

RESEARCH ARTICLE

A comparative study of the EAT-Lancet diet and the Mediterranean diet in relation to neuroimaging biomarkers and cognitive performance

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Abstract

BACKGROUND: The impact of the sustainable EAT-Lancet planetary health diet on brain and cognitive health remains unclear. This study compared the impact of the EAT-Lancet diet with the well-established cognitive-beneficial Mediterranean diet (MeDi) in relation to neuroimaging biomarkers and cognitive performance among older adults.

METHODS: The study included 615 dementia-free 70-year-olds from the Swedish population-based Gothenburg H70 Birth Cohort study. Dietary adherence was measured with EAT-Lancet diet and MeDi scores. Neuroimaging measures included cortical thickness, hippocampal volume, small vessel disease, and deep learning-derived brain age. Cognitive performance was assessed with a global cognitive composite score.

RESULTS: In multi-adjusted models, higher adherence to the EAT-Lancet diet was associated with higher total mean cortical thickness, and thicker cortex in Alzheimer's disease-signature regions, while a higher adherence to the MeDi was associated with better cognitive performance.

DISCUSSION: The results indicate the beneficial effects of both the EAT-Lancet and the MeDi on brain health.

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KEYWORDS

Alzheimer's disease, brain age, cognitive impairment, EAT-Lancet diet, Mediterranean diet, neuroimaging, small vessel disease

HIGHLIGHTS

- There were no indications of detrimental effects of adhering to the EAT-Lancet diet.
- Adhering to the EAT-Lancet planetary health diet was associated with thicker cortex.
- Results confirm links between the Mediterranean diet and better cognitive function.

1 | BACKGROUND

The Mediterranean diet (MeDi) is one of the most extensively studied dietary patterns in relation to brain and cognitive health, and higher adherence has been linked to greater brain integrity, slower cognitive decline, and reduced dementia risk.^{1–4} However, findings are inconsistent and direct pathways linking diet with cognitive impairment in old age remain unclear.^{5,6}

Indirectly, diet may be linked to dementia by contributing to non-communicable diseases such as obesity, diabetes, and cardiovascular disease.⁶ Adhering to unhealthy diets, characterized by high calorie, sugar, ultra-processed, and animal-derived foods (e.g., Western diets), not only exacerbates the burden of non-communicable diseases, but also contributes to global environmental degradation.^{7,8} In response, the EAT-Lancet Commission presented a new environmentally sustainable healthy reference diet in 2019, constructed to reduce non-communicable diseases and malnutrition.⁹ The EAT-Lancet diet emphasizes plant-based foods, such as whole grains, fruits, vegetables, nuts, and legumes, and limiting animal-based foods, sugar, and saturated fats.⁹ Greater adherence to the EAT-Lancet diet has been associated with a lower risk of cancer-, cardiovascular-, and all-cause mortality,¹⁰ decreased risk of stroke,¹¹ coronary events,¹² and diabetes type 2.^{13,14} Additionally, it has been suggested that higher adherence to the EAT-Lancet diet may reduce the risk of cognitive impairment in old age.¹⁵ However, its impact on brain and cognitive health among older adults remains largely unexplored.

In older adults, structural brain alterations and cognitive deficits may reflect changes due to cerebrovascular pathologies or neurode-

generative diseases such as Alzheimer's disease (AD).¹⁶ Hippocampal atrophy and cortical thinning in AD-sensitive regions may indicate early neurodegenerative changes, and cerebral small vessel disease (CSVD) is commonly observed in aging individuals.^{17,18} Together, neurodegenerative and cerebrovascular alterations can contribute to an older-appearing brain.¹⁹ In this context, brain age, as estimated from brain magnetic resonance imaging (MRI), may serve as a valuable biological marker of brain aging.¹⁹

Given the increased focus on incorporating environmental sustainability into general dietary guidelines, it is important to understand how planetary health diets, such as the EAT-Lancet diet, impact brain and cognitive health.²⁰ The EAT-Lancet diet is constructed to be adaptable to diverse global culinary traditions and to achieve global equity in access to healthy food, and improve food production and environmental sustainability. While the EAT-Lancet diet and the MeDi promote similar foods, intake levels and combinations of foods can differ between the diets. For example, the EAT-Lancet diet is overall more restrictive in animal-based foods than the MeDi and does not recommend alcohol as part of a healthy diet (a low to moderate intake of alcohol, especially wine, is often included in the MeDi).^{9,21} Comparing adherence to the EAT-Lancet diet with the MeDi in relation to neuroimaging biomarkers and cognitive performance among older adults can offer valuable insights into the impact of the EAT-Lancet diet on brain health, potential pathways involved, and whether the impact of the diet differs from the well-established cognitive-beneficial MeDi.

Our hypothesis was that both the EAT-Lancet diet and the MeDi are beneficial for brain health, but that the impact of the diets may differ. The aim of this study was to investigate adherence to the EAT-Lancet

diet and the MeDi in relation to brain MRI markers of cortical thickness (global and AD-signature regions), hippocampal volume, CSVD, predicted brain age, and cognitive function among 70-year-olds without dementia. Additionally, we explored the potentially modifying effect of sex in this context, as factors that could postpone the development of cognitive impairment may differ by the sex assigned at birth.²²

2 | METHODS

2.1 | Study design and participants

Cross-sectional data were obtained from the Swedish population-based Gothenburg H70 Birth Cohort Study (H70 study) in 2014–2016.²³ All residents in Gothenburg born in 1944 on birth dates ending with 0, 2, 5, or 8 were selected as potential participants, and 1203 participated (72% response rate). The systematic selection procedure was implemented to enhance the likelihood of obtaining a representative sample with respect to diversity, equity, and inclusion (DEI). The study comprised a 1-day general examination at the Neuropsychiatric Clinic at Sahlgrenska University Hospital, as well as several additional examinations.²³ A clinical cognitive examination was performed as part of the general examination ($n = 1196$ participants). All participants were invited to participate in the brain MRI and dietary examinations. There were 861 individuals who participated in the dietary examination,²⁴ and 791 individuals that performed an MRI.²³ Non-participation in the examinations was due to several reasons (e.g., declining participation, no response, discomfort, or contraindications), described in detail previously.^{23,24} Participants with dementia were excluded from this study. The final sample included 615 participants with both diet and MRI data. The participant flowchart can be found in Figure 1.

RESEARCH IN CONTEXT

- 1. Systematic review:** We used traditional sources such as PubMed to review the literature. Given the increased focus on incorporating environmental sustainability into dietary guidelines, it is important to understand how planetary health diets, such as the EAT-Lancet diet, impact brain and cognitive health in aging populations. While the Mediterranean diet has been extensively studied in this context, associations between the EAT-Lancet diet and neuroimaging biomarkers remain unexplored, and only a few studies have investigated associations between the EAT-Lancet diet and cognitive function.
- 2. Interpretation:** Our study linked higher adherence to the EAT-Lancet diet with markers of brain health and confirmed previous research linking higher adherence to the Mediterranean diet with better cognitive performance. We found no indications of the detrimental effects of adhering to the EAT-Lancet diet.
- 3. Future directions:** Intervention studies are needed to confirm that adhering to the EAT-Lancet diet is beneficial for brain and cognitive health in older adults.

2.2 | Dietary examination procedure

The diet history (DH) method used in this study was a semi-structured face-to-face interview conducted by registered dietitians, estimating habitual food intake during the preceding 3 months, as described previously.^{23,24} The protocol for the interview consisted of a meal-

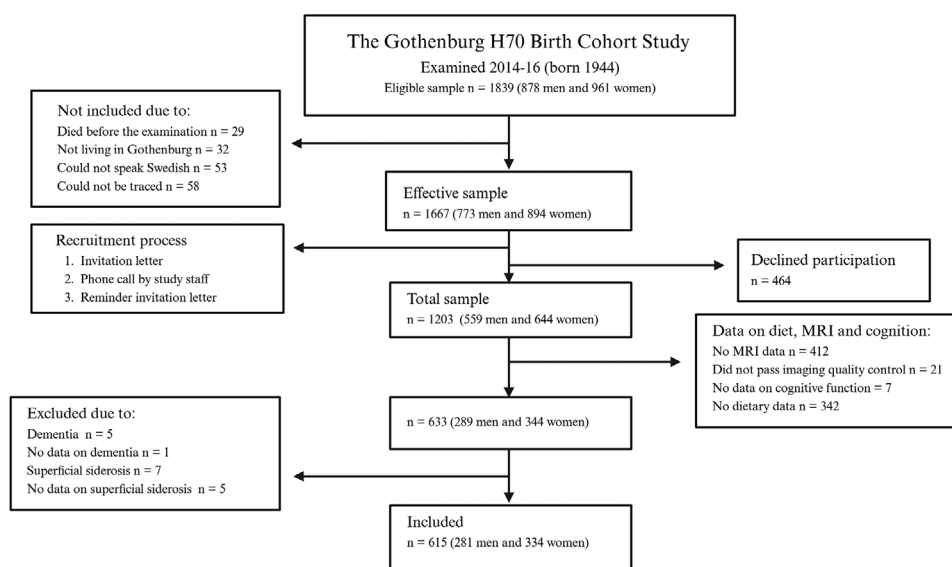


FIGURE 1 Participant flowchart in the Gothenburg H70 Birth Cohort study

pattern interview with questions on foods consumed, usual frequencies and portion sizes of foods. Pictures of foods from the Swedish Food Agency (SFA) were used during the interviews to estimate individual portion sizes of reported food items. Dietary intake was registered as gram of food items usually consumed per day/week/month in the nutritional calculation computer program Dietist Net Pro, containing the SFAs nutrient database of 2015.²⁴

2.3 | Dietary variables

Mean daily energy, alcohol, nutrients, and food intake were estimated based on results from the DH interview. Dietary adherence was measured with an EAT-Lancet dietary index (score 0–42), and a MeDi index (score 0–9). The scores were transformed for comparability by dividing the EAT-Lancet score (range 0–42) by 4.2, and the MeDi score (range 0–9) by 0.9, with results presented per 10% in increment scores.

2.3.1 | The EAT-Lancet diet score

The EAT-Lancet diet score used in this study was a replicate of the score constructed by Stubbendorff et al. in 2022,¹⁰ based on the EAT-Lancet diet proposed by the EAT-Lancet Commission in 2019.⁹ Reported food intake was divided into food components based on amounts in grams in uncooked weight per day (Table S1). The food components were classified as either “emphasized foods” or “limited foods”. Emphasized foods were vegetables, fruits, legumes, whole grains, nuts, fish, and unsaturated fat. Food components classified as limited were beef and lamb, pork, poultry, eggs, dairy, potatoes, and added sugar. The index consists of 14 food components, with a possible range of 0–3 points for each component; 0 points indicate low adherence, and 3 points indicate high adherence (Table S2). The total possible score range is 0 (nonadherence) to 42 points (perfect adherence = 14 × 3 points). The construction of the EAT-Lancet diet index has been described in detail previously.¹⁰

2.3.2 | The MeDi score

The MeDi score used in this study was a modified version of the commonly used score by Trichopoulou et al.²¹ Nine food components were included in the score (Table S3), and each component was adjusted to daily energy intakes of 2500 kcal (10.5 MJ) for men and 2000 kcal (8.5 MJ) for women. A value of 0 or 1 was assigned using the sex-specific median as cutoff for each component. Emphasized foods were whole grains, vegetables, legumes, fruits, nuts, fish, and unsaturated fat. Limited foods were red meat (including processed meat), and dairy products. For emphasized foods, participants with an intake above the median cutoff were assigned a value of 1, while participants with an intake below the median cutoff were assigned a value of 0. For limited foods, participants with an intake below the median were assigned a

value of 1, while participants with an intake above the median were assigned a value of 0. For alcohol, a value of 1 was assigned to men who consumed between 10 and 50 g of alcohol per day, and to women who consumed between 5 and 25 g of alcohol per day (based on cutoffs from the original score by Trichopoulou et al.).²¹ Participants with an alcohol intake above or below the sex-specific alcohol range were assigned a 0. The diet score ranged from 0 (nonadherence) to 9 (perfect adherence).

2.4 | Brain MRI acquisition

All participants were scanned on a 3.0T Philips Achieva system (Philips Medical Systems). The imaging protocol included a three-dimensional (3D) T1-weighted turbo field echo (TFE) sequence to assess structural changes, a T2-weighted sequence to exclude other pathologies (e.g., tumors) and to evaluate enlarged perivascular spaces (PVS), a fluid-attenuated inversion recovery (FLAIR) sequence for detecting white matter hyperintensities (WMH) and lacunes, and venous blood oxygen level dependent sequence (VenoBOLD) for the detection of microbleeds.²⁵ Cortical reconstruction and volumetric segmentation of subcortical gray matter volumes were performed on the T1-weighted images using the FreeSurfer 7.2 image analysis pipeline, described in detail previously.²⁶

Large infarcts (>15 mm), lacunes (3–15 mm), intracerebral hemorrhage, enlarged PVS, cortical superficial siderosis, and cerebral microbleeds (CMBs) were assessed by an experienced radiologist blinded to clinical data.²⁷ Small vessel disease markers were defined according to the Standards for Reporting Vascular Changes.²⁸

Biological brain age is a theoretical concept of a measurement developed to track the state of a person's biophysiological brain aging, in an attempt to unveil why individuals with the same chronological age present different atrophy patterns (aging heterogeneity). The brain age model is based on a convolutional neural network, trained on 18843 raw T1-weighted brain MRIs of cognitively unimpaired individuals, with an average age of 65.4 ± 9.0 years, from seven different cohorts (AddNeuroMed, ADNI, AIBL, Genic, UK Biobank and the H70-study), using a 10-fold cross-validation approach. Images were only rigid registered to the Montreal Neuroscience Institute (MNI) atlas space before being used as input to the model. Four approaches were used to validate the brain age model: (1) the hold-out method, (2) advanced 10-fold cross-validation with two external cohorts (AddNeuroMed and J-ADNI), (3) adding external data during training in the cross-validation, and (4) cross-validation with skull-stripped brain images. The third approach resulted in the smallest mean absolute error (MAE), which was therefore used in the current manuscript. The models showed MAE levels comparable to previous studies, indicating strong performance with the advantage of requiring only one preprocessing step, described in detail previously.¹⁹ No age bias correction was necessary as all participants were 70 years old.

Quality control was carried out on all MRI data according to previously described procedures.²⁹ Data were managed and processed through The Hive database system.³⁰

2.4.1 | Brain MRI markers

Total mean cortical thickness was derived by averaging the cortical thickness of the right and left hemisphere. An AD-signature cortical thickness measure was derived by averaging cortical thicknesses of entorhinal, inferior temporal, middle temporal, and fusiform regions (AD-signature meta-regions of interest [meta-ROIs]) from the Desikan-Killiany Atlas.^{31–33} The AD-signature regions were adjusted for surface area. This adjustment was performed since the regions included in the AD-signature meta-ROI differ in size.³¹ In addition, whole-brain surface-based analyses were performed to explore associations between dietary patterns and cortical thickness in a non-hypothesis driven manner.

Hippocampal volume was adjusted for total intracranial volume (TIV). The adjustment was performed by using residuals of a least-square derived linear regression between hippocampal volume (y) and TIV (x).³⁴

Predicted brain age was analyzed as the difference between the individual's chronological age and the predicted brain age, also known as the "brain age gap" (BAG). A negative value indicates a biologically younger brain, and a positive value indicates a biologically older brain compared to chronological age.

A CSVD score including measures of WMHs, CMBs, enlarged PVs, and lacunes was generated as a measure of overall CSVD burden.³⁵ WMHs were assessed with the Fazekas scale applied on FLAIR dichotomized into none/punctuate (Fazekas 0–1) or confluent (Fazekas 2–3), lacunes and CMBs were dichotomized into none or present (≥ 1), and PVS in basal ganglia were dichotomized into 0–10 or ≥ 11 . A summary CSVD score (ranging 0–4) was generated by awarding one point for each of the following CSVD marker feature: confluent WMHs (Fazekas's score 2–3), ≥ 1 lacunes, ≥ 1 CMBs, and ≥ 11 PVS in basal ganglia. Due to the few participants with a score of 4 ($n = 1$), participants with scores of 3 and 4 were combined into one category ($n = 17$). Therefore, the final CSVD score ranged between 0 (low burden) and 3 (high burden).

2.5 | Dementia diagnosis

Dementia was diagnosed following the Diagnostic and Statistical Manual of Mental Disorders, third edition revised, using information from comprehensive neuropsychiatric examinations, and information from close informants, described in detail previously.^{23,36}

2.6 | Assessment of cognitive function

The cognitive examination was a semi-structured interview conducted by trained research staff (e.g., research nurse or medical doctor).²³ Cognitive performance was measured using a global cognitive composite score, derived from eight cognitive tests covering five cognitive domains: executive function (Digit Span Backward and Figure Logic), perceptual speed (Figure Identification-Psif), verbal fluency (phonemic fluency derived from the Controlled Oral Word Association-FAS

and semantic fluency derived from "animals" task), episodic memory (12-object recall, and 12-object delayed recall), and visuospatial abilities (Koh's block test), described previously.^{23,37} The participants had to have information on at least three cognitive tests to be included. The single tests were standardized into z-scores and averaged within each domain. The global cognitive composite score was then generated by averaging the z-scores of the five cognitive domains.³⁷ There were 589 participants with data on five cognitive domains (96%). There were 563 participants (91.5%) with data on eight tests, 35 (5.7%) with data on seven tests, six participants (1%) with data on six tests, three participants (0.5%) with data on five tests, two participants (0.3%) with data on four tests, and five participants (0.8%) with data on three tests. Missing data per test: Digit Span Backward; $n = 12$, Figure logic; $n = 18$, Figure Identification-Psif; $n = 11$, Controlled Oral Word Association-FAS; $n = 33$, Semantic fluency derived from "animals" task, $n = 4$, 12-object recall; $n = 5$, and 12-object delayed recall; $n = 6$, and block design; $n = 21$. One participant had no cognitive composite score data. Cognitive function was also rated in accordance with a Swedish version of the Mini-Mental State Examination (MMSE).³⁸ Two participants had missing data on the MMSE.

2.7 | Characteristics and potential confounders

Information on characteristics and potential confounders was obtained through semi-structured interviews and health examinations, described in detail previously.²³ Sex, education, physical activity, smoking, body mass index (BMI), diabetes, and hypertension were considered potential confounders. Educational level was divided into three categories based on Swedish education classifications: compulsory primary education, secondary education, and higher education. Smoking was defined as either present smoking or not smoking. Physical activity was divided into four categories based on an updated version of the Saltin-Grimby physical activity level scale; physically inactive, some light physical activity, regular physical activity and training, and regular hard physical training,³⁹ and then dichotomized into inactive/ light physical activity or regular physical activity/hard physical training. BMI was measured as kg body weight/ body height meter². Diabetes was measured as diabetes yes/no. Hypertension was measured as $\geq 140/90$ mmHg (yes/no). apolipoprotein E (APOE) $\epsilon 4$ status was dichotomized into carrier/non-carrier. There were missing data on physical activity for four participants, smoking for one participant, diabetes for one participant, and 14 missing for APOE $\epsilon 4$.

2.8 | Statistical analyses

The student's independent t-test was performed to compare age, brain age, total mean cortical thickness, AD-signature cortical thickness, hippocampal volume, BMI, and estimated energy intake between women and men. The Mann-Whitney U test was performed to compare the dietary scores, MMSE scores, cognitive performance, BAG, and alcohol intake. The chi-squared test was performed to compare CSVD burden, educational level, physical activity level, smoking status, diabetes,

hypertension, and APOE $\epsilon 4$ status between women and men. Continuous variables were presented as means (standard deviation [SD]) or medians (interquartile range [IQR]), and proportions as number and percentage (%).

Analyses were performed with linear or ordinal logistic regression models to explore cross-sectional associations between the diets and markers of brain integrity and cognitive performance. Dependent variables in the linear regression models were total mean cortical thickness, mean cortical thickness in AD-signature regions, hippocampal volume, predicted brain age (estimated as BAG), and a global cognitive composite score. The dependent variable in the ordinal logistic regression model (cumulative logit model) was the CSVD score. Independent variables were the EAT-Lancet and MeDi scores, with adherence presented per 10% in increment score (higher score = higher adherence). Potential confounders were identified from the literature. We performed the analyses adjusted for sex, education, physical activity, smoking, BMI, diabetes, and hypertension. In additional analyses, we excluded BMI, hypertension, and diabetes, as these factors potentially could mediate the association. We also performed a basic model (only adjusted by sex). The fully adjusted model was used as the main model, and results are based on this model unless otherwise stated. Potential sex*diet interactions were explored in relation to the MRI measures and cognitive performance with linear and ordinal regression models, adjusted for potential confounding. In addition, analyses were performed stratified by biological sex.

2.8.1 | Sensitivity analyses

Given that alcohol was included in the MeDi score, sensitivity analyses were performed to explore the impact of alcohol on associations between the EAT-Lancet diet and the MRI measures and cognitive performance (the same cutoffs for alcohol consumption were used as in the MeDi score).

2.8.2 | Additional analyses

Associations between the potential confounders and the brain health markers were investigated with linear and ordinal logistic regression models.

It has been suggested that APOE $\epsilon 4$ status (carrier/non-carrier) may modify the association between diet and AD.⁴⁰ Potential APOE $\epsilon 4$ *diet interactions were explored in relation to the MRI measures and cognitive performance with linear and ordinal regression models, adjusted for potential confounding. In addition, analyses were performed stratified by APOE $\epsilon 4$ status.

2.8.3 | Statistics

Assumptions underlying the linear regression models were controlled. Normality was assessed by examining P-P plots and histograms of the

residuals. Multicollinearity was tested by a variance inflation factor (VIF) and by examining the correlation matrix of continuous predictors. For the ordinal logistic regression model, the proportional odds assumptions were controlled with a likelihood ratio test, and linearity for quantitative predictors was assessed by creating scatterplots of each quantitative predictor against the ordinal response variable. The whole-brain surface-group analyses were performed using vertex-based general linear model (GLM) with Qdec (Query, design, estimate, contrast) in FreeSurfer adjusted for sex, and in models stratified by sex. Statistical significance was evaluated using Monte Carlo z-field simulation with a cluster forming threshold of $p < 0.05$ (vertex-z-threshold = 1.3).²⁶

Results from the regression models were interpreted based on estimates (β -Coefficients for the linear regression models, and OR for the ordinal logistic regression model) with 95% confidence interval (CI). False discovery rate (FDR) correction was applied to explore potential Type 1 errors in the main linear and ordinal regression analyses.

The statistical analyses were performed in IBM SPSS STATISTICS 29, and R version 4.1.2.

3 | RESULTS

3.1 | Characteristics of the study population

Participant characteristics are reported in Table 1. There were 334 women, and 281 men included in this study. The median EAT-Lancet score was 23 (IQR: 21, 25) for women, and 22 for men (IQR: 19, 23). The median MeDi score was 5 (IQR: 3, 6) for women, and 5 (IQR: 3, 6) for men (Table 1). Boxplots of the transformed dietary scores (score range: 0–10) can be found in Figure 2. Women had higher total mean cortical thickness compared to men, but there was no evidence of a difference in cortical thickness in AD-signature regions, hippocampal volume, predicted brain age, BAG, CSVD burden, or cognitive performance (measured with the global cognitive composite score) (Table 1). The MMSE score was high among both men (median score: 29) and women (median score: 30) (Table 1).

3.2 | Dietary adherence in relation to MRI measures and cognitive function

3.2.1 | Cortical thickness

In the surface group analyses (adjusted by sex), positive associations were found between higher adherence to the EAT-Lancet diet, and to the MeDi in relation to cortical thickness in both hemispheres (Figure 3, Table S4).

A higher adherence to the EAT-Lancet diet was associated with higher total mean cortical thickness (β : 0.012 [95% CI: 0.004, 0.019], p : 0.002, FDR adjusted p : 0.009), and thicker cortex in AD-signature regions (β : 0.011 [95% CI: 0.002, 0.020], p : 0.012, FDR adjusted p : 0.043) (Table 2). These associations were found also when cardiovascu-

TABLE 1 Characteristics of dementia-free participants from the Gothenburg H70 Birth Cohort Study

Parameter	Total sample N = 615 Median (IQR)	Women N = 334 Median (IQR)	Men N = 281 Median (IQR)	p-value
EAT-Lancet score (0–42)	22 (20, 25)	23 (21, 25)	22 (19, 23)	<0.001
Mediterranean score (0–9)	5 (3, 6)	5 (3, 6)	5 (3, 6)	0.691
Alcohol intake (gram/day)	8.5 (2.3, 17.9)	6.4 (1.7, 12.7)	11.7 (4.4, 22.5)	<0.001
MMSE score (0–30)	29 (29, 30)	30 (29, 30)	29 (29, 30)	0.191
Global cognitive composite score (z-score) ^a	0.155 (–0.288, 0.564)	0.208 (–0.232, 0.578)	0.096 (–0.311, 0.513)	0.136
Brain age gap (years) ^b	0.40 (–0.50, 1.40)	0.50 (–0.50, 1.50)	0.20 (–0.50, 1.30)	0.209
	Mean (SD)	Mean (SD)	Mean (SD)	
Age (years)	70.5 (0.3)	70.5 (0.2)	70.5 (0.3)	0.349
Predicted brain age (years)	71.5 (1.8)	71.5 (1.8)	71.4 (1.9)	0.548
Total mean cortical thickness (mm)	2.35 (0.08)	2.36 (0.07)	2.34 (0.08)	0.003
AD-signature cortical thickness (mm) ^c	2.72 (0.09)	2.72 (0.09)	2.72 (0.10)	0.671
Hippocampus volume (adjusted for total intracranial volume, mm ³)	3920 (329)	3921 (301)	3920 (360)	0.972
BMI (kg/m ²)	25.7 (4.2)	25.6 (4.7)	25.8 (3.6)	0.450
Energy intake (kcal/day)	2162 (517)	1993 (451)	2364 (518)	<0.001
	N (%)	N (%)	N (%)	
CSVD score (0–3) ^d				0.205
0	386 (63)	211 (64)	175 (62)	
1	157 (25)	91 (27)	66 (24)	
2	53 (9)	23 (7)	30 (11)	
3	17 (3)	7 (2)	10 (4)	
Diabetes (yes)	51 (8)	20 (6)	31 (11)	0.023
Hypertension (≥140/90 mmHg)	424 (69)	237 (71)	187 (67)	0.239
APOE ε4 (carrier)	200 (33)	97 (35)	103 (32)	0.436
Physical activity (regular physical activity)	519 (85)	280 (85)	239 (85)	0.792
Education				<0.001
Compulsory primary education	40 (7)	13 (4)	27 (9)	
Secondary education	270 (44)	175 (52)	95 (34)	
Higher education	305 (50)	146 (44)	159 (57)	
Smoking (non-smoking)	570 (93)	309 (93)	261 (93)	0.966

Notes: There were missing data for cerebral small vessel disease (CSVD) for two participants, global cognitive composite score for one participant, Mini-Mental State Examination (MMSE) for two participants, physical activity level for four participants, smoking status for one participant, diabetes data for one participant, and apolipoprotein E (APOE) ε4 status for 14 participants. The student's independent *t*-test was performed to compare age, brain age, total mean cortical thickness, AD-signature cortical thickness, hippocampal volume, body mass index (BMI), and estimated energy intake between women and men. The Mann–Whitney *U* test was performed to compare the dietary scores, MMSE scores, cognitive performance, BAG, and alcohol intake. The chi-squared test was performed to compare CSVD burden, educational level, physical activity level, smoking status, diabetes, hypertension, and APOE ε4 status between women and men.

^aThe global cognitive composite score (z-score) was derived from eight cognitive tests covering five cognitive domains: executive function, perceptual speed, verbal fluency, episodic memory, and visuospatial abilities.

^bBrain age gap (BAG) is the difference between chronological age and predicted brain age.

^cAlzheimer's disease (AD)-signature: Averaging cortical thicknesses of entorhinal, inferior temporal, middle temporal, and fusiform regions, adjusted for surface area.

^dThe global cerebral small vessel disease (CSVD) score ranged from 0 (no cerebrovascular burden) to 3 (high cerebrovascular burden), including measures of white matter hyperintensities, cerebral microbleeds, enlarged perivascular spaces in basal ganglia, and lacunes.

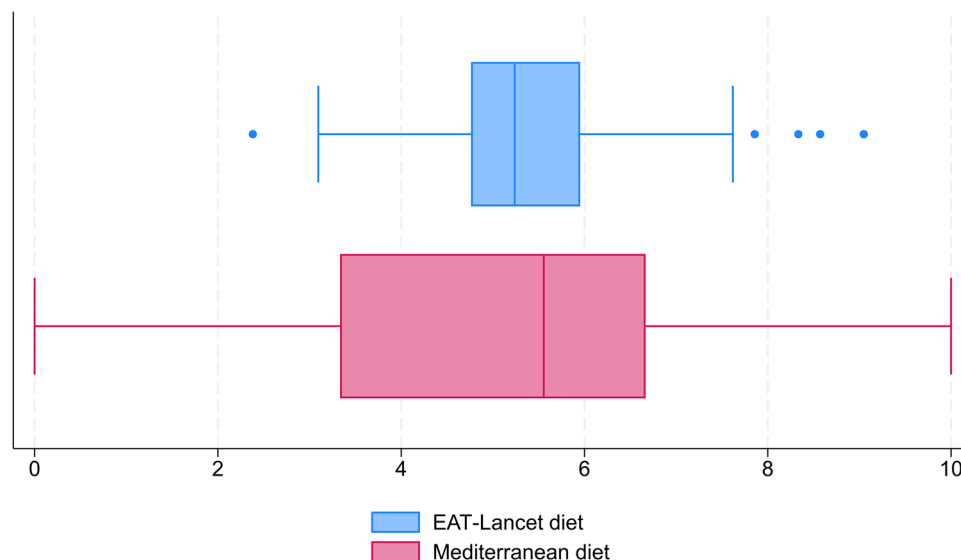


FIGURE 2 Adherence to the EAT-Lancet diet and the Mediterranean diet by 10% in increment score. The scores were transformed for comparability by dividing the EAT-Lancet diet score (range 0–42) by 4.2, and the Mediterranean diet score (range 0–9) by 0.9

lar risk factors (BMI, hypertension, and diabetes) were excluded from the models (Table S5). A positive association between the MeDi and total mean cortical thickness was detected in the basic model (adjusted by sex). However, this association did not remain statistically significant when education, lifestyle, and cardiovascular risk factors were added to the model, and there was no evidence of an association between the MeDi and cortical thickness in AD-signature regions (Table 2, Table S5).

3.2.2 | Hippocampal volume

No evidence of an association between the EAT-Lancet diet and hippocampal volume, or between the MeDi and hippocampal volume was detected (Table 2, Table S5).

3.2.3 | BAG

There was evidence of an association between higher adherence to the MeDi and lower BAG (younger appearing brain) in the basic model (Table S5). However, this association did not remain statistically significant when education, lifestyle, and cardiovascular risk factors were added to the model (Table 2, Table S5). Nor was there any evidence of an association between the EAT-Lancet diet and BAG (Table 2, Table S5).

3.2.4 | CSVD

There was no evidence of an association between the EAT-Lancet diet and CSVD burden, or between the MeDi and CSVD burden (Table 2, Table S5).

3.2.5 | Cognitive performance

There was an association between higher adherence to the MeDi and better cognitive performance (β : 0.035 [95% CI: 0.011, 0.060], p : 0.005, FDR adjusted p : 0.022) (Table 2). This association was found also when cardiovascular risk factors (BMI, hypertension, and diabetes) were excluded from the model (Table S5). No association was detected between the EAT-Lancet diet and cognitive performance in the total population (Table 2, Table S5).

3.2.6 | Sex-related differences

Stratified by sex, the unadjusted surface group analyses showed positive associations between the EAT-Lancet diet and cortical thickness in both hemispheres among men, but no evidence of an association was detected among women (Figure 3, Table S4). Additionally, positive associations between the MeDi and cortical thickness were found in both hemispheres among men, and in the right hemisphere among women (Figure 3, Table S4).

There was evidence of an interaction between sex and the EAT-Lancet diet in relation to total mean cortical thickness (p : 0.040). Among men, a higher adherence to the EAT-Lancet diet was associated with higher total mean cortical thickness (β : 0.020 [95% CI: 0.008, 0.032], p : 0.001, FDR adjusted p : 0.013), but there was no evidence of an association among women (Table 3). There was evidence of an interaction between sex and the MeDi in relation to CSVD burden (p : 0.032), but no association between the MeDi and CSVD was found among either women or men (Table 3). No other evidence of sex*dietary score interactions was detected in relation to the MRI measures or cognitive performance. The results from the analyses performed stratified by sex, can be found in Table 3 and Table S6.

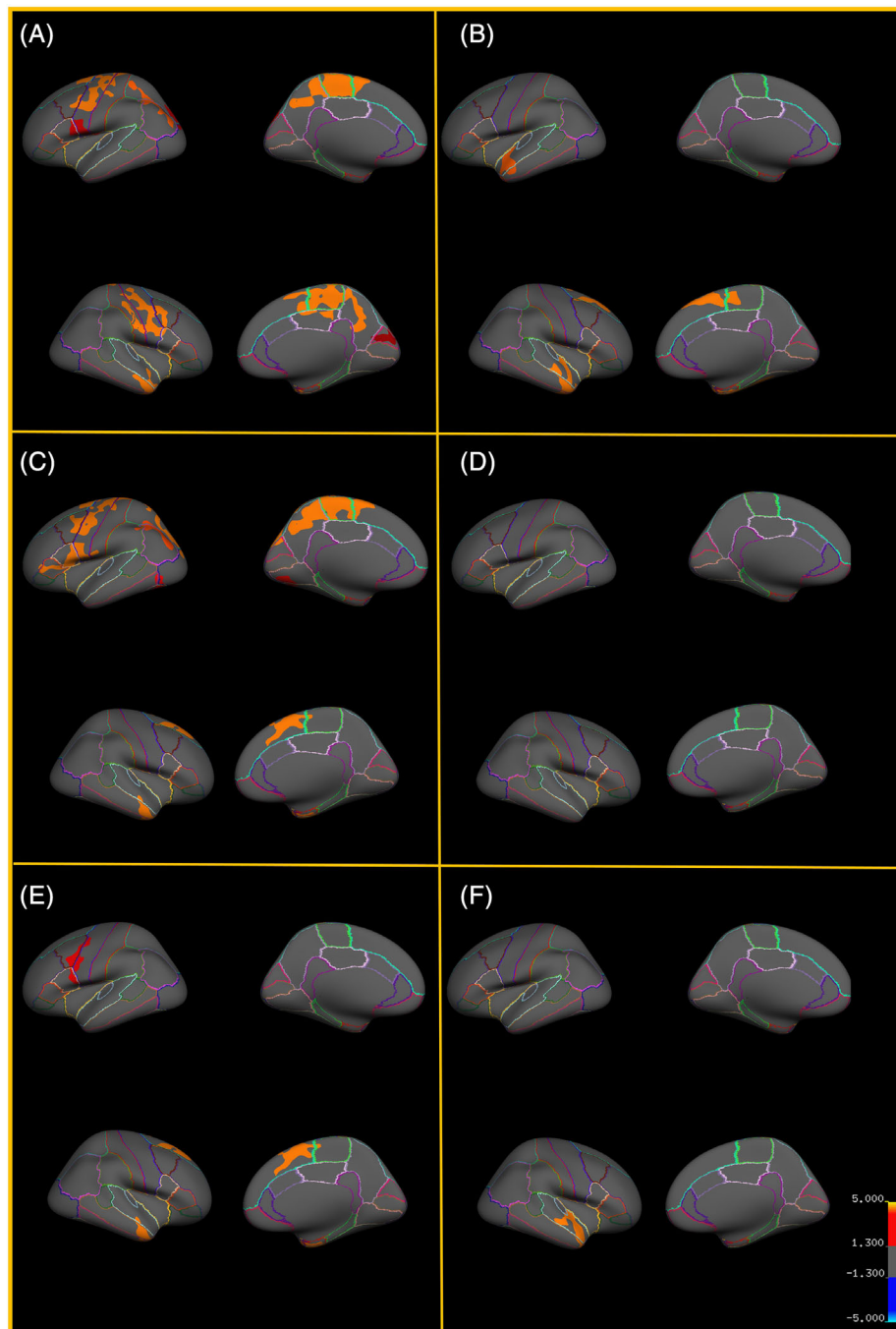


FIGURE 3 Adherence to the EAT-Lancet diet (A) and the Mediterranean diet (B) in relation to cortical thickness, shown on the inflated cortical surface of the left hemisphere (top row) and the right hemisphere (bottom row). Warm colors indicate positive associations (orange/red), and cold colors have negative associations (blue). The analyses were adjusted for sex. (C) Associations between the EAT-Lancet diet and cortical thickness among men. (D) Associations between the EAT-Lancet diet and cortical thickness among women (unadjusted models). (E) Associations between the Mediterranean diet and cortical thickness among men. (F) Associations between the Mediterranean diet and cortical thickness among women (unadjusted models). Data from the analyses can be found in Table S4

3.2.7 | Sensitivity analyses

The associations between the EAT-Lancet diet and the MRI measures and cognitive performance remained when the models were adjusted for alcohol consumption (Table S7).

3.2.8 | Additional analyses

There was no evidence of an interaction between either diet and APOE $\epsilon 4$ status in relation to the brain health markers (Table S8). In the analyses performed stratified by APOE $\epsilon 4$ status (carrier/non-carrier),

TABLE 2 Associations of the EAT-Lancet diet and the Mediterranean diet with neuroimaging biomarkers and cognitive function

N = 615			
Total mean cortical thickness	β (95% CI)	p-value	Adjusted p-value ^f
EAT-Lancet diet	0.012 (0.004, 0.019)	0.002	0.009
Mediterranean diet	0.003 (−0.001, 0.006)	0.121	0.233
AD-signature cortical thickness ^a	β (95% CI)	p-value	
EAT-Lancet diet	0.011 (0.002, 0.020)	0.012	0.043
Mediterranean diet	0.003 (−0.001, 0.007)	0.109	0.226
Hippocampal volume ^b	β (95% CI)	p-value	
EAT-Lancet diet	6.96 (−23.55, 37.48)	0.654	0.763
Mediterranean diet	1.78 (−12.22, 15.77)	0.803	0.854
Brain age gap ^c	β (95% CI)	p-value	
EAT-Lancet diet	−0.118 (−0.288, 0.052)	0.174	0.314
Mediterranean diet	−0.060 (−0.139, 0.018)	0.129	0.240
Cerebral small vessel disease ^d	OR (95% CI)	p-value	
EAT-Lancet diet	0.96 (0.79, 1.17)	0.691	0.783
Mediterranean diet	1.05 (0.96, 1.14)	0.318	0.494
Cognitive performance ^e	β (95% CI)	p-value	
EAT-Lancet diet	0.023 (−0.031, 0.077)	0.399	0.558
Mediterranean diet	0.035 (0.011, 0.060)	0.005	0.022

Notes: Linear regression β -coefficients or ordinal logistic regression odds ratio (OR) with 95% confidence intervals (CIs) are presented. The analyses were adjusted for sex, education, smoking, physical activity level, BMI, hypertension and diabetes. There were missing data for: cerebral small vessel disease (CSVD) for two participants, global cognitive composite score for one participant, physical activity level for four participants, smoking status for one participant, and diabetes data for one participant. In total, there were six participants with missing data on potential confounders.

^aAlzheimer's disease (AD)-signature: Averaging cortical thicknesses of entorhinal, inferior temporal, middle temporal, and fusiform regions, adjusted for surface area, measured in mm.

^bHippocampal volume was adjusted for total intracranial volume, measured in mm³.

^cBrain age gap (BAG) is the difference in years between chronological age and predicted biological age. A negative value indicates a biologically younger brain, and a positive value a biological older brain, compared to chronological age.

^dThe CSVD score ranged from 0 (no cerebrovascular burden) to 3 (high cerebrovascular burden).

^eThe global cognitive composite score (z-score) was derived from eight cognitive tests covering five cognitive domains: executive function, perceptual speed, verbal fluency, episodic memory, and visuospatial abilities.

^fFalse discovery rate (FDR) correction was applied to explore potential Type 1 errors.

we found associations between higher adherence to the EAT-Lancet diet and higher total mean cortical thickness among both $\epsilon 4$ carriers and non-carriers, and thicker cortex in AD-signature regions among $\epsilon 4$ non-carriers. Additionally, we found an association between higher adherence to the EAT-Lancet diet and lower BAG (younger appearing brain) among APOE $\epsilon 4$ carriers (Table S8). There were associations between higher adherence to the MeDi and thicker cortex in AD-signature regions, and higher cognitive performance among APOE $\epsilon 4$ non-carriers, while there was an association between higher adherence to the MeDi and lower BAG (younger appearing brain) among APOE $\epsilon 4$ carriers (Table S8). After FDR correction, only the association between the EAT-Lancet diet and total mean cortical thickness among APOE $\epsilon 4$ carriers remained statistically significant (β : 0.016 [95% CI: 0.005, 0.028], p : 0.006, FDR adjusted p : 0.037). There was a borderline association between higher adherence to the MeDi and thicker cortex in AD-signature regions among APOE $\epsilon 4$ non-carriers after FDR correction (β : 0.007 [95% CI: 0.002, 0.012], p : 0.009, FDR adjusted p : 0.053).

Associations between the potential confounders and the brain health markers can be found in Table S9.

4 | DISCUSSION

In this cross-sectional study of dementia-free 70-year-olds, both the EAT-Lancet diet and the MeDi were associated with markers of brain health. Specifically, a higher adherence to the EAT-Lancet diet was associated with higher total mean cortical thickness and thicker cortex in regions typically affected in early AD. Moreover, we found associations between higher adherence to the MeDi and thicker cortex and lower (younger) predicted brain age, but these associations did not remain statistically significant when the models were adjusted for education, lifestyle, and cardiovascular risk factors. Additionally, the results confirm previous research linking higher adherence to the MeDi with better cognitive performance. We found no associations between either diets and CSVD burden or hippocampal volume.

TABLE 3 Associations of the EAT-Lancet diet and the Mediterranean diet with neuroimaging biomarkers and cognitive function among men and women

Men, n = 281			
Women, n = 334			
Total mean cortical thickness	β (95% CI)	p-Value	Adjusted p-value^f
EAT-Lancet diet			
Men	0.020 (0.008, 0.032)	0.001	0.013
Women	0.005 (−0.004, 0.013)	0.296	0.558
Mediterranean diet			
Men	0.003 (−0.002, 0.009)	0.208	0.417
Women	0.002 (−0.002, 0.006)	0.418	0.633
AD-signature cortical thickness^a	β (95% CI)	p-Value	
EAT-Lancet diet			
Men	0.019 (0.004, 0.034)	0.012	0.075
Women	0.004 (−0.007, 0.014)	0.465	0.674
Mediterranean diet			
Men	0.004 (−0.003, 0.010)	0.231	0.438
Women	0.002 (−0.003, 0.007)	0.348	0.580
Hippocampal volume^b	β (95% CI)	p-Value	
EAT-Lancet diet			
Men	0.62 (−52.25, 53.48)	0.982	0.983
Women	6.70 (−29.96, 43.36)	0.719	0.816
Mediterranean diet			
Men	0.78 (−22.84, 24.40)	0.948	0.958
Women	2.00 (−15.02, 19.01)	0.818	0.879
Brain age gap^c	β (95% CI)	p-Value	
EAT-Lancet diet			
Men	−0.127 (−0.393, 0.140)	0.350	0.571
Women	−0.096 (−0.319, 0.127)	0.399	0.631
Mediterranean diet			
Men	−0.103 (−0.222, 0.015)	0.087	0.232
Women	−0.014 (−0.118, 0.090)	0.790	0.868
Cerebral small vessel disease^d	OR (95% CI)	p-Value	
EAT-Lancet diet			
Men	0.88 (0.65, 1.19)	0.404	0.631
Women	1.06 (0.82, 1.37)	0.644	0.785
Mediterranean diet			
Men	0.97 (0.85, 1.09)	0.674	0.813
Women	1.12 (0.99, 1.26)	0.058	0.207
Cognitive performance^e	β (95% CI)	p-Value	
EAT-Lancet diet			
Men	−0.052 (−0.140, 0.036)	0.246	0.481
Women	0.071 (0.004, 0.139)	0.038	0.146

(Continues)

TABLE 3 (Continued)

Cognitive performance ^e	β (95% CI)	<i>p</i> -Value	
Mediterranean diet			
Men	0.033 (−0.006, 0.072)	0.099	0.241
Women	0.037 (0.006, 0.068)	0.020	0.106

Notes: Linear regression β -coefficients or ordinal logistic regression OR with 95% confidence intervals are presented. The model was adjusted for education, smoking, physical activity level, body mass index (BMI), diabetes, and hypertension. There was missing data for: cerebral small vessel disease (CSVD) for two participants, global cognitive composite score for one participant, physical activity level for four participants, smoking status for one participant, and diabetes for one participant. In total, there was missing data for six participants.

^aAlzheimer's disease (AD)-signature: Averaging cortical thicknesses of entorhinal, inferior temporal, middle temporal, and fusiform regions, adjusted for surface area, measured in mm.

^bHippocampal volume was adjusted for total intracranial volume, measured in mm³.

^cBrain age gap (BAG) is the difference in years between chronological age and predicted biological age. A negative value indicates a biologically younger brain, and a positive value a biological older brain, compared to chronological age.

^dThe CSVD score ranged from 0 (no cerebrovascular burden) to 3 (high cerebrovascular burden).

^eThe global cognitive composite score (z-score) was derived from eight cognitive tests covering five cognitive domains: executive function, perceptual speed, verbal fluency, episodic memory, and visuospatial abilities.

^fFalse discovery rate (FDR) correction was applied to explore potential Type 1 errors.

The results from previous studies investigating associations between the MeDi and neuroimaging biomarkers (e.g., gray and white matter volume, total brain volume, cortical thickness, hippocampal volume, and WMH) are inconclusive, and associations between the EAT-Lancet diet and neuroimaging biomarkers remain unexplored.^{1,41} In our study, we found associations between both diets and measures of cortical thickness. However, only the associations with the EAT-Lancet diet remained statistically significant after adjustment for education, lifestyle, and cardiovascular risk factors. Furthermore, we found that associations between the EAT-Lancet diet and cortical thickness were driven mainly by men. This may be explained by the differences between men and women in adherence to the EAT-Lancet diet and total mean cortical thickness (both were lower among men than women). There was no difference in adherence to the MeDi between men and women. The construction of the dietary scores could be a partial explanation for this, as the MeDi score is based on sex-specific median cutoffs, while the EAT-Lancet diet has the same score ranges for men and women. Whether the associations between the EAT-Lancet diet and cortical thickness are AD-related is difficult to determine, as associations were found also with other cortical regions. Furthermore, we found no associations with hippocampal volume, a region often affected in the early stages of AD.⁴²

Few studies have explored associations between dietary patterns and BAG, a potential biological marker of resilience.⁴³ An intervention study (mean age 63 years) found that a healthy diet intervention (based on the general American dietary guidelines) was associated with a reduction in BAG (younger appearing brain), suggesting the beneficial effects of a healthy diet on brain health.⁴⁴ In our study, we found a similar direction of association between the MeDi and BAG. However, the association did not remain statistically significant after adjustment for education, lifestyle, and cardiovascular risk factors. Additionally, no association was found between the EAT-Lancet diet and BAG. Nor between either of the diets and CSVD. Notably, most participants had

a low CSVD score (88% with a score of 0–1), indicating an overall low CSVD burden in this population.

Results from our study support previous research linking higher adherence to the MeDi with better cognitive performance.^{45,46} Furthermore, our study is among the few that have examined associations between the EAT-Lancet diet and cognitive performance. Previous studies have found links between higher adherence to the diet and better cognitive performance.^{15,47,48} A study from the Singapore Chinese Health Study found that higher adherence to the EAT-Lancet diet at baseline (mean age 53 years) was associated with a lower risk of poor cognitive function at follow-up (mean age 73 years).⁴⁷ A study from the Brazilian longitudinal study of adult health found that among participants ≥ 60 years (baseline mean age 51.6 years, median follow-up time was 8 years), higher adherence was associated with slower memory decline.⁴⁸ A Dutch study including cognitively healthy community-dwelling older adults (>65 years, mean age 72 years), found that higher adherence to the EAT-Lancet diet was associated with better global cognitive functioning, and slower cognitive decline over a 2-year period.¹⁵ In our study, there was no evidence of an association between the EAT-Lancet diet and cognitive performance in the total population. Nor did we find evidence of an interaction between the EAT-Lancet diet and sex in relation to cognitive performance.

In the analyses performed stratified by APOE $\epsilon 4$ status, we found evidence indicating the beneficial effects of both diets in relation to markers of brain health among both APOE $\epsilon 4$ carriers and non-carriers. However, we found no evidence of an interaction between the diets and APOE $\epsilon 4$ status in relation to the brain health markers, and only the association between the EAT-Lancet diet and total mean cortical thickness among $\epsilon 4$ carriers remained after FDR correction. Thus, the results indicating a potentially modifying effect of APOE $\epsilon 4$ status should be interpreted with caution.

We can only speculate on why the EAT-Lancet diet was associated with the measures of cortical thickness, while the MeDi was associated with cognitive performance. Potentially, we may have found associa-

tions between the EAT-Lancet diet and cortical thickness that have not yet influenced cognitive performance. Furthermore, due to the cross-sectional design of the study, causality and the direction of associations cannot be determined. Thus, we cannot rule out the possibility of a reversed association between the MeDi and cognitive performance. That is, those with higher cognitive performance may make healthier dietary choices in line with the more well-established MeDi. However, while there were differences in the impact of the diets, the results from our study indicate similar directions of associations between the diets in relation to the MRI measures and cognitive performance. Potentially, the inclusion of alcohol in the MeDi score could be one reason for the differences in results. However, when we adjusted the EAT-Lancet models for alcohol, the results remained. Another difference is that the EAT-Lancet diet score considered sugar intake, a dietary factor that has been linked to an increased risk of dementia and cognitive decline among older adults.^{49,50} A third factor that could affect the results is the differences in how the dietary scores were constructed. The EAT-Lancet score is categorized based on predefined food intake levels, while the MeDi score was categorized based on the median population intake (wider range of adherence). The methodology of constructing dietary adherence scores may also be a factor that potentially could explain inconsistencies in results from previous research.^{51,52}

Although the MeDi and similar diets, such as the Dietary Approaches to Stop Hypertension (DASH) and the Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND),⁵³ are similar to the EAT-Lancet diet by emphasizing plant-based foods, they were not designed to achieve global equity in access to healthy food, improve food production and environmental sustainability as the EAT-Lancet diet is.⁹ The intake ranges in the EAT-Lancet reference diet allows the diet to be adaptable to diverse culinary traditions. Thus, similarities to the MeDi may vary between populations globally. However, the EAT-Lancet diet is generally more restrictive in animal-based foods compared to the MeDi. Concerns have been raised that high adherence to the EAT-Lancet diet may have negative consequences on the brain by having a too severe limit on animal products (e.g., nutrient deficiencies).⁵⁴ In our study, we found no indications that adhering to the EAT-Lancet diet would be detrimental to the brain. However, there were few participants with a score close to perfect adherence to the EAT-Lancet diet.

Measuring dietary adherence is complex, and there is a wide range of food and nutrient combinations that could impact risk through several metabolic pathways. It has been suggested that pathways linking diet with cognitive impairment in old age may involve inflammatory and cardiometabolic factors (e.g., glucose and lipid metabolism, and hypertension).^{55,56} In a previous study on the same sample as in our study, we found that higher adherence to a high-protein and alcohol dietary pattern (Western-style) was associated with overall thinner cortex, and thinner cortex in AD-signature regions.⁵⁷ Altogether, the results from this and the previous study indicate that the impact of dietary patterns may vary depending on food combinations, potentially due to synergistic or additive effects of nutrients and other bioactive food components on metabolic pathways.⁵⁸ Additionally, previous studies have found that the combined effect of education and lifestyle

factors such as diet, physical activity, and smoking may affect the risk of cognitive impairment differently compared to individual factors.^{6,59} The results from our study support this notion, as only the more robust associations between the diets and the brain health markers remained in the models adjusted by education, lifestyle, and cardiovascular risk factors.

4.1 | Strengths and limitations

Strengths of this study are the comprehensive dietary, cognitive, and MRI examinations performed by trained staff on a systematically selected and well-characterized population-based sample of 70-year-olds. However, due to the cross-sectional design of the study, causality and the direction of associations cannot be determined. Furthermore, as in all observational studies, residual confounding cannot be entirely ruled out. Potential measurement errors may have been limited by the use of trained and specialized research staff that performed the interviews, health examinations and diagnostics. A previous study showed that the MRI sample was slightly healthier and higher educated than the non-MRI sample,⁶⁰ which potentially could have weakened the detection of an association. Additionally, the comparability of the transformed dietary scores (10% increment score) may have been limited by methodological differences in constructing the scores. However, both the MeDi score and the EAT-Lancet diet score were constructed based on scores previously found to measure adherence to the diets,^{21,51} and while there is an overlap in the food groups between the diets, we believe that the scores can capture differences in the diets. Finally, the proportion of participants born outside Sweden (15.5%) was slightly lower than that reported among 70-year-olds in Gothenburg (19.5%). Additionally, non-Swedish speakers were excluded from participation ($n = 53$).²³ Consequently, the generalizability of the results may be limited to populations with characteristics similar to those of the 70-year-olds examined in this study. Nonetheless, the mechanistic insights may be applicable also to other groups.

5 | CONCLUSION

This study linked higher adherence to both the EAT-Lancet diet and the MeDi with markers of brain health. A higher adherence to the EAT-Lancet planetary health diet was associated with higher total mean cortical thickness, and thicker cortex in AD-signature regions, while a higher adherence to the MeDi was associated with better cognitive performance. We found no indications of detrimental effects of adhering to the EAT-Lancet planetary health diet in relation to neuroimaging biomarkers or cognitive performance.

AUTHOR CONTRIBUTIONS

Conception and design of the study: Jessica Samuelsson, Anna Stubben-dorff, and Anna Marseglia. *Acquisition of data:* Ingmar Skoog, Lina Rydén, Johan Skoog, Olof Lindberg, Sarah Shams, Caroline Darta-tora, Silke Kern, and Eric Westman. *Interpretation of data:* Jessica Samuelsson, Anna Stubben-dorff, Anna Marseglia. *Data analysis:* Jessica

Samuelsson. *Drafting the article:* Jessica Samuelsson. *Revising the article critically for important intellectual content:* Anna Stubbendorff, Anna Marseglia, Olof Lindberg, Caroline Dartora, Nira Cedres, Sarah Shams, Silke Kern, Lina Rydén, Johan Skoog, Eric Westman, and Ingmar Skoog. All authors read and approved the manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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CONFLICT OF INTEREST STATEMENT

Silke Kern has served at scientific advisory boards, speaker, and/or as a consultant for Roche, Eli Lilly, Geras Solutions, Optoceutics, Biogen, Eisai, Merry Life, Triolab, Novo Nordisk, and Bioarctic, unrelated to the

present study content. The remaining authors have nothing to disclose. Author disclosures are available in the [Supporting Information](#).

DATA AVAILABILITY STATEMENT

Deidentified data from this study will be made available upon request with investigator support, after approval of a proposal, and with a signed data access agreement. For data access, please contact the corresponding author at jessica.samuelsson@neuro.gu.se.

CONSENT STATEMENT

The study was approved by the Regional Ethics Review Board in Gothenburg, Sweden (Reference number 869-13). The participants gave written informed consent to participate in the examinations according to the Helsinki declaration.

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SUPPORTING INFORMATION

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