Associations between lifestyle, genetic risk for Alzheimer's disease, and longitudinal brain atrophy in UK Biobank (N=2214)

Authors: Yating You[1], Laura M. Lyall[1], Frederick K. Ho[1]*, Claire E. Hastie[1]*†, Donald M. Lyall[1]*†

(*Joint senior authors)

Institutions

[1]School of Health and Wellbeing, University of Glasgow, Glasgow, United Kingdom G12 8TB

†**Corresponding authors**

Claire E. Hastie, PhD, School of Health and Wellbeing, University of Glasgow, Glasgow, United Kingdom G12 8TB

Email: Claire.Hastie@glasgow.ac.uk

Donald M. Lyall, PhD, School of Health and Wellbeing, University of Glasgow, Glasgow, United Kingdom G12 8TB

Email: Donald.Lyall@glasgow.ac.uk

Abstract

INTRODUCTION: Modifiable behaviours such as smoking, diet, alcohol intake, sedentariness, and physical inactivity are associated with brain health, but longitudinal evidence in adults without dementia is limited.

METHODS: Among 2214 UK Biobank participants with two MRI scans over 2.2 years, unweighted lifestyle scores (ranging 0 - 10) were derived from five behaviours and classified as unfavourable, moderate, or favourable. Linear regression examined associations, and *APOE* e4 genotypic interactions, with changes in 16 brain volumetric markers.

RESULTS: Compared with favourable lifestyle, unfavourable lifestyle showed significantly greater grey matter (2059 mm^3; 0.046 standard deviations [SDs]) and left hippocampal (36.5 mm^3; 0.044 SD) atrophy. Moderate-risk drinking was linked to higher total brain atrophy (2075 mm^3; 0.063 SD), while high-risk drinking and low physical activity associated with accelerated regional grey matter loss. No effects were found for smoking, diet, or sedentariness. High-risk drinking was associated with greater frontal lobe atrophy, particularly among *APOE* ε4 carriers.

DISCUSSION: Lifestyle variables showed modest associations with brain atrophy, with alcohol drinking appearing most influential, with significant modification by *APOE* e4 genotype.

KEYWORDS

Brain health; atrophy; longitudinal; lifestyle; *APOE* e4; alcohol intake

1. BACKGROUND

With longer life expectancy, the prevalence of brain impairment and neurodegenerative diseases are increasing, such as dementia, which affected cognitive ability, memory, and the ability to perform daily activities in 57 million people worldwide in 2019.[1-3] Dementia is a global public health problem, and the number of people living with this disease is predicted to increase to 153 million by 2050.[2] Causes of dementia may include multiple diseases or injuries that directly and indirectly lead to brain damage and deterioration in cognitive function; Alzheimer's disease (AD), as the most common form, accounts for 60-70% of cases.[3] Apolipoprotein *E* gene (*APOE*) e4 allele is known as the strongest genetic risk factor for AD.[4] Although effective and broadly indicated pharmacological treatments for dementia are still lacking, the Lancet Commission on dementia suggests that around 45% of dementia might be preventable by implementing interventions on modifiable risk factors, for example, smoking, excessive alcohol consumption, obesity, and physical inactivity.[1] Understanding the relationships between modifiable risk factors and brain structural changes is a priority to prevent or delay dementia.

Brain structure is a relatively sensitive mediator of cognitive health, and a more proximal phenotype to exposures, compared with cognitive test scores which are widely used to explore different abilities,[5,6] but remains incompletely explored. Associations between several modifiable risk factors and poorer brain health have been demonstrated through structural magnetic resonance imaging (MRI) phenotypes, for example, smoking and smaller grey matter volumes,[7] unhealthy diet and poorer brain connectivity,[8] and habitual sedentary behaviour with poorer white matter health,[9] and excessive alcohol drinking with smaller grey matter volumes and poorer white matter tract integrity.[10] Yet, it is difficult to infer potential causality because of limitations

in these cross-sectional designs: these findings could reflect either differences in baseline levels, reverse causation, or long-term accumulated effects.[11] Longitudinal studies could isolate the change aspects and provide better tests of causality, which so far remain scarce.[12]

Though human cognitive function changes continuously throughout life, preventive interventions in early-life might be effective for late-life brain health and cognitive outcomes.[13] A few studies have provided longitudinal evidence on the associations between lifestyle and brain structural changes, such as, moderate and heavy alcohol drinking with greater decrease in cortical thickness of medial orbitofrontal cortex among 179 participants;[14] null associations between the Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND) diet score and brain structural changes in UK Biobank.[15] These studies were limited by small sample sizes or examining only a single lifestyle variable with brain structural changes, and neglected real-world clustering of risky lifestyle factors within individuals. Convincing evidence that healthy lifestyle variables, either alone or in combination, can protect brain health and prevent dementia is lacking.[16] Thus, large-scale cohorts with repeated neuroimaging data are warranted to elucidate the impacts of daily lifestyle variables on subtle but clinically meaningful brain structural changes over time while accounting for the genetic risk, and their interactions.

In the current study, we aim to examine whether and how individual/overall lifestyle(s), including smoking, alcohol drinking, diet, sedentary behaviour, and physical activity, influence atrophy in global brain measures as well as regional grey matter volumes in the frontal lobe, considering *APOE* e4 risk and its interactions among people living without dementia between two-timepoint scans.

2. Methods

2.1 Study design and participants

Data for the current study were obtained from the UK Biobank, which is a large community-based cohort with 502,359 participants aged 37-73 years.[17] From 2006 to 2010, participants who attended one of 22 assessment centres completed the baseline assessments and questionnaires on physical, lifestyle, sociodemographic and medical characteristics. In 2014, MRI scanning of the heart, brain and abdomen for a sub-group of participants began; this is ongoing until the aim of 100,000 participants being scanned is reached. As of September 2023, 71,091 participants aged 44-85 years had attended the MRI assessment for the first time. Brain structural MRI data being processed at the first scan are available for 46,398 participants, and repeat imaging at the second scan for 4,784 participants. Participants who reported chronic neurological diseases before the first scan which could directly affect cognitive function were excluded (see **Table S1**). We mainly focused on lifestyle variables and covariates collected at the time of first MRI scan as the baseline measures, and brain structural phenotypes in two scans. This research was completed using UK Biobank project number 17689.

2.2 Lifestyle

2.2.1 Individual lifestyle variables

Participants self-reported their health related lifestyles at the first scan, including smoking status, alcohol intake, diet, sedentary behaviour duration and physical activity (**Table S2**). The intercorrelations among lifestyle variables are shown in **Table S4**.

Three levels (namely optimal, moderate, poor) for each lifestyle variable were defined based on public health guidelines. Smoking status was classified as never,

former, and current smoker.[7] Alcohol drinking was defined here as low, moderate, and high risk, being defined by types, frequencies and units of weekly alcohol intake and grouped based on UK national guidelines: 0–14 units as low risk of disease; 15–35 units for females or 15–50 units for males as moderate risk; > 35 units for females and > 50 units for males as high risk.[18] Diet was categorized as healthy, moderate, and unhealthy based on a diet score for cardiovascular diseases sharing similar risk factors with dementia rather than the MIND diet,[19] because information on 24-hour diet recall being used to construct the MIND diet score were not collected when participants attended the first MRI scan. This current score was derived from the food frequency questionnaire, and constructed by the unweighted sum of adherence to the UK dietary guidelines, including: processed meat, red meat individually less than twice per week, total fish more than twice per week, consumption of semi- and skimmed, soya milk, no spread intake, more than five bowls of cereal intake, no salt added to food, more than six glasses of water and more than five servings per day of fruits and vegetables. There is currently no guideline for sedentary behaviour, only being recommended to limit the amount of time being sedentary by WHO; and using the WHO guidelines for physical activity of 150-300 minutes moderate or 75-150 minutes vigorous activity weekly would result in a highly left-skewed distribution.[20] Tertiles were therefore used for categories of sedentary behaviour (time [in hours] spent driving, using a personal computer, and watching television), and physical activity (weekly metabolic equivalents task units [METs] minutes of walking, moderate and vigorous activity) as low, medium and high levels[21].

2.2.2 Unweighted lifestyle score and lifestyle categories

We assigned 0,1, and 2 points for each lifestyle variable based on the adherence to poor, moderate and optimal lifestyle behaviour, respectively. Two points were

assigned for membership of each respective optimal level: never smoking; low risk drinking; healthy diet; low duration of sedentary behaviour; high level METs. One point was assigned for each of moderate-level lifestyles, such as former smoking, moderate risk drinking, moderate diet, medium duration sedentariness, and medium METs; and 0 for poor ones. An overall lifestyle score was summed across these five three-level lifestyle variables using an unweighted score, ranging from 0 to 10, with a higher score indicating a healthier lifestyle. Based on the distribution of frequencies of participants' lifestyle scores (see **Figure S1**), participants who scored 0, 1, 2 or 3 were classed as unfavourable lifestyle; 4, 5, or 6 as moderate lifestyle; 7, 8, 9, or 10 as favourable lifestyle.[10] For example, someone who never smoked and had low risk drinking (two points each), moderate diet (one point), low sedentariness (two points) and high METs (two points) would receive nine points and be included in the favourable lifestyle group. We used this method which prioritized clinical relevance and interpretability over statistical convenience, rather than tertiles which might mask meaningful biological patterns.

2.3 Imaging data

Brain structural markers were measured using MRI performed with a 3 Tesla Siemens Skyra scanner (Siemens Healthineers) with VD13 software and a 32-channel head coil since 2014.[22] In the current study, we used data from T1-weighted imaging, including global brain volumetric measures of grey matter, white matter, total brain; hippocampal volumes: left hippocampus, right hippocampus, hippocampal asymmetry (left minus right); volumetric measures of grey matter in frontal lobe (including frontal pole; superior frontal gyrus; middle frontal gyrus; inferior frontal gyrus, pars triangularis; inferior frontal gyrus, pars opercularis; frontal medial cortex; frontal orbital cortex; frontal operculum cortex, see **Table S3**); these regions were selected as they have

shown association with cognitive deficits.[23] Additionally, we included the volume of white matter hyperintensities from the T2 FLAIR structural scan as this is strongly associated with dementia.[24] The primary outcomes of interest were grey matter volumes, white matter volumes, total brain volumes, white matter hyperintensities volumes, left/right hippocampal volumes, hippocampal asymmetry and volumes of grey matter in frontal lobe regions (all uncorrected for head size).

2.4 Genetic data

UK Biobank genotyping was conducted by Affymetrix using a bespoke BiLEVE Axiom array for ~50,000 participants and the remaining 450,000 on the Affymetrix UK Biobank Axiom array. All genetic data were quality controlled by UK Biobank.[25] The *APOE* e genotype is directly genotyped. The two *APOE* e single nucleotide polymorphisms— rs7412 and rs429358—were both in Hardy-Weinberg equilibrium ($p > 0.05$) assessed with PLINK V1.90.[26] Further information on the genotyping process is available (ukbiobank.ac.uk/scientists-3/geneticdata). For enough granularity to test lifestyle interactions, a dominant *APOE* e4 model - e3/e4 and e4/e4 collated vs. e2/e2, e2/e3 and e3/e3, was used as previous research showed that about 2% of the cohort were e4 homozygotes.[27] *APOE* e2/e4 was removed as standard practice because it has potentially both risk and protective alleles.[28]

2.5 Covariates

We used information from questionnaires completed at the first scan which recorded sociodemographic factors including age, sex (male or female), Townsend deprivation index (categorized as quintiles);[29] health factors on body mass index (BMI) as underweight, normal weight, overweight, or obese;[30] sleep durations as short (<7 hours), normal (7-9 hours) or long (>9 hours),[31] social isolation (yes or no),[32] history

of diabetes (yes or no), hypertension (yes or no), and depression (yes or no). Genetic and imaging covariates were also included, such as genotypic arrays, the first 10 principal components for stratification, MRI sites (n=4), intracranial volume (ICV), which was generated by summing the volumes of white matter, grey matter, and ventricular cerebrospinal fluid at the first scan,[33] and time intervals, which were the number of days between the dates of attending two scans. Since these measures were ascertained prior to brain imaging, they cannot be mediators and were treated as confounders (associated with both exposures and outcomes).

2.6 Statistical analysis

Characteristics of participants were described, stratified by the dominant *APOE* e4 model (presence versus absence), with Chi-square tests for categorical variables, t-tests for normally distributed continuous variables, and Mann-Whitney U tests for not normally distributed continuous variables; MRI volumes were combined across hemispheres (summing left and right) for grey matter in the frontal lobe. For white matter hyperintensities, outlier values greater than 5 standard deviations (SDs) from the sample mean were excluded; data were log-transformed due to a positively skewed distribution.

We used the raw change scores to examine the longitudinal associations between lifestyle, *APOE* e4 genotype, and brain atrophy by linear regression, where standardised betas, intuitive unstandardised betas and standard errors (SEs) were all reported. The outcome variables were defined as the differences of raw brain structural volumes (in mm^3) between follow-up and baseline scans (e.g. brain volumetric markers in the second scan minus markers in the first scan) and the main predictor was the lifestyle variable in each regression model. Each model was fully adjusted for

corresponding brain structural values in the first scan; sociodemographic factors: age, sex, Townsend deprivation categories; genetic and imaging related factors: genotypic arrays, MRI sites, the first 10 principal components, ICV, and time intervals; health and social factors: BMI, sleep duration, isolated status, history of diabetes, hypertension, and depression. Positive betas indicate that the exposure group had less volume loss (i.e., attenuated atrophy) compared to the reference group, whereas negative betas indicate greater volume loss (i.e., accelerated atrophy), see **Figure S2**.

We firstly examined the general associations of lifestyle categories (including unfavourable, moderate, and favourable lifestyles) and brain atrophy, additionally for continuous lifestyle scores. To further interpret the association, we computed adjusted marginal means of brain structural changes across lifestyle categories using *margins* in Stata, holding other covariates at their observed values. Then, the intuitive contributions of individual lifestyle variables on raw brain changes were investigated in two phases: 1) we estimated the associations of individual lifestyle variable with brain changes without adjusting for other lifestyle variables; 2) all lifestyle variables were included in one regression model simultaneously, being adjusted mutually in one multiple linear regression model for each brain MRI variable of interest. Interactions between *APOE* e4 status with lifestyle categories, and individual lifestyle variable, on brain structural atrophy were also tested.

Analyses were conducted in Stata v.18 and R (v4.2.3). We report two-sided P-values throughout and false discovery rate (FDR) correction was applied to keep the error rate at 0.05.

3. Results

3.1 Characteristics of participants

A total of 2214 participants were included with complete information on lifestyle factors, *APOE* e4 genotype, and covariates in the first scan and brain structural markers of two scans (**Figure 1)**. The median (IQR) of follow up was 2.25 (0.30) years. The 2214 participants had a mean (SD) age of 61.3 (7.3) years in the first scan and 1099 (49.6%) were female (**Table 1**). There were 547 (24.7%) participants carrying at least one copy of the e4 allele. Among e4 carriers, there were 250 (45.7%) participants with moderate lifestyles, followed by 249 (45.5%) with favourable lifestyles and 48 (8.8%) with unfavourable lifestyles. *APOE* e4 carriers were more likely to be younger (Cohen's d= 0.11, P=0.031) and have smaller white matter volume (Cohen's d= 0.10, P=0.036), and left hippocampal volume (Cohen's d= 0.12, P=0.018) in the first scan.

3.2 Associations between lifestyle, APOE e4 status, and longitudinal brain atrophy

3.2.1 Lifestyle categories

As shown in **Figure 2** (with supporting information in **Table S5**), compared with favourable lifestyle, unfavourable lifestyle was significantly associated with greater brain atrophy in grey matter and left hippocampal volumes, but not with other brain structural phenotypes. Participants with favourable lifestyle experienced a mean atrophy of 7883.8 mm^3 atrophy in grey matter and 63.6 mm^3 in left hippocampus independently, over a median follow-up of two years. Compared with the favourable lifestyle group, unfavourable lifestyle was associated with 2059.2 mm^3 more atrophy in grey matter, equivalent to 0.046 standard deviation (SD) greater decline (95% CI =-3966.5 to -152.0, P=0.034), and 36.5 mm^3 more atrophy in left hippocampus, equivalent to 0.044 SD greater decline (95% CI =-72.5 to -0.4, P=0.048). Additionally, a one-point increment in lifestyle score (out of 10 points) was associated with less grey matter loss (unstandardised β = 318.1, 95% CI =32.9 to 603.2, standardised β = 0.047,

P=0.029), and less hippocampal asymmetry (unstandardised β = 6.4, 95% CI =0.2 to 12.6, standardised β = 0.044, P=0.042) in **Table S6**. However, none of these associations remained significant after correction for multiple testing ($p_{(FDR)}$ >0.05).

3.2.2 Individual lifestyle variable

Figure 3 presents the heatmap of associations of individual and simultaneous lifestyle variables on longitudinal brain atrophy. In **Figure 3A** with supporting information in **Table S7**, we observed significant impacts of single lifestyle variables on certain investigated brain markers. For example, for alcohol drinking, compared with low-risk drinking, high-risk drinking was associated with greater atrophy of 57.3 mm^3 in left hippocampal volume, corresponding to 0.062 SD greater loss (P=0.004), and accelerated decreased volumes of 48.9 mm^3 in inferior frontal gyrus, pars triangularis, corresponding to 0.048 SD greater loss (P=0.023), while moderate drinking was linked to accelerated total brain atrophy of 2075.4 mm^3, corresponding to 0.063 SD greater loss (P=0.003), especially in grey matter volumes with 1336 mm^3 more atrophy, corresponding to 0.054 SD greater loss (P=0.012). For physical activity, compared with participants with high METs, those with low METs showed greater atrophy of 1255.4 mm3 in grey matter volumes, equvilent to 0.05 SD greater decrease (P=0.035), and those with medium METs attenuated white matter atrophy of 1413.7 mm^3 , equvilent to 0.05 SD greater decrease (P=0.035). These significant associations of each lifestyle variable on brain imaging markers remained largely consistent even when we included all lifestyle variables in one simultaneous regression model (**Figure 3B** with supporting information in **Table S8)**, although high-risk drinking's effect on left hippocampus reduced slightly from -0.062 SD to -0.055 SD. After FDR correction, only moderate drinking and total brain atrophy remained statistically significant ($p_{(FDR)}$ =0.045); all other associations became non-significant ($p_{(FDR)}$ > 0.05). No significant

associations were observed for smoking, diet or sedentary behaviour with brain structural atrophy in either univariable or multivariable models (all P>0.05).

3.3 Interaction of lifestyle and *APOE* e4 status on brain structural phenotypes

Two-way interaction tests of lifestyle categories × *APOE* e4 status for each brain imaging marker did not reveal significant interactions in **Table S9**. However, in two-way interaction tests of each individual lifestyle variable × *APOE* e4 status on brain structural changes in **Table S10**, significant interactions were found between high-risk drinking and *APOE* e4 status on regional grey matter atrophy in frontal lobe as well as moderate drinking and sedentary behaviour with regional brain changes. After correcting for multiple testing, only the interaction of high-risk drinking and *APOE* e4 status on regional grey matter atrophy in frontal lobe survived, including frontal pole, superior frontal gyrus, inferior frontal gyrus, pars triangularis, and frontal operculum cortex ($p_{(FDR)}$ <0.05). Based on this finding, we then performed subgroup analyses stratified by *APOE* e4 status (**Table S11)**, which showed among e4 non-carriers, moderate drinking subtly accelerated atrophy in grey matter in frontal lobe regions except for frontal operculum cortex (standardised β ranges from -0.064 to -0.051, P<0.05), but among e4 carriers, we observed greater decreased volumes (standardised β ranges from -0.093 to -0.072, P<0.05) between high drinking and frontal lobe volumes. None of these associations remained significant when correcting for multiple testing.

4. Discussion

In this longitudinal study, we showed that lifestyle and genetic risk for AD were associated with accelerated structural changes in a range of brain phenotypes over a period of up to 7 years. Longitudinal associations were nominally found between an

overall unfavourable lifestyle, and grey matter and left hippocampal atrophy. Among individual lifestyle variables, alcohol drinking showed the most consistent effects on brain atrophy: moderate drinking was associated with total brain atrophy, as well as high drinking and declined volumes in the left hippocampus and frontal lobe at the follow-up scan. Moreover, we observed evidence of interaction between *APOE* e4 status and alcohol intake, with e4 carriers showing greater brain atrophy to the adverse effects of high-risk drinking.

This is the first study to demonstrate that unfavourable lifestyles accelerate longitudinal grey matter and left hippocampus atrophy nominally, although associations were no longer significant after correcting for multiple comparisons. However, for each lifestyle variable, they had impacts on certain brain volumetric changes.

Alcohol drinking was the most consistent lifestyle factor associated with brain atrophy in our study. Moderate drinking was associated with greater total brain atrophy after multiple testing, compared with low risk drinking. Our finding is also partly supported by a Mendelian randomization study reporting that moderate alcohol consumption was associated with higher brain iron, whose accumulation represented a potential mechanism for alcohol-related cognitive decline.[34] High-risk drinking was associated with greater atrophy in left hippocampus and grey matter in inferior frontal gyrus, pars triangularis, generally in line with prior studies.[35,36] This might be because of functional lateralization, which meant the left hippocampus was more involved in verbal memory processing and it was often negatively impacted by high alcohol consumption on cognitive function, making the impact on the left hippocampus more obvious.[37] When including all lifestyle factors in one regression model, high-risk drinking was associated with less atrophy in left hippocampus based on the reduced beta. This might be

because the detrimental effects of high alcohol consumption may be mitigated through other lifestyle modifications, such as maintaining a balanced diet, engaging in regular physical activity, and avoiding smoking and long duration sedentariness. Evidence suggests that these healthy habits can enhance metabolic resilience, and reduce systemic inflammation, thereby counteracting alcohol-induced oxidative stress.[38]

We also observed that physical inactivity was associated with grey matter atrophy. However, compared with high level METs, medium levels of physical activity were related to less white matter atrophy, namely, better brain ageing. This could be explained by moderate exercise leading to increased cerebral blood flow and neurotrophic factors, which may have a positive impact on angiogenesis and neurogenesis.[39] These effects translate to beneficial effects on structural brain measures associated with cognitive function.[40] High activity levels might be associated with metabolic strain, oxidative stress, and inflammatory responses,[41] which could counteract the neuroprotective effects. We found that medium and high sedentariness were not associated with longitudinal brain atrophy. This is inconsistent with other studies which reported the relationship between sedentary behaviour and reduced white matter health.[42,43] This might be due to overall time use patterns, as sedentary behaviour per se may not be detrimental when individuals compensate by engaging in sufficient physical activity during their non-sedentary time. We still cannot ignore the possibility that the multiple detrimental cardiovascular and metabolic effects led by sedentary behaviour can be intermediate risk factors for dementia, such as hypertension.[44] Other metabolic effects, including insulin resistance, and blood lipids, also have a negative impact on white matter health, which in turn might increase the risk of dementia.[45]

Notably, although multiple significant cross-sectional associations between smoking, and diet and lower brain volumes have been reported,[7,8] we found null associations between smoking or diet with longitudinal brain atrophy in the investigated brain structural markers. Of them, current or former smoking was not associated with brain changes in the current study. Our finding is inconsistent with previous research stating that smoking was associated with decreased structural integrity of multiple brain regions among elderly people without dementia. [46] This might be explained by the impacts of smoking on brain changes being distributed by other factors, or that the measurement of smoking is less precise than other, i.e. non-misclassification bias, and thus associations could not be detected. We cannot neglect the impact of chronic exposure of noxious agents in cigarette smoking, which may directly compromise neuronal and cellular membrane functions of cerebral tissue and lead to cardiovascular and cerebrovascular disease.[46]

Furthermore, we found no significant associations of moderate or unhealthy diet with brain atrophy. We used a developed diet score from the food frequency questionnaire at the first scan designated for cardiovascular diseases which shared similar risk factors with cerebrovascular diseases.[19] Although the MIND diet is well-known to slow cognitive decline and lower risks of all-cause dementia,[47] data on 24-hour diet recall which is used to construct the MIND diet score was not collected at the first MRI scan in the UK Biobank, which meant we were unable to explore its impacts on brain changes properly. However, a prior study showed no significant associations between MIND diet and longitudinal brain structural changes by accessing the first wave of imaging data being taken long after dietary assessments.[15]

Significant interactions were found between high-risk drinking and *APOE* e4 status on grey matter volume decline in frontal lobe. Non-low risk drinking was significantly

associated with decreased volumes of grey matter in frontal lobe regardless of *APOE* e4 status. However, *APOE* e4 carriers may be more vulnerable to the effects of alcohol-related neurodegeneration due to more brain atrophy compared with non-carriers. Our finding is supported by one study showing that heavy drinking history was associated with an earlier onset of AD by 2–3 years among *APOE* e4 carriers.[48] However, it contrasted with another study stating *APOE* e4 did not moderate the relationship between alcohol use and cognitive performance.[49] This study was limited by a smaller sample size (N=818) and missing covariates of medical conditions. The findings remained unclear and further research on interaction tests are needed.

Major strengths were the relatively large sample size with long-term follow-up (up to 7 years), repeated brain MRI data for conducting longitudinal analyses, and simultaneous inclusion of multiple daily lifestyle factors that allowed us to investigate their individual and combined effects on brain changes. Moreover, the use of raw brain changes, adjusted for baseline brain phenotypes, yielded intuitive and robust results.

However, limitations remain. First, our findings might be underestimated potentially because of healthy volunteer bias. We have previously observed prevalent healthy bias in the imaging sub-sample from the already biased UK Biobank baseline sample.[50] Second, lateralized effects of lifestyle factors on longitudinal brain ageing might exist as we investigated the summed left/right phenotypes in volumes of grey matter in the frontal lobe in analyses. For future studies, it might be interesting to examine the associations of specific lifestyle factors and left/right phenotype changes to explore potential underlying mechanisms. Third, while these associations highlight the neuroimaging consequences of specific lifestyle factors, the interplay between individual factors and white matter tracts remains underexplored. Future research should prioritize longitudinal investigations into how lifestyle factors influence white

matter microstructural changes to elucidate their independent and synergistic effects. Fourth, despite excluding participants with at least one neurological condition in the current study, those with cognitive impairments were not specifically identified in this population-based sample. Thus, the results might be overestimated. Fifth, despite the longitudinal design, and the adjustment of a comprehensive list of confounders, residual confounding cannot be ruled out as with all other observational studies. Last but not least, potential reverse causality might exist; although we have shown evidence consistent with causal effects, we cannot conclude that the lifestyle factors themselves.

Our findings have several important implications. First, alcohol drinking consistently showed adverse effects, suggesting that this lifestyle variable may be a key modifiable target for preserving brain health. Notably, our findings identified associations of moderate intake with greater longitudinal brain atrophy: there has been a long-standing perception of moderate alcohol consumptionas safe, underscoring the need for cautious public health recommendations. Second, the significant interaction between *APOE* e4 status and alcohol use highlights the potential role of genetic susceptibility in modifying lifestyle effects on brain ageing. This supports the notion that prevention strategies should increasingly consider gene–environment interactions and be tailored to vulnerable subgroups such as *APOE* e4 carriers. Together, these implications emphasise the value of integrating lifestyle modification with personalised risk assessment in efforts to mitigate neurodegeneration and promote healthy brain ageing.

Our findings showed an overall unfavourable lifestyle was associated with greater longitudinal atrophy in grey matter and left hippocampus over time. Moderate and high-risk drinking accelerated brain atrophy, compared with low-risk drinking. Among

APOE e4 carriers, high-risk drinking may be an important modifiable risk factor for brain atrophy, indicating a gene - lifestyle interaction in brain ageing. These findings advocate for public health strategies prioritizing relevant lifestyle interventions to delay cognitive aging and prevent dementia.

ACKNOWLEDGEMENTS

The authors thank all participants and staff of the UK Biobank study. This work uses data provided by patients and collected by the NHS as part of their care and support. The UK Biobank was established by the Wellcome Trust, Medical Research Council, Department of Health, Scottish Government and Northwest Regional Development Agency. UK Biobank has also had funding from the Welsh Assembly Government and the British Heart Foundation.

AUTHOR CONTRIBUTIONS

Study concept: YY, FKH, DML, CEH.

Obtained data: DML.

Design: YY, FKH, DML, CEH.

Conducted analyses: YY.

Drafted original manuscript: YY, LML, FKH, DML, CEH.

Reviewed for intellectual content: all co-authors.

FUNDING INFORMATION

YY acknowledges financial support from China Scholarship Council.

CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to disclose.

CONSENT STATEMENT

All human subjects provided informed consent.

SUPPORTING INFORMATION

Supplementary information is available at website.

FIGURE LEGENDS

FIGURE 1. Flowchart summarising participants selection and inclusion processes, including the reasons for exclusion of participants

FIGURE 2. Margin plots for predicted brain structural volumes by lifestyle categories

Unstandardized betas and 95% confidence intervals were calculated using linear regression models (in mm^3), where lifestyle categories are regressed on raw changes of grey matter volumes (A), white matter volumes (B), total brain volumes (C), left hippocampal volumes (D), right hippocampal volumes (E), white matter hyperintensity volumes (F), hippocampal asymmetry (G), frontal pole (H), superior frontal gyrus (I), middle frontal gyrus (J), inferior frontal gyrus, pars triangularis (K), inferior frontal gyrus, pars opercularis (L), frontal medial cortex (M), frontal orbital cortex (N), frontal operculum cortex (O) with the reference of people having favourable level lifestyle, adjusted for corresponding baseline brain structural volumes, age, sex, genotypic array, four MRI assessment centres, first ten genetic principal components, *APOE*4 presence, deprivation index, BMI, sleep duration, isolated status, history of diabetes, hypertension, depression, intracranial volume among N=2214 participants. * denotes significant associations ($P<0.05$).

FIGURE 3. Heatmap of longitudinal associations of individual lifestyle variable individually (A.) and simultaneously (B.) modelled on brain structural markers

Standardized betas were calculated using linear regression models, where each three-level lifestyle factor regressed on raw changes of brain structural markers individually (A), then an overall lifestyle factors regressed on brain metrics simultaneously (B) among N=2214 participants with the reference of people having healthy lifestyle, such

as never smoking, low risk drinking, healthy diet, low sedentariness duration and high METs. Models were fully adjusted for corresponding baseline brain structural volumes, age, sex, genotypic array, four MRI assessment centres, first ten genetic principal components, *APOE4* presence, deprivation index, BMI, sleep duration, isolated status, history of diabetes, hypertension, depression, intracranial volume. Stronger associations are indicated by darker shades, light/dark red indicates a positive association ($P<0.05$), light/dark purple indicates a negative association ($P<0.05$). * denotes significant associations ($P<0.05$).

REFERENCES

1. Livingston G, Huntley J, Liu KY, et al. Dementia prevention, intervention, and care: 2024 report of the Lancet standing Commission. *The Lancet*. 2024;doi:10.1016/s0140-6736(24)01296-0

2. Nichols E, Steinmetz JD, Vollset SE, et al. Estimation of the global prevalence of dementia in 2019 and forecasted prevalence in 2050: an analysis for the Global Burden of Disease Study 2019. *The Lancet Public Health*. 2022/02/01/ 2022;7(2):e105-e125. doi:https://doi.org/10.1016/S2468-2667(21)00249-8

3. WHO. Dementia. WHO. Accessed May 22nd, 2025. https://www.who.int/en/news-room/fact-sheets/detail/dementia

4. Serrano-Pozo A, Das S, Hyman BT. APOE and Alzheimer's disease: advances in genetics, pathophysiology, and therapeutic approaches. *The Lancet Neurology*. 2021/01/01/ 2021;20(1):68-80. doi:https://doi.org/10.1016/S1474-4422(20)30412-9

5. Dhana K, Aggarwal NT, Rajan KB, Barnes LL, Evans DA, Morris MC. Impact of the Apolipoprotein E ε4 Allele on the Relationship Between Healthy Lifestyle and Cognitive Decline: A Population-Based Study. *American Journal of Epidemiology*. 2021;190(7):1225-1233. doi:10.1093/aje/kwab033

6. Jareebi MA, Fullerton J, Kancheva AK, et al. Associations and interactions between premorbid cognitive health, apolipoprotein e4 genotype, and incident Alzheimer's disease in UK Biobank (N = 252,340). *npj Dementia*. 2025/06/18 2025;1(1):8. doi:10.1038/s44400-025-00013-3

7. Elbejjani M, Auer R, Jacobs DR, Jr., et al. Cigarette smoking and gray matter brain volumes in middle age adults: the CARDIA Brain MRI sub-study. *Transl Psychiatry*. Feb 11 2019;9(1):78. doi:10.1038/s41398-019-0401-1

8. Jensen DEA, Leoni V, Klein-Flügge MC, Ebmeier KP, Suri S. Associations of dietary markers with brain volume and connectivity: A systematic review of MRI studies. *Ageing Res Rev*. Sep 2021;70:101360. doi:10.1016/j.arr.2021.101360

9. Maasakkers CM, Weijs RWJ, Dekkers C, et al. Sedentary behaviour and brain health in middle-aged and older adults: A systematic review. *Neurosci Biobehav Rev*. Sep 2022;140:104802. doi:10.1016/j.neubiorev.2022.104802

10. You Y, Ward J, Ho FK, Lyall DM, Hastie CE. Associations and interactions between APOE e4 genotype and lifestyle with brain structural phenotypes. *Brain Communications*. 2025;7(5)doi:10.1093/braincomms/fcaf350

11. Spector PE. Do Not Cross Me: Optimizing the Use of Cross-Sectional Designs. *Journal of Business and Psychology*. 2019/04/01 2019;34(2):125-137. doi:10.1007/s10869-018-09613-8

12. Menard SW. *Longitudinal research*. vol 76. Sage; 2002.

13. Tucker-Drob EM. Cognitive Aging and Dementia: A Life Span Perspective. *Annu Rev Dev Psychol*. Dec 2019;1:177-196. doi:10.1146/annurev-devpsych-121318-085204

14. Binnewies J, Nawijn L, van Tol MJ, van der Wee NJA, Veltman DJ, Penninx B. Associations between depression, lifestyle and brain structure: A longitudinal MRI study. *Neuroimage*. May 1 2021;231:117834. doi:10.1016/j.neuroimage.2021.117834

15. Chen H, Dunk MM, Wang B, et al. Associations of the Mediterranean-DASH Intervention for Neurodegenerative Delay diet with brain structural markers and their changes. *Alzheimer's & Dementia*. 2024;20(2):1190-1200. doi:10.1002/alz.13521

16. Reuben DB, Kremen S, Maust DT. Dementia Prevention and Treatment: A Narrative Review. *JAMA Intern Med*. May 1 2024;184(5):563-572. doi:10.1001/jamainternmed.2023.8522

17. Sudlow C, Gallacher J, Allen N, et al. UK Biobank: An Open Access Resource for Identifying the Causes of a Wide Range of Complex Diseases of Middle and Old Age. *PLOS Medicine*. 2015;12(3):e1001779. doi:10.1371/journal.pmed.1001779

18. NHS. Alcohol units. April 12th, 2024. https://www.nhs.uk/live-well/alcohol-advice/calculating-alcohol-units/

19. Petermann-Rocha F, Ho FK, Foster H, et al. Nonlinear Associations Between Cumulative Dietary Risk Factors and Cardiovascular Diseases, Cancer, and All-Cause Mortality: A Prospective Cohort Study From UK Biobank. *Mayo Clin Proc*. Sep 2021;96(9):2418-2431. doi:10.1016/j.mayocp.2021.01.036

20. World Health O. *WHO guidelines on physical activity and sedentary behaviour: at a glance*. World Health Organization; 2020.

21. Jetté M, Sidney K, Blümchen G. Metabolic equivalents (METS) in exercise testing, exercise prescription, and evaluation of functional capacity. *Clin Cardiol*. Aug 1990;13(8):555-65. doi:10.1002/clc.4960130809

22. Littlejohns TJ, Holliday J, Gibson LM, et al. The UK Biobank imaging enhancement of 100,000 participants: rationale, data collection, management and future directions. *Nature Communications*. 2020/05/26 2020;11(1):2624. doi:10.1038/s41467-020-15948-9

23. Engelborghs S, Maertens K, Mariën P, et al. Behavioural and neuropsychological correlates of frontal lobe features in dementia. *Psychological Medicine*. 2006;36(8):1173-1182. doi:10.1017/s003329170600777x

24. Kandel BM, Avants BB, Gee JC, et al. White matter hyperintensities are more highly associated with preclinical Alzheimer's disease than imaging and cognitive markers of neurodegeneration. *Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring*. 2016;4(1):18-27. doi:https://doi.org/10.1016/j.dadm.2016.03.001

25. Bycroft C, Freeman C, Petkova D, et al. The UK Biobank resource with deep phenotyping and genomic data. *Nature*. 2018/10/01 2018;562(7726):203-209. doi:10.1038/s41586-018-0579-z

26. Purcell S, Neale B, Todd-Brown K, et al. PLINK: A Tool Set for Whole-Genome Association and Population-Based Linkage Analyses. *The American Journal of Human Genetics*. 2007/09/01/ 2007;81(3):559-575. doi:https://doi.org/10.1086/519795

27. Lyall DM, Cox SR, Lyall LM, et al. Association between APOE e4 and white matter hyperintensity volume, but not total brain volume or white matter integrity. *Brain Imaging Behav*. Oct 2020;14(5):1468-1476. doi:10.1007/s11682-019-00069-9

28. Wisdom NM, Callahan JL, Hawkins KA. The effects of apolipoprotein E on non-impaired cognitive functioning: A meta-analysis. *Neurobiology of Aging*. 2011/01/01/ 2011;32(1):63-74. doi:https://doi.org/10.1016/j.neurobiolaging.2009.02.003

29. Townsend P, Phillimore P, Beattie A. *Health and deprivation: inequality and the North*. Routledge; 2023.

30. Obesity WHOCo, World Health O. Obesity : preventing and managing the global epidemic : report of a WHO consultation. Geneva: World Health Organization; 2000.

31. Ferrie JE, Shipley MJ, Cappuccio FP, et al. A Prospective Study of Change in Sleep Duration: Associations with Mortality in the Whitehall II Cohort. *Sleep*. 2007;30(12):1659-1666. doi:10.1093/sleep/30.12.1659

590 32. Foster HME, Gill JMR, Mair FS, et al. Social connection and mortality in UK
591 Biobank: a prospective cohort analysis. *BMC Medicine*. 2023/11/10 2023;21(1):384.
592 doi:10.1186/s12916-023-03055-7
593 33. Lyall DM, Royle NA, Harris SE, et al. Alzheimer's Disease Susceptibility Genes
594 APOE and TOMM40, and Hippocampal Volumes in the Lothian Birth Cohort 1936.
595 *PLoS ONE*. 2013;8(11):e80513. doi:10.1371/journal.pone.0080513
596 34. Topiwala A, Wang C, Ebmeier KP, et al. Associations between moderate alcohol
597 consumption, brain iron, and cognition in UK Biobank participants: Observational and
598 mendelian randomization analyses. *PLOS Medicine*. 2022;19(7):e1004039.
599 doi:10.1371/journal.pmed.1004039
600 35. Binnewies J, Nawijn L, Brandmaier AM, et al. Lifestyle-related risk factors and
601 their cumulative associations with hippocampal and total grey matter volume across
602 the adult lifespan: A pooled analysis in the European Lifebrain consortium. *Brain*
603 *Research Bulletin*. 2023/08/01/ 2023;200:110692.
604 doi:https://doi.org/10.1016/j.brainresbull.2023.110692
605 36. Momenan R, Steckler LE, Saad ZS, van Rafelghem S, Kerich MJ, Hommer DW.
606 Effects of alcohol dependence on cortical thickness as determined by magnetic
607 resonance imaging. *Psychiatry Res*. Nov 30 2012;204(2-3):101-11.
608 doi:10.1016/j.pscychresns.2012.05.003
609 37. Fanselow MS, Dong HW. Are the dorsal and ventral hippocampus functionally
610 distinct structures? *Neuron*. Jan 14 2010;65(1):7-19.
611 doi:10.1016/j.neuron.2009.11.031
612 38. Crews FT, Nixon K. Mechanisms of neurodegeneration and regeneration in
613 alcoholism. *Alcohol Alcohol*. Mar-Apr 2009;44(2):115-27. doi:10.1093/alcalc/agn079

614 39. Rashid MH, Zahid MF, Zain S, Kabir A, Hassan SU. The Neuroprotective Effects
615 of Exercise on Cognitive Decline: A Preventive Approach to Alzheimer Disease.
616 *Cureus*. Feb 11 2020;12(2):e6958. doi:10.7759/cureus.6958
617 40. Chieffi S, Messina G, Villano I, et al. Neuroprotective Effects of Physical Activity:
618 Evidence from Human and Animal Studies. *Front Neurol*. 2017;8:188.
619 doi:10.3389/fneur.2017.00188
620 41. Meng Q, Su CH. The Impact of Physical Exercise on Oxidative and Nitrosative
621 Stress: Balancing the Benefits and Risks. *Antioxidants (Basel)*. May 7
622 2024;13(5)doi:10.3390/antiox13050573
623 42. Maasakkers CM, Weijs RWJ, Dekkers C, et al. Sedentary behaviour and brain
624 health in middle-aged and older adults: A systematic review. *Neuroscience &*
625 *Biobehavioral Reviews*. 2022/09/01/ 2022;140:104802.
626 doi:https://doi.org/10.1016/j.neubiorev.2022.104802
627 43. Arnardottir NY, Koster A, Domelen DRV, et al. Association of change in brain
628 structure to objectively measured physical activity and sedentary behavior in older
629 adults: Age, Gene/Environment Susceptibility-Reykjavik Study. *Behavioural Brain*
630 *Research*. 2016/01/01/ 2016;296:118-124.
631 doi:https://doi.org/10.1016/j.bbr.2015.09.005
632 44. Claassen JA. New cardiovascular targets to prevent late onset Alzheimer
633 disease. *Eur J Pharmacol*. Sep 15 2015;763(Pt A):131-4.
634 doi:10.1016/j.ejphar.2015.05.022
635 45. Carter S, Hartman Y, Holder S, Thijssen DH, Hopkins ND. Sedentary Behavior
636 and Cardiovascular Disease Risk: Mediating Mechanisms. *Exerc Sport Sci Rev*. Apr
637 2017;45(2):80-86. doi:10.1249/jes.0000000000000106

638 46. Durazzo TC, Insel PS, Weiner MW. Greater regional brain atrophy rate in
639 healthy elderly subjects with a history of cigarette smoking. *Alzheimer's & Dementia*.
640 2012/11/01/ 2012;8(6):513-519. doi:https://doi.org/10.1016/j.jalz.2011.10.006
641 47. Chen H, Dhana K, Huang Y, et al. Association of the Mediterranean Dietary
642 Approaches to Stop Hypertension Intervention for Neurodegenerative Delay (MIND)
643 Diet With the Risk of Dementia. *JAMA Psychiatry*. 2023;80(6):630.
644 doi:10.1001/jamapsychiatry.2023.0800
645 48. Harwood DG, Kalechstein A, Barker WW, et al. The effect of alcohol and
646 tobacco consumption, and apolipoprotein E genotype, on the age of onset in
647 Alzheimer's disease. *Int J Geriatr Psychiatry*. May 2010;25(5):511-8.
648 doi:10.1002/gps.2372
649 49. Herring D, Paulson D. Moderate alcohol use and apolipoprotein E-4 (ApoE-4):
650 Independent effects on cognitive outcomes in later life. *Journal of Clinical and*
651 *Experimental Neuropsychology*. 2018/04/21 2018;40(4):326-337.
652 doi:10.1080/13803395.2017.1343803
653 50. Lyall DM, Quinn T, Lyall LM, et al. Quantifying bias in psychological and physical
654 health in the UK Biobank imaging sub-sample. *Brain Communications*.
655 2022;4(3):fcac119. doi:10.1093/braincomms/fcac119

656