

BMJ Open Associations of lifestyle and vascular risk factors with Alzheimer's brain biomarker changes during middle age: a 3-year longitudinal study in the broader New York City area

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ABSTRACT

Objective To investigate the associations between lifestyle and vascular risk factors and changes in Alzheimer's disease (AD) biomarkers (beta-amyloid load via ¹¹C-PiB PET, glucose metabolism via ¹⁸F-FDG PET and neurodegeneration via structural MRI) and global cognition in middle-aged asymptomatic participants at risk for AD.

Design Prospective, longitudinal.

Setting The study was conducted at New York University Langone/Weill Cornell Medical Centres in New York City.

Participants Seventy cognitively normal participants from multiple community sources, aged 30–60 years with lifestyle measures (diet, intellectual activity and physical activity), vascular risk measures and two imaging biomarkers visits over at least 2 years, were included in the study.

Outcome measures We examined MRI-based cortical thickness, fluoro-deoxy-glucose (FDG) glucose metabolism and PiB beta-amyloid in AD-vulnerable regions. A global cognitive z-score served as our summary cognition measure. We used regression change models to investigate the associations of clinical, lifestyle and vascular risk measures with changes in AD biomarkers and global cognition.

Results Diet influenced changes in glucose metabolism, but not amyloid or cortical thickness changes. With and without accounting for demographic measures, vascular risk and baseline FDG measures, lower adherence to a Mediterranean-style diet was associated with faster rates of FDG decline in the posterior cingulate cortex ($p \leq 0.05$) and marginally in the frontal cortex ($p = 0.07$). *None of the other lifestyle variables or vascular measures showed associations with AD biomarker changes.* Higher baseline plasma homocysteine was associated with faster rates of decline in global cognition, with and without accounting for lifestyle and biomarker measures ($p = 0.048$). None of the lifestyle variables were associated with cognition.

Conclusions Diet influenced brain glucose metabolism in middle-aged participants, while plasma homocysteine explained variability in cognitive performance. These findings suggest that these modifiable risk factors affect

Strengths and limitations of this study

- A key strength of this study is the availability of healthy, cognitively normal middle-aged individuals with multiple lifestyle and vascular risk measures and neuroimaging scans at least 2 years apart.
- Another strength of our study was our ability to look at diet, intellectual and physical activity and vascular risk factors and our statistical model enabled us to assess these risk factors simultaneously.
- Given the participants were cognitively normal and between ages 30 and 60 years, it is unlikely that we would see substantial changes in amyloid burden, an age-dependent phenomenon and associated cognitive changes without lifestyle enrichment strategies this early in life.
- We caution that we carefully screened the study participants to include healthy individuals without severe cardiac or cerebrovascular disease, which limits the generalisability of our results to the entire population.

AD risk through different pathways and support further investigation of risk reduction strategies in midlife.

INTRODUCTION

Unless effective strategies for prevention are found, the prevalence of Alzheimer's disease (AD), the most common form of dementia that affects nearly 34 million people worldwide, is expected to triple by 2050.¹

Leading a healthy lifestyle in combination with strategies to reduce vascular disease risk is increasingly viewed as preventative against cognitive decline and dementia.² Findings from population-attributable risk models estimate that one in every three AD cases may be accounted for by modifiable risk factors,

such as midlife hypertension, obesity, diabetes and several lifestyle factors.^{3 4}

Most studies in this field have focused on the effects of lifestyle and cardiovascular factors on cognitive decline or incidence of dementia as outcome measures.⁵ However, there is evidence that AD pathophysiology develops up to 20 years upstream of cognitive symptoms,^{6 7} namely in midlife. As such, studies investigating biological markers of AD are needed to determine whether lifestyle and vascular risk impact the emergence and progression of brain AD endophenotype.

Studies involving older adults, with or without mild cognitive impairment, have found both positive and null associations between intellectual and physical activity and AD biomarkers.^{8–14} The mixed results of these studies may be due to not taking diet or vascular risk into account, and focusing on elderly populations. Of those that included cognitively normal, middle-aged individuals, physical activity has been shown to attenuate age-related brain biomarker changes,¹⁵ and insulin resistance has been positively associated with cerebral hypometabolism, atrophy and amyloid deposition^{16–18} and negatively related to regional cerebral blood flow.¹⁹ We observed that adherence to a Mediterranean diet (MeDi) was positively associated with MRI-based cortical thickness in middle-aged individuals at cross-section, after accounting for intellectual activity, physical activity and vascular risk measures.²⁰

Herein, we present a 3-year multimodality brain imaging study aimed at assessing the association of multiple lifestyle and vascular risk factors with change in AD biomarkers, as measured by amyloid-beta (A β) deposition on ¹¹C-PiB PET, glucose metabolism via ¹⁸F-FDG PET and neurodegeneration via MRI, in a cohort of cognitively normal, middle-aged individuals at risk for AD.

METHODS

Participants

Study participants were recruited from a longitudinal brain imaging study conducted at New York University (NYU) Langone School of Medicine and Weill Cornell Medical College (WCMC) between 2010 and 2016. The study aimed to examine risk factors for AD among clinically and cognitively normal middle-aged adults. Details about the study design have previously been published.^{21 22} Briefly, participants were derived from multiple community sources, including individuals interested in research participation and family members and caregivers of impaired patients.

All participants received clinical, laboratory, neuropsychological and brain imaging exams including MRI and FDG PET and PiB PET at baseline and at least 2 years later. To be included in this study, participants had to be aged 30–60 years at baseline, with education \geq 12 years, Clinical Dementia Rating=0, Global Deterioration Scale \leq 2, Mini Mental State Examination \geq 27, Hamilton

Depression Scale $<$ 16 and normal cognitive test performance for age and education.²³ Those with past or current medical conditions that can affect brain structure or function (ie, cardiovascular disease, stroke, diabetes, head trauma, any neurodegenerative diseases, depression, hydrocephalus, intracranial mass and infarcts on MRI) and those taking psychoactive medications were excluded.

A family history of AD that included at least one first-degree relative whose AD onset was after age 60 years was elicited using standardised questionnaires.²² Apolipoprotein E (APOE) genotypes were determined using standard quantitative PCR procedures.²² Participants were grouped as positive versus negative family history, and as APOE4 carriers versus non-carriers. Participants with a family history of AD and/or APOE4 positivity were considered at increased risk for AD.

Standard protocol approvals, registrations and patient consents

All participants provided informed consent to participate in this study.

Patient and public involvement

Patients and or public were not involved in the planning or execution of the study. Results were not disseminated to study participants.

Global cognition measure

The neuropsychological battery of tests was previously described.²³ At both time points, we assessed three cognitive domains from the following tests: memory (immediate and delayed recall of a paragraph and immediate and delayed recall of paired associates), executive function (Wechsler Adult Intelligence Scale (WAIS) digit symbol substitution) and language (WAIS vocabulary).

We computed a global cognitive summary score by first z-scoring each measure within each domain and averaging each component of the three domains listed above. Global cognition, calculated as the average of the composite memory, executive function and language variables at each time point, was used as an outcome variable.

Vascular risk-related measures

Vascular risk factors included in the model were: a) body mass index (BMI); b) presence of hypertension, conservatively based on either current antihypertensive treatment or blood pressure assessments; c) plasma cholesterol and/or homocysteine, obtained after overnight fasting using standard laboratory procedures and d) insulin resistance, measured with the Quantitative Insulin Sensitivity Check Index (QUICKI)²⁴ derived from fasting plasma insulin (via ELISA kit) and fasting plasma glucose, where lower QUICKI scores reflect greater insulin resistance.

Lifestyle variables

Dietary data regarding average food consumption over the prior year were obtained using the Harvard Willett semi-quantitative food frequency questionnaire.^{20 25}

Briefly, food items were categorised into 30 food groups based on similarities in food and nutrient composition, and intake (g/day) of each food group was calculated by summing the intakes of food group items. For the construction of MeDi scores, we first regressed caloric intake and calculated the derived residuals of daily intake for each of the following categories: dairy, meat, fruits, vegetables, legumes, cereals and fish. Individuals were assigned a value of one for each beneficial component (fruits, vegetables, legumes, cereals and fish) whose consumption was at or above the sex-specific median; a value of one for each harmful component (meat and dairy products) whose consumption was below the median; a value of one for a ratio of monounsaturated fats to saturated fats above the median and a value of one for mild-to-moderate alcohol consumption. These values were summed to generate a MeDi score, with a higher score indicating higher MeDi adherence.

The Minnesota Leisure Time Physical Activity questionnaire was used to estimate physical activity.²⁶ For each activity, information was collected on the frequency and duration of engagement, which was multiplied by an activity-specific intensity code indicating calorie expenditure. The activity-dependent scores were summed to obtain the overall intensity of physical activity per person during the last 12 months and converted to metabolic equivalents.

Intellectual activity throughout life was assessed using a validated 25-item interview in which participants were asked to report how often they engaged in common cognitively demanding activities with minimal dependence on socioeconomic statuses, such as reading books or newspapers, writing letters or e-mails, going to the library and playing games, at different ages.^{14 27} Previous studies have described this instrument in detail and reported high internal consistency and positive associations of intellectual activity with educational and cognitive performance.²⁷

AD biomarkers

All subjects received MRI, PiB PET and FDG PET scans at least 2 years apart following standardised procedures.^{21 28 29}

Participants received 3T volumetric T1-MPRAGE scans at both time points. Freesurfer V.5.3 with a longitudinal processing pipeline was used to obtain entorhinal (EC) and posterior cingulate cortex (PCC) thickness on longitudinal MRI scans.³⁰ These regions of interest (ROIs) were chosen based on previous reports of AD-related and lifestyle-related changes at the preclinical AD stages.^{20 31} Total intracranial volumes (TIV) were also estimated and used as a covariate.

PET images were acquired with PET/CT scanners operating in three-dimensional mode and analysed using a fully automated image-processing pipeline.^{32 33} Statistics on image voxel values were extracted from automatically labelled cortical regions of interest using the automated anatomic labelling atlas.³⁴ We selected PCC/precuneus as the target AD-related region of interest and frontal cortex

(including prefrontal and medial frontal regions) as the target ageing-related region.³⁵ For each region of interest, PiB uptake was divided by cerebellar grey matter uptake, and FDG uptake was normalised by the global activity.

Statistical analysis

Statistical analyses were performed using Stata, V.13. We conducted two types of analyses to examine the associations of age, sex, APOE4 genotype, lifestyle variables (diet, intellectual activity and physical activity) and vascular risk variables (BMI, plasma cholesterol, plasma homocysteine, hypertension and insulin resistance) with AD biomarkers and cognition.

The first analysis consisted of a partial correlation analysis to evaluate the direct associations between the predictors and dependent variables at baseline and over time. We estimated these associations using partial Pearson's correlations (r_s) and adjusted for the effects of age, gender and APOE status. The PIB variables had skewed distributions and were log transformed, and MRI measures were adjusted by TIV.

In the second analysis, we used regressed change models³⁶ to evaluate lifestyle and vascular measures as predictors of change in biomarker values and global cognition. Regressed change models, as opposed to difference score models, overcome several of the disadvantages of difference score measures.³⁶ For example, difference scores are often negatively correlated with baseline values and are doubly affected by unreliability and missing data points in the measures.

We considered continuous variables including age (years), education (years), diet, exercise and intellectual activity scores, BMI, QUICKI scores and lab measures. Sex (female vs male) and APOE genotype (presence of either one or two vs absence of $\epsilon 4$ alleles) were used as dichotomous variables with female sex and APOE4 positivity as the reference. Presence or absence of hypertension was used as a dichotomous variable with the absence of the condition used as the reference.

In each model, we predicted regressed change in each outcome measure by running a series of regression models that isolated the effect of our predictors on the outcome measure at follow-up while holding the baseline measures constant. Additionally, the baseline biomarker measures were examined as predictors of change in cognition in addition to the other predictors. For each model, we used a backward elimination procedure to remove non-significant covariates and form the most parsimonious model.

We fit four separate models for each outcome measure:

- ▶ Model 1: full model with all predictor variables included.
- ▶ Model 2: full model with non-significant adjustment variables removed.
- ▶ Model 3: reduced model with lifestyle predictors only, and non-significant adjustment variables removed.
- ▶ Model 4: reduced model with vascular predictors only, and non-significant adjustment variables removed.

Table 1 Clinical and demographic characteristic at baseline

| | |
|---|---------------------|
| Sample size (n) | 70 |
| Age (years) | 49 (8), range 30–60 |
| Female, no. (%) | 48 (69) |
| Education (years) | 16 (2) |
| Caucasians, no. (%) | 56 (80) |
| Positive family history of AD, no. (%) | 47 (67) |
| APOE4 carriers, no. (%) | 27 (39) |
| Positive subjective complaints, no. (%) | 48 (69) |
| Time to follow-up (years) | 3 (1), range 2–3.5 |
| Lifestyle measures | |
| Mediterranean diet scores | 4 (2), range 1–9 |
| Physical activity scores | 9 (5), range 1–37 |
| Intellectual activity scores | 4 (1), range 2–5 |
| Vascular risk measures | |
| Body mass index (kg/m ²) | 25 (4) |
| Presence of hypertension, no. (%) | 10 (14) |
| QUICKI scores | 0.32 (0.03) |
| Plasma cholesterol/HDL ratio | 3.3 (0.8) |
| Plasma homocysteine (µmol/L) | 7.9 (6.2) |
| Neuropsychological measures | |
| Mini Mental State Examination | 29 (1) |
| Paragraph Recall, immediate | 7.2 (2.5) |
| Paragraph Recall, delayed | 9.8 (2.8) |
| Paired Associates Recall, immediate | 6.4 (2.5) |
| Paired Associates Recall, delayed | 7.3 (2.6) |
| Object naming | 55 (9) |
| Design test | 8.1 (2.3) |
| Digit symbol substitution | 66 (13) |
| WAIS vocabulary | 68 (8) |

Values are presented as mean (SD), unless otherwise specified. AD, Alzheimer's disease; APOE, apolipoprotein E; QUICKI, Quantitative Insulin Sensitivity Check Index; WAIS, Wechsler Adult Intelligence Scale.

The resulting unstandardised beta-coefficients (β_s) can be interpreted as partial correlations. All results were considered statistically significant at $p < 0.05$.

RESULTS

Participants

A total of 86 participants completed baseline imaging evaluations. Six participants did not complete the follow-up evaluations. Of the remaining 80 participants, 10 had incomplete lifestyle questionnaires and were excluded. The remaining 70 participants were examined in this study.

Participants' characteristics are shown in [table 1](#). The average age was 49 years, ranging from 30 to 60 years, with 69% of participants being women. While none of

the participants had cognitive impairment, 69% reported subjective memory complaints, as determined using the Global Deterioration Scale.³⁷ Sixty-seven per cent of participants reported a family history of AD and 39% had at least one copy of the APOE4 allele.

Models for prediction of cognitive changes

None of the adjustment variables were associated with cognition at baseline or longitudinally. At baseline, higher intellectual activity was associated with better cognition, with and without adjusting for age, sex and APOE status ($r_s \geq 0.401$, $p < 0.01$; online supplementary tables 1–3).

Longitudinal results are summarised in [table 2](#). After accounting for baseline cognition, higher baseline plasma homocysteine was associated with faster rates of decline in global cognition scores ($p = 0.048$). None of the lifestyle variables were directly associated with cognitive changes.

The baseline biomarkers did not predict cognitive changes, except for a negative non-significant association between baseline FDG uptake in the frontal cortex and faster rates of declines in global cognition ($p = 0.11$). Therefore, including the baseline biomarkers in the models did not significantly shift the relationships between cognition and the lifestyle or vascular variables.

Models for prediction of amyloid accumulation

Baseline results are summarised in online supplementary table 1. None of the clinical, lifestyle or vascular risk variables were associated with baseline PiB uptake.

Longitudinal results are summarised in [table 3](#). APOE4 status was marginally positively associated with faster rates of amyloid deposition in the frontal cortex ($p = 0.084$). None of the other vascular variables were associated with changes in amyloid measures.

Physical activity was marginally negatively associated with faster rates of amyloid changes in the PCC ($p \leq 0.106$), while MeDi adherence was marginally negatively associated with amyloid changes in the frontal cortex in models accounting for lifestyle and vascular factors ($p \leq 0.104$).

Models for prediction of FDG changes

Baseline results are summarised in online supplementary table 2. Among the lifestyle variables, frontal FDG uptake was positively associated with intellectual activity ($r_s = 0.27$, $p = 0.042$). None of the vascular variables showed associations with baseline FDG uptake.

Longitudinal results are summarised in [table 4](#). Older age was marginally associated with increased rates of FDG declines in the frontal cortex ($p = 0.091$), although not in the PCC. None of the other clinical variables were associated with changes in FDG uptake. With and without accounting for baseline FDG uptake, lower MeDi adherence was associated with faster rates of FDG declines in the PCC ($p \leq 0.048$) and marginally in the frontal cortex ($p \leq 0.106$). None of the vascular variables were associated with FDG changes.

Table 2 Prediction of changes in global cognition

| | Model 1* | Model 2† | Model 3‡ | Model 4§ |
|------------------------------|------------------------|------------------------|-----------------------|------------------------|
| Mediterranean diet | -0.012 (0.046) | -0.013 (0.048) | -0.029 (0.046) | |
| Physical activity | 0.001 (0.008) | -0.001 (0.008) | -0.004 (0.008) | |
| Intellectual activity | 0.089 (0.128) | 0.044 (0.128) | 0.103 (0.128) | |
| Plasma homocysteine | -0.068 (0.034) p=0.061 | -0.063 (0.032) p=0.066 | | -0.066 (0.032) p=0.048 |
| Plasma cholesterol | 0.001 (0.002) | 0.001 (0.002) | | 0.001 (0.002) |
| Body mass index | 0.007 (0.014) | 0.006 (0.014) | | 0.006 (0.014) |
| QUICKI scores | 0.343 (3.965) | 0.537 (3.813) | | 0.798 (3.837) |
| Hypertension | -0.080 (0.117) | -0.056 (0.118) | | -0.055 (0.117) |
| Global cognition at baseline | 0.872 (0.132) p<0.001 | 0.827 (0.143) p<0.001 | 0.801 (0.146) p<0.001 | 0.842 (0.132) p<0.001 |
| Sex | -0.023 (0.078) | | | |
| APOE status | 0.104 (0.079) | | | |
| Age | 0.006 (0.012) | | | |
| Time to follow-up | -0.000 (0.000) | | | |
| Constant | -0.097 (0.654) | -0.125 (0.620) | 0.005 (0.068) | -0.167 (0.621) |

Values are presented as unstandardised beta-coefficients (SE). Only significant and marginally significant p values are reported in the table.

*Model 1: full model with all variables examined.

†Model 2: full model without non-significant adjustment variables.

‡Model 4: model with vascular variables only, and without non-significant adjustment variables.

§Model 3: model with lifestyle variables only, and without non-significant adjustment variables.

APOE, apolipoprotein E; QUICKI, Quantitative Insulin Sensitivity Check Index.

Models for prediction of MRI changes

Baseline results are summarised in online supplementary table 3. None of the clinical, lifestyle and vascular risk variables were associated with baseline MRI measures.

Longitudinal results are summarised in table 5. APOE4 status showed a positive, non-significant association with faster EC thickness reduction (p=0.149). None of the other variables were associated with changes in MRI measures.

Discussion

The main findings of this study are as follows: (1) during middle age, MeDi adherence predicts changes in glucose metabolism detected via FDG PET, but not changes in amyloid deposition or cortical thickness, (2) baseline plasma homocysteine was the only predictor of cognitive changes and (3) exercise and intellectual activity did not predict changes in AD biomarkers or cognition. As such, the present findings do not support an association between physical or intellectual activity and brain AD biomarker changes in middle-aged participants, but do contribute support to diet and vascular risk factors playing a role instead.

MeDi adherence predicted changes in FDG PET hypometabolic biomarkers while accounting for possible risk factors such as age, sex, APOE status, vascular measures and physical and intellectual activity. Lower MeDi adherence was associated with faster rates of FDG declines in the PCC, an early site of cerebral glucose utilisation decline in AD.³⁵ Progressive PCC hypometabolism is a well-established finding in at-risk individuals,^{21 38}

and accurately predicts the decline from mild cognitive impairment to AD.³⁵ Our data suggest that the neuro-protective effects of the MeDi may lie in its ability to preserve brain metabolic activity, which may in turn help delay the onset of cognitive impairment.³⁹ Additionally, higher plasma homocysteine, a well-known risk factor for AD,^{40 41} predicted declines in cognition and also showed borderline associations with increased rates of metabolic decline.

Altogether, these data suggest that diet and homocysteine-related vascular risk may influence brain ageing and AD through different, yet to some extent interconnected pathways. Hence, adopting a healthy diet, particularly the MeDi, in combination with vascular risk management in midlife might be protective against future AD.

Hypometabolic changes observed with FDG are believed to emerge downstream to A β accumulation.³¹ While we did not find direct effects of lifestyle or vascular risk factors on A β pathology, lower MeDi adherence was marginally, although non-significantly, associated with faster rates of A β deposition. This suggests that the associations between lower MeDi adherence and increased metabolic declines may be related to emerging A β plaque pathology and/or increasing soluble A β (which is undetectable with PET).

Furthermore, A β deposition in plaques is an age-dependent phenomenon, with 0% of cognitively normal individuals aged between 45 and 49 years testing positive for A β , and just under 6% aged between 50 and 59 years testing positive for A β .⁴² Considering that all our participants

Table 3 Prediction of PiB PET amyloid deposition

| | Model 1* | Model 2† | Model 3‡ | Model 4§ |
|--------------------------------|------------------------|------------------------|------------------------|-----------------------|
| PCC | | | | |
| Mediterranean diet | -0.017 (0.016) | -0.018 (0.017) | -0.011 (0.016) | |
| Physical activity | -0.005 (0.003) p=0.106 | -0.005 (0.003) | -0.005 (0.003) p=0.096 | |
| Intellectual activity | 0.053 (0.053) | 0.021 (0.052) | 0.016 (0.051) | |
| Plasma homocysteine | -0.013 (0.012) | -0.006 (0.012) | | -0.010 (0.012) |
| Plasma cholesterol | -0.002 (0.001) | -0.001 (0.001) | | -0.001 (0.001) |
| Body mass index | -0.004 (0.005) | -0.005 (0.005) | | -0.006 (0.005) |
| QUICKI scores | -1.720 (1.550) | -2.155 (1.581) | | -2.016 (1.575) |
| Hypertension | -0.048 (0.041) | -0.026 (0.037) | | -0.019 (0.036) |
| PCC PiB uptake at baseline | 0.094 (0.238) | 0.194 (0.259) | 0.156 (0.261) | 0.232 (0.252) |
| Sex | 0.020 (0.031) | | | |
| APOE status | 0.042 (0.029) | | | |
| Age | 0.007 (0.004) | | | |
| Time to follow-up | 0.000 (0.000) | | | |
| Constant | 0.394 (0.256) | 0.465 (0.264) p=0.088 | 0.126 (0.028) p<0.001 | 0.447 (0.263) p=0.090 |
| Frontal cortex | | | | |
| Mediterranean diet | -0.016 (0.011) p=0.104 | -0.018 (0.011) p=0.102 | -0.011 (0.011) | |
| Physical activity | -0.000 (0.002) | -0.001 (0.002) | -0.001 (0.002) | |
| Intellectual activity | 0.050 (0.036) | 0.031 (0.036) | 0.019 (0.036) | |
| Plasma homocysteine | -0.001 (0.008) | -0.001 (0.008) | | -0.002 (0.008) |
| Plasma cholesterol | -0.001 (0.001) | -0.001 (0.001) | | -0.001 (0.001) |
| Body mass index | -0.001 (0.003) | -0.001 (0.003) | | -0.001 (0.003) |
| QUICKI scores | -1.293 (1.008) | -1.497 (1.012) | | -1.184 (1.001) |
| Hypertension | -0.005 (0.029) | -0.005 (0.026) | | 0.001 (0.025) |
| Frontal PiB uptake at baseline | 0.000 (0.143) | 0.003 (0.145) | 0.001 (0.144) | 0.026 (0.140) |
| Sex | 0.017 (0.019) | | | |
| APOE status | 0.033 (0.019) p=0.084 | | | |
| Age | 0.000 (0.002) | | | |
| Time to follow-up | -0.000 (0.000) | | | |
| Constant | 0.234 (0.167) | 0.256 (0.168) | 0.010 (0.018) p<0.001 | 0.208 (0.166) |

See legend to [table 2](#). Only significant and marginally significant p values are reported in the table.

APOE, apolipoprotein E; PCC, posterior cingulate cortex; QUICKI, Quantitative Insulin Sensitivity Check Index.

were cognitively normal and between 30 and 60 years of age, very few (if any) would have had substantial amyloid burden, making this cohort an ideal population for testing primary prevention strategies.

As with other studies in asymptomatic at-risk individuals,^{32 33 43} imaging biomarkers were not associated with cognitive measures, most likely because our participants were all cognitively normal and younger than 60 years at baseline. Previous studies have demonstrated that associations between brain biomarkers and cognition are evident in clinical AD patients, such as those with clear brain pathology, but not among normal populations.⁴⁴ A longer follow-up duration may allow for additional pathological and cognitive changes to manifest. We performed

an additional sensitivity analysis to test for associations between biomarkers and domain-specific changes in memory, attention and language, which left our conclusions substantially unchanged (see online supplementary eappendix).

We did not find a significant statistical relationship between intellectual and physical activity and biomarker changes. There is mixed evidence for the role of physical activity on brain ageing. A recent randomised controlled trial showed that aerobic exercise interventions resulted in improved cardiorespiratory fitness, which in turn improved memory and reduced brain atrophy in the elderly.⁴⁵ Animal models have also suggested that physical activity has the potential to alleviate tau

Table 4 Prediction of FDG PET metabolic changes

| | Model 1* | Model 2† | Model 3‡ | Model 4§ |
|--------------------------------|------------------------|------------------------|------------------------|-----------------------|
| PCC | | | | |
| Mediterranean diet | 0.010 (0.005) p=0.050 | 0.010 (0.005) p=0.048 | 0.010 (0.005) p=0.043 | |
| Physical activity | -0.000 (0.001) | -0.000 (0.001) | -0.000 (0.001) | |
| Intellectual activity | 0.005 (0.015) | 0.004 (0.015) | 0.004 (0.014) | |
| Plasma homocysteine | 0.004 (0.004) | 0.004 (0.003) | | 0.004 (0.004) |
| Plasma cholesterol | 0.000 (0.000) | 0.000 (0.000) | | -0.000 (0.000) |
| Body mass index | -0.001 (0.001) | -0.001 (0.001) | | -0.001 (0.001) |
| QUICKI scores | 0.165 (0.480) | 0.184 (0.438) | | 0.049 (0.459) |
| Hypertension | 0.001 (0.013) | 0.003 (0.011) | | -0.000 (0.011) |
| PCC FDG uptake at baseline | 0.573 (0.194) p=0.006 | 0.587 (0.183) p=0.002 | 0.566 (0.184) p=0.003 | 0.515 (0.184) p=0.004 |
| Sex | -0.003 (0.010) | | | |
| APOE status | 0.001 (0.008) | | | |
| Age | 0.000 (0.001) | | | |
| Time to follow-up | -0.000 (0.000) | | | |
| Constant | 1.154 (0.080) p<0.001 | 1.154 (0.083) p<0.001 | 1.182 (0.007) p<0.001 | 1.173 (0.076) p<0.001 |
| Frontal cortex | | | | |
| Mediterranean diet | -0.011 (0.007) | -0.012 (0.007) p=0.106 | -0.012 (0.007) p=0.072 | |
| Physical activity | 0.001 (0.001) | 0.000 (0.001) | 0.001 (0.001) | |
| Intellectual activity | 0.010 (0.020) | 0.008 (0.019) | 0.005 (0.019) | |
| Plasma homocysteine | 0.003 (0.005) | 0.002 (0.005) | | 0.002 (0.005) |
| Plasma cholesterol | 0.001 (0.000) | 0.000 (0.000) | | 0.001 (0.000) |
| Body mass index | 0.002 (0.002) | 0.003 (0.002) | | 0.003 (0.002) |
| QUICKI scores | -0.116 (0.690) | -0.100 (0.669) | | 0.102 (0.668) |
| Hypertension | 0.017 (0.018) | 0.009 (0.015) | | 0.013 (0.015) |
| Frontal FDG uptake at baseline | 0.202 (0.112) p=0.093 | 0.239 (0.107) p=0.040 | 0.196 (0.104) p=0.085 | 0.235 (0.101) p=0.036 |
| Sex | 0.007 (0.011) | | | |
| APOE status | -0.006 (0.012) | | | |
| Age | -0.001 (0.001) p=0.091 | | | |
| Time to follow-up | -0.000 (0.000) | | | |
| Constant | 1.209 (0.114) p<0.001 | 1.197 (0.111) p<0.001 | 1.174 (0.010) p<0.001 | 1.166 (0.110) p<0.001 |

See legend to [table 2](#). Only significant and marginally significant p values are reported in the table. APOE, apolipoprotein E; PCC, posterior cingulate cortex; QUICKI, Quantitative Insulin Sensitivity Check Index.

hyperphosphorylation.⁴⁶ However, a previous longitudinal study in non-demented elderly reported absent to minimal associations between physical and intellectual activity and brain AD biomarker changes.⁸ In our study, physical activity was only marginally negatively associated with PCC amyloid deposition. Since we did not find significant relationships between intellectual and physical activity and biomarker changes, we tested to see if we had adequate power to detect these associations (see online supplementary eappendix). Based on the sensitivity analysis, we had adequate power to detect associations of interest, indicating that the null results are not necessarily attributable to methodology or sample size concerns.

Additionally, the null results in our cohort are consistent with findings from large-scale, community-based studies in the elderly.^{8,9} Therefore, we offer that the strongest arguments of the study are the significant findings that manifest themselves despite the above limitations. That said, clinical trials are needed to test whether these lifestyle interventions may alter the rate of change in AD biomarkers and cognition. Recent clinical trials provided encouraging evidence that multimodal lifestyle and vascular risk interventions improve cognition in the elderly.⁴⁷

Worth noting is that we assumed linearity in the rate of change in biomarkers and cognition, which is reasonable for short time frames, as in this 3-year study, but possibly

Table 5 Prediction of MRI-based cortical thickness change

| | Model 1* | Model 2† | Model 3‡ | Model 4§ |
|---|-----------------------|-----------------------|-----------------------|-----------------------|
| Entorhinal cortex | | | | |
| Mediterranean diet | 0.061 (0.042) | 0.049 (0.042) | 0.061 (0.040) | |
| Physical activity | -0.010 (0.008) | -0.009 (0.008) | -0.008 (0.008) | |
| Intellectual activity | -0.180 (0.112) | -0.110 (0.111) | -0.120 (0.106) | |
| Plasma homocysteine | 0.012 (0.029) | 0.012 (0.029) | | 0.006 (0.029) |
| Plasma cholesterol | -0.001 (0.002) | -0.002 (0.002) | | -0.003 (0.002) |
| Body mass index | -0.000 (0.011) | 0.001 (0.012) | | 0.003 (0.012) |
| QUICKI scores | 3.542 (4.008) | 2.844 (4.075) | | 1.726 (4.345) |
| Hypertension | -0.035 (0.093) | -0.072 (0.083) | | -0.088 (0.085) |
| Entorhinal cortex thickness at baseline | 0.407 (0.167) p=0.018 | 0.382 (0.168) p=0.025 | 0.361 (0.162) p=0.031 | 0.400 (0.157) p=0.012 |
| Sex | 0.096 (0.079) | | | |
| APOE status | -0.092 (0.064) | | | |
| Age | -0.009 (0.008) | | | |
| Time to follow-up | -0.0007 (0.0002) | | | |
| Constant | 2.710 (0.654) p<0.001 | 2.784 (0.667) p<0.001 | 3.303 (0.059) p<0.001 | 2.956 (0.710) p<0.001 |
| PCC | | | | |
| Mediterranean diet | 0.003 (0.016) | 0.002 (0.015) | 0.002 (0.015) | |
| Physical activity | -0.002 (0.003) | -0.002 (0.003) | -0.001 (0.003) | |
| Intellectual activity | -0.034 (0.047) | -0.015 (0.045) | -0.019 (0.041) | |
| Plasma homocysteine | 0.009 (0.012) | 0.008 (0.011) | | 0.009 (0.010) |
| Plasma cholesterol | -0.000 (0.001) | -0.000 (0.001) | | -0.000 (0.001) |
| Body mass index | -0.002 (0.005) | -0.001 (0.005) | | -0.001 (0.005) |
| QUICKI scores | 0.801 (1.643) | 0.794 (1.577) | | 0.698 (1.581) |
| Hypertension | 0.052 (0.038) | 0.037 (0.033) | | 0.035 (0.033) |
| PCC thickness at baseline | 0.390 (0.205) p=0.099 | 0.459 (0.209) p=0.050 | 0.508 (0.205) p=0.023 | 0.506 (0.182) p=0.011 |
| Sex | 0.012 (0.032) | | | |
| APOE status | -0.020 (0.028) | | | |
| Age | -0.003 (0.004) | | | |
| Time to follow-up | 0.000 (0.000) | | | |
| Constant | 2.321 (0.267) p<0.001 | 2.311 (0.260) p<0.001 | 2.418 (0.024) p<0.001 | 2.326 (0.260) p<0.001 |

See legend to [table 2](#). Only significant and marginally significant p values are reported in the table. All MRI models are adjusted for total intracranial volume (data not shown).

APOE, apolipoprotein E; PCC, posterior cingulate cortex; QUICKI, Quantitative Insulin Sensitivity Check Index.

different for more extended periods of observation. For instance, increasing pathological burden with age may cause acceleration in cognitive and biomarker changes. Also, due to the relatively small sample size, we did not examine interactions between the different biomarkers, which may be influenced by lifestyle and vascular risk factors.

We caution that lifestyle habits were self-reported, and as self-reported lifestyle questionnaires are vulnerable to error, this may have reduced our ability to detect additional associations between lifestyle factors and AD risk.

Lastly, while our results are pertinent to healthy, middle-aged research participants without severe

cardiac or cerebrovascular disease, results may differ in the elderly, in patients with dementia and in those with vascular or metabolic diseases. Studies with larger samples and longer follow-up times are needed to assess the generalisability of these findings in community-based populations with a higher variability in socioeconomic and medical status.

Our study has a number of strengths. While previous studies focused on elderly with no dementia, including those with cognitive impairment, this longitudinal biomarker study focused on cognitively intact, middle-aged individuals. There is a consensus that lifestyle interventions have the highest chances of success when

implemented well before old age,⁵ making our results particularly relevant to efforts aimed at preventing AD.

Furthermore, the majority of previous studies looked at intellectual and physical activity, but not at diet. We demonstrated that diet does, in fact, influence the rate of change in metabolic AD biomarkers, whereas intellectual and physical activity do not appear to do so.

Lastly, our statistical model enabled us to simultaneously assess multiple lifestyle and vascular risk factors, yielding a more comprehensive understanding of the associations between these modifiable risk factors and AD risk. A combined reduction in several modifiable AD risk factors is projected to have a more significant impact than any one factor alone.⁴

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