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Mediterranean diet and preserved brain structural connectivity in older subjects

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Abstract

Introduction: The Mediterranean diet (MeDi) has been related to a lower risk of Alzheimer's disease; yet, the underlying mechanisms are unknown. We hypothesized that protection against neurodegeneration would translate into higher gray matter volumes, whereas a specific association with preserved white matter microstructure would suggest alternative mechanisms (e.g., vascular pathways).

Methods: We included 146 participants from the Bordeaux Three-City study nondemented when they completed a dietary questionnaire and who underwent a 3-T magnetic resonance imaging at an average of 9 years later, including diffusion tensor imaging.

Results: In multivariate voxel-by-voxel analyses, adherence to the MeDi was significantly associated with preserved white matter microstructure in extensive areas, a gain in structural connectivity that was related to strong cognitive benefits. In contrast, we found no relation with gray matter volumes.

Discussion: The MeDi appears to benefit brain health through preservation of structural connectivity. Potential mediation by a favorable impact on brain vasculature deserves further research.

Keywords: Neuroimaging; Diffusion tensor imaging; Voxel-based morphometry; Mediterranean diet; Prospective studies; Risk factors in epidemiology

1. Introduction

The traditional Mediterranean diet (MeDi) is characterized by an abundant consumption of plant foods, a moderate intake of fish and alcohol, and low intakes of meats and dairy products, with monounsaturated fatty acids as the main fat source provided by olive oil. The beneficial effect of the MeDi on cardiovascular mortality is well established [1]. Adherence to the MeDi has also been associated with a lower risks of Alzheimer's disease (AD) dementia and cognitive

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decline [2–5], stroke, and depression [6], which all appear to have a strong vascular component [7–9]. The protective effect of the MeDi on stroke was confirmed in a large intervention study [10], and the MeDi was related to less cerebral infarcts at magnetic resonance imaging (MRI) [11]. However, mediation by vascular comorbidities was not evidenced in studies of dementia or cognitive decline [4,12], suggesting that nonvascular mechanisms (e.g., neurodegenerative pathways) may also be involved. Hence, more research is needed to elucidate the neurobiological basis of the relation of the MeDi to brain health.

Examining how the MeDi relates to the preservation of brain structure (i.e., gray matter [GM] volume and white matter [WM] connectivity) is critical to understand these pathways. Indeed, on the one hand cerebrovascular disease has been associated with alterations of WM microstructure [13,14], which may start decades before brain ischemic injury visible at MRI [15], and on the other hand GM atrophy in the medial temporal lobe is a typical early feature of AD [16]. Hence, we hypothesized that an association of the MeDi with higher GM volumes in AD regions may indicate involvement of neurodegenerative mechanisms and that a specific relationship with preserved WM microstructure (with no relation to GM volumes) would be suggestive of mechanisms partly independent of AD-related neurodegeneration, including possibly vascular pathways. Our objective was to examine the association between higher adherence to the MeDi and preserved brain GM volume and WM microstructure at an average of 9 years later, in older individuals from the Three-City (3C) study.

2. Methods

2.1. Study population

The 3C study is a prospective cohort initiated in 1999–2000 with the objective to study vascular risk factors of dementia. In total, 9294 noninstitutionalized community dwellers aged ≥65 years were included in three French cities (Bordeaux [N = 2104], Dijon [N = 4931], and Montpellier [N = 2259]) [17]. The protocol of 3C study was approved by the Consultative Committee for the Protection of Persons participating in Biomedical Research at Kremlin-Bicêtre University Hospital, Paris, France, and all participants provided written informed consent. Data collected at baseline included sociodemographic and lifestyle information, symptoms and medical complaints, blood pressure and anthropometric measurements, and neuropsychological testing and a blood biobank. Five follow-up examinations were performed at 2, 4, 7, 10, and 12 years after baseline examination. At each visit, all potential dementia cases were identified based on their neuropsychological performances and reviewed by an independent committee of neurologists to obtain a consensus on its diagnosis and etiology according to the criteria of the *Diagnostic and Statistical Manual of Mental Disorders*, *Fourth Edition* [18].

In 2001–2002, a comprehensive dietary survey was conducted among 1811 participants in Bordeaux (94% of those still alive included at baseline), of whom 1712 had no missing dietary data. We excluded 31 individuals with dementia at the time of dietary assessment. Of the 1681 remaining nondemented individuals, 351 died and 1044 were reexamined at the 10-year follow-up visit in 2010–2011 (Supplementary Fig. 1). Among them, 225 participants were invited to an MRI examination using a 3-T machine, allowing accurate investigation of WM microstructure through diffusion tensor imaging (DTI; We primarily selected participants included in a previous MRI substudy and enriched our sample with individuals with cognitive deficits suggestive of dementia at the 10-year visit; to ensure that such selection of "at risk" participants did not bias results, we conducted sensitivity analyses, as detailed in the "Methods" Section 2.6.3 subsequently). The present study is based on the 146 Bordeaux 3C study nondemented participants who provided information on their diet in 2001–2002, underwent brain MRI in 2010–2011 including DTI, were free of tumor or major cerebrovascular pathologies at MRI, and had no missing data for main potential confounders.

2.2. Dietary assessment and the MeDi score

The dietary survey was conducted at home by a specifically trained dietician who administered a food frequency questionnaire (FFQ) and a 24-hour dietary recall [19,20]. Data from these questionnaires were validated in an independent 3C study subsample [21]. In the FFQ, frequency of consumption of 148 foods and beverages was recorded in 11 classes, converted into a number of servings per week, and then aggregated into 20 food per beverage groups, as detailed previously [19]. The groups considered to be a part of a MeDi were identified: vegetables; fruits; legumes; cereals including bread, pasta, and rice; fish; meats; dairy products; and alcohol. The 24-hour recall was used to estimate nutrient and total energy intake and the ratio of monounsaturated-to-saturated fatty acids.

We computed a MeDi 9-point score [4] based on the original score as described by Trichopoulou et al. [22], which included nine components. For components supposed to be beneficial to health (vegetables, fruits, legumes, cereals, fish, and a higher monounsaturated-to-saturated fatty acid ratio), 1 point was given if individual consumption was greater than the sex-specific median in our population and 0, otherwise. For alcohol, of which "moderate" consumption is considered beneficial, 1 point was given for consumption between 4 and 15 glasses/wk in men and 0 and 2 glasses in women (i.e., the second quartile of intake in our population). For components hypothesized to be detrimental (i.e., meats and dairy products), 1 point was given for a consumption less than the sex-specific median and 0, otherwise. A

MeDi score was then computed by summing individual binary scores for each component. Thus, the score could range from 0 to 9, with higher scores indicating greater dietary adherence to a MeDi.

2.3. Assessment of brain structure

2.3.1. MRI acquisition

In 2010–2011, MRI examination was performed using an Achieva 3-T scanner (Philips Medical System, The Netherlands). Anatomic high-resolution MRI volumes were acquired in transverse plane using a three-dimensional Multiplanar reconstruction acquisition gradient echo (MPRAGE) T1-weighted sequence, and diffusion-weighted images were performed using a single-shot echo-planar sequence with diffusion gradients applied in 21 noncollinear directions (Supplementary Methods).

2.3.2. MRI processing

Brain GM and WM volumes were assessed using voxel-based morphometry (VBM) [23,24], and WM microstructure was examined through DTI using tract-based spatial statistics (TBSS) pipeline [25] within FMRIB Software Library (FSL). DTI parameters evaluate both the directionality and magnitude of water diffusion in brain tissue. Within WM, the diffusion of water is restricted along axonal bundles; thus, higher directionality and lower magnitude of diffusion generally indicate preserved architecture of WM tracts [26]. Fractional anisotropy (FA) represents the degree of directionality of water diffusivity along fibers (a higher FA indicates higher directionality of diffusion and preserved microstructure); axial diffusivity and radial diffusivity quantify the magnitude of diffusion along the principal and perpendicular directions of fibers, respectively, and mean diffusivity (MD) represents a global measure of diffusion (lower axial diffusivity, radial diffusivity, and MD indicate lower magnitude of diffusion and preserved microstructure). Details on MRI processing were provided in the Supplementary Methods.

2.4. Cognitive assessment

A battery of neuropsychological tests was administered by psychologists at baseline and at each follow-up examination. Supplementary Methods provide the details on the cognitive battery used in the cohort.

2.5. Other variables

Covariates were assessed at the time of dietary assessment except vascular risk factors, which were determined at the cohort baseline (an average of 1.5 years before dietary assessment), the unique time point with concomitant clinical and blood measurements.

Covariates included age, gender, educational level, body mass index (BMI), smoking, and total energy intake. Regular exercise was defined as practicing a sport at least 1 h/wk, having at least 1 hour of intensive leisure activity per week (e.g., running, swimming, hiking), or at least 1 hour of more moderate activities (e.g., walking, household) per day. Vascular risk factors included history of cardiovascular or cerebrovascular disease, hypertension (blood pressure $\geq$140/90 mm Hg or treated), diabetes (glucoses level $\geq$130 mg/dL [7 mmol/L] or treated), and hypercholesterolemia (total cholesterol $\geq$240 mg/dL [6.2 mmol/L]).

Furthermore, to reduce the possibility of reverse causation (which occurs when individuals with cognitive impairment modify their diets), we adjusted our analyses for cognitive status at the time of dietary assessment. We focused on semantic memory, an early predictor of AD dementia [27], using the Isaacs' Set Test (IST) (Supplementary Methods).

2.6. Statistical analyses

2.6.1. Relationship between MeDi adherence and GM and WM volumes

We examined on a voxel-by-voxel basis the relationship between the MeDi score (used as a continuous variable) and GM and WM volumes at an average of 9 years later, using linear regression within Statistical Parametric Mapping (SPM). Analyses were first adjusted for age, gender, education, carrying at least one ε4 allele for the apolipoprotein E (*APOE*) gene (ie, *APOE* ε4 carrier status), and total intracranial volume. In a second model, we added energy intake, physical activity, BMI, smoking, vascular risk factors, and the IST score. For all VBM analyses, we used a statistical threshold of $P < .05$ after corrections for multiple comparisons using topological false discovery rate [28] and a significant threshold cluster of 100 voxels.

2.6.2. Relationship between MeDi adherence and WM microstructure

We examined the relationships between the MeDi score and DTI parameters using a linear regression model within FSL. As with VBM analyses, models were first adjusted for age, gender, education, and *APOE* ε4 carrier status; we secondarily added our full set of covariates. In TBSS analyses, statistical inference was based on permutation-based statistics with 5000 permutations and threshold-free cluster enhancement [29], with a threshold of $P < .05$ corrected for multiple comparisons. The WM atlas of the Johns Hopkins University [30] was used to identify WM tracts that were significantly associated with the MeDi score.

2.6.3. Supplementary analyses

We performed a series of secondary analyses, which were all described in details in the Supplementary Methods. First, we analyzed the stability of dietary habits between MeDi assessment in 2001–2002 and the MRI examination in 2010–2011, using available information from two FFQs in 2003–2004 and 2006–2007. Second, to determine whether

the associations between the MeDi and brain structure were because of a particular food group, we evaluated MeDi components separately. Third, we examined whether the association between the MeDi and preserved brain structure had a favorable impact on cognition. Using the cognitive battery assessed at the time of MRI, we defined an episodic memory score, a score of processing speed/executive function, and a composite score of global cognition. We focused on the brain WM regions in which imaging parameters were significantly associated with the MeDi in the main analysis, and we investigated whether individual parameter values in the corresponding WM region were related to better cognitive scores, using linear regressions adjusted for age, gender, and education.

Finally, we examined the robustness of our findings in several sensitivity analyses. We tested any departure from the linearity assumption, and we ensured that our results were independent of the burden of white matter hyperintensities (WMH; Supplementary Methods). We also conducted a sensitivity analysis excluding incident dementia cases (n = 4) and individuals with suspected dementia based on their neuropsychological evaluation (n = 18).

3. Results

At the time of dietary assessment, the mean age of participants was 73.0 years (range, 67.7–83.2). The MeDi score ranged from 0 to 8 and was normally distributed. In total, 26% of the participants were classified within a low score range (0–3), indicating poor adherence to the MeDi; 47% had medium scores (4 or 5); and 27% had higher scores (6–8) representing a top adherence to the MeDi.

Compared with individuals with medium or high MeDi adherence, participants with lower adherence were more often intensive smokers and had slightly higher BMI; they also practiced less regularly physical activity, although the difference was not statistically significant (Table 1). Age, education, *APOE* ε4 carrier status, history of cardiovascular diseases, hypertension, and hypercholesterolemia did not differ significantly across categories of MeDi adherence. In general, there was a large distribution of intake of each MeDi component from the lowest to the highest categories of MeDi score (Table 2).

3.1. MeDi adherence and GM and WM volumes

MRI examination was performed 8.9 years on average (standard deviation = 0.2) after dietary assessment (range, 8.4–9.9 years). In VBM analyses adjusted for multiple comparisons, we did not find any significant association between the MeDi score and GM volumes in any brain area. Likewise, the MeDi was not associated with WM volumes.

3.2. MeDi adherence and WM microstructure

In contrast, in TBSS analyses, we found strong associations between the MeDi score and DTI parameters, indicating that higher MeDi adherence was associated with a general pattern of preserved WM microstructure in multiple bundles (Fig. 1).

Table 1
Baseline characteristics of the study participants according to the MeDi score, the Bordeaux sample of the 3C study (N = 146)

	Low adherence	Medium adherence	High adherence	
	MeDi score (0–3)	MeDi score (4–5)	MeDi score (6–8)	
Characteristics	n = 38	n = 69	n = 39	*P* value*
Mean age, y (SD)	73.3 (3.8)	72.4 (3.5)	73.9 (3.7)	.10
Male	44.7	31.9	48.7	.17
Education				
Primary school or less	18.4	30.4	25.6	.47
Secondary	23.7	27.5	18.0	
High school	34.2	26.1	25.6	
University	23.7	15.9	30.8	
APOE ε4	13.2	14.5	25.6	.25
Regular physical activity	27.0	48.4	32.4	.07
Smoking, mean number of packs per year (SD)	18.7 (31.3)	7.3 (13.0)	7.4 (16.4)	.04
Mean BMI (SD)	28.4 (4.3)	25.8 (3.8)	26.9 (3.0)	.01
History of cardiovascular or cerebrovascular diseases	23.7	14.5	25.6	.30
Hypertension	73.7	56.5	76.9	.05
Hypercholesterolemia	42.1	56.5	53.9	.35
Diabetes	7.9	3.0	5.3	.48
Mean IST score (SD)	33.6 (6.7)	32.6 (6.5)	33.4 (6.6)	.74

Abbreviations: MeDi, Mediterranean diet; 3C, Three-City; SD, standard deviation; *APOE* ε4, ε4 allele of the apolipoprotein E gene; BMI, body mass index; IST, Isaacs' set test.

NOTE. Values are percentages unless otherwise indicated. Percentages are of nonmissing values.

*Estimated using χ^2 tests or Fisher's exact tests for categorical variables and analyses of variance for continuous variables, across categories of the MeDi score.

Table 2
Mean energy and MeDi component intakes by categories of the MeDi score, the Bordeaux sample of the 3C study (N = 146)

	Low adherence	Medium adherence	High adherence
	MeDi score (0–3)	MeDi score (4–5)	MeDi score (6–8)
Dietary variables	n = 38	n = 69	n = 39
Mean total energy intake, kcal/d (SD)	1536.3 (541.8)	1701.5 (519.8)	1695.6 (607.8)
Mean MeDi score components intake, servings/d (SD)			
Vegetables	15.0 (5.1)	18.7 (6.2)	24.2 (5.5)
Legumes	0.5 (0.5)	0.5 (0.7)	0.8 (0.4)
Cereals	17.4 (7.0)	22.9 (6.8)	23.4 (4.5)
Fruits	11.7 (9.2)	13.6 (6.8)	15.6 (5.4)
Fish	1.9 (1.4)	2.7 (1.5)	3.5 (1.7)
Meat	5.4 (2.3)	4.8 (2.4)	4.4 (2.4)
Dairy products	19.4 (7.4)	15.6 (6.4)	13.6 (7.1)
Mean monounsaturated-to-saturated fatty acid ratio (SD)	0.8 (0.3)	0.9 (0.5)	1.1 (0.3)
Mean alcohol intake, glasses/d (SD)	14.5 (16.6)	7.0 (9.4)	10.2 (11.3)

Abbreviations: MeDi, Mediterranean diet; 3C, Three-City; SD, standard deviation.
NOTE. Values are percentages unless otherwise indicated. Percentages are of nonmissing values.

In multivariate analyses adjusted for age, gender, education, and *APOE* ε4 allele and controlling for multiple comparisons, a higher MeDi score was associated with lower diffusivity values in extensive WM areas, including the whole corpus callosum (genu, body, and splenium), anterior and posterior thalamic radiations, paracingulate gyrus cingulum, and parahippocampal fornix (Fig. 1). Consistently, a higher MeDi score was associated with higher FA values in the corpus callosum, anterior and posterior thalamic radiations, and inferior frontooccipital fasciculus; yet, significant associations with FA values were somewhat less extended than those found with diffusivity values (Fig. 1).

After controlling for a large set of potential confounders, the relationship between the MeDi score and FA values did not remain statistically significant. However, the relation of the MeDi score to diffusivity values, largely distributed within the whole WM skeleton, remained materially unchanged (Supplementary Fig. 2).

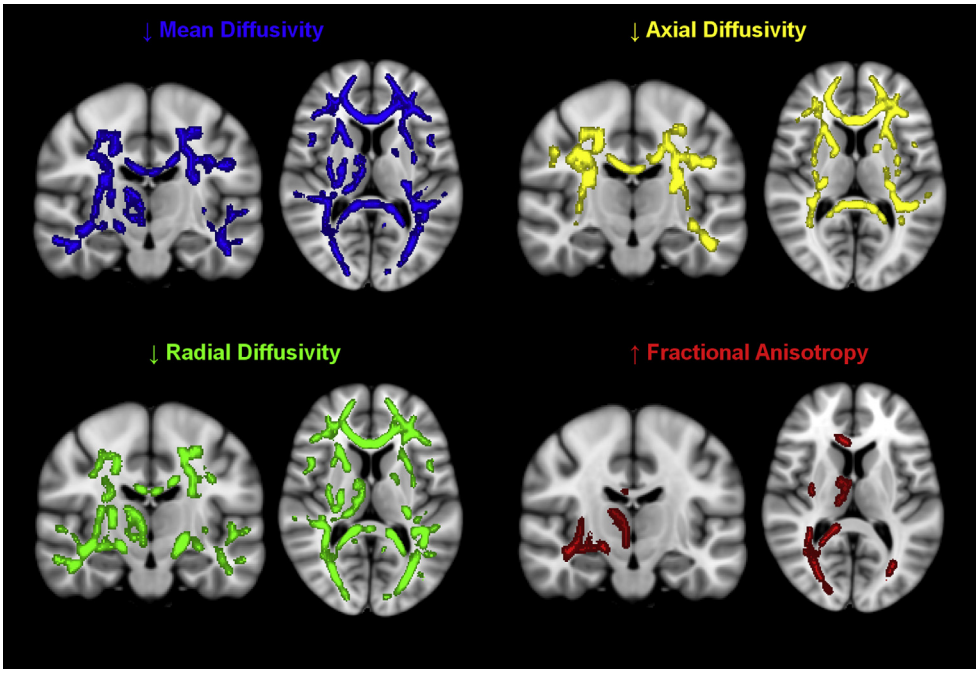

Fig. 1. Association between higher MeDi score, lower diffusivity values (mean, axial, and radial diffusivities), and higher FA in older subjects from the Bordeaux sample of the 3C study (N = 146). Areas of the WM skeleton where each 1-point increase of the MeDi score was significantly associated with lower diffusivity (i.e., mean, axial, and radial diffusivities) and higher FA values, after adjustment for age, gender, education, and *APOE* ε4 allele carrier status. TBSS results were displayed at $P < .05$, TFCE corrected, and overlaid on the MNI template. R, right side. Abbreviations: FA, fractional anisotropy; 3C, Three-City; WM, white matter; MeDi, Mediterranean diet; *APOE* ε4, ε4 allele of the Apolipoprotein E gene; TBSS, tract-based spatial statistics; TFCE, threshold-free cluster enhancement; MNI, Montreal Neurological Institute.

3.3. Supplementary analyses

In secondary analyses investigating the evolution of food habits, average consumption of most MeDi components appeared reasonably stable across MeDi score categories between MeDi assessment and brain imaging (Supplementary Results). Moreover, when we considered separately the nine MeDi components, few individual components were significantly associated with DTI parameters, and associations were generally weaker than with the total MeDi score (Supplementary Results).

In supplementary analyses investigating the cognitive function, we found that lower MD and higher FA in the region that appeared preserved by the MeDi were generally strongly associated with higher cognitive scores (Supplementary Results). For example, the effect estimates we found for episodic memory scores comparing extreme quintiles of MD and FA in our region of interest were comparable with the effect estimates obtained for decrease of 8–10 years of age. In other words, preserved WM microstructure with higher adherence to the MeDi appeared to delay cognitive aging by up to 10 years.

In sensitivity analyses, the MeDi was not significantly associated with total WMH volume; hence, expectedly, further adjustment of our models for WMH volume did not alter findings (Supplementary Results), suggesting that our results were not influenced by the WMH burden. Finally, the results remained virtually unchanged after exclusion of incident dementia cases or of individuals with suspected dementia based on their cognitive performances.

4. Discussion

In our cohort of older subjects, greater adherence to the MeDi was associated, up to a decade after dietary assessment, with preserved microstructure in extensive areas of the WM—a gain in structural connectivity which appeared related to strong cognitive benefits (equivalent to up to 10 years of delay in cognitive aging for those in the top quintile of indices of tissue integrity). None of the individual components was strongly associated with DTI parameters, which supports our hypothesis that overall diet quality may be more important to preserve brain structure than any single food. In contrast, we did not find any association between the MeDi score and GM or WM volumes. These results are important, as they provide evidence that healthy diets such as the MeDi may have a substantial beneficial impact on brain structure—which appears largely underlain by a preservation of brain structural connectivity.

WM connectivity alterations seem to explain part of the cognitive deficits in brain aging [14,26,31]. By linking the MeDi to improved WM microstructure and cognitive function, our study establishes that preserved structural connectivity may be the common anatomical substrate of the well-documented link between the MeDi and lower risks of cognitive decline and related diseases [1–6]. Hence, our results both support and largely extend previous findings on the MeDi and brain diseases and conditions with aging. Yet, research on the MeDi and brain structure has been extremely limited so far, and to our knowledge, no study has confronted at the same time WM microstructure and GM atrophy. A single, small study of healthy adults reported associations between the MeDi and increased cortical thickness in 10 preselected regions [32]. Conversely, as in our study, the larger Prospective Investigation of the Vasculature in Uppsala Seniors study did not find any association between the MeDi and GM volumes [33]. In contrast to studies of brain volumes, associations between the MeDi and a lower burden of cerebrovascular disease have been consistently reported [11,34]; the results of a broad impact on WM connectivity reported here certainly extend these previous findings.

The biological mechanisms underlying alterations of WM connectivity with aging are still unclear, and the pathophysiological interpretation of our findings certainly deserves further investigation. Still, our results may provide a few clues to start deciphering these pathways. First, the strong relation of the MeDi with WM microstructure in extensive areas (with no specific involvement of tracts generally altered in AD, e.g., the cingulum and fornix) along with the absence of meaningful association with GM atrophy (specifically in AD regions, e.g., the hippocampus) suggests that mechanisms are not primarily related to AD neurodegeneration [35–40]. It remains possible that our study was underpowered to detect associations with volumes; however, we were able to detect the effect of age, suggesting sufficient power in this sample to capture well-established risk factors for brain atrophy. Nonetheless, any effect of the MeDi to GM volume would be at best modest compared to the magnitude of associations we found with DTI parameters.

Second, the extended pattern of WM microstructural changes associated with the MeDi in our study is similar to alterations reported in cerebral vascular diseases [14] or in older subjects with higher blood pressure [41]. Hence, it is possible that mechanisms may rely on vascular pathways, although this interpretation remains speculative. Moreover, the beneficial effect of the MeDi on vascular risk factors (e.g., lipid profile, blood pressure, insulin resistance, adiposity, inflammation, and oxidative stress [42–47]) is well established. So overall, there is a strong biological plausibility for a role of the MeDi in preserving brain vascular health. Yet, we did not find evidence that the relation of the MeDi to WM structure was mediated by standard vascular risk factors. However, alterations of WM microstructure may accumulate from middle age [15], and vascular factors measured in the late life as in our cohort may incompletely capture long-term exposures. It is thus possible that the MeDi exerts lifelong beneficial effects on brain

vasculature and microstructure starting long before detectable vascular lesions. Certainly, the temporal relationships between diet and brain structure, as well as vascular mediators over the life course, deserve further research.

Our study has important strengths. We used a large population-based sample and a comprehensive dietary assessment, and MRI was based on a 3-T scanner, which offers a better sensitivity than a 1.5-T scans. Moreover, analyses were controlled for a large number of potential confounders, and we conducted a series of sensitivity analyses to assess the robustness of our findings. However, there are also some limitations. First, we did not assess DTI in 2001–2002; so, we were not able to adjust for brain microstructure at the time of dietary assessment. However, nutritional exposure preceded brain imaging by several years, and we adjusted our analyses for cognition at the time of the dietary questionnaire, and both these aspects strongly limited the possibility of reverse causation. At the same time, using a single dietary assessment may have caused some misclassification in our analyses. However, we ensured that average intakes of most MeDi components were reasonably stable across MeDi score categories, suggesting that the participants did not modify their diets during the study period. Another potential limitation pertains to the inclusion of individuals who accepted brain imaging and were generally healthier than the overall cohort, and it is possible that selection of participants with both better diets and a healthier brain may have biased results toward the null (i.e., underestimation of associations). Furthermore, adherence to the MeDi was ascertained according to a sample-specific score, which limits the generalizability of results to other populations. Finally, in observational studies, there is always a risk of confounding, and although we adjusted for many potential confounders, residual confounding may still persist.

In summary, in our large sample of French older subjects, higher adherence to the MeDi was associated with preserved WM microstructure in multiple brain areas up to a decade after dietary assessment. It was recently demonstrated that adopting a MeDi lowers the risk of stroke in individuals at high vascular risk [10]. Our results extend these findings by suggesting a strong beneficial effect of the MeDi on brain connectivity. Certainly, these data may provide additional support for promoting a healthy diet to maintain optimal brain health with aging.

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Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jalz.2015.06.1888.

RESEARCH IN CONTEXT

1. Systematic review: The Mediterranean diet (MeDi) has been associated with lower risks of Alzheimer's disease and cerebrovascular diseases. Yet, a very limited number of studies have examined MeDi and brain structure, and we found no investigation of white matter microstructure, which appears to be altered by vascular risk factors early in the life course.
2. Interpretation: Our findings provide novel mechanistic knowledge on diet and the brain, by suggesting a strong impact of healthy diets on structural connectivity in older subjects, with no meaningful effect on gray matter volumes. Overall, these results support involvement of vascular rather than neurodegenerative mechanisms, in accordance with the previous literature on the MeDi and less vascular risk factors and related diseases.
3. Future directions: Potential mediation by a beneficial impact on brain vasculature and the time course of the effect of healthy diets on brain structure over the life span, both deserve further research.

References

[1] Sofi F, Abbate R, Gensini GF, Casini A. Accruing evidence on benefits of adherence to the Mediterranean diet on health: An updated systematic review and meta-analysis. Am J Clin Nutr 2010; 92:1189–96.

[2] Scarmeas N, Stern Y, Tang MX, Mayeux R, Luchsinger JA. Mediterranean diet and risk for Alzheimer's disease. Ann Neurol 2006; 59:912–21.

[3] Scarmeas N, Stern Y, Mayeux R, Manly JJ, Schupf N, Luchsinger JA. Mediterranean diet and mild cognitive impairment. Arch Neurol 2009; 66:216–25.

[4] Feart C, Samieri C, Rondeau V, Amieva H, Portet F, Dartigues JF, et al. Adherence to a Mediterranean diet, cognitive decline, and risk of dementia. JAMA 2009;302:638–48.
[5] Singh B, Parsaik AK, Mielke MM, Erwin PJ, Knopman DS, Petersen RC, et al. Association of Mediterranean diet with mild cognitive impairment and Alzheimer's disease: A systematic review and meta-analysis. J Alzheimers Dis 2014;39:271–82.
[6] Psaltopoulou T, Sergentanis TN, Panagiotakos DB, Sergentanis IN, Kosti R, Scarmeas N. Mediterranean diet and stroke, cognitive impairment, depression: A meta-analysis. Ann Neurol 2013;74: 580–91.
[7] Viswanathan A, Rocca WA, Tzourio C. Vascular risk factors and dementia: How to move forward? Neurology 2009;72:368–74.
[8] Sahathevan R, Brodtmann A, Donnan GA. Dementia, stroke, and vascular risk factors: A review. Int J Stroke 2012;7:61–73.
[9] Valkanova V, Ebmeier KP. Vascular risk factors and depression in later life: A systematic review and meta-analysis. Biol Psychiatry 2013; 73:406–13.
[10] Estruch R, Ros E, Salas-Salvado J, Covas MI, Corella D, Aros F, et al. Primary prevention of cardiovascular disease with a Mediterranean diet. N Engl J Med 2013;368:1279–90.
[11] Scarmeas N, Luchsinger JA, Stern Y, Gu Y, He J, DeCarli C, et al. Mediterranean diet and magnetic resonance imaging-assessed cerebrovascular disease. Ann Neurol 2011;69:257–68.
[12] Scarmeas N, Stern Y, Mayeux R, Luchsinger JA. Mediterranean diet, Alzheimer disease, and vascular mediation. Arch Neurol 2006; 63:1709–17.
[13] Reijmer YD, Freeze WM, Leemans A, Biessels GJ. The effect of lacunar infarcts on white matter tract integrity. Stroke 2013; 44:2019–21.
[14] Lawrence AJ, Chung AW, Morris RG, Markus HS, Barrick TR. Structural network efficiency is associated with cognitive impairment in small-vessel disease. Neurology 2014;83:304–11.
[15] Maillard P, Seshadri S, Beiser A, Himali JJ, Au R, Fletcher E, et al. Effects of systolic blood pressure on white-matter integrity in young adults in the Framingham Heart Study: A cross-sectional study. Lancet Neurol 2012;11:1039–47.
[16] Sperling RA, Aisen PS, Beckett LA, Bennett DA, Craft S, Fagan AM, et al. Toward defining the preclinical stages of Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 2011;7:280–92.
[17] Three-City Study Group. Vascular risk factors and risk of dementia: Design of the Three-City Study and baseline characteristics of the study population. Neuroepidemiology 2003;22:316–25.
[18] American Psychiatric Association. Diagnostic and statistical manual of mental disorders (IV). 4th ed. Washington, DC: American Psychiatric Press; 1994.
[19] Samieri C, Jutand MA, Feart C, Capuron L, Letenneur L, Barberger-Gateau P. Dietary patterns derived by hybrid clustering method in older people: Association with cognition, mood, and self-rated health. J Am Diet Assoc 2008;108:1461–71.
[20] Feart C, Jutand MA, Larrieu S, Letenneur L, Delcourt C, Combe N, et al. Energy, macronutrient and fatty acid intake of French elderly community dwellers and association with socio-demographic characteristics: Data from the Bordeaux sample of the Three-City Study. Br J Nutr 2007;98:1046–57.
[21] Simermann J, Barberger-Gateau P, Beer C. Validation of a Food Frequency Questionnaire in older population. 25th Annual congress of SFNEP: Clinical nutrition and metabolism. Montpellier, France: Elsevier; 2007. p. S69–70.
[22] Trichopoulou A, Costacou T, Bamia C, Trichopoulos D. Adherence to a Mediterranean diet and survival in a Greek population. N Engl J Med 2003;348:2599–608.
[23] Ashburner J, Friston KJ. Voxel-based morphometry—The methods. Neuroimage 2000;11:805–21.
[24] Good CD, Johnsrude IS, Ashburner J, Henson RN, Friston KJ, Frackowiak RS. A voxel-based morphometric study of ageing in 465 normal adult human brains. Neuroimage 2001;14:21–36.
[25] Smith SM, Jenkinson M, Johansen-Berg H, Rueckert D, Nichols TE, Mackay CE, et al. Tract-based spatial statistics: Voxelwise analysis of multi-subject diffusion data. Neuroimage 2006; 31:1487–505.
[26] Filippi M, van den Heuvel MP, Fornito A, He Y, Hulshoff Pol HE, Agosta F, et al. Assessment of system dysfunction in the brain through MRI-based connectomics. Lancet Neurol 2013;12: 1189–99.
[27] Amieva H, Le Goff M, Millet X, Orgogozo JM, Peres K, Barberger-Gateau P, et al. Prodromal Alzheimer's disease: Successive emergence of the clinical symptoms. Ann Neurol 2008;64:492–8.
[28] Chumbley JR, Friston KJ. False discovery rate revisited: FDR and topological inference using Gaussian random fields. Neuroimage 2009; 44:62–70.
[29] Smith SM, Nichols TE. Threshold-free cluster enhancement: Addressing problems of smoothing, threshold dependence and localisation in cluster inference. Neuroimage 2009;44:83–98.
[30] Mori S, Oishi K, Jiang H, Jiang L, Li X, Akhter K, et al. Stereotaxic white matter atlas based on diffusion tensor imaging in an ICBM template. Neuroimage 2008;40:570–82.
[31] Kantarci K, Senjem ML, Avula R, Zhang B, Samikoglu AR, Weigand SD, et al. Diffusion tensor imaging and cognitive function in older adults with no dementia. Neurology 2011;77:26–34.
[32] Mosconi L, Murray J, Tsui WH, Li Y, Davies M, Williams S, et al. Mediterranean diet and magnetic resonance imaging-assessed brain atrophy in cognitively normal individuals at risk for Alzheimer's disease. J Prev Alzheimers Dis 2014;1:23–32.
[33] Titova OE, Ax E, Brooks SJ, Sjogren P, Cederholm T, Kilander L, et al. Mediterranean diet habits in older individuals: Associations with cognitive functioning and brain volumes. Exp Gerontol 2013; 48:1443–8.
[34] Gardener H, Scarmeas N, Gu Y, Boden-Albala B, Elkind MS, Sacco RL, et al. Mediterranean diet and white matter hyperintensity volume in the Northern Manhattan Study. Arch Neurol 2012; 69:251–6.
[35] Zhang Y, Schuff N, Camacho M, Chao LL, Fletcher TP, Yaffe K, et al. MRI markers for mild cognitive impairment: Comparisons between white matter integrity and gray matter volume measurements. PLoS One 2013;8:e66367.
[36] Damoiseaux JS, Smith SM, Witter MR, Sanz Arigita EJ, Barkhof F, Scheltens P, et al. White matter tract integrity in aging and Alzheimer's disease. Hum Brain Mapp 2009;30:1051–9.
[37] Zhang Y, Schuff N, Jahng GH, Bayne W, Mori S, Schad L, et al. Diffusion tensor imaging of cingulum fibers in mild cognitive impairment and Alzheimer disease. Neurology 2007;68:13–9.
[38] Acosta-Cabronero J, Williams GB, Pengas G, Nestor PJ. Absolute diffusivities define the landscape of white matter degeneration in Alzheimer's disease. Brain 2010;133:529–39.
[39] Clerx L, Visser PJ, Verhey F, Aalten P. New MRI markers for Alzheimer's disease: A meta-analysis of diffusion tensor imaging and a comparison with medial temporal lobe measurements. J Alzheimers Dis 2012;29:405–29.
[40] Kantarci K, Schwarz CG, Reid RI, Przybelski SA, Lesnick TG, Zuk SM, et al. White matter integrity determined with diffusion tensor imaging in older adults without dementia: Influence of amyloid load and neurodegeneration. JAMA Neurol 2014; 71:1547–54.
[41] Salat DH, Williams VJ, Leritz EC, Schnyer DM, Rudolph JL, Lipsitz LA, et al. Inter-individual variation in blood pressure is associated with regional white matter integrity in generally healthy older adults. Neuroimage 2012;59:181–92.
[42] Estruch R, Martinez-Gonzalez MA, Corella D, Salas-Salvado J, Ruiz-Gutierrez V, Covas MI, et al. Effects of a Mediterranean-style diet on

cardiovascular risk factors: A randomized trial. Ann Intern Med 2006; 145:1–11.
[43] Romaguera D, Norat T, Mouw T, May AM, Bamia C, Slimani N, et al. Adherence to the Mediterranean diet is associated with lower abdominal adiposity in European men and women. J Nutr 2009;139:1728–37.
[44] Chrysohoou C, Panagiotakos DB, Pitsavos C, Das UN, Stefanadis C. Adherence to the Mediterranean diet attenuates inflammation and coagulation process in healthy adults: The ATTICA Study. J Am Coll Cardiol 2004;44:152–8.
[45] Mena MP, Sacanella E, Vazquez-Agell M, Morales M, Fito M, Escoda R, et al. Inhibition of circulating immune cell activation: A molecular antiinflammatory effect of the Mediterranean diet. Am J Clin Nutr 2009;89:248–56.
[46] Konstantinidou V, Covas MI, Munoz-Aguayo D, Khymenets O, de la Torre R, Saez G, et al. In vivo nutrigenomic effects of virgin olive oil polyphenols within the frame of the Mediterranean diet: A randomized controlled trial. FASEB J 2010;24:2546–57.
[47] Casas R, Sacanella E, Urpi-Sarda M, Chiva-Blanch G, Ros E, Martinez-Gonzalez MA, et al. The effects of the mediterranean diet on biomarkers of vascular wall inflammation and plaque vulnerability in subjects with high risk for cardiovascular disease. A randomized trial. PLoS One 2014;9:e100084.