. However, the absence of associations among the individual tractography measures suggests that regional effects are not present, in relation to the diet variables used in the current study. Given the lack of parallel associations of diet with cognitive *and* neuroimaging measures, we cannot entirely rule out the possibility that the observed diet-cognitive associations are the result of unmeasured antecedent genetic, and/or environmental, confounders. Finally, given the sample comprised relatively healthy volunteers from an affluent area of Scotland, the findings may have limited generalisability.

4.2. Conclusions

In conclusion, our study suggests that closer adherence to a Mediterranean diet might be associated with better overall- and domain-specific cognitive functioning in later life, but not with larger global brain volumes or better white matter integrity. Nor were there neuroimaging deficits associated with

eating a more processed diet. This study is only one of a few in the literature which has examined cognitive and neuroimaging outcomes in the same sample, which is important if we are to begin to elucidate whether diets can be 'neuroprotective'. Further longitudinal studies and intervention trials are warranted to replicate our results and to explore whether closer, long-term Mediterranean diet adherence can influence cognitive and brain aging trajectories over time.

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Declarations of Interest

None.

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Table 1 Factor loadings (>0.3) for items on the two dietary patterns

Food item	Mediterranean pattern	Processed pattern
Vegetables[a]	0.311 – 0.601	-0.288 – 0.244
French dressing	0.543	-0.168
Fruit[b]	0.308 – 0.490	0.017 – 0.185
Legumes	0.382	0.010
Oily fish	0.374	-0.190
Salad dressing	0.374	0.130
Vegetable soup	0.367	0.120
White fish	0.358	0.010
Wholemeal bread	0.348	-0.153
Wine	0.338	-0.202
Sauces (white, cheese, gravy)	0.336	0.310
Brown rice	0.314	-0.072
White rice	0.304	0.109
Pies (meat)	-0.143	0.557
Fruit pies (ready-made)	0.010	0.536
White bread	-0.176	0.501
Milk-based pudding (home)	0.040	0.500
Sausages	-0.074	0.470
Sponge puddings (ready-made)	0.050	0.468
Beef	-0.037	0.459
Chips	-0.093	0.459
Buns/pastries (ready-made)	0.030	0.458
Pork	-0.053	0.427
Bacon	0.025	0.425
Fried fish	-0.047	0.423
Cakes	0.028	0.413
Dairy desserts	-0.042	0.402
Plain biscuits	0.131	0.395
Ice cream	0.036	0.393
Baked beans	0.026	0.390
Chocolate biscuits	0.014	0.379
Chocolate bars	-0.057	0.377
Tinned fruit	-0.036	0.371
Luncheon meats	-0.179	0.370
Ham	-0.014	0.364
Roast potatoes	0.112	0.343
Sweets	0.007	0.342
Meat soup	0.074	0.335
Non-roast potatoes	0.182	0.307

Note. [a]Individual vegetable item loadings: green salad/lettuce/cucumber/celery (.601), sweet peppers (.593); onions (.576); garlic (.572); marrow/courgettes (.566); tomato (.538); broccoli/spring greens/kale (.525); spinach (.516); mushrooms (.516); avocado (.500); leeks (.458); carrots (.446), green beans/broad beans/runner beans (.442); parsnips/turnips/swedes (.431); watercress (.404); cabbage (.368); peas (.336); sweetcorn (.330); cauliflower (.320); beansprouts (.313); beetroot (.311). [b]Individual fruit item loadings: strawberries/raspberries/kiwi fruit (.490); peaches/plums/apricots (.448); apples (.360), pears (.358), oranges/satsumas/mandarins (.344), melon (.324); grapes (.323); bananas (.308)

Table 2 Characteristics of the sample as a function of the dietary patterns

	Mediterranean pattern				Processed pattern			
	Low	Medium	High	P-value	Low	Medium	High	P-value
N	170	171	170		170	171	170	
Women, %	40.0	52.6	58.2	0.003	62.9	47.4	42.4	0.002
Age, years	79.5	79.3	79.2	0.072	79.3	79.3	79.4	0.399
Education, years	10.6	10.8	11.3	<0.001	11.1	10.7	10.9	0.002
Age 11 IQ	100.7	101.6	105.9	0.003	105.3	101.8	100.7	0.013
APOE e4, %	25.6	29.1	30.9	0.571	32.1	27.8	25.9	0.451
Current smoker, %	5.9	4.1	1.8	0.146	3.5	5.3	2.9	0.516
Ever smoker, %	53.5	47.9	34.7	0.002	45.4	50.3	40.6	0.198
Body mass index	28.0	27.1	26.7	0.035	26.5	27.2	28.3	0.001
Physical activity				0.020				0.019
Levels low 1&2	36.1	30.0	28.4		28.7	35.6	32.6	
Level med 3	47.9	60.6	50.9		51.1	50.8	55.4	
Levels high 4&5	16.0	9.4	20.7		20.1	13.6	12.0	
Alcohol intake, units/wk	7.7	7.6	11.7	0.001	10.7	7.9	8.3	0.058
Hypertension, %	64.1	57.3	53.5	0.133	52.9	59.6	62.4	0.193
Diabetes, %	15.4	12.9	8.8	0.180	12.9	11.7	12.9	0.850
Stroke, %	15.4	11.8	10.0	0.311	11.8	11.2	14.1	0.698
High cholesterol, %	47.3	50.9	48.2	0.794	50.6	52.0	43.8	0.267
HADS-A score	3.8	4.0	4.5	0.119	4.1	4.1	4.0	0.914
HADS-D score	3.4	2.7	2.7	0.004	2.7	3.0	3.1	0.263
MMSE score	28.6	28.8	29.0	0.027	29.0	28.8	28.7	0.171

Note. HADS-A, Hospital Anxiety and Depression Score-Anxiety subscale; HADS-D, Hospital Anxiety and Depression Score-Depression subscale; MMSE, Mini-Mental State Examination

Continuous variables are reported as mean values and categorical variables are reported as percentages.

Significance ($P < 0.05$) was tested using Analysis of variance (ANOVA) or Chi-Square tests, as appropriate.

Table 3 Associations between dietary pattern scores, global and domain-specific cognitive function, and structural neuroimaging indices

		Mediterranean pattern						Processed pattern					
		Model 1 age, sex		Model 2 before age 11 IQ		Model 3 with age 11 IQ		Model 1 age, sex		Model 2 before age 11 IQ		Model 3 with age 11 IQ	
	N	β	P-value	β	P-value	β	P-value	β	P-value	β	P-value	β	P-value
Cognitive function													
Global cognitive function	410	0.147	**0.003^**	0.130	**0.023**	0.094	**0.043**	-0.163	**0.001^**	-0.181	**0.001^**	-0.088	0.055
Visuospatial ability	494	0.143	**0.001^**	0.163	**0.002^**	0.113	**0.019**	-0.089	**0.045**	-0.106	**0.036**	-0.032	0.493
Processing speed	437	0.026	0.587	-0.008	0.881	-0.024	0.653	-0.118	**0.013^**	-0.148	**0.006^**	-0.070	0.189
Memory	470	0.142	**0.002^**	0.166	**0.002^**	0.105	**0.029**	-0.144	**0.001^**	-0.162	**0.002^**	-0.081	0.087
Verbal ability	505	0.234	**<0.001^**	0.218	**<0.001^**	0.121	**0.002^**	-0.213	**<0.001^**	-0.224	**<0.001^**	-0.130	**0.001^**
Neuroimaging													
TBV	358	-0.050	0.317	-0.068	0.242	-0.065	0.279	-0.052	0.306	-0.078	0.174	-0.061	0.309
GMV	358	-0.027	0.613	-0.064	0.286	-0.089	0.156	0.015	0.771	0.023	0.696	0.015	0.815
NAWMV	358	0.017	0.744	-0.034	0.574	-0.046	0.459	-0.055	0.295	-0.108	0.067	-0.062	0.315
WMHV	358	-0.033	0.543	0.039	0.520	0.070	0.264	-0.001	0.980	0.023	0.708	0.017	0.910
gFA	319	-0.020	0.749	-0.092	0.179	-0.096	0.174	-0.095	0.140	-0.125	0.076	-0.137	0.063
gMD	319	0.026	0.687	0.059	0.410	0.066	0.372	-0.014	0.830	-0.001	0.999	0.020	0.794

Note. β, standardised beta regression coefficients; TBV, total brain volume; GMV, grey matter volume; NAWMV, normal appearing white matter volume; WMHV, white matter hyperintensity volume; gFA, general factor of Fractional Anisotropy; gMD, general factor of Mean Diffusivity

Model 1 = adjusted for age and sex

Model 2 = adjusted for age, sex, physical activity, alcohol intake, smoking, diabetes, stroke, hypertension, hypercholesterolaemia, *APOE* e4 carrier status

Model 3 = model 2 + age 11 IQ

Significance ($P < 0.05$) was tested using linear regression. Statistically significant P-values are reported in bold typeface. ^ denotes significance following FDR correction.

Table 4 Associations of Mediterranean dietary pattern components with cognitive function

	Mediterranean pattern components						
	Fruit	Vegetables	Green leafy veg	Legumes	Wholegrains	Fish	Red meat
	β (P-value)	β (P-value)	β (P-value)	β (P-value)	β (P-value)	β (P-value)	β (P-value)
Global cognitive function							
Model 1	0.102 **(0.039)**	0.087 (0.081)	0.150 **(0.003)^**	0.030 (0.543)	0.034 (0.588)	0.071 (0.146)	-0.145 **(0.003)^**
Model 2	0.136 **(0.016)^**	0.055 **(0.034)**	0.132 **(0.019)**	0.019 (0.723)	0.015 (0.830)	0.082 (0.138)	-0.149 **(0.005)^**
Model 3	0.107 (0.058)	0.082 (0.138)	0.078 (0.160)	0.016 (0.710)	0.003 (0.966)	0.060 (0.174)	-0.114 **(0.009)^**
Visuospatial ability							
Model 1	0.129 **(0.004)^**	0.061 (0.172)	0.151 **(0.001)^**	0.036 (0.421)	0.092 (0.103)	0.068 (0.121)	-0.118 **(0.008)^**
Model 2	0.162 **(0.001)^**	0.076 (0.141)	0.161 **(0.001)^**	0.043 (0.374)	0.073 (0.245)	0.071 (0.149)	-0.130 **(0.007)^**
Model 3	0.108 **(0.024)**	0.074 (0.191)	0.106 **(0.025)**	0.055 (0.227)	0.058 (0.335)	0.043 (0.349)	-0.085 (0.063)
Processing speed							
Model 1	0.059 (0.224)	0.000 (0.998)	0.069 (0.157)	0.039 (0.410)	-0.072 (0.233)	0.033 (0.492)	-0.161 **(0.001)^**
Model 2	0.069 (0.213)	0.049 (0.378)	0.042 (0.441)	0.024 (0.651)	-0.101 (0.138)	0.048 (0.370)	-0.161 **(0.002)^**
Model 3	0.109 (0.092)	0.009 (0.887)	0.040 (0.533)	0.002 (0.796)	-0.101 (0.138)	0.039 (0.456)	-0.129 **(0.011)^**
Memory							
Model 1	0.067 (0.146)	0.104 **(0.024)**	0.115 **(0.012)^**	0.030 (0.510)	0.033 (0.569)	0.117 **(0.010)^**	-0.077 (0.089)
Model 2	0.152 **(0.003)^**	0.102 (0.054)	0.134 **(0.010)^**	0.009 (0.852)	0.054 (0.418)	0.122 **(0.016)^**	-0.094 (0.060)
Model 3	0.104 **(0.029)**	0.077 (0.108)	0.079 (0.095)	0.014 (0.765)	0.021 (0.730)	0.075 (0.104)	-0.049 (0.281)
Verbal ability							
Model 1	0.132 **(0.003)^**	0.166 **(<0.001)^**	0.226 **(<0.001)^**	0.079 (0.079)	0.054 (0.347)	0.106 **(0.017)^**	-0.147 **(0.001)^**
Model 2	0.155 **(0.002)^**	0.125 **(0.014)^**	0.204 **(<0.001)^**	0.068 (0.165)	0.079 (0.207)	0.112 **(0.024)**	-0.170 **(<0.001)^**
Model 3	0.053 (0.168)	0.088 **(0.022)**	0.110 **(0.004)^**	0.046 (0.204)	0.033 (0.485)	0.072 **(0.049)**	-0.119 **(0.001)^**

Note. β, standardised beta regression coefficients
Model 1 = adjusted for age and sex
Model 2 = adjusted for age, sex, physical activity, alcohol intake, smoking, diabetes, stroke, hypertension, hypercholesterolaemia, *APOE* e4 carrier status
Model 3 = model 2 + age 11 IQ
Significance ($P < 0.05$) was tested using linear regression. Statistically significant P-values are reported in bold typeface. ^ denotes significance following FDR correction.