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Mediterranean diet, micro- and macronutrients, and MRI measures of cortical thickness

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Abstract

INTRODUCTION—The Mediterranean diet (MeDi) is associated with reduced risk of cognitive impairment, but it's unclear whether it's associated with better brain imaging biomarkers.

METHODS—Among 672 cognitively normal participants (mean age: 79.8 years, 52.5% men), we investigated associations of MeDi score and MeDi components with magnetic resonance imaging measures of cortical thickness for the 4 lobes separately and averaged (average lobar).

RESULTS—Higher MeDi score was associated with larger frontal, parietal, occipital, and average lobar cortical thickness. Higher legume and fish intakes were associated with larger

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cortical thickness: legumes with larger superior parietal, inferior parietal, precuneus, parietal, occipital, lingual, and fish with larger precuneus, superior parietal, posterior cingulate, parietal, inferior parietal. Higher carbohydrate and sugar intakes were associated with lower entorhinal cortical thickness.

DISCUSSION—In this sample of elderly persons, higher adherence to MeDi was associated with larger cortical thickness. These cross-sectional findings require validation in prospective studies.

Keywords

Cortical thickness; Diet; Fish; Fruit; Legumes; Macronutrients; Nutrition; Sugar; Vitamins; Cross-sectional studies; Biomarkers; Magnetic resonance imaging; Structural brain changes

1. Introduction

The absence of effective disease modifying treatments for cognitive impairment underscores the need for preventive measures to reduce the burden of late life cognitive impairment including mild cognitive impairment (MCI) and Alzheimer's dementia (AD). Certain diets show promising, preventive effects on brain aging and cognitive impairment in observational studies and in clinical trials [1–3]. Higher adherence to the Mediterranean diet (MeDi) is associated with a lower risk for AD [4–8]. Prospectively, we showed that a high percentage of daily calories derived from protein and fat were associated with a reduced risk of incident MCI, whereas a high percentage from carbohydrates was associated with an increased risk of incident MCI [9]. We and others showed that cross-sectionally, components of the MeDi diet (vegetables, fruit, moderate alcohol intake) and high intake of mono (MUFA) and polyunsaturated (PUFA) fatty acids were associated with a reduced odds ratio for mild cognitive impairment (MCI) [10, 11]. Other investigators report beneficial effects of micronutrients (specifically, vitamins) on risk of cognitive impairment [12–14]. Despite these beneficial effects of diet on cognition, the associations of dietary measures with structural brain changes assessed using magnetic resonance imaging (MRI) are not established.

The few published studies on diet and imaging biomarkers suggest that higher adherence to a MeDi dietary pattern is associated with a reduced odds ratio for infarctions [15], larger cortical thickness, and larger brain volumes [16, 17]. However, further studies are needed to better understand the associations of the MeDi pattern and components of the MeDi with MRI biomarkers for specific brain regions that are involved in ageing or AD-related neurodegeneration and atrophy. Our objective was to study the cross-sectional associations of the MeDi and components of the MeDi with global and regional MRI measures of cortical thickness.

2. Methods

2.1. Study design and participants

The details of the population-based Mayo Clinic Study of Aging (MCSA) have previously been published [18]. Briefly, all residents from Olmsted County, Minn., USA, aged 70–89 years on October 1, 2004, were identified using the medical records-linkage system of the

Rochester Epidemiology Project (REP) [19]. Potential participants were selected using an age- and sex-stratified random sampling strategy, and eligible participants (without dementia, not in hospice or terminally ill) were recruited. From August 2005, MRI imaging was offered to participants at the clinical evaluation. Food Frequency Questionnaire (FFQ) were mailed to participants beginning in 2006 and were not linked to a particular evaluation. This study includes persons who were 70 years and older, cognitively normal when they completed the FFQ, and underwent MRI. Ethical considerations: All study protocols were approved by the Mayo Clinic and Olmsted Medical Center institutional review boards, and participants provided signed informed consent prior to participation.

2.2. Clinical evaluation

Participants underwent a clinical evaluation by a nurse or study coordinator. The interview by the study coordinator included questions about education, memory (participant), the Functional Activities Questionnaire and Clinical Dementia Rating scale (informant) [20, 21], and weight and height were measured. They underwent neuropsychometric testing administered by a psychometrist; 9 tests were used to assess performance in memory, executive function, visuospatial skills and language domains [18, 22]. A physician evaluation included assessment of global cognition using the Short Test of Mental Status [23] and a neurologic examination. The nurse or coordinator, psychometrist and physician who evaluated the participant and a neuropsychologist reviewed all the information for a participant and assigned a diagnosis of normal cognition, MCI, or dementia by consensus using previously published criteria [18, 22, 24]. Medical conditions were abstracted from the medical records.

2.3. Measurement of dietary food intake

Participants reported dietary intakes in the prior 12 months using a modified Block 1995 Revision of the Health habits FFQ [25] which consisted of 128 items [9–11]. Respondents indicated the usual portion size (small, medium, large; the medium portion was specified), and how often they consumed the food (never or <1 per month, 1–3 per month, 1 per week, 2–4 per week, 5–6 per week, 1 per day, 2–3 per day, 4–5 per day, 6+ per day). The questionnaire data were analyzed using The Food Processor SQL nutrition analysis software program (version 10.0.0, ESHA Research, Salem, Oregon, USA). Daily intake of foods, micronutrients, macronutrients, total daily caloric intake, and percentage of total caloric intake from each macronutrient (% protein, % fat, and % carbohydrate) were computed.

A MeDi score was computed as previously described [7, 9, 10, 26]. Energy-adjusted nutrient intakes were computed from the residual of each nutrient regressed on total caloric intake (kcal) [27]. Using a sex specific median cutoff, a value of 0 was assigned for consumption below, and 1 for values at or above the median for beneficial foods (vegetables, legumes, fruit, cereal/grains, and fish). Conversely, a value of 1 was assigned for consumption below, and 0 for consumption above the median for foods considered unfavorable in excess (meat, dairy products). Fat intake was estimated from the ratio of MUFA to saturated fats (SFA); a value of 1 was assigned for a ratio at or above the median and 0 otherwise. Alcohol intake was assigned a score of 1 for intake of 5 to < 25 g/day for women and 10 to < 50 g/day for men, and 0 otherwise. The total MeDi score ranged from 0 to 9 (maximum adherence).

2.4. MRI measures

MRI was performed on 3T systems. The cortical surface was parcellated using Freesurfer (v 5.3). Six summary cortical thickness measures were calculated: an average cortical thickness for each of the 4 lobes from regions of interest (ROIs): parietal (ROIs from precuneus, superior parietal, inferior parietal, supramarginal, and postcentral cortex), temporal (superior temporal, middle temporal, inferior temporal, banks of superior temporal sulcus, transverse temporal, fusiform and entorhinal cortex), frontal (ROIs from superior frontal, rostral middle frontal, caudal middle frontal, inferior frontal, lateral and medial orbitofrontal, paracentral, precentral and frontal pole), and occipital (ROIs from lateral occipital, lingual, cuneus, and pericalcrine regions); average lobar cortical thickness (average thickness from the ROIs for the 4 lobes); and a composite ROI thickness measure representing an AD signature cortical thickness (ROIs from entorhinal, inferior temporal, middle temporal, and fusiform cortex) [28]. *A priori* individual cortical thickness measures of interest included ROIs associated with atrophy or AD-related neurodegeneration: entorhinal, inferior parietal, superior parietal, posterior cingulate, middle temporal, superior temporal, inferior temporal, temporal pole, supramarginal, precuneus, dorsolateral prefrontal (superior frontal, rostral and caudal middle frontal), inferior frontal (pars orbitalis, pars triangularis, pars opercularis), fusiform and lingual [29–31]. Hippocampal volume (HVa) was estimated from the summed right and left volumes from Freesurfer (v 5.3) and adjusted for TIV.

2.5. Statistical analyses

Examination of residuals of regression of total MeDi on summary imaging measures suggested a linear association. Therefore, the associations of dietary measures (MeDi score, components of MeDi, macro and micronutrients) with summary MRI measures and individual ROIs were examined using general linear models for the left and right thickness combined. Due to the discrete nature of the total MeDi score and the differences in units and distributions of the dietary variables (foods [g/d], macronutrients [g/d or %], micronutrients [mg/d or mcg/d]), dietary variables were log-transformed (linolenic acid, linoleic acid, vitamin B2, B6, C, B carotene and folate) or square root-transformed (vegetables and whole grains/cereal) where necessary (i.e. substantially skewed), and standardized by the mean and standard deviation to create z scores.

The basic models were adjusted for age, sex, education, body mass index (BMI), and total energy intake. The fully adjusted models additionally included depressive symptoms (from Beck's Depression Inventory II), diabetes, hypertension, stroke, coronary heart disease, congestive heart failure, peripheral vascular disease, atrial fibrillation, and dyslipidemia; we also examined potential confounding by APOE $\epsilon 4$ allele ($\epsilon 2/\epsilon 4$, $\epsilon 3/\epsilon 4$, or $\epsilon 4/\epsilon 4$). The associations of dietary measures with thickness measures were examined for left and right hemispheres separately, and averaged. The associations for left and right hemispheres were very similar and consistent with the average; therefore only results based on the averaged thicknesses are reported.

Potential interaction (effect modification) by APOE $\epsilon 4$ allele, sex, and moderate exercise (based on self-report at baseline) was examined. Adjustment for multiple comparisons was not performed in order to identify potential associations that could be examined in definitive

prospective studies [32]. Statistical testing was performed at the conventional 2-tailed alpha level of $P < 0.05$. All analyses were performed using SAS version 9.4 (Cary Institute, NC).

3. Results

Table 1 shows the characteristics of the participants included in the study ($n = 672$) vs. those who did not participate in MRI studies ($n = 398$). Participants who completed an MRI had a higher education level and a lower frequency of vascular diseases compared to MRI non-participants, but they did not differ in regard to sex, APOE $\epsilon 4$ allele, diabetes, body mass index, history of smoking, dyslipidemia, or total MeDi score. The median [25th, 75th interquartile range] time between FFQ and MRI was 6.2 (3.6, 12.7 months); 74% of scans were performed after the FFQ. The distribution of the dietary intakes overall and by MeDi categories (0–3, 4–5, 6–9) is presented in the Supplementary Table.

3.1. Association of total MeDi score with summary cortical thickness measures

A higher MeDi score was associated with larger frontal, average lobar, parietal, and occipital lobe cortical thickness (CT); beta estimates ranged from .007 to .011 (Figure 1A). MeDi was marginally associated with temporal (beta, .009, $p = .07$) and AD signature CT (beta, .009, $p = .09$). A higher MeDi score was also associated with larger CT in several individual ROIs: superior temporal, dorsolateral prefrontal, middle temporal, fusiform, precuneus and lingual with beta estimates ranging from .010 to .014, and marginally significant associations for superior parietal (beta, .011; $p = 0.05$), inferior parietal (beta, .009; $p = .07$) and inferior frontal (beta, .008, $p = .09$); Figure 1B). There were no significant interactions of MeDi with APOE $\epsilon 4$ allele, sex or moderate exercise in regard to the summary measures and MeDi was not associated with hippocampal volume (the data are not presented).

3.2. Association of MeDi components, macro- and micronutrients with cortical thickness measures

Four of the five beneficial MeDi components were positively associated with CT measures. Specifically, higher fish intake was associated with larger CT summary measures for parietal and average lobar CT, and was marginally associated with AD signature CT ($p = .06$), temporal ($p = .06$) and frontal ($p = .08$) CT (Figure 2A). Fish intake was also associated with several individual CT measures: precuneus, superior parietal, posterior cingulate, supramarginal, middle temporal, and inferior parietal, and marginally associated with fusiform CT ($p = .05$). Higher intake of legumes was associated with larger parietal and occipital CT, and with larger thickness in ROIs for superior parietal, inferior parietal, precuneus and lingual CT (Figure 2B). Higher intake of total vegetables was associated with larger dorsolateral prefrontal and superior parietal CT; vegetables without legumes were associated with larger middle temporal, superior parietal, and dorsolateral prefrontal CT (Table 2). Intake of whole grains/cereals was associated with larger temporal pole and superior temporal CT in the fully adjusted model (Table 2, model 2). In contrast, fruit intake (without fruit juice) was negatively associated with inferior parietal, supramarginal, superior parietal, parietal, and precuneus CT (Figure 2C).

Table 2 presents associations of other MeDi component foods not included in computing the MeDi score, percentage macronutrients, and vitamins, with CT measures. Positive associations (higher intake with larger CT) were observed for omega-3 fatty acids and linolenic acid (an omega-3 PUFA) with superior temporal CT; linoleic acid (an omega-6 PUFA) with superior temporal, precuneus, middle temporal and parietal CT; vitamins B1 and B2 with superior temporal and temporal pole CT; vitamin B6 with superior temporal and middle temporal; folate with superior temporal; and beta carotene with dorsolateral prefrontal and temporal pole CT. Surprisingly, higher red meat was associated with larger entorhinal CT. Negative associations (higher intake with lower CT) were observed for % carbohydrate and % sugar with entorhinal CT and red meat with inferior and superior temporal CT (Table 2, model 1). MUFA/saturated fat ratio and dairy were not associated with CT measures. The estimates were unchanged with adjustment for APOE ε4 allele (data not presented). Food components that were marginally associated with CT measures (.05 P .10) in the fully adjusted models are presented in Table 3.

4. Discussion

In this population-based sample of elderly participants, higher adherence to a Mediterranean dietary pattern was associated with larger cortical thickness of the summary measures and with several individual ROIs that undergo age-related or AD-related neurodegeneration. Higher intakes of foods that are considered beneficial for cognition as well as B vitamins were associated with larger cortical thickness. In contrast, higher intakes of foods that are considered non-beneficial at high levels and higher percentages of calories from carbohydrates and sugar were associated with lower cortical thickness. These cross-sectional findings suggest that a healthy or MeDi dietary pattern is associated with larger cortical thickness in several brain regions.

Synaptic dysfunction and loss of synapses may lead to neuronal loss, cortical thinning, and cognitive impairment. Although we did not evaluate cognition as an dependent measure in the present study, the findings have implications for maintaining cognitive function. Positive associations of total MeDi score and beneficial components of MeDi (fish, vegetables, legumes, and whole grains/cereals) were observed with average cortical thickness in parietal and frontal lobes and with ROIs such as superior temporal, dorsolateral prefrontal, entorhinal, and fusiform ROIs that mediate or support memory, executive function, attention and language, and are associated with atrophy in dementia [30].

Fish (fatty fish in particular) is an important source of omega-3 fatty acid that is reported to have beneficial effects on brain structure and function [33, 34]. Indeed, fish, omega-3 fatty acids and linolenic acid (an omega-3 PUFA) were associated with larger cortical thickness in the present study. Vegetables and legumes may be important because of their high micronutrient content (vitamins, minerals, and phytochemicals), anti-oxidant and anti-inflammatory effects as well as other factors.

Most vegetables (e.g. broccoli, cabbage, cauliflower, mushrooms, green beans) consist of complex carbohydrates or complex starches that have a zero or low glycemic index and low glycemic load, as do legumes (e.g. beans, lentils, and chickpeas). Vegetables are also

beneficial because they have a low caloric density, increase satiety, and thereby can help reduce weight gain. Legumes are also high in plant protein. Thus, in general, vegetables are less likely to adversely impact glucose metabolism and neuronal integrity. A few vegetables, however, have a high glycemic index and glycemic load (e.g. corn and potatoes) and could adversely impact glucose and insulin metabolism and cortical thickness. Fewer yet, have a relatively moderate to high glycemic index, but a very low glycemic load (e.g. parsnip, carrots, and beets). Overall, our findings are consistent with the anticipated beneficial effect of vegetables. Whole grains and cereals may also have beneficial effects for the same reasons as described for vegetables.

Fruit on the other hand, is a beneficial MeDi component and a source of antioxidants and vitamins, but was negatively associated with cortical thickness. Several fruits have a high content of simple sugars and a high glycemic index that may offset the benefits at high intakes. Our findings are consistent with a study from the Washington Heights-Inwood Community Project, that also reported that higher fruit intake was associated with lower temporal and hippocampal volumes [17]. The association of fruit with cortical thickness, however, should be interpreted in the context of the study design and the age of study participants. Older persons may have a high intake of fruit because it is perceived to be healthy, easily digested, requires little preparation, and tastes good. However, moderation of fruit intake may be necessary, particularly for diets deficient in other beneficial foods, and because older adults are typically less active and the mitigating effects of physical activity or exercise may not be realized. The association of fruit with cortical thickness in the present study, therefore, may not be applicable to younger age groups who are more active and have a more varied and healthy diet. Our findings, however, raise the question that in elderly persons, high intake of foods with a high glycemic index or high glycemic load, whether as fruit or as highly refined carbohydrates, may disrupt insulin signaling, impair glucose metabolism, and thereby contribute to neuronal loss, reduced cortical thickness, and cognitive impairment. Indeed, we previously reported that high percentage intakes of daily calories derived from carbohydrate and sugar was associated with an increased risk of MCI [9].

Our findings are in keeping with other studies on diet and MRI biomarkers. In a cross-sectional study, higher adherence to the MeDi was associated with larger cortical thickness in the entorhinal, orbitofrontal and the posterior cingulate cortex regions [16]. In the Washington Heights-Inwood Community Aging Project, higher MeDi score, higher fish intake and lower meat intake were positively associated with larger mean cortical thickness, and lower red meat intake was associated with larger cortical thickness in the superior-frontal region [17]. In a clinical trial among older adults, parietal, frontal and cingulate cortex volumes increased or were maintained in persons treated with omega-3 fatty acid supplementation, exercise and cognitive stimulation, but decreased in the control arm [34]. The positive association of MeDi with larger thickness in the frontal lobe suggests that the MeDi may favorably modulate cortical thickness through vascular mechanisms; this is consistent with the known beneficial effects of the MeDi on cardiovascular health and with the reported association of frontal lobe atrophy with cerebrovascular disease [35, 36]. Our findings are also consistent with positive associations of micronutrients (vitamins) and omega-3 fatty acids with larger total brain volume in non-demented persons [13].

The present findings are also consistent with reported beneficial effects of MeDi and MeDi components on risk of mild cognitive impairment and AD dementia in prospective [4, 26, 37] and cross-sectional studies [10, 11]. Higher plasma levels of omega-3 fatty acid were associated with a reduced risk of dementia in the Framingham Heart Study [38] and in the Atherosclerosis Risk in Communities study [39]. In a clinical trial among MCI patients, B vitamins had beneficial effects on cognition in persons with high omega-3 fatty acids [40]. Micronutrients (vitamins) have also been positively associated with cognition [26, 41, 42].

In general, associations of non-beneficial components of the MeDI with cortical thickness measures were as expected. Saturated and trans fats are unhealthy due to adverse cardiovascular effects, and have been associated with greater cognitive decline and risk of dementia [4, 43–45]. High red meat intake has been shown to be detrimental to cognition including dementia [4]. Consistent with this, we observed a negative association of red meat with inferior and superior parietal cortical thickness. However, we also unexpectedly observed a positive association with larger entorhinal cortex thickness. The potential mechanism is unclear; we speculate that it could relate to some beneficial components of lean red meat (e.g. iron, protein, MUFA and PUFA) [46] and beneficial effects in increasing satiety and reducing weight gain. Fatty red meats and processed meats on the other hand are unlikely to be beneficial due to their high saturated fat content. Our findings remain to be validated.

In contrast to studies on cognitive impairment [44, 47], we did not find significant beneficial associations of MUFA/saturated fat ratio with MRI biomarkers. Failure to observe associations of MeDi or MeDi components with hippocampal volume is consistent with findings from the Alzheimer's Disease Neuroimaging Initiative in which presymptomatic individuals had significantly reduced cortical thickness in AD vulnerable regions compared to controls, but did not differ in regard to hippocampal volume [29].

There are potential limitations to our study. The FFQ was not administered concurrently with MRI, but the diet or MRI biomarkers are unlikely to have changed markedly in the short time interval between completing the FFQ and imaging. The cross-sectional design precludes our ability to make causal inferences; however, it allows us to generate hypotheses for future studies. Despite the potential for reporting bias, FFQs assessing intakes over longer periods as in this study are reportedly more reliable than short term recall [48]. Furthermore, FFQs reliably rank individuals in regard to food intake and are useful for large epidemiologic studies, in contrast to daily diaries that are not feasible for large epidemiologic studies. We did not adjust for multiple comparisons to reduce the likelihood of falsely rejecting potentially relevant associations [32]. Despite this, several observed associations are biologically plausible and consistent with the expected associations based on published literature. Finally, MRI participants were healthier than non-participants; thus, we may have underestimated the strength of the associations.

Our study has several strengths. The population-based design reduced potential selection bias. The study consisted of a large sample of participants who were cognitively normal and unaware of their brain morphology when completing the FFQ, thereby minimizing potential recall bias in reporting of dietary intakes. Participants were characterized as cognitively

normal by 3 independent evaluators and underwent state of the art MRI. The study assessed associations of several dietary measures with MRI biomarkers of atrophy or neurodegeneration, generating hypotheses for prospective studies. If validated prospectively, the associations will inform the development of non-pharmacologic interventions for maintaining cortical thickness and thereby reducing the risk of cognitive impairment and AD dementia.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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RESEARCH IN CONTEXT

1. **Systematic review:** The authors reviewed the literature using established methods (PubMed) to identify abstracts and publications that have investigated the associations of dietary measures with brain magnetic resonance imaging measures. Despite the abundance of studies on the association of the Mediterranean and other dietary pattern or nutrients with cognition, few studies examined the association of diet with brain MRI measures.
2. **Interpretation:** We observed positive associations of higher MeDi Score with cortical thickness measures. We hypothesize that a potential mechanism for the beneficial association of the Mediterranean diet on cognition is that adherence to this diet may maintain cortical thickness. Since cortical thinning is associated with late life mild cognitive impairment and dementia, the current findings have implications for diet as a lifestyle measure that may reduce the risk of these conditions.
3. **Future directions:** The current cross-sectional study cannot assess causality. Therefore, in a future study, we will prospectively investigate whether persons with higher adherence to the Mediterranean diet have a reduced risk of cortical atrophy assessed from longitudinal changes in cortical thickness measures during follow-up in the Mayo Clinic Study of Aging.

Figure 1.

Forest plots for associations (beta estimates [*P*-values]) of total MeDi score with cortical thickness for a) The 6 summary measures: average frontal, temporal, parietal, occipital, average composite thickness for the 4 lobes, and an AD signature cortical thickness. b) Individual regions of interest (ROIs). The squares represent beta estimates from general linear models adjusted for age, sex, education, BMI, vascular risk factors, stroke and depressive symptoms. The dark solid horizontal lines represent the 95% confidence intervals.

Figure 2.

Forest plots of associations (beta estimates [*P*-values]) of components of MeDi score for (A) Fish; (B) Legumes; (C) Fruit; with cortical thickness for regions of interest (ROIs) for summary measures (listed first) and individual ROIs. The squares represent beta estimates from general linear models, adjusted for age, sex, education, BMI, vascular risk factors, stroke and depressive symptoms.

Table 1

Characteristics of participants and non-participants in imaging studies

	MRI n=672	No MRI n=398	P value
Age, mean (SD)	79.8 (5.0)	80.6 (5.4)	0.015
Men, n (%)	353 (52.5)	193 (48.5)	0.20
Education, mean (SD)	14.2 (2.9)	13.8 (3.0)	0.032
APOE ε4 carrier, n (%)	156 (23.2)	96 (24.2)	0.70
BMI, mean (SD)	27.4 (4.6)	28.0 (5.7)	0.12
Diabetes, n (%)	99 (14.7)	73 (18.3)	0.12
Hypertension, n (%)	517 (76.9)	328 (82.4)	0.034
Dyslipidemia, n (%)	545 (81.1)	330 (82.9)	0.46
Stroke, n (%)	25 (3.7)	33 (8.3)	0.001
Congestive heart failure, n (%)	42 (6.3)	74 (18.6)	<0.001
Coronary artery disease, n (%)	256 (38.1)	181 (45.5)	0.018
Vascular conditions, mean (SD) *	2.9 (1.6)	3.4 (1.7)	<0.001
Smoking:			
Never	64 (50.4)	56 (44.4)	0.56
Former	50 (39.4)	53 (42.1)	
Current	13 (10.2)	30 (11.9)	
Depressive symptoms †	27 (4.0)	27 (6.8)	0.046
Global z score ‡	0.5 (0.9)	0.3 (0.8)	<0.001
MeDi score, median (IQR)	4.0 (3.0 – 5.0)	4.0 (3.0– 5.0)	0.052
FFQ to MRI, median (IQR) months §	6.2 (3.6 – 12.7)	NA	
MCI at time of imaging, n (%)	22 (3.3)	NA	
Imaging measures: //			
Parietal cortical thickness, mm	2.03 (1.95, 2.11)	NA	
Temporal cortical thickness, mm	2.65 (2.55, 2.74)	NA	
Frontal cortical thickness, mm	2.30 (2.22, 2.37)	NA	
Occipital cortical thickness, mm	1.75 (1.69, 1.81)	NA	
AD signature cortical thickness, mm	2.77 (2.67, 2.85)	NA	

MeDi, Mediterranean diet total score; MRI, magnetic resonance imaging; BMI, body mass index; FFQ, food frequency; SD, standard deviation; IQR, interquartile range. Data are based on participants with non-missing data only. P-values are based on the chi-square test for categorical variables and Kruskal-Wallis test for continuous variables.

* Number of vascular conditions (diabetes, hypertension, coronary heart disease, peripheral vascular disease, obesity, congestive heart failure, atrial fibrillation, dyslipidemia, and stroke).

† Depressive symptoms were assessed from the Beck Depression Inventory II.

‡ Composite global cognitive score based on memory, executive function, language and visuospatial skills domain z scores.

§ Time between completion of food frequency questionnaire and MRI imaging.

// Median (25th, 75th percentile)

Table 2
Association of scaled dietary foods and vitamins with cortical thickness in regions of interest*

		Model 1 [†]			Model 2 [‡]		
Dietary measures	Cortical thickness	Beta	95% CI	p	Beta	95% CI	p
Positive associations							
Vegetables [§]	Dorsolateral prefrontal	.011	.001, .021	.027	.013	.003, .023	.012
	Superior parietal	.013	.002, .024	.021	.014	.003, .025	.015
	Temporal pole	.020	−.000, .041	.055	.024	.004, .045	.021
	Superior temporal	.009	−.002, .020	.117	.011	.001, .022	.037
Red meat	Entorhinal	.032	.007, .058	.013	.036	.011, .061	.006
Omega 3 fatty acid	Superior temporal	.013	.001, .024	.029	.013	.002, .024	.026
Linolenic	Superior temporal	.013	.001, .024	.027	.013	.002, .025	.019
Linoleic acid	Superior temporal	.014	.003, .026	.015	.014	.003, .026	.013
	Precuneus	.011	.001, .021	.027	.012	.001, .022	.025
	Middle temporal	.012	.001, .023	.032	.012	.001, .023	.034
	Parietal	.009	.000, .018	.05	.009	−.000, .018	.050
Vitamin B1	Superior temporal	.013	.002, .025	.019	.014	.003, .025	.016
	Temporal pole	.021	−.000, .042	.054	.024	.002, .045	.030
Vitamin B2	Superior temporal	.011	−.000, .022	.05	.012	.001, .023	.032
	Temporal pole	.023	.002, .044	.034	.027	.006, .048	.013
Vitamin B6	Superior temporal	.014	.003, .025	.010	.013	.003, .024	.016
	Middle temporal	.011	.001, .022	.037	.011	.001, .021	.037
Folate	Superior temporal	.012	.001, .023	.026	.012	.001, .023	.036
B carotene	Dorsolateral prefrontal	.010	−.000, .020	.052	.011	.001, .021	.033
	Temporal pole	.020	−.001, .041	.058	.022	.001, .043	.044
Negative associations							
Red meat	Inferior temporal	−.012	−.023, −.001	.037	−.010	−.021, .001	.074
	Superior temporal	−.012	−.023, −.000	.042	−.010	−.021, .001	.073
% carbohydrates	Entorhinal	−.034	−.059, −.009	.008	−.035	−.060, −.010	.006
% sugar	Entorhinal	−.034	−.059, −.009	.007	−.036	−.061, −.011	.005

* Associations of MeDi components, %macronutrients, and vitamins with cortical thickness measures. Dietary measures were log or square root transformed where necessary, and standardized.

[†]Model 1 is adjusted for age, sex, education, body mass index and total energy intake.

[‡]Model 2 is additionally adjusted for diabetes, hypertension, vascular risk factors (coronary heart disease, peripheral vascular disease, congestive heart failure, atrial fibrillation, dyslipidemia), stroke, and depressive symptoms.

[§]Vegetables excluding legumes was associated with larger dorsolateral prefrontal (beta, .013; $p = .014$), middle temporal (beta, .012; $p = .028$), superior parietal (beta, .011; $p = .048$) cortical thickness; models were adjusted for variables in Model 2.

Table 3

Multivariable models for marginally significant associations of scaled dietary foods and nutrients with cortical thickness in regions of interest

		Model *		
Dietary measures	Cortical thickness	Beta	95% CI	P
Positive associations				
Vegetables	Middle temporal	.010	-.001, .020	.07
Linolenic	Middle temporal	.010	-.001, .020	.08
B carotene	Lingual	.007	-.001, .015	.09
	Middle temporal	.009	-.002, .019	.10
	Superior frontal	.011	-.000, .022	.06
	Superior parietal	.010	-.000, .021	.06
	Orbitofrontal	.008	-.002, .018	.10
Vitamin C	Temporal pole	.018	-.003, .039	.09
Negative associations				
% sugar	Precuneus	-.010	-.019, .000	.05
	Parietal	-.008	-.017, .001	.08
	Composite lobar	-.007	-.014, .001	.07
	AD signature	-.010	-.020, .001	.07
% saturated fat	Lingual	-.007	-.016, .001	.09
	Middle temporal	-.010	-.021, .001	.07
% total fat	Inferior temporal	-.011	-.022, .001	.06

MUFA/SFA, monounsaturated fat/saturated fat ratio. BMI, body mass index. Dietary measures are log or square root transformed where necessary, and standardized.

* Estimates for association of MeDi components with imaging measures were .05 P .1. The model is adjusted for age, sex, education, total energy intakes, BMI, diabetes, hypertension, coronary heart disease, peripheral vascular disease, congestive heart failure, atrial fibrillation, dyslipidemia, stroke, and depressive symptoms.