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Higher Dietary Inflammatory Index scores are associated with brain MRI markers of brain aging: Results from the Framingham Heart Study Offspring cohort

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Abstract

Introduction: We investigated cross-sectional associations between the Dietary Inflammatory Index (DII) and measures of brain volume and cerebral small vessel disease among participants of the Framingham Heart Study Offspring cohort.

Methods: A total of 1897 participants (mean ± standard deviation, age 62±9) completed Food Frequency Questionnaires and brain magnetic resonance imaging (MRI).

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CONFLICTS OF INTEREST

Dr. Melo van Lent is vice-chair of the Alzheimer's Association ISTAART Nutrition Metabolism and Dementia Professional Interest Area; Hannah Gokingco, Meghan I. Short, Dr. Changzheng Yuan, Dr. José R. Romero, Dr. Charles S. DeCarli, Dr. Alexa Beise, Dr. Sudha Seshadri, Dr. Jayandra J. Himali, and Dr. Mini E. Jacob declare no conflicts of interest; Dr. Paul Jacques is part of the Danone North America Essential Dairy and Plant-Based Advisory Board.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

Results: Higher (pro-inflammatory) DII scores, averaged across a maximum of three time points, were associated with smaller total brain volume (beta ± standard error: −0.16 ± 0.03; $P < .0001$) after adjustment for demographic, clinical, and lifestyle covariates. In addition, higher DII scores were associated with smaller total gray matter volume (−0.08 ± 0.03; $P = .003$) and larger lateral ventricular volume (0.04 ± 0.02; $P = .03$). No associations were observed with other brain MRI measures.

Discussion: Our findings showed associations between higher DII scores and global brain MRI measures. As we are one of the first groups to report on the associations between higher DII scores and brain volume, replication is needed to confirm our findings.

Keywords

apolipoprotein E ε4; brain volume; cerebral microbleeds; Framingham Heart Study; inflammatory diet; silent brain infarcts

1 | BACKGROUND

Systemic inflammatory processes in the body, including the brain, can be influenced by diet,[1] leading to its important contributory role in brain aging. Findings from an animal study performed in aged rats showed that a high fat diet activated pro-inflammatory marker interleukin (IL)-1 beta in both hippocampus and amygdala derived microglia.[2] The effect of nutrition on neuroinflammation in humans is yet to be directly estimated, however, anti-inflammatory dietary factors consumed in the Mediterranean diet have been linked to lower concentrations of inflammatory markers including high-sensitivity C-reactive protein (CRP), IL-6, tumor necrosis factor alpha (TNF-α), and monocyte chemoattractant protein 1.[3] High inflammatory activity in the brain measured in cell line studies has in turn been linked to vascular brain pathology and neurodegeneration.[4] In addition, population-based studies have found associations between circulating inflammatory markers and magnetic resonance imaging (MRI) markers of brain aging and incident dementia.[5,6] A healthy diet may therefore be a key modifiable lifestyle factor that may help to slow brain aging and prevent vascular brain injury.

Systematic reviews have reported promising effects of a wide range of individual nutrients, such as vitamin D and omega 3 fatty acids—key micronutrients for cognitive health[7,8]—on inflammatory markers.[9] However, effects of individual nutrients are often hard to detect, so the combined nutrient potential of multiple dietary components is often captured using comprehensive scores.[10] Using such scores, several observational studies have identified the combined inflammatory potential of nutrients, bio-active compounds, and whole foods on markers of systemic inflammation.[11–14]

The Dietary Inflammatory Index (DII) is an index that has been specifically designed to capture the inflammatory potential of diet[15] and has shown association with cognitive impairment and memory.[16–20] However, we have limited information on the role of diet-driven inflammation on subclinical MRI brain markers of neurodegeneration and vascular brain damage[21–23] that serve as early risk indicators for dementia and appear decades before the clinical onset of dementia. Thus far, two studies found that higher scores of

an inflammation-related nutrient pattern and higher adherence to a “Western” pattern were associated with smaller brain volume outcomes.[22,23] However, both these studies were limited by small sample sizes, dietary assessment that was restricted to one examination cycle, and nutrient patterns that were difficult to extrapolate to other populations. These also did not examine important markers of cerebral small vessel disease such as silent brain infarcts and cerebral microbleeds. A third study showed no association between the energy-adjusted DII (eDII) and brain volume outcomes in a small study sample.[21] Thus the question whether dietary inflammatory content can influence brain MRI measures (i.e., MRI markers of brain aging: total brain volume, total gray matter volume, lateral ventricular volume, and hippocampal volume; and MRI markers of cerebral small vessel disease: white-matter hyperintensities, silent brain infarcts, and cerebral microbleeds) known to be associated with incident dementia[24] has not been answered thoroughly.

Therefore, we aimed to cross-sectionally examine the effect of dietary inflammatory content as measured by the average of up to three DII scores on MRI markers of brain aging and cerebral small vessel disease in a large community-based dementia-free sample of the Framingham Heart Study (FHS) Offspring cohort. The DII scores in this cohort represent usual dietary intake over a mean period of 7 years; the MRI measures capture vascular and neurodegenerative burden accumulated over time in this dementia-free population that are likely to worsen with age. The FHS thus provided an exceptional opportunity for rigorous evaluation of associations between dietary inflammatory content and MRI markers of brain aging in an asymptomatic population.

2 | METHODS

The FHS involves ongoing population-based cohorts from the town of Framingham, Massachusetts, USA. The Original cohort was established in 1948 with the aim to identify factors that contribute to the development of cardiovascular disease.[25] In 1971, the Offspring cohort was established, including children of the original cohort and their spouses.[26] The Offspring cohort enrolled 5124 participants who have been studied over nine examination cycles, approximately once every 4 years. All participants provided written informed consent. The study protocol was approved by the institutional review board at Boston University Medical Center.

For the present study, we assessed self-reported dietary intake from participants of the Offspring cohort using a food frequency questionnaire (FFQ) administered at examination cycles 5 (1991–1995), 6 (1995–1998), and 7 (1998–2001). A flow chart of included and excluded participants is shown in Figure 1. Examination cycle 7 was defined as baseline for this study because data on both covariates and outcome were obtained at this time point. To be included in the present investigation, participants were required to have completed the FFQ at examination cycle 7 and at least one other time point (examination cycles 5 or 6). Participants were excluded if they had no dietary intake data available (e.g., due to the length of the FFQ and the time it takes to fill out the FFQ) or an abnormal estimated total energy intake (<600–>3999 kcal for women or <600–>4199 kcal for men) and/or >13 missing items (n = 643).[27] Further, we included data from participants who completed brain MRI scans (i.e., silent brain infarcts [SBI], n = 1897; total brain volume [TBV], hippocampal volume

[HPV], lateral ventricular volume [LVV], total gray matter volume [TGMV], $n = 1871$; white-matter hyperintensity volume [WMHV], $n = 1852$; cerebral microbleeds [CMB], $n = 423$). Participants were excluded if no brain MRI scan data was available (e.g., due to MRI scanner time, claustrophobia, and/or participants needed to come in for an additional study center visit at a later date). Participants underwent a brain MRI scan on average 0.7 ± 0.7 years after examination cycle 7. At last, we excluded participants with prevalent dementia, stroke, or other significant neurological disease, such as significant head trauma, subdural hematoma, or multiple sclerosis ($n = 70$).

2.1 | Dietary inflammatory index

The DII index for the present study was calculated using the validated 131-item Harvard semi-quantitative FFQ,[28,29] which assesses dietary intake over the past year. Participants were asked how often they consumed food items (i.e., from never or <1 per month to >6 per day), the type of food item, and whether food items were homemade or readymade.[30] A commonly used portion size was given for each food item. In addition, the FFQ included questions on most frequently eaten breakfast cereal, types of fats and oils, and frequency of consumption of fried foods. Intakes of food components (i.e., nutrients, food items, or food groups) were computed by multiplying the frequency of consumption of each food item by the nutrient content of the specified portions.[30]

The DII index for the present study consists of 31 dietary components including anti-inflammatory nutrients, pro-inflammatory nutrients, whole foods, and caffeine from food intake only (i.e., not including supplement intake).[15] The dietary components are categorized as (1) anti-inflammatory: alcohol, beta carotene, caffeine, dietary fiber, folic acid, magnesium, thiamin, riboflavin, niacin, zinc, monounsaturated fat, polyunsaturated fat, omega-3 fat, omega-6 fat, selenium, vitamins B6, A, C, D, E, green/black tea, pepper, and garlic; and (2) pro-inflammatory: vitamin B12, iron, carbohydrates, cholesterol, total energy intake, protein, saturated fat, and total fat. A total of 14 components of the Shivappa et al. DII (i.e., turmeric, thyme/oregano, rosemary, eugenol, ginger, onion, trans fat, isoflavones, flavan-3-ol, flavones, flavonols, flavonones, anthocyanidins, and saffron) were not available in our FFQ. The formula of the DII has been described elsewhere.[15] In brief, the DII is based on a set of literature-based dietary component–specific inflammatory effect scores, dietary intake data from the population under study, and a representative world database that provides a mean and standard deviation for consumption of each dietary component in the global population.[15] These then become the multipliers to express an individual's exposure relative to the "standard global mean" as a Z-score:[15] subtracting the "standard global mean" (i.e., from the world database) from the amount reported by the study participants and dividing this value by the world standard deviation.[15] To minimize the effect of "right skewing," this value is converted to a percentile score.[15] To achieve a symmetrical distribution with values centered on 0 (null) and bounded between −1 (maximally anti-inflammatory) and +1 (maximally pro-inflammatory), each percentile score is doubled and then "1" is subtracted.[15] The centered percentile value for each dietary component is then multiplied by its respective "overall dietary component–specific inflammatory effect score" to obtain the "dietary component–specific DII score."[15] Finally, all of the "dietary component–specific DII scores" are summed to create the "overall DII score" for

an individual (range from −4.47 to +4.06, higher scores indicating pro-inflammatory DII scores).[15]

At FHS we had the opportunity to assess dietary intake over a decade. As data from a FFQ is prone to recall bias and to account for reverse causality, we averaged the DII scores across examination cycle 7 (1998–2001) and at least one of the prior examination cycles: 5 (1991–1995) and 6 (1995–1998); 86% of participants completed all three FFQs from our largest brain volume (n = 1897) outcome sample. There were only very minor differences between participants with data on three versus two time points (data not shown). Thus, the DII was assessed over a maximum of 10 years (Pearson correlations between pairs of the three examination-specific DII scores ranged between 0.630 and 0.692).

2.2 | Assessment of brain volume and white-matter injury

MRI examinations were conducted using a Siemens 1.5-T scanner (Siemens Medical Solutions) using T1-weighted coronal spoiled gradient-recalled echo acquisition and fluid-attenuated inversion recovery sequences with standard MRI parameters. Further information about the imaging methodology has been reported elsewhere.[31] We examined brain volumes (TBV, HPV, LVV, and TGMV), SBIs, CMB, and WMHV on MRI cross-sectionally. Brain volumes were expressed as a percentage of total intracranial volume (i.e., adjusting for difference in head size). TBV was calculated as the total brain parenchymal volume. LVV was calculated by analyzing central cerebrospinal fluid spaces, excluding the temporal horn. Further, SBIs were identified according to Standards for ReportIng Vascular Changes on Neuroimaging (STRIVE) criteria.[32] CMB were defined using standard criteria[33] as rounded or ovoid hypointense lesions on T2*-GRE weighted sequence.[34] WMHV was natural logarithmically transformed to normalize skewed distributions. Analysis of MRI images was completed by operators (i.e., a team of very skilled brain imaging analysts with neurology oversight, neurologists, and neuroradiologists) who were blind to any participants' personal identifying information.[35]

2.3 | Statistical analysis

SAS Software 9.4 (SAS Institute) was used to perform separate multivariable linear (for continuous outcomes) and logistic (for binary outcomes) regressions to examine the associations between the DII score and outcomes.

The main results are presented as adjusted beta coefficients accompanied by standard errors. The beta estimates represent the change in units of each respective outcome per one unit higher in the DII score. Odds ratios and 95% confidence intervals (CIs) are presented for the binary outcomes SBI and CMB. A P-value <.05 and <.10 was considered statistically significant for our main analyses and for our tests of interactions, respectively. Missing data were excluded from analysis (Apolipoprotein $\varepsilon 4$[*APOE* $\varepsilon 4$; n = 41], body mass index [BMI; n = 5], physical activity [n = 122], smoking status [n = 1], total to high-density lipoprotein [HDL] cholesterol ratio [n = 10], anti-cholesterol medication [n = 1], prevalent diabetes [n = 7], cardiovascular disease [CVD; n = 1], adiponectin [n = 342], CD40 [n = 18], CRP [n = 17], 8-EPI-isoprostane [n = 281], fibrinogen [n = 16], IL-6 [n = 18], IL-18 [n = 91], intercellular adhesion molecule [ICAM; n = 16], resistin [n = 335], and

TNF-α [n = 488]). Confounders were selected based on the published literature (Table S4 in supporting information).[36–42] Model 1 was adjusted for age, age squared, sex, and the time interval between examination cycle 7 (i.e., baseline FFQ and covariates assessment) and the measurement of MRI outcomes. Model 2 was additionally adjusted for education, *APOE* ε4 status, lifestyle factors (BMI, physical activity, smoking status, and total energy intake), and cardiometabolic factors (total to HDL cholesterol ratio and anti-cholesterol medication). For our secondary analyses, we tested for interactions between the DII score and *APOE* ε4 status and sex separately using model 2. We performed stratified analyses in cases in which significant interactions were observed, adjusting for model 2 covariates. Further, we investigated the mediating effects of diabetes mellitus, hypertension, CVD, and inflammatory markers in model 2 on significant associations found in the main analyses.

3 | RESULTS

3.1 | Cohort demographics

Table 1 details the sample characteristics. The mean DII score was −0.26 ± 1.74, indicating that this sample's diets were on average anti-inflammatory relative to the global mean. Additionally, a comparison of participants included in our study sample and those who were not showed that participants who were not included in the study sample were slightly older, less educated, and were more likely to smoke (data not shown).

3.2 | Dietary Inflammatory Index scores and brain volume and silent brain infarcts

In the present study we investigated the effect of one unit higher DII scores on MRI markers of brain aging and cerebral small vessel disease. We observed that higher (pro-inflammatory) DII scores were associated with smaller TBV in the first linear model (beta ± standard error: −0.12 ± 0.03, P < .0001; Table 2). After additional adjustment for education, *APOE* ε4, total energy intake, lifestyle factors, total cholesterol to HDL cholesterol ratio, and the use of anti-cholesterol medication the association remained (model 2: −0.16 ± 0.03, P < .0001). Additionally, compared to the first quartile (i.e., most anti-inflammatory), the third and fourth DII score quartiles (i.e., most pro-inflammatory) were associated with progressively smaller TBV. These associations remained after full adjustment (model 2: quartile 3: −0.36 ± 0.14, P = .01; quartile 4: −0.64 ± 0.16, P < .0001; P for trend <.0001).

Further, higher DII scores were linearly associated with larger LVV in model 2, but not in model 1 (model 2: 0.04 ± 0.02, P = .03). In addition, compared to the first quartile, the second and third DII score quartiles were associated with larger LVV (model 2: quartile 2: 0.17 ± 0.07, P = .01; quartile 3: 0.16 ± 0.07, P = .02), but not the fourth quartile (model 2: quartile 4: 0.13 ± 0.08, P = .10).

We observed a significant linear association between higher DII scores and TGMV, which remained after adjustments for model 2 covariates (model 2: −0.08 ± 0.03, P = .003). Our categorical analyses revealed that, compared to the first quartile, the fourth DII score quartile was associated with smaller TGMV (model 2: −0.30 ± 0.13, P = .02).

Finally, we observed an overall significant P for trend (.03) for the association between higher DII scores and increased odds for SBIs. Compared to the first quartile, the fourth DII

score quartile was associated with increased odds for SBIs (model 2: odds ratio [OR], 95% CI: 1.77, 1.05–3.00). No associations were observed between the DII and the other structural MRI markers of brain aging and cerebral small vessel disease after adjusting for the full set of covariates. Further, we found that additional adjustment for TNF-α attenuated the effect estimates (>10%) of the associations between the continuous DII score and TBV and LVV in model 2 (no evidence of collinearity between the DII and TNF-α was found). Adjustment for 8-epi-isoprostane diminished the association between DII score and LVV; the association was no longer significant (no evidence of collinearity between the DII and 8-epi-isoprostane was found, data not shown). Adjustments for prevalent diabetes, CVD, hypertension, and other inflammatory markers did not change the results.

3.3 | Secondary analyses—interactions in the association between higher Dietary Inflammatory Index scores and brain volumes and brain injury

We observed a significant interaction between DII scores and the *APOE* ε4 variable in models testing association between DII and HPV (Table S1 in supporting information). Among *APOE* ε4 non-carriers' participants only, one unit higher in DII scores were significantly and independently associated with smaller HPV (beta ± standard error: −0.002 ± 0.001, $P = .02$). In addition, compared to the first quartile, the fourth DII score quartile was associated with smaller HPV (model 2: −0.01 ± 0.004, $P = 0.01$; Table S2 in supporting information). Among participants with an *APOE* ε4 allele we observed that, compared to the first quartile, the second DII score quartile was marginally associated with larger HPV (model 2: 0.01 ± 0.007, $P = .04$), but there was no overall trend of association between DII score and HPV in those individuals.

Further, we observed a significant interaction between higher DII scores and sex when investigating WMHV (Table S1). We observed an association between higher DII scores and larger WMHV among men (model 2: 0.06 ± 0.02, $P = .02$), but not among women (Table S3 in supporting information).

4 | DISCUSSION

In the present study we investigated a large study sample of the community-based FHS Offspring cohort and found that DII scores were associated with global brain MRI markers of brain aging and cerebral small vessel disease, but not with regional MRI markers. In addition, we observed that 8-epi-isoprostane may be an important mediator in this association. Further, we found that the associations between the DII and regional markers of brain aging may be modified by *APOE* ε4 status and markers of cerebral small vessel disease by sex. Our results indicate that inflammatory content in diet may have important implications to global markers of brain aging and markers of cerebral small vessel disease, thereby offering a promising opportunity for preventive intervention.

4.1 | Higher Dietary Inflammatory Index scores and brain volume and SBIs

Our findings that higher DII scores were associated with smaller TBV and TGMV and higher odds for SBIs are to some extent in line with previous observational studies that investigated inflammatory dietary patterns.[22,43] Consistent with our findings, the

Washington Heights-Inwood Columbia Aging Project study (WHICAP) reported that higher scores of an inflammation-related nutrient pattern low in calcium, vitamins, folate, and omega-3 poly-unsaturated fatty acids intake and high in cholesterol intake have been associated with smaller TBV and TGMV.[22] In addition, the Australian Longitudinal Study on Women's Health showed that higher DII scores were associated with increased odds for cerebrovascular disease.[43] Further, we observed no associations between the DII and HPV, WMHV, and CMB, which agrees with findings from the Cognition and Diabetes in Older Tasmanians study, which also observed no association between the eDII and HPV, WMV, WMHV, and CMB; and the WHICAP study, which showed no association with WMHV.[21,22] In addition the Cognition and Diabetes in Older Tasmanians study also observed no associations between the eDII and all other brain structure outcomes.[21] This may be due to a lack of power (n = 641), as the age range across studies is comparable to our study and the percentages of participants with a history of diabetes and hypertension (50%) is higher compared to our participants; one would expect an association between the eDII and brain outcomes in more vulnerable (i.e., participants with comorbidities) participants.

4.2 | Effect modifications

We hypothesized that the associations between the DII and brain outcomes may differ by *APOE* ε4 status and sex. We observed that higher DII scores were associated with smaller HPV among *APOE* ε4 non-carriers. The APOE gene plays a role in fat metabolism where the *APOE* ε4 allele tends to catabolize more omega-3 fatty acids (i.e., anti-inflammatory compounds) in *APOE* ε4 carriers compared to the catabolism process among non-carriers.[44] One would expect that higher DII scores would be associated with smaller HPV among *APOE* ε4 carriers, as the DII for this subgroup may be more proinflammatory. However, we observed that higher DII scores were associated with smaller HPV in *APOE* ε4 non-carriers but not in *APOE* ε4 carriers, which was not intuitive. In a previous investigation in the FHS Offspring cohort, we found a contradictory finding; the association between higher Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND) diet scores (i.e., higher scores are considered anti-inflammatory) and better neuropsychological performance was true for *APOE* ε4 carriers but not for *APOE* ε4 non-carriers.[30] Other studies that investigated inflammatory nutrient pattern/scores in relation to brain MRI markers either did not observe an interaction between the inflammatory dietary pattern/scores and *APOE* ε4, or *APOE* ε4 data were not available.[21,22,43] In summary, the interaction between DII and *APOE* ε4 carrier status on brain aging warrants further investigations.

Further, we observed an association between higher DII scores and larger WMHV among men, but not among women. These differential effects of the DII across the sexes may be explained by women in our sample having residual confounding of a healthier lifestyle. In addition, other unmeasured sex-related factors that are protective for women in terms of vascular brain changes may also be there. As we are the first to investigate this DII and sex interaction, we encourage future studies to replicate our findings in their study population. Further, our mediation analysis showed evidence of the role of inflammatory markers with the relationship between the DII and brain volumes; further studies are required to explore the biological mechanism of this association.

4.3 | Implications

At present no cure for dementia exists; thus, there is a pressing need for preventive interventions in the preclinical phase, starting with the identification and further examination of modifiable risk factors, such as diet.

In our study we found evidence of an association between DII scores and global markers of brain volumes and vascular brain injury, which are early markers of dementia. Moreover, previous studies have shown associations between the DII and risk factors of dementia.[45] Our findings indicate potential for prevention by dietary modification.

A closer look at the most pro-inflammatory components of the DII (i.e., saturated fat, trans fats, and total energy intake), confirms that these are indeed well-known diet components that contribute to the worsening of vascular health, when consumed in abundance.[46,47] Fortunately, replacement of saturated fats with other macronutrients, such as polyunsaturated fats (i.e., anti-inflammatory), has been related to a reduced risk for cardiovascular disease[48] offering a promising opportunity for reducing risk for dementia. Thus, the presented study contributed to our understanding of the biological mechanisms underlying the global and regional brain volume changes in pre-clinical (Alzheimer's disease [AD]) dementia populations. Global measures indicate global changes in brain volume due to age-related neuronal loss, whereas regional volumes are more specific to types of neurodegenerative disease such as AD. When replicated in future large community-based studies these findings could reveal potential for future dietary- and multi-domain interventions for prevention of brain volume loss.

4.4 | Strengths and limitations

Strengths of this study include our large population-based sample, highly reliable rating of brain MRI markers to comprehensively investigate MRI markers of brain aging and cerebral small vessel disease, assessment of diet using a validated FFQ, and the ability to average dietary intake over a number of time points to estimate dietary intake over a maximum of 10 years of follow-up. In addition, we were able to adjust for many important confounders, including lifestyle and risk factors for dementia.

However, we acknowledge that the present study has limitations. First, to assess dietary intake of our participants we used a FFQ, which is subject to measurement error and recall bias. To mitigate the effects of recall bias, we excluded participants with dementia, stroke, and/or other neurological diseases from the analyses. In addition, we adjusted for total energy intake in model 2 to account for potential systematic measurement error.[49] And we made use of the opportunity to construct a cumulative DII score based on at least two examination cycles instead of using dietary intake data information based on one examination cycle. Most cohort studies are often limited to one dietary intake assessment method at one point in time. However, we acknowledge the possible presence of non-differential misclassification while using this dietary assessment method, which may have led to bias toward the null.[50] Second, we were able to compose the DII by including 31 dietary components, while the original DII score consists of 45 components. However, our quantity of components is in line with the study of Zabetian-Targhi et al., which investigated

the association between the eDII and brain volumes including 27 components,[21] and studies that examined the DII with cognition, which composed a DII score ranging between 26 and 35 components.[16–20] Third, the present study is observational, which precludes conclusions about the causality of the observed associations due to potential reverse causality. However, the DII score was constructed over three consecutive visits over a maximum of 10 years of follow-up, which makes such a reverse causation bias less likely. Fourth, the subgroup analyses might have lacked power and increased the likelihood of a type 1 error. Last, generalizability of our findings to other races/ethnicities may be limited as individuals included in our study were White individuals of European ancestry. However, the DII accounts for that to a certain extent by including a mean and standard deviation of a representative world database, which we used in our calculation.[13]

In conclusion, in our community-based sample, DII scores were associated with global markers of brain aging and cerebral small vessel disease, with smaller HPV in those with no *APOE ε*4 allele, and with larger WMHV in men. These findings are in line with other studies that investigated inflammatory dietary patterns and scores. We encourage future studies to replicate our main findings, and to investigate the associations among subgroups such as *APOE ε*4 carriers and non-carriers and men and women.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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RESEARCH IN CONTEXT

1. Systematic Review:

With the use of online databases such as PubMed, we reviewed published studies. Higher Dietary Inflammatory Index (DII) scores have been associated with cognitive impairment and worse memory. However, we have limited information on the role of diet-driven inflammation on subclinical magnetic resonance imaging (MRI) brain markers of neurodegeneration and vascular brain damage. The relationship between the energy-adjusted DII and structural MRI outcomes of brain aging has been investigated only once in a small study sample; no significant relationships were found.

2. Interpretation:

Our findings show a relationship between higher DII scores and global brain MRI markers of brain aging and cerebral small vessel disease.

3. Future Directions:

Replication studies are needed across diverse populations. In addition, research should investigate the impact of the DII across different subgroups at risk for dementia, including persons who are carriers/non-carriers of the apolipoprotein E $\varepsilon 4$ gene and men and women.

HIGHLIGHTS

- Higher Dietary Inflammatory Index (DII) scores were associated with smaller total brain volume.
- Higher DII scores were associated with smaller total gray matter volume.
- Higher DII scores were associated with larger lateral ventricular volume.
- Higher DII scores were not associated with regional brain magnetic resonance imaging measures.
- Results differed by important demographic factors, including sex and apolipoprotein $\varepsilon 4$.

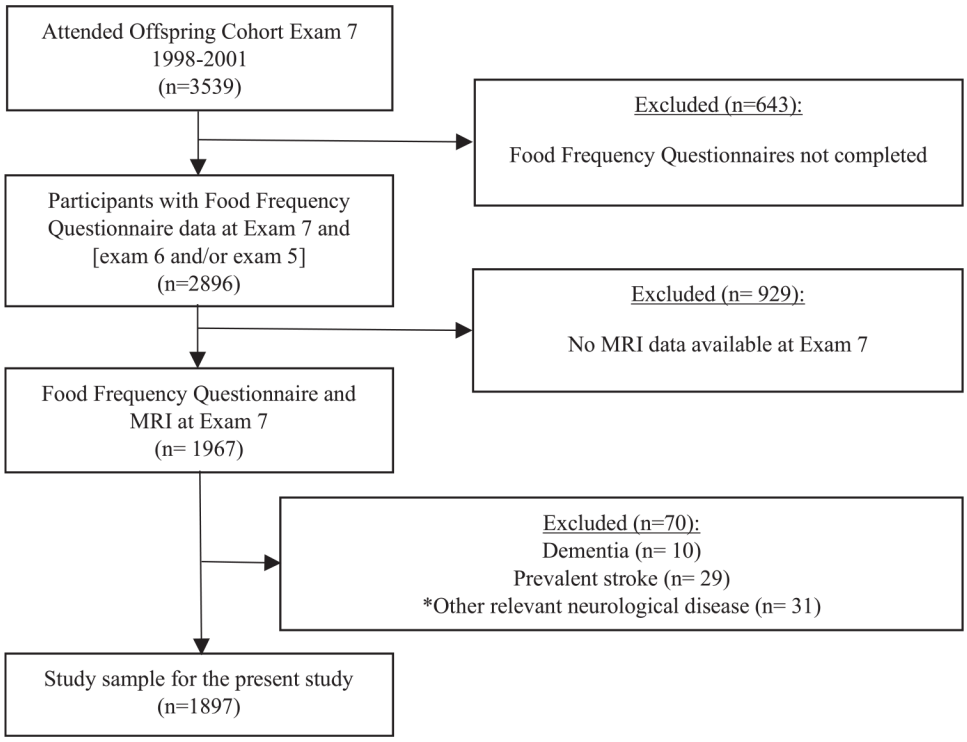

FIGURE 1.

Flow chart of the participants included in the study. *n*, number; MRI, magnetic resonance imaging. *Other relevant neurological disease known to impact cognition includes illness or injury such as traumatic brain injury, primary brain tumor, or multiple sclerosis

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TABLE 1

Baseline characteristics of participants included in the study

Variable	Overall (*n* = 1897)	DIIQ1 (*n* = 474)	DIIQ2 (*n* = 474)	DIIQ3 (*n* = 475)	DIIQ4 (*n* = 474)	*P* value
Age, years	62 ± 9	64 ± 9	62 ± 10	62 ± 9	61 ± 9	<.0001
Time between Exam 7 to MRI exam, years	0.7 ± 0.7	0.8 ± 0.8	0.7 ± 0.7	0.7 ± 0.7	0.8 ± 0.8	.33
Men, *n* (%)	866 (45.7)	217(45.8)	223(47.1)	204 (43.0)	222 (46.8)	.56
Apolipoprotein E ε4 allele, *n* (%)	421(22.7)	109 (23.4)	109(23.6)	109(23.3)	94 (20.4)	.60
Education, *n* (%						<.0001
No high school degree	54 (2.9)	11 (2.3)	21 (4.4)	12 (2.5)	10(2.1)	
High school degree	525 (27.7)	91 (19.2)	118 (24.9)	146 (30.7)	170 (35.9)	
Some college	556(29.3)	137 (28.9)	129(27.2)	132 (27.8)	158 (33.3)	
College graduate	762 (40.2)	235 (49.6)	206 (43.5)	185 (39.0)	136 (28.7)	
BMI, kg/m^2	27.9 ± 5.2	27.4 ± 5.0	27.9 ± 5.1	28.2 ± 5.3	28.1 ± 5.3	.09
PA Index	37.9 ± 6.3	38.2 ± 6.0	37.7 ± 5.9	37.8 ± 6.4	37.7 ± 6.8	.51
Total energy intake, kcal	1848 ± 585	2262±543	1971±537	1701± 474	1458±452	<.0001
Current smoker, *n* (%)	211 (11.1)	26(5.5)	35 (7.4)	58(12.2)	92 (19.4)	<.0001
Total cholesterol, mg/dL	201 ± 37	197 ± 34	199 ± 36	201 ± 35	208 ± 39	<.0001
HDL cholesterol, mg/dL	54±17	54±17	54±16	53 ± 16	53 ± 18	.69
Total to HDL cholesterol ratio	4.1 ± 1.3	3.9 ± 1.3	4.0 ± 1.3	4.1 ± 1.4	4.2 ± 1.5	.001
Lipid-lowering medication, *n* (%)	356 (18.8)	99 (20.9)	93(19.6)	84(17.2)	80(16.9)	.38
Diabetes, *n* (%)	211(11.2)	57(12.1)	47 (9.9)	56(11.8)	51 (10.8)	.71
Prevalent CVD, *n* (%)	784 (41.4)	203 (42.8)	194 (40.9)	196(41.4)	191 (40.3)	.88
History of hypertension, *n* (%)	1030 (54.3)	271(57.2)	253(53.4)	250(52.6)	256 (54.0)	.51
Adiponectin, μg/ml	10.1 ± 6.4	10.5 ± 6.5	10.1 ± 6.9	9.8 ± 5.8	10.0 ± 6.1	.41
Cluster of differentiation 40, ng/ml	3.4 ± 4.8	3.9 ± 5.4	3.2 ± 4.6	3.4 ± 4.8	2.9 ± 4.2	.01
C-reactive protein, mg/L	4.0 ± 5.8	3.6 ± 5.2	3.7 ± 6.0	4.5 ± 6.4	4.1 ± 5.3	.09
8-EPI-isoprostane, ng/mmol	16,482 ± 10,362	14,786 ± 9893	16,325±10,711	16,855 ± 10,308	18,046 ± 10,279	.0001
Fibrinogen	0.3 ± 0.1	0.3 ± 0.1	0.3 ± 0.1	0.3 ± 0.1	0.3 ± 0.1	.97
Interleukin-6, pg/ml	3.8 ± 5.0	3.4 ± 3.5	3.9 ± 5.3	4.0 ± 6.1	4.0 ± 4.9	.17
Interleukin-18, pg/ml	257±129	256±135	245 ± 110	254±116	275 ± 150	.01
Intercellular adhesion molecule, ng/ml	254 ± 75	248 ± 72	247 ± 70	256 ± 71	265 ± 86	.0004
Resistin, ng/ml	14.3 ± 7.4	14.4 ± 9.2	14.1 ± 6.9	14.3 ± 6.5	14.4 ± 6.7	.93

Variable	Overall (*n* = 1897)	DIIQ1 (*n* = 474)	DIIQ2 (*n* = 474)	DIIQ3 (*n* = 475)	DIIQ4 (*n* = 474)	*P* value
Tumor necrosis factor-*α*, pg/ml	1.4 ± 1.2	1.4 ± 1.0	1.4 ± 1.5	1.5 ± 1.3	1.4 ± 0.8	.54
DII score	−0.26 ± 1.74	−2.54 ± 0.66	−0.88 ± 0.39	0.42 ± 0.37	1.95 ± 0.66	<.0001
Total brain volume, % of ICV	77.3 ± 2.6	77.2 ± 2.6	77.4 ± 2.6	77.3 ± 2.6	77.3 ± 2.7	.59
Hippocampal volume, % of ICV	0.5 ± 0.05	0.5 ± 0.05	0.5 ± 0.05	0.5 ± 0.05	0.5 ± 0.05	.26
Lateral ventricular volume, % of ICV	1.9 ± 1.0	1.9 ± 1.0	1.9 ± 1.2	1.9 ± 1.1	1.8 ± 0.9	.12
Total gray matter volume, % of ICV	40.3 ± 1.7	40.3 ± 1.6	40.4 ± 1.8	40.4 ± 1.8	40.2 ± 1.8	.48
White matter hyperintensity volume, % of ICV, median [Q1, Q3]	0.04 [0.02,0.08]	0.04 [0.02, 0.07]	0.04 [0.02, 0.08]	0.04 [0.02, 0.08]	0.04 [0.02, 0.07]	.27
Silent brain infarct, *n* (%)	210(11.1)	50(10.6)	53(11.2)	50(10.5)	57(12.0)	.88
Cerebral microbleeds, *n* (%)	22(5.2)	6(5.7)	5 (5.3)	6(5.6)	5 (4.4)	.97

Notes: Mean ± SD reported, unless specified otherwise. A *P*-value < .05 was considered statistically significant.

Abbreviations:BMI, bodymass index;CVD, cardiovascular disease;DII, Dietary Inflammatory Index; dL, deciliter;HDL, high-density lipoprotein; ICV, intracranial volume; kcal, kilocalorie; kg, kilogram; L, liter; MRI, magnetic resonance imaging; m, meter; mmol, millimole; mg, milligram; ml, milliliter; *n*, number of participants; ng, nanograms; PA, physical activity; pg, picogram;Q, quartile.

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TABLE 2

Association between Dietary Inflammatory Index (DII) and brain MRI measures

	Dietary Inflammatory Index scores										
Brain volumes	**Continuous**		**Quintile 1**		**Quintile 2**		**Quintile 3**		**Quintile 4**		***P* for trend**
Total brain volume [a]	*n* = 1871		*n* = 467		*n* = 468		*n* = 468		*n* = 468		
	β ± SE	***P*** [*]	**β ± SE**	***P*** [*]	**β ± SE**	***P*** [*]	**β ± SE**	***P*** [*]	**β ± SE**	***P*** [*]	
Model 1	−0.12 ± 0.03	<.0001	*Reference*		−0.10 ± 0.13	.43	−0.28 ± 0.13	.02	−0.50 ± 0.13	<.0001	<.0001
Model 2	−0.16 ± 0.03	<.0001	*Reference*		−0.16 ± 0.14	.23	−0.36 ± 0.14	.01	−0.64 ± 0.16	<.0001	<.0001
Hippocampal volume [a]	*n* = 1871		*n* = 467		*n* = 468		*n* = 468		*n* = 468		
	β ± SE	***P*** [*]	**β ± SE**	***P*** [*]	**β ± SE**	***P*** [*]	**β ± SE**	***P*** [*]	**β ± SE**	***P*** [*]	
Model 1	−0.0003 ± 0.0006	.67	*Reference*		0.004 ± 0.003	.23	0.003 ± 0.003	.28	−0.001 ± 0.003	.64	.63
Model 2	−0.001 ± 0.0008	.09	*Reference*		0.003 ± 0.003	.37	0.001 ± 0.003	.78	−0.007 ± 0.004	.09	.08
Lateral ventricular volume [a]	*n* = 1871		*n* = 467		*n* = 468		*n* = 468		*n* = 468		
	β ± SE	***P*** [*]	**β ± SE**	***P*** [*]	**β ± SE**	***P*** [*]	**β ± SE**	***P*** [*]	**β ± SE**	***P*** [*]	
Model 1	0.02 ±0.01	.14	*Reference*		0.16 ± 0.06	.01	0.13 ±0.06	.03	0.07 ± 0.06	.24	.36
Model 2	0.04 ± 0.02	.03	*Reference*		0.17 ± 0.07	.01	0.16 ± 0.07	.02	0.13 ± 0.08	.10	.13
Total gray matter volume [a]	*n* = 1871		*n* = 467		*n* = 468		*n* = 468		*n* = 468		
	β ± SE	***P*** [*]	**β ± SE**	***P*** [*]	**β ± SE**	***P*** [*]	**β ± SE**	***P*** [*]	**β ± SE**	***P*** [*]	
Model 1	−0.08 ± 0.02	.0001	*Reference*		−0.11 ± 0.10	.27	−0.14 ± 0.10	.18	−0.33 ± 0.10	.002	.002
Model 2	−0.08 ± 0.03	.003	*Reference*		−0.09 ± 0.11	.45	−0.08 ± 0.12	.53	−0.30 ± 0.13	.02	.04
White matter hyperintensity volume [a,b]	*n* = 1852		*n* = 463		*n* = 463		*n* = 463		*n* = 463		
	β ± SE	***P*** [*]	**β ± SE**	***P*** [*]	**β ± SE**	***P*** [*]	**β ± SE**	***P*** [*]	**β ± SE**	***P*** [*]	
Model 1	0.03 ± 0.01	.02	*Reference*		0.08 ± 0.06	.16	0.11 ± 0.06	.07	0.14 ± 0.06	.02	.02
Model 2	0.02 ± 0.02	.12	*Reference*		0.10 ± 0.06	.10	0.12 ± 0.07	.08	0.12 ± 0.08	.10	.11
Silent brain infarcts	*n* = 1897		*n* = 474		*n* = 474		*n* = 475		*n* = 474		
	OR [95% CI]	***P*** [*]	**OR [95% CI]**	***P*** [*]	**OR [95% CI]**	***P*** [*]	**OR [95% CI]**	***P*** [*]	**OR [95% CI]**	***P*** [*]	
Model 1	1.04 [0.96,1.13]	.38	*Reference*		1.10 [0.73,1.67]	.65	1.08 [0.71,1.63]	.74	1.30 [.86,1.96]	.21	.25
Model 2	1.10 [0.99,1.23]	.08	*Reference*		1.22 [0.77,1.93]	.39	1.34 [0.82, 2.18]	.24	1.77 [1.05, 3.00]	.03	0.03
Cerebral microbleeds	*n* = 423		*n* = 105		*n* = 106		*n* = 106		*n* = 106		

Brain volumes	Dietary Inflammatory Index scores										
	Continuous		Quintile 1		Quintile 2		Quintile 3		Quintile 4		*P* for trend
	OR [95% CI]	*P* *	OR [95% CI]	*P* *	OR [95% CI]	*P* *	OR [95% CI]	*P* *	OR [95% CI]	*P* *	
Model 1	1.00 [0.78,1.28]	.99	*Reference*		0.99 [0.28, 3.53]	.98	1.59 [0.48, 5.25]	.45	0.95 [0.24, 3.69]	.94	.82
Model 2	0.90 [0.65,1.26]	.54	*Reference*		1.17 [0.28,4.86]	.83	1.17 [0.28,4.93]	.83	0.56 [0.09, 3.44]	.53	.65

Abbreviations: CI, confidence interval; HDL, high-density lipoprotein; MRI, magnetic resonance imaging; *n*, number;OR, odds ratio; SE, standard error.

*Notes:*Model 1: Age at magnetic resonance imaging (MRI) exam, age-squared at MRI exam, sex, and time from exam to exam MRI. Model 2: Model 1+education, apolipoprotein E *ε*4 status, body mass index, smoking status, physical activity index score, total energy intake, total cholesterol to HDL cholesterol ratio, and the use of anti-cholesterol medication.

[a]Percentages of intercranial volume.

[b]White matter hyperintensity volume is log transformed.

*A *P*-value <.05 was considered statistically significant.

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