REPORT

The associations of energy adjusted dietary inflammatory index with brain structure and cognitive function

Dashan Zheng,[1,3] Bingting Zhuo,[1,3] Guzhengyue Zheng,[1] Junjie Hua,[1] Junguo Zhang,[1] Chongjian Wang,[2] Yuhua Wang,[1] Zilong Zhang,[1] and Hualiang Lin[1,*]

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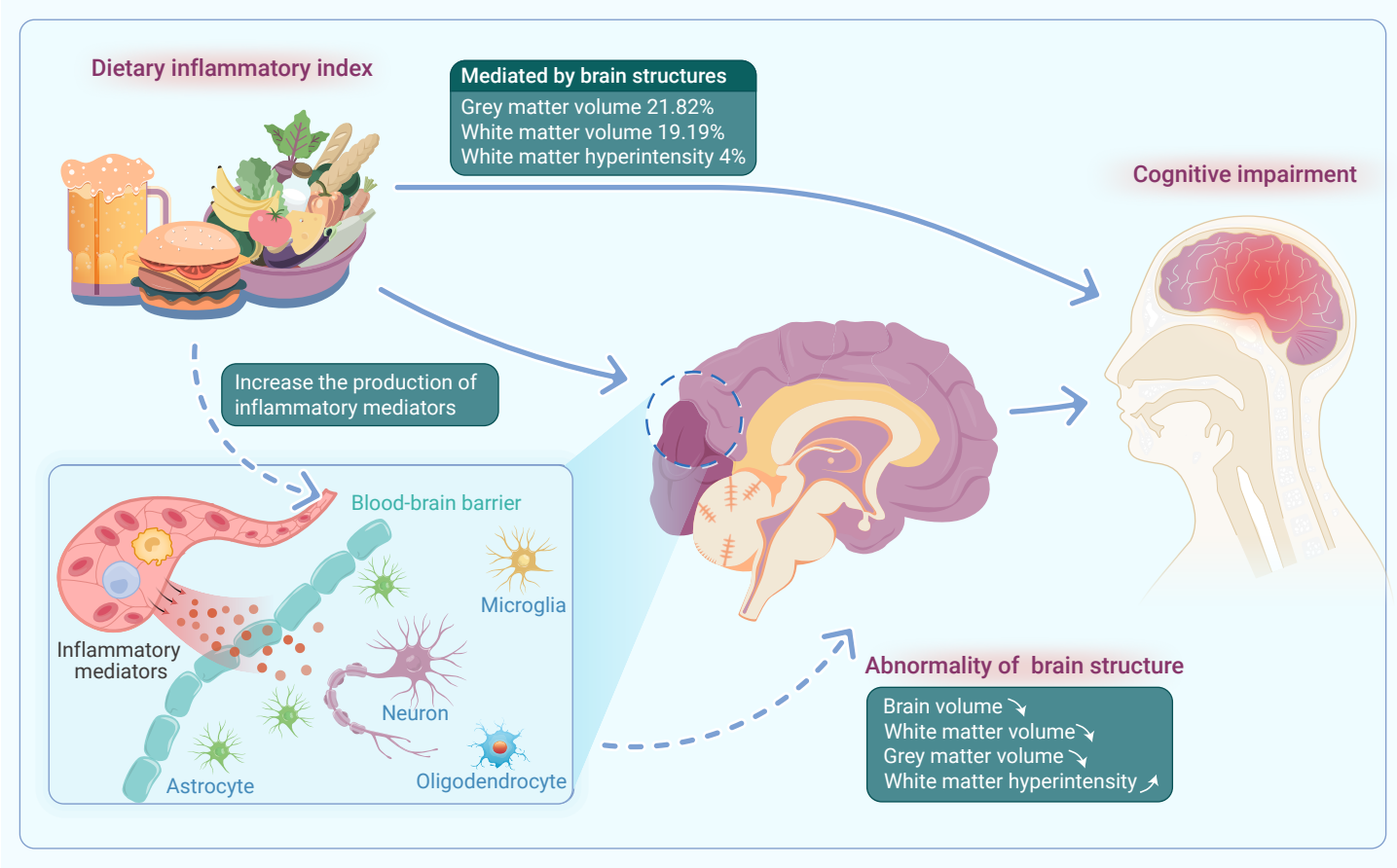
GRAPHICAL ABSTRACT



PUBLIC SUMMARY

- Higher dietary inflammatory index links to more severe brain structure abnormalities.
- Brain structure abnormalities mediate the "inflammatory diet-cognition" association.
- Controlling inflammatory diet may protect rain structure and cognitive function.

REPORT

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Limited research exists on the mediating effect of brain structure in the association between dietary inflammatory index (DII) and cognitive impairment. To address this issue, this analysis utilized data from a cohort of 15,526 participants in the UK Biobank who underwent brain magnetic resonance imaging (MRI) during 2014-2020. We assessed the associations between energy adjusted DII (E-DII, calculated by 28 components) and cognitive function (represented by fluid intelligence scores, FIS), as well as the brain structures, including total brain volume (TBV), white matter volume (WMV), white matter hyperintensities volume (WMHV) and grey matter volume (GMV) of 76 cortices, 14 subcortices and 28 cerebellum regions. We further estimated the mediation effects of brain structures on the association between E-DII and cognitive function. From this analysis, we observed that higher E-DII was associated with reduced TBV, GMV, WMV, FIS and higher WMHV. Each one unit increase in E-DII was associated with 0.025(0.007, 0.041) FIS decrease, 937.93 mm^3 (95% CI: 494.48.07, 1,381.38) GMV decrease, 675.02 mm^3 (95% CI: 279.02, 1,071.02) WMV decrease and 93.80 mm^3 (95% CI: 41.45, 146.14) WMHV increase. Furthermore, GMV, WMHV, WMV were found to significantly mediate the association between E-DII and cognitive function, accounting for 21.82% (95% CI: 11.26%, 33.24%), 19.19% (95% CI: 8.52%, 30.63%) and 4% (95% CI: 1.31%, 7.99%). These results indicated that controlling of inflammatory diet could prevent brain structures abnormalities and might reduce the risk of cognitive impairment.

INTRODUCTION

Cognitive impairment is a major global public health issue, affecting 19% of adults aged 50 years and older.[1,2] Mild cognitive ability decline could generate dissatisfaction, and further cause adverse health consequences, and severe cognitive impairment may progress to dementia, such as Alzheimer's disease.[3] Therefore, it is crucial to investigate the risk factors associated with cognitive impairment and understand the underlying biological mechanisms.

Epidemiological and experimental studies have reported numerous risk factors,[4] among which chronic inflammation and its triggers may be vital contributors to cognitive impairment.[3] As a long-term exposure, dietary patterns can trigger body's inflammatory response over a long duration, and further affect the cognitive function.[5,6] The dietary inflammatory index (DII) has been suggested as a potential indicator for evaluating the inflammatory impact of the diet. Several studies have examined the association between DII and cognitive impairment.[7] For example, one study based on the National Health and Nutrition Examination Survey observed that higher DII was associated with cognitive function impairment.[8] Another population-based study also showed that higher DII could lead to cognitive declines and increase the risk of dementia.[2]

Existing studies have mainly attributed the underlying mechanism between DII and cognitive impairment to neurological damage in the brain, but the quantitative estimates of the mediating effect of the brain neurological damage have not been elucidated.[9,10] Furtherly, the association between DII and neurological damage in specific brain regions also remains unknown.[11] Utilizing more detailed brain magnetic resonance imaging (MRI) matrices focused on specific regions, rather than solely assessing overall brain volume, could not only enhance the precision in identifying brain structures susceptible to inflammatory effects but also holds potential significance in revealing the mechanisms linking inflammation and brain damage, thereby informing dietary interventions for clinical patients.[12]

To rectify these research gaps, we conducted this study by collecting the MRI images data (including total brain volume, total white matter volume, white matter hyperintensities, total grey matter volume, as well as the specific GMV of 38 brain cortices and 7 subcortices in each hemisphere, 28 cerebellum regions and brain stem), dietary components, and the fluid intelligence score (FIS) from UK Biobank with the aims to examine the associations between E-DII and MRI metrics of different brain regions, and further investigate the mediating of these MRI metrics on the association between E-DII and cognitive function.

MATERIALS AND METHODS

Participants

This study made use of data from the UK Biobank, which is a prospective cohort comprising over 500,000 participants aged between 40 and 69 years. The study protocol details have been previously outlined and documented.[13] Briefly, the participants were enrolled from 22 assessment centers located throughout the United Kingdom. The baseline survey was administered to gather comprehensive demographic, health examination, and medical information of the participant from 2016 to 2020.[14]

The UK Biobank administered 24-hour dietary recall surveys at baseline, and a subgroup in the first and second follow-up (177,379 participants were surveyed at all three follow-ups). In addition, UK Biobank launched its first imaging visit among a sample of 42,786 participants at the second follow-up between 2014 and 2020, during which the fluid intelligence score was also collected (45,041 participants). We selected 20,581 participants who provided E-DII components, intelligence scores, and brain imaging data, and excluded participants with missing data for dietary components, MRIs in the brain regions of interest, and other important covariates (4,856 participants). Furthermore, 34 participants were excluded from the study due to their history of Parkinson's disease or dementia before the initial imaging visit. The remaining 15,691 participants comprised our final analytical sample (Figure 1).

The acquisition of MRI data

The UK Biobank's imaging data were acquired using a standard Siemens Skyra 3T scanner, which was equipped with a 32-channel RF receiver head coil. The imaging matrix was tilted downward by 16 degrees along the AC-PC line, following standard protocols.[15,16] All imaging data in this study were expressed in cubic millimeters (mm^3), including total brain volume (TBV), total white matter volume (WMV), white matter hyperintensities (WMHV), total grey matter volume (GMV), as well as the specific GMV of 38 brain cortices, and 7 subcortices in each hemisphere, 28 cerebellum regions and brain stem. A lower GMV, WMV and a higher WMHV reflects the neurological abnormalities or impairment of brain.

To provide a more concise presentation of cortical grey matter volume, we consolidated the GMV of 49 biliteral cortical structures into 38 in each hemisphere based on the parcellations derived from the Harvard-Oxford cortical and subcortical atlases (Table S1).[17]

The assessment of E-DII

The process of developing and validating the E-DII have been previously documented.[18] The E-DII is calculated based on 45 dietary components,

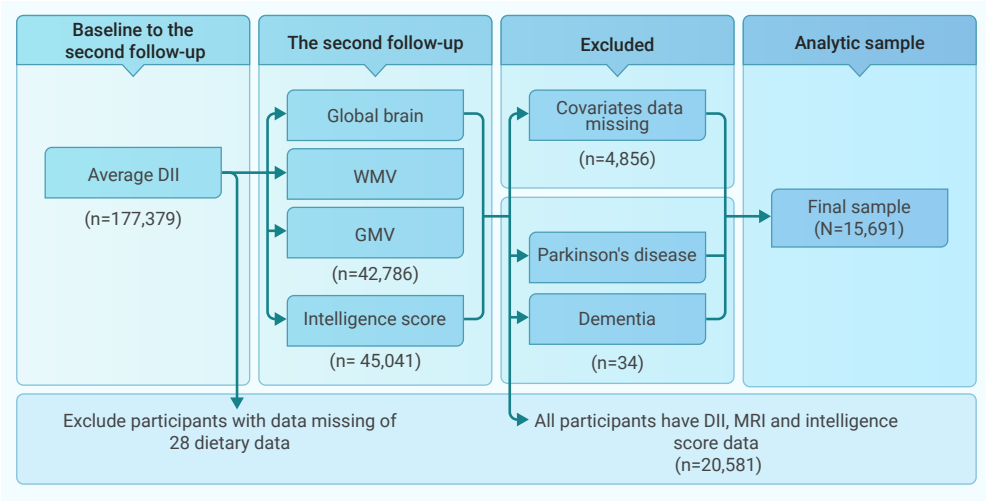

Figure 1. The flowchart for this study.

which include individual foods, nutrients, and bioactive components.[7] These components are associated with six inflammatory biomarkers, including C-reactive protein, IL-1β, IL-4, IL-6, IL-10, tumor necrosis factor-α. Of the 45 dietary components used to calculate the dietary inflammatory index, data were missing for 17 components in the UK Biobank.[19] Therefore, only 28 components were utilized for the E-DII calculation, including energy, alcohol, total fat, protein, carbohydrate, beta-carotene, cholesterol, fiber, folate, iron, magnesium, monounsaturated fatty acids, polyunsaturated fatty acids, niacin, riboflavin, thiamin, vitamin A, vitamin B12, vitamin B6, vitamin C, vitamin D, vitamin E, saturated fat, selenium, zinc, trans-fat, n-3 fatty acids n-6 fatty acids.

Several steps were performed to obtain E-DII in this analysis. First, the mean nutrient or food intake from 24-hour dietary recall surveys (baseline, first follow-up, and second follow-up) was calculated to obtain the intake of each dietary component. Second, the energy intake for each dietary component was adjusted using the nutrient density approach to control for confounding factors and accurately predict the effect of diet.[20] Third, the Z-score for each dietary component was determined by subtracting the mean of the database from the component's value and dividing the result by the standard deviation. Fourth, the Z-scores were subsequently transformed into percentile scores, which were multiplied by two and then reduced by one. Finally, an individual's E-DII was calculated by multiplying the converted Z-scores with the corresponding component-specific inflammatory effect score and summing the results. A lower E-DII score suggests a dietary pattern that is characterized by lower inflammation, while a higher score indicates a dietary pattern that may be more pro-inflammatory.

The fluid intelligence score

The fluid intelligence score in UK Biobank is calculated as an unweighted sum of correct answers to 13 questions that assess reasoning and problem-solving abilities.[21,22] Participants who were unable to complete all the questions within the two-minute time limit were assigned a score of zero for each unanswered question. Despite being relatively simple, the scores from the UK Biobank cognitive test have demonstrated strong concurrent validity and retest reliability.[23] A lower fluid intelligence score is often highly correlated with a decline in one's ability to live and activities independently.[24]

Covariates

According to the directed acyclic graph (DAG, Figure S1), we selected a series of covariates in this study. The covariates were operationalized as follows: age (years), sex (male and female), race (white and others), annual household income (greater than £100000, 52000 to 100000, 31000 to 51999, 18000 to 30999, less than 18000, and unknown), alcohol intake (heavy, moderate, occasional and never), smoking status (current, previous, never and no answer), the history of cancer, international physical activity questionnaire (IPAQ) (low, moderate, high), hypertension (yes and no), stroke (yes and no), hemoglobin A1c (percentage points), body mass index (BMI), and fine particulate matter.[25,26] HbA1c were measured at baseline and were further converted into percentages according to the American Diabetes Association clinical practice guideline.[27] Based on the Seca 240 cm and Tanita BC418MA body composition analyzers without thick clothing and shoes, the height and weight of participants were measured and used to calculate BMI (kg/m^2).[28,29] The IPAQ short form asked about three levels of activities: walking, moderate physical activities and vigorous physical activities, and an assigned corresponding metabolic equivalent (MET, equals to one kilocalorie per hour per kilogram of body weight): 3.3 for walking, 4.0 for moderate physical activity and 8.0 for vigorous physical activity.[30] The IPAQ was used to assess self-reported physical activity levels, which were classified into three categories: low (< 600 MET-min/week, minutes of MET each week), moderate (600 MET-min/week to 3000 MET-min/week), and high (≥ 3000 MET-min/week).[31]

Statistical analysis

To investigate the association between E-DII, brain MRI metrics and fluid intelligence score, and to explore whether the brain MRI metrics act as a potential mediator on the association between E-DII and fluid intelligence score, we adopted a two-stage statistical analysis.

In the first stage, the multivariable linear regression models were built to assess the associations between E-DII and brain MRI metrics, as well as between brain MRI metrics and fluid intelligence score. Specifically, we conducted separate analyses for each brain region (including TBV, WMV, WMHV, total GMV, and GMV of 117 brain regions) to investigate the relationships between E-DII and 121 brain MRI metrics, as well as between 121 brain MRI metrics and fluid intelligence score. Therefore, to avoid the type I error caused by multiple comparisons when explaining the associations between "E-DII ~ brain structure" and "brain structure ~ FIS", we performed FDR correction with "121" as correction parameter. Secondly, based on the significant association between exposure (E-DII) and mediator (brain MRI metrics), as well as the association between the mediator and the outcome (fluid intelligence score), we performed the mediation analysis to examined whether brain MRI metrics mediated the association between exposure and outcome. Specifically, for the mediation analysis, we performed both single and multiple mediation models in a structure equation modelling (SEM) framework by using the R package "*bruceR*". The single mediation models were built to provide the proportion of indirect effects on the association between E-DII and fluid intelligence score attributed to different brain MRI metrics, including TBV, total GMV, total WMV and WMHV. Furtherly, to quantify the unique mediation effect of those brain structures variable, we also built a multiple mediation models, which entered total GMV, total WMV and volume of WMHV simultaneously. Notably, the covariates selected through DAG were included in both linear regression and mediation models.

Sensitivity analysis

Several sensitivity analyses were performed. Firstly, individuals with TBV outside the range of 3 standard deviations were excluded to explore whether abnormal brain volume can affect the stability of the results. Secondly, given the difference in the position of each participant's brain relative to the scanner, we further included the scanner table position, scanner transverse (Y), lateral (X) and longitudinal (Z) brain position in an adjusted model (alongside the covariates confirmed by the DAG).

All the statistical analyses were performed using R software (version: 4.1.1). Two-sided tests were used for all P values, and statistical significance was determined at a threshold of FDR-corrected $P < 0.05$.

RESULTS

Descriptive results

We enrolled 15,691 participants for this study, with a mean age of 54.84

years. Among these participants, 51.3% were females and 48.7% were white (Table 1). The E-DII ranged from -5.57 to 5.23, with a mean of 0.15 and a standard deviation of 1.77. The fluid intelligence scores of the participants in this study ranged from 0 to 13, with a mean of 6.91 and a standard deviation of 2.04. The mean volumes of the TBV, total GMV, total WMV and WMHV were 1,167,775 mm^3, 548,910.3 mm^3, 618,864.2 mm^3, and 4,832.77 mm^3. Furthermore, we conducted descriptive analyses of GMV in 117 specific cerebral structures, including 38 cortices and 7 subcortices in each cerebral hemisphere, as well as brain stem and 28 cerebellum regions (Tables S2-S3).

The associations between E-DII and total GMV, WMV, WMHV and TBV

We observed that higher E-DII was associated with poorer brain health outcome and lower fluid intelligence score (Table 2). Specifically, for each one unit increment of E-DII, we observed 0.024 (95% CI: 0.007, 0.041) reduction of fluid intelligence score, 93.80 mm^3 (95% CI: 41.45, 146.14) increase of WMHV mm^3 and 1,612.96 mm^3 (95% CI: 826.81, 2,399.12) reduction of total brain volume, including 937.93 mm^3 (95% CI: 494.48, 1,381.38) of GMV and 675.02 mm^3 (95% CI: 279.02, 1,071.02) of WMV.

The associations between E-DII and GMV of cerebellum regions, brain stem and cerebral subcortices

We further examined the association between each on unit increase of E-DII and changes of GMV (mm^3) (Table S4). We found that the GMV of 25 cerebellum regions was inversely associated with increment of E-DII, and 9 of those regions remained significant after FDR correction (Figure 2), including biliteral V cerebellum (Right: -5.681 mm^3, 95% CI: -8.94, -2.68, $P_{FDR} < 0.01$ and Left: -6.69 mm^3, 95% CI: -9.87, -3.51, $P_{FDR} < 0.01$), VI cerebellum (Right: -5.69 mm^3, 95% CI: -24.15, -7.23, $P_{FDR} < 0.01$ and Left: -18.11 mm^3, 95% CI: -26.73, -9.48, $P_{FDR} < 0.01$) and VIIIb cerebellum (Right: -7.94 mm^3, 95% CI: -12.56, -3.32, $P_{FDR} < 0.01$ and Left: -6.56 mm^3, 95% CI: -10.85, -2.26, $P_{FDR} < 0.05$), as well as the crus I cerebellum (-17.95 mm^3, 95% CI: -31.00, -1.63, $P_{FDR} < 0.05$) and right VIIIa cerebellum (-8.45 mm^3, 95% CI: -14.52, -2.38, $P_{FDR} < 0.05$). However, we found no significant association between E-DII and GMV of brain stem.

Moreover, the relationship between E-DII and regional GMV of cerebral subcortices was further estimated (Table S5). All the GMV of those subcortices demonstrated negative associations with E-DII, and significant asociations could be found in biliteral hippocampus (Right: β = -7.11 mm^3, 95% CI: -10.54, -3.68, $P_{FDR} < 0.01$ and Left: β = -7.11, 95% CI: -9.8, -2.79, $P_{FDR} < 0.01$).

The associations between E-DII and GMV of cerebral cortices

For the cerebral cortices, 28 out of 76 regions exhibited significant relationships between E-DII and GMV, and 23 of them remained significant after FDR correction (Figure 3 & Table S6). These grey matter reduction regions mainly distributed in frontal lobe (central opercular cortex, frontal orbital cortex, subcallosal cortex and frontal pole), parietal lobe (angular gyrus, precuneous cortex and parietal operculum cortex) and temporal lobe (temporal pole, insular cortex, temporal occipital fusiform cortex and planum temporale). For example, each one unit increase of E-DII was associated with a 35.96 mm^3 (95%CI: 11.92, 60.00) GMV reduction in right frontal pole and a 18.73 mm^3 (95%CI: 8.78, 28.69) reduction in right temporal pole.

Mediating role of brain structure in the association between E-DII and fluid intelligence score

Considering the association of "E-DII - brain abnormalities" and "brain abnormalities - fluid intelligence score" (Table S7), we estimated the single mediation proportions and the unique mediation effect of different brain structure neuroimaging metrics (total GMV, total WMV and WMHV) contribute to the association (Figure 4 & Table S8) of "E-DII - fluid intelligence score". The single mediation effects on the relationship between E-DII and fluid intelligence score were strongest for brain GMV ($\beta_{indirect\ effect}$= -0.0055, 95% CI: -0.08, -0.003) with a mediating proportion of 21.82% (95% CI: 11.26%, 33.24%). In addition, significant indirect effect could also be found in WMV ($\beta_{indirect\ effect}$= -0.0045, 95% CI: -0.007, -0.002) and WMHV ($\beta_{indirect\ effect}$= -0.001, 95% CI: -0.002, -0.0003), corresponding to a mediation proportion of 19.19% (95% CI: 8.52%, 30.63%) and 4.00% (95% CI: 1.31%, 7.99%) respectively. We further quantified the unique mediation effect of those MRI metric

Table 1. Descriptive summary of the demographic characteristics

	Mean or Number of participants	Standard deviation or proportion
Age (year)	54.89	7.48
E-DII	0.15	1.77
Total Brain Volume	1167775	110594.8
Total grey matter volume (mm^3)	548910.3	61376.72
Total white matter volume (mm^3)	618864.2	55090.16
White matter hyperintensities volume (mm^3)	4832.77	6305.28
Fluid intelligence score	6.91	2.04
Body mass index	26.37	4.15
HbA1c (%)	34.91	5.08
Sex		
Male	7641	48.7%
Female	8050	51.3%
Race		
White	15255	97.2%
Others	433	2.8%
$PM_{2.5}$ ($\mu g/m^3$)	9.88	1.03
Annual household income		
Greater than 100,000	1327	8.5%
52,000 to 100,000	4375	27.9%
31,000 to 51,999	4448	28.3%
18,000 to 30,999	3074	19.6%
Less than 18,000	1476	9.4%
Unknow	991	6.3%
Alcohol intake		
Never	637	4.1%
Occasional	2889	18.4%
Moderate	8484	54.1%
Heavy	3681	23.4%
Smoking status		
Never	9655	61.5%
Previous	5102	32.5%
Current	910	5.8%
Prefer not to answer	24	0.2%
IPAQ		
Low	2892	18.4%
Moderate	6675	42.5%
High	6124	39.1%
Cancer		
None	14621	93.2%
Benign	47	0.3%
Malignant	1023	6.5%

Table 2. The associations between DII, brain neuroimaging and fluid intelligence score

	Estimate (95% CI)	P_{FDR}
Total brain volume (mm^3)	-1612.96 (-2399.12, -826.81)	0.002
Total grey matter volume (mm^3)	-937.93 (-1381.38, -494.48)	0.002
Total white matter volume (mm^3)	-675.02 (-1071.02, -279.02)	0.009
Volume of white matter hyperintensities (mm^3)	93.8 (41.45, 146.14)	0.003
Fluid intelligence score	-0.024 (-0.041, -0.007)	0.009

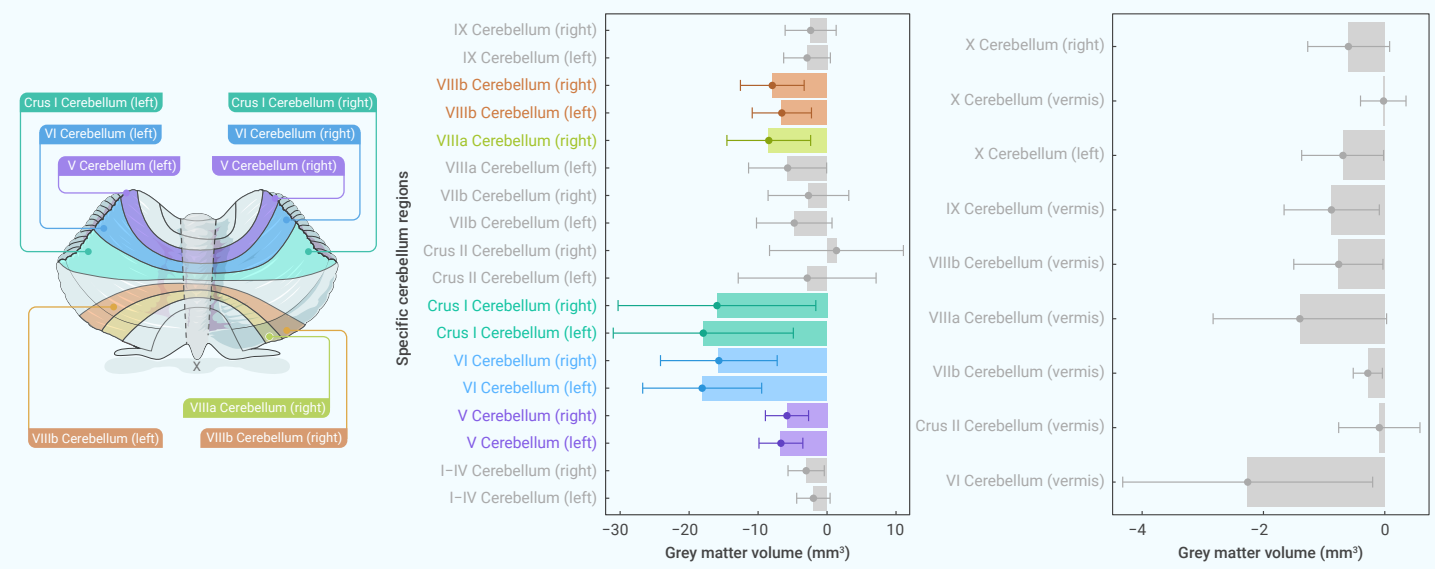

Figure 2. The changes in GMV of specific cerebellum regions for each unit increase in E-DII.

by using multiple mediation analysis (Figure 4 & Table S9). In multi-mediation models, WMV emerged the largest unique contribution to the association ($\beta_{\text{indirect effect}}$= -0.003, 95% CI: -0.005, -0.001) between E-DII and fluid intelligence score. Similarly, the association between E-DII and fluid intelligence score was also mediated by the GMV ($\beta_{\text{indirect effect}}$= -0.002, 95% CI: -0.004, -0.001) and WMHV ($\beta_{\text{indirect effect}}$= -0.001, 95% CI: -0.003, -0.001)

Sensitivity analysis

According to the results of sensitivity analysis, our results remained stable under varying conditions. Firstly, the outcomes of the sensitivity analysis, which excluded participants with TBV outside the range of 3 SD, aligned with our main findings (Tables S10-S12). Secondly, the mediation effects of brain MRI metrics (total GMV, total WMV, TBV and WMHV) on the association between E-DII and fluid intelligence score adjusted by scanner-brain position was also similar to our original findings (Tables S13-S15).

DISCUSSION

To our knowledge, this is the first study to investigate associations between E-DII and specific brain structures, as well as the first to explore the mediating effect of brain structures on the relationship between E-DII and cognitive impairment. In this study, we observed that higher E-DII was associated with lower GMV (including 8 regions of cerebellum, 25 regions of cerebral cortices and 4 regions of cerebral subcortices), lower total WMV and higher WMHV. Additionally, we discovered that the abnormalities of total GMV, total WMV and WMHV mediate the relationship between E-DII and fluid intelligence score.

Aline with previous findings, we observed significant associations of E-DII with brain MRI metrics and FIS, for example, each 1 unit increase of E-DII was associated with 0.024 (95%CI: 0.007, 0.041) decrease of FIS and 1,612.96 mm^3 (95%CI: 826.81, 2,399.12) reduction of total brain volume. These associations indicated that dietary inflammatory factors could impact the normality of brain structure and cognitive function.[2,10] Although few studies have directly demonstrated the correlation between E-DII and brain structure,[32] numerous studies have indicated that the abnormalities of brain structure could be due to diet-induced inflammation. For instance, a longitudinal study revealed that individuals who followed an inflammation-related nutrient pattern exhibited significant associations with cognitive impairment.[33] Another cohort study also reported that people with higher intake of alcohol and animal foods was associated with relative lower brain GMV.[34] Furthermore, higher Mediterranean diet pattern was also found to associated with a lower WMHV.[35] However, the findings of Zabetian-Targhi et al. demonstrate no significant correlation between E-DII and brain structures.[12] This discrepancy may be attributed to the following reasons: Firstly, the sample size of our study was larger, which may result in more accurate outcomes. Secondly, the participants in our study were younger, and age being a substantial factor in brain structure may render the effects of E-DII less noticeable.[36]

Our study found significant associations between higher E-DII and GMV reduction, predominantly distributed in prefrontal lobe, temporal, and parietal lobe, as well as hippocampal, which have been previously reported to be associated with inflammatory markers.[37,38] Interestingly, most of the regions of E-DII associated GMV in our study were also found to be associated with cognitive decline (such as the subcallosal cortex, angular gyrus and frontal pole), which aligns with established findings from neurocognitive studies indicating that inflammation has a stronger association with declines in processing ability than in other domains such as the visual and hearing abilities.[39,40] The possible explanation for this specificity is that variations in tissue responses, vascular dilation, blood flow, and permeability across different regions of the central nervous system result in distinct characteristics in the presence of inflammatory markers.[38] In addition, the E-DII associated structures in our findings were also the structures particularly associated with Alzheimer's disease.[41]

We further estimated that TBV, GMV, WMV and WMHV could all mediate the association of "E-DII~FIS" with mediation proportion of 23.57%, 21.82%, 19.19% and 4% respectively. These findings were also consisted with several

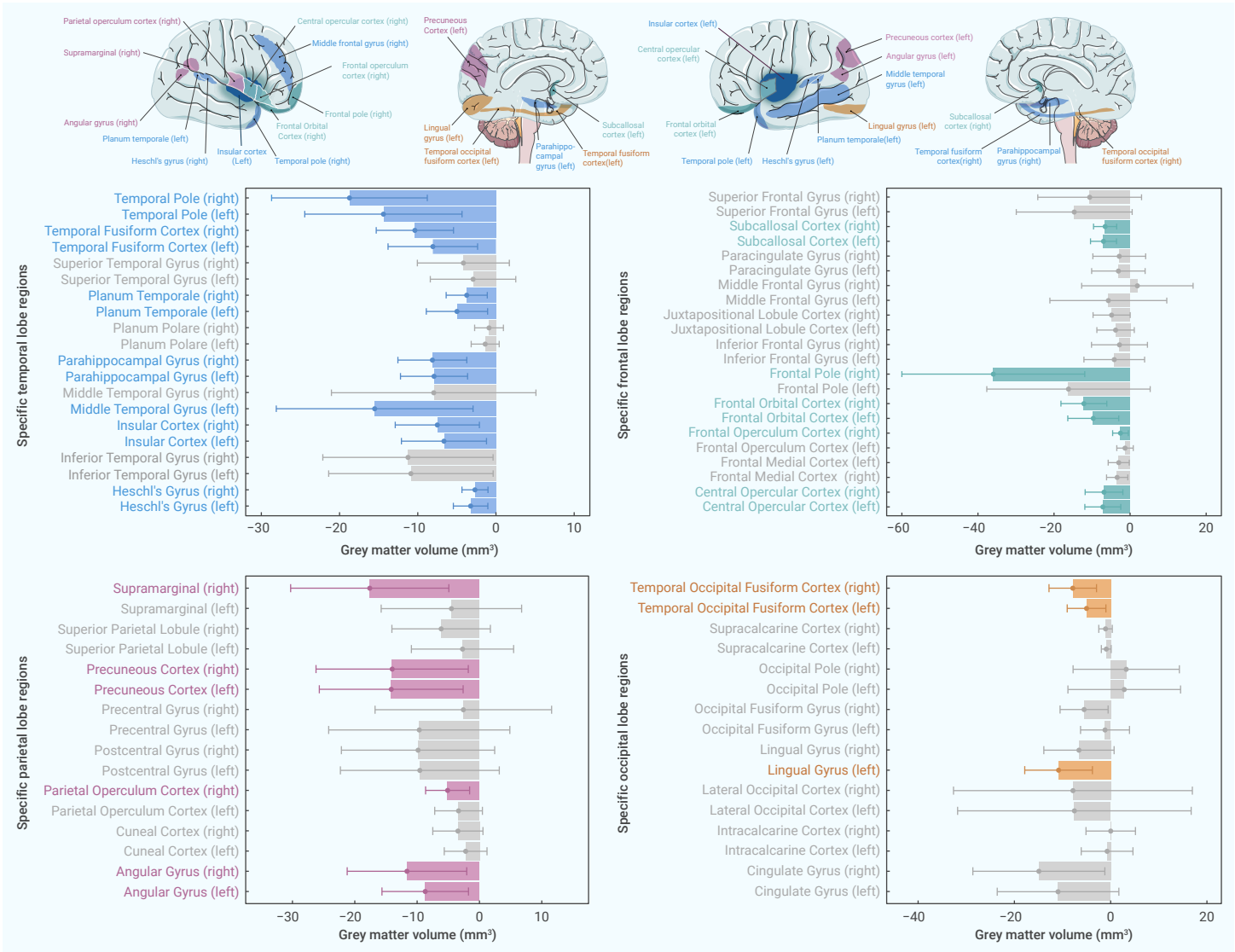

Figure 3. The changes in GMV of specific cerebral cortices for each unit increase in E-DII.

studies indicated that brain structures might play an vital role in the association between inflammatory diet and cognitive function. For instance, Frith et al. suggested that the memory and cognitive damage caused by E-DII could be a result of E-DII induced brain neuroinflammation and impairment.[11] Another review also noted that an inflammatory diet might lead to brain-related oxidative stress and further impair cognitive performance.[42] Notably, the proportion of mediators in this study is relatively large, which also suggests that inflammatory diet to a large extent directly affects cognition by affecting brain structure. In addition, although the indirect effects were small which was due to the small total effect, as FIS represents problem-solving capacity and is considered independent of learning, experience as well as education, even slight decrease cannot be ignored.[23]

In additional, the results from the multiple mediation analysis unveiled nuanced distinctions from the single mediation models. Specifically, the brain GMV showed the strongest mediation proportion in our single mediation models, while WMV exhibited the strongest unique mediation effect in our multiple mediation model. This suggested that the mediation effects of different brain structures (GMV, WMV and WMHV) were not completely distinct, and there were potential connections between them, which need further exploration.

Several mechanisms could help explain the observed associations between E-DII, brain structure abnormalities, and the mediation association of brain MRI metrics on the relationship "E-DII ~ cognitive function". Previous findings suggested that E-DII may lead to an increase in the cellular production of proinflammatory mediators such as C-reactive protein, TNF-α, IL-6, and IL-1β, resulting in the establishment of a chronic subclinical systemic inflammatory state.[2] Those peripheral inflammation mediators have been shown to disrupt the blood-brain barrier, allowing them to enter the brain where they continue to harm neurons and glial cells.[43,44] This perpetuates a chronic inflammatory brain state, which contributes to a decline in neurotrophic support,[44] leading to various neurodegenerative pathways and ultimately causing brain atrophy and white matter hyperintensities.[40] Finally, the neurodegeneration of specific brain structures associated with cognitive processes eventually lead to impaired cognition.

Several limitations should also be noted in this study. Firstly, due to the limitations of sample size, fluid intelligence score and MRI data were both collected at the second follow-up, which may lead bidirectional causality, that is, abnormal brain structures may also be a manifestation of cognitive impairment. However, it is worth noting that the current evidence of the association between brain structures and cognitive damage is unlikely to explain the direction of "cognitive impairment → brain structure".[45] Moreover, due to the utilization of cross-sectional data in this study, it is difficult to investigate the casual association, and analyzing individual brain MRI metric changes becomes challenging.

CONCLUSION

In summary, we observe significant relationships between E-DII and brain structures. Also, we produce preliminary evidence that brain structures might

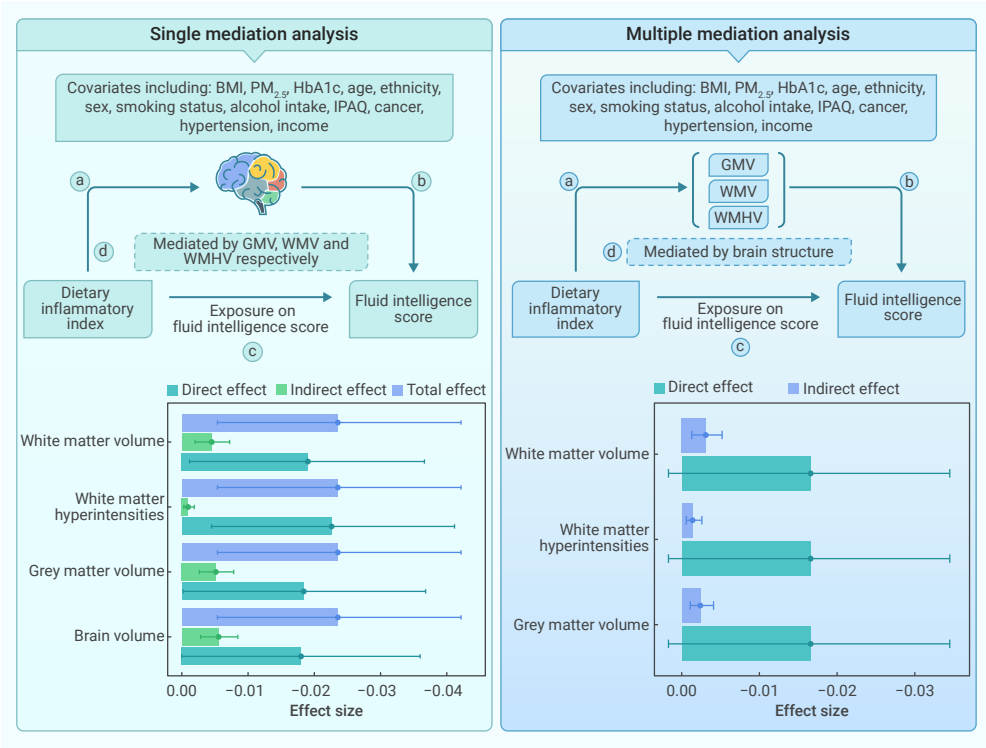

Figure 4. Brain MRI metrics partly mediate the association between DII and fluid intelligence score.

have mediation effects on the relationship between inflammatory diet and cognitive function, which suggests that the controlling of inflammatory diet could effectively prevent brain structures abnormalities and further reduce the risk of cognitive impairment.

REFERENCES

1. Pais, R., Ruano, L., P Carvalho, O., et al. (2020). Global cognitive impairment prevalence and incidence in community dwelling older adults-a systematic review. Geriatrics **5**: 4. DOI: 10.3390/geriatrics5010004.
2. Charisis, S., Ntanasi, E., Yannakoulia, M., et al. (2021). Diet inflammatory index and dementia incidence: A population-based study. Neurology **97**: 2381–2391. DOI: 10.1212/WNL.0000000000012973.
3. Sartori, A.C., Vance, D.E., Slater, L.Z., et al. (2012). The impact of inflammation on cognitive function in older adults: Implications for healthcare practice and research. J. Neurosci. Nurs. **44**: 206–217. DOI: 10.1097/JNN.0b013e3182527690.
4. Zhang, Q., Wu, Y., Han, T., et al. (2019). Changes in cognitive function and risk factors for cognitive impairment of the elderly in China: 2005-2014. Int. J. Environ. Res. Public Health **16**: 16. DOI: 10.3390/ijerph16162847.
5. Khoo, J., Piantadosi, C., Duncan, R., et al. (2011). Comparing effects of a low-energy diet and a high-protein low-fat diet on sexual and endothelial function, urinary tract symptoms, and inflammation in obese diabetic men. J. Sex. Med. **8**: 2868–2875. DOI: 10.1111/j.1743-6109.2011.02417.x.
6. Jia, Y., Yan, S., Sun, M., et al. (2022). Association between dietary inflammatory index and cognitive impairment: A meta-analysis. Front. Aging Neurosci. **14**: 1007629. DOI: 10.3389/fnagi.2022.1007629.
7. Shivappa, N., Steck, S.E., Hurley, T.G., et al. (2014). Designing and developing a literature-derived, population-based dietary inflammatory index. Public Health Nutr. **17**: 1689–1696. DOI: 10.1017/S1368980013002115.
8. Sun, M., Wang, L., Guo, Y., et al. (2022). The association among inflammatory diet, glycohemoglobin, and cognitive function impairment in the elderly: Based on the NHANES 2011-2014. J. Alzheimers Dis. **87**: 1713–1723. DOI: 10.3233/JAD-215688.
9. Li, R., Zhan, W., Huang, X., et al. (2021). Association of dietary inflammatory index (DII) and depressive disorders. J. Inflamm. Res. **14**: 6959–6973. DOI: 10.2147/JIR.S344002.
10. Melo Van Lent, D., Gokingco, H., Short, M.I., et al. (2022). Higher dietary inflammatory index scores are associated with brain MRI markers of brain aging: Results from the Framingham heart study offspring cohort. Alzheimers Dement. **19**: 621–631 DOI: 10.1002/alz.12685.
11. Frith, E., Shivappa, N., Mann, J.R., et al. (2018). Dietary inflammatory index and memory function: Population-based national sample of elderly Americans. Br. J. Nutr. **119**: 552–558. DOI: 10.1017/S0007114517003804.
12. Zabetian-Targhi, F., Srikanth, V.K., Smith, K.J., et al. (2021). Associations between the dietary inflammatory index, brain volume, small vessel disease, and global cognitive function. J. Acad. Nutr. Diet. **121**: 915–924. DOI: 10.1016/j.jand.2020.11.004.
13. Chen, L., Cai, M., Li, H., et al. (2022). Risk/benefit tradeoff of habitual physical activity and air pollution on chronic pulmonary obstructive disease: Findings from a large prospective cohort study. BMC Med. **20**: 70. DOI: 10.1186/s12916-022-02274-8.
14. Caleyachetty, R., Littlejohns, T., Lacey, B., et al. (2021). United Kingdom Biobank (UK Biobank): JACC focus seminar 6/8. J. Am. Coll. Cardiol. **78**: 56–65. DOI: 10.1016/j.jacc.2021.03.342.
15. Alfaro-Almagro, F., Jenkinson, M., Bangerter, N.K., et al. (2018). Image processing and quality control for the first 10,000 brain imaging datasets from UK Biobank. Neuroimage **166**: 400–424. DOI: 10.1016/j.neuroimage.2017.10.034.
16. Miller, K.L., Alfaro-Almagro. F., Bangerter, N.K., et al. (2016). Multimodal population brain imaging in the UK Biobank prospective epidemiological study. Nat. Neurosci. **19**: 1523–1536. DOI: 10.1038/nn.4393.
17. Daviet, R., Aydogan, G., Jagannathan, K., et al. (2022). Associations between alcohol consumption and gray and white matter volumes in the UK Biobank. Nat. Commun. **13**: 1175. DOI: 10.1038/s41467-022-28735-5.
18. Asadi, Z., Yaghooti-Khorasani, M., Ghazizadeh, H., et al. (2020). Association between dietary inflammatory index and risk of cardiovascular disease in the Mashhad stroke and heart atherosclerotic disorder study population. IUBMB Life **72**: 706–715. DOI: 10.1002/iub.2172.
19. Shi, Y., Lin, F., Li, Y., et al. (2023). Association of pro-inflammatory diet with increased risk of all-cause dementia and Alzheimer's dementia: A prospective study of 166,377 UK Biobank participants. BMC Med. **21**: 266. DOI: 10.1186/s12916-023-02940-5.
20. Hebert, J.R., Shivappa, N., Wirth, M.D., et al. (2019). Perspective: The dietary inflammatory index (DII)-lessons learned, improvements made, and future directions. Adv. Nutr. **10**: 185–195. DOI: 10.1093/advances/nmy071.
21. Sudlow, C., Gallacher, J., Allen, N., et al. (2015). UK biobank: An open access resource for identifying the causes of a wide range of complex diseases of middle and old age. PLoS Med. **12**: e1001779. DOI: 10.1371/journal.pmed.1001779.
22. Schulz, C.A., Weinhold, L., Schmid, M., et al. (2023) Analysis of associations between dietary patterns, genetic disposition, and cognitive function in data from UK Biobank. Eur. J. Nutr. **62**: 511–521. DOI: 10.1007/s00394-022-02976-y.
23. Duchowny, K.A., Ackley, S.F., Brenowitz, W.D., et al. (2022). Associations between handgrip strength and dementia risk, cognition, and neuroimaging outcomes in the UK Biobank cohort study. JAMA Netw. Open **5**: e2218314. DOI: 10.1001/jamanetworkopen.2022.18314.
24. Kievit, R.A., Fuhrmann, D., Borgeest, G.S., et al. (2018). The neural determinants of age-related changes in fluid intelligence: A pre-registered, longitudinal analysis in UK Biobank. Wellcome Open Res. **3**: 38. DOI: 10.12688/wellcomeopenres.14241.2.
25. Textor, J., Hardt, J., and Knüppel, S. (2011) DAGitty: A graphical tool for analyzing causal diagrams. Epidemiology **22**: 745. DOI: 10.1097/EDE.0b013e318225c2be.
26. Park, S.K., Jung, J.Y., Kang, J.G., et al. (2019). Left ventricular geometry and risk of incident hypertension. Heart **105**: 1402–1407. DOI: 10.1136/heartjnl-2018-314657.
27. Di Pino, A., Scicali, R., Calanna, S., et al. (2014). Cardiovascular risk profile in subjects with prediabetes and new-onset type 2 diabetes identified by HbA(1c) according to American Diabetes Association criteria. Diabetes Care **37**: 1447–1453. DOI: 10.2337/dc13-2357.
28. Tyrrell, J., Jones, S.E., Beaumont, R., et al. (2016). Height, body mass index, and socioeconomic status: Mendelian randomisation study in UK Biobank. BMJ **352**: i582. DOI: 10.1136/bmj.i582.
29. Zheng, D., Cai, M., Qian, Z., et al. (2023) The associations of glycosylated hemoglobin with grey matter volume and depression: Investigating mediating role of grey matter volume. Global Trans. **5**: 107–116. DOI: 10.1016/j.glt.2023.06.004.
30. Craig, C.L., Marshall, A.L., Sjöström, M., et al. (2003). International physical activity questionnaire: 12-country reliability and validity. Med. Sci. Sports Exerc. **35**: 1381–1395. DOI: 10.1249/01.MSS.0000078924.61453.FB.
31. Bull, F.C., Al-Ansari, S.S., Biddle, S., et al. (2020). World Health Organization 2020 guidelines on physical activity and sedentary behaviour. Br. J. Sports Med. **54**: 1451–1462. DOI: 10.1136/bjsports-2020-102955.
32. Frye, B.M., Craft, S., Register, T.C., et al. (2021). Diet, psychosocial stress, and Alzheimer's disease-related neuroanatomy in female nonhuman primates. Alzheimers Dement. **17**: 743–744. DOI: 10.1002/alz.12232.
33. Gu, Y., Manly, J.J., Mayeux, R.P., et al. (2018). An inflammation-related nutrient

pattern is associated with both brain and cognitive measures in a multiethnic elderly population. Curr. Alzheimer Res. **15**: 493–501. DOI: 10.2174/1567205015666180101145619.
34. Kokubun, K., and Yamakawa, Y. (2019). Association between food patterns and gray matter volume. Front. Hum. Neurosci. **13**: 384. DOI: 10.3389/fnhum.2019.00384.
35. Song, S., Gaynor, A.M., Cruz, E., et al. (2022). Mediterranean diet and white matter hyperintensity change over time in cognitively intact adults. Nutrients **14**: 3664. DOI: 10.3390/nu14173664.
36. Cox, S.R., Ritchie, S.J., Tucker-Drob, E.M., et al. (2016). Ageing and brain white matter structure in 3,513 UK Biobank participants. Nat. Commun. **7**: 13629. DOI: 10.1038/ncomms13629.
37. Bettcher, B.M., Wilheim, R., Rigby, T., et al. (2012). C-reactive protein is related to memory and medial temporal brain volume in older adults. Brain Behav. Immun. **26**: 103–108. DOI: 10.1016/j.bbi.2011.07.240.
38. Janowitz, D., Habes. M., Toledo, J.B., et al. (2020). Inflammatory markers and imaging patterns of advanced brain aging in the general population. Brain Imaging Behav. **14**: 1108–1117. DOI: 10.1007/s11682-019-00058-y.
39. Heringa, S.M., van den Berg, E., Reijmer, Y.D., et al. (2014). Markers of low-grade inflammation and endothelial dysfunction are related to reduced information processing speed and executive functioning in an older population - the Hoorn Study. Psychoneuroendocrinology **40**: 108–118. DOI: 10.1016/j.psyneuen.2013.11.011.
40. Conole, E.L.S., Stevenson, A.J., Muñoz Maniega, S., et al. (2021). DNA methylation and protein markers of chronic inflammation and their associations with brain and cognitive aging. Neurology **97**: e2340–e2352. DOI: 10.1212/WNL.0000000000012997.
41. Montagne, A., Nation, D.A., Sagare, A.P., et al. (2020). APOE4 leads to blood-brain barrier dysfunction predicting cognitive decline. Nature **581**: 71–76. DOI: 10.1038/s41586-020-2247-3.
42. Freeman, L.R., Haley-Zitlin, V., Rosenberger, D.S., et al. (2014). Damaging effects of a high-fat diet to the brain and cognition: A review of proposed mechanisms. Nutr. Neurosci. **17**: 241–251. DOI: 10.1179/1476830513Y.0000000092.
43. Hsuchou, H., Kastin, A.J, Mishra, P.K., et al. (2012). C-reactive protein increases BBB permeability: Implications for obesity and neuroinflammation. Cell Physiol. Biochem. **30**: 1109–1119. DOI: 10.1159/000343302.
44. Miller, A.H., Maletic, V., and Raison, C.L. (2009). Inflammation and its discontents: The role of cytokines in the pathophysiology of major depression. Biol. Psychiatry **65**: 732–741. DOI: 10.1016/j.biopsych.2008.11.029.
45. Edison, P. (2020). Brain connectivity and cognitive impairment. Brain Connect. **10**: 329–330. DOI: 10.1089/brain.2020.29013.ped.

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AUTHOR CONTRIBUTIONS

D.Z. contributed to data cleaning, and had primary responsibility for writing the manuscript. B.Z., G.Z., J.H., J.Z., C.W., Y.W. and Z.Z. contributed to the revision of the manuscript and interpretation of the findings. H.L. contributed to the analysis and directed this study. In addition, H.L. is the guarantor of this article.

DECLARATION OF INTERESTS

The authors declare no competing interests.

ETHICAL STATEMENT AND PATIENT CONSENT

This study was conducted using publicly available de-identified data; therefore, it did not require additional ethical approval or patient consent.

DATA AND CODE AVAILABILITY

The data that support the findings of this study are available from the UK Biobank project site, subject to the registration and application process. Further details can be found at https://www.ukbiobank.ac.uk.

SUPPLEMENTAL INFORMATION

It can be found online at https://doi.org/10.59717/j.xinn-med.2023.100036

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