



Characterising the covariance pattern between lifestyle factors and structural brain measures: a multivariable replication study of two independent ageing cohorts

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ARTICLE INFO

Article history:

Received 9 February 2023

Revised 12 July 2023

Accepted 20 July 2023

Available online 26 July 2023

Keywords:

Old age

White matter hyperintensities

Modifiable lifestyle factors

Magnetic resonance imaging (MRI)

ABSTRACT

Modifiable lifestyle factors have been shown to promote healthy brain ageing. However, studies have typically focused on a single factor at a time. Given that lifestyle factors do not occur in isolation, multivariable analyses provide a more realistic model of the lifestyle–brain relationship. Here, canonical correlation analyses (CCA) examined the relationship between nine lifestyle factors and seven MRI-derived indices of brain structure. The resulting covariance pattern was further explored with Bayesian regressions. CCA analyses were first conducted on a Danish cohort of older adults ($n = 251$) and then replicated in a British cohort ($n = 668$). In both cohorts, the latent factors of lifestyle and brain structure were positively correlated (UK: $r = .37$, $p < 0.001$; Denmark: $r = .27$, $p < 0.001$). In the cross-validation study, the correlation between lifestyle–brain latent factors was $r = .10$, $p = 0.008$. However, the pattern of associations differed between datasets. These findings suggest that baseline characterisation and tailoring towards the study sample may be beneficial for achieving targeted lifestyle interventions.

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1. Introduction

The concept of dementia prevention by modifying lifestyle factors is inherently appealing. It promises to alter dementia risk in a way that

pharmacological medicine has yet to achieve. It has been suggested that up to 40% of dementia cases could be prevented or delayed by attenuating risks such as low education, midlife hearing loss, obesity, hypertension, late-life depression, smoking, physical inactivity, diabetes, and social isolation (Livingston et al., 2020). Prevalence of dementia is the most common outcome measure for studies investigating factors that decrease dementia risk, yet changes in brain structure can be observed years before dementia is diagnosed (Tondelli et al., 2012). Grey matter volume, white matter hyperintensities, and indices of white matter microstructure have been shown to vary with alcohol consumption (Topiwala et al., 2017), physical activity (Dunas et al., 2021), late-life depression (Demnitz et al., 2020), level of education (Nyberg et al., 2021), smoking (Gray et al., 2020), and degree of social activity (Anatürk et al., 2018). These structural brain measures can be

Abbreviations: BFinc, Inclusion Bayes factor; BIANCA, Brain Intensity AbNormality Classification Algorithm; CCA, Canonical correlation analysis; CES-D, Center for Epidemiological Studies Depression Score; eTIV, Estimated total intracranial volume; FA, Fractional anisotropy; MD, Mean diffusivity; LISA, Live active Successful Aging study; PASE, Physical Activity Scale for the Elderly; PSQI, Pittsburgh Sleep Quality Index; WMH, White matter hyperintensities.

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repeatedly mapped with magnetic resonance imaging (MRI), and their dynamic change with age may provide a better reflection of the interplay between decline in brain health and individual lifestyle.

To date, most studies have focused on the relationship between a single individual risk factor and brain health. Given that risk factors do not occur in isolation, multivariable analyses, where several measures are considered simultaneously, may provide a more realistic model of the association of modifiable lifestyle factors on brain ageing. With this aim, composite scores of dementia risk have been developed wherein each risk factor is typically given a binary score (denoting the absence or presence of the risk factor) and then summed. In a meta-analysis of 6 studies using composite risk factor scores, a dose-dependent relationship between modifiable risk factors and dementia incidence was observed (Peters et al., 2019). In one such dementia risk score, the Lifestyle for Brain Health (LIBRA) index, a one-point increase has been related to a 19% higher risk of dementia (Schiepers et al., 2018), as well as larger white matter hyperintensity volumes (Heger et al., 2021). In the UK Biobank, a healthy lifestyle score (0–5) based on five modifiable factors was associated with total grey matter volume and smaller white matter hyperintensity volumes (Pan et al., 2023). Yet while composite scores may capture additive effects, they are blind to the clustering nature of risk factors (Peters et al., 2019) and often incorrectly assume that all factors contribute equally to the risk of dementia onset. Further, since risk factors naturally co-occur, potentially due to shared underlying mechanisms, composite scores may also be overestimating resulting risks.

As an alternative, the use of multivariate methods can identify distinct behavioural patterns in lifestyle factors that confer a greater risk to brain health. For instance, when considering self-reported health behaviours, one study identified that diet (low fruit and vegetable consumption) and low physical activity were the main contributors to a latent factor associated with poorer memory (Kesse-Guyot et al., 2014). Others have used a combination of latent class and regression analyses to identify distinct clusters of lifestyle factors (diet, exercise, socialisation, church attendance, alcohol consumption and smoking) associated with subsequent dementia onset (Norton et al., 2012). Similarly, Cox and colleagues estimated a latent construct of vascular risk factors (e.g., smoking, hypertension, diabetes, and body mass index (BMI)) found to be associated with global structural MRI measures (Cox et al., 2019). To develop interventions promoting healthy brain ageing, we must reach a better understanding of the clustering of risk factors in the years preceding dementia onset—a long preclinical period which can span more than 2 decades (Josefsson et al., 2019).

This study applies a multivariate approach to investigate the association between lifestyle factors with MRI-derived measures of brain structure. One of the greatest challenges for fitting such models is that large datasets are required. Fortunately, the last decade has seen tremendous growth in the scale, scope, and accessibility of neuroimaging datasets in well-characterised cohorts. Using data from two such cohorts, this study aimed to (1) identify a covariance pattern between lifestyle factors associated with dementia risk and MRI-derived measures of brain structure; and (2) distinguish which lifestyle factors account for the most variance in brain structure measures. Modifiable lifestyle factors were selected to best reflect the risk factors outlined in the Lancet report on dementia prevention (Livingston et al., 2020). The indices of brain structure consisted of global MRI measures typically associated with age-related changes (global grey matter, white matter hyperintensities, cortical thickness, and global fractional anisotropy [FA] and mean diffusivity [MD]). In addition to the global measures, hippocampal volume was selected as a region of interest given its accelerated decline in ageing (Fjell et al., 2014). To test the individual covariation between lifestyle factors and MRI measures of brain structure, we identified modes of covariation using canonical

correlation analysis (CCA). CCA is a multivariate method used to investigate relationships between 2 sets of variables (Zhuang et al., 2020). Here, we applied CCA to identify a joint covariance pattern between lifestyle measures and indices of brain structure. Given 2 vectors of random variables, lifestyle factors and MRI indices of brain structure in this case, CCAs find the linear combinations of these 2 vectors which have maximum correlation with each other. To test the generalizability of our results, analyses were first conducted in a Danish cohort of older adults ($n = 251$) and then replicated in a cohort of British older adults ($n = 668$).

2. Methods

2.1. Study samples

2.1.1. LISA study

Participants in the Live active Successful Aging (LISA) study were community-dwelling older adults (ages 62–70 years). The LISA study is a randomised controlled trial of a 12-month supervised and monitored muscle strength training intervention (Eriksen et al., 2016). Only baseline data were included in this analysis. Potential participants were excluded if they engaged in more than 1 hour per week of strenuous exercise, had a current diagnosis of severe medical disease (e.g., active cancer), a musculoskeletal disease that could inhibit training, or used medication that could influence the effect of training (e.g., androgens). In the current analysis, we also excluded participants who reported a diagnosis of a neurological disorder ($n = 30$), had no T1-weighted MRI brain scan ($n = 117$), missing lifestyle or MR data ($n = 42$), or displayed significant artefacts on their MRI scan ($n = 11$). The LISA study was registered on [ClinicalTrials.gov](https://clinicaltrials.gov) (NCT02123641) and complies with the declaration of Helsinki. Ethical approval was received from the Ethical Committees of the Capital Region of Denmark (No. H-3-2014-017) and the Danish Data Protection Agency.

2.1.2. Whitehall II MRI sub-study

The replication sample was drawn from the Whitehall II MRI sub-study, described in detail elsewhere (Filippini et al., 2014). Briefly, the Whitehall II study is a prospective cohort of British civil servants established in 1985 (Marmot and Brunner, 2005). In the MRI sub-study, 800 Whitehall participants were randomly selected to attend an additional assessment phase at the University of Oxford. Participants were community dwelling-older adults (aged 60–85 years) with no history of neurological illness. In this analysis, participants were excluded if they presented significant abnormality or artefacts on structural MRI scans ($n = 47$) or had missing MRI or lifestyle measures ($n = 85$). The Whitehall II MRI sub-study has been registered on [ClinicalTrials.gov](https://clinicaltrials.gov) (NCT03335696). Ethical approval for the Whitehall II study was obtained from the University College London Medical School Committee on the Ethics of Human Research. The Whitehall II Imaging sub-study received ethical approval from the Oxford Central University Research Ethics Committee, and informed written consent was obtained from all participants.

2.2. Lifestyle measures

For each cohort, a single outcome measure was selected to best reflect either each exposure construct of interest or each modifiable lifestyle factor suggested by Livingston and colleagues (2020) (Tables 1 and 2). A full overview of the measures collected in the LISA and Whitehall II studies is available in Eriksen et al. (2016) and Filippini et al. (2014), respectively. If an exposure was not measured in both cohorts (e.g., air pollution, traumatic brain injury, and hearing loss), they were not included in the present study. Since only 6 participants reported having type 2 diabetes in the LISA study, this

Table 1

Overview of the lifestyle measures selected for analyses in each cohort

Construct of interest	Selected variable	
	LISA study	Whitehall II MRI
Sleep quality	"How often is your sleep poor or restless?" ^a	Score on the Pittsburgh Sleep Quality Index (PSQI) (Buysse et al., 1989)
Physical activity	Physical Activity Scale for the Elderly (PASE) (Washburn et al., 1993)	Community Healthy Activities Model Program for Seniors (CHAMPS) Questionnaire (Stewart et al., 2001)
Alcohol consumption	Units per week	Units per week
Loneliness	"Are there times when you are alone, when you would rather be together with others?" ^b	"Please tell me how often you have felt this way during the past week: <i>I felt lonely</i> ." ^c
Obesity	BMI	BMI
Blood pressure	Systolic blood pressure	Systolic blood pressure
Diabetes (type 2)	Yes/no	Yes/no
Smoking	Years of smoking	Current smoking status (yes/no)
Depressive symptoms	Depressive subscore of the Symptom Checklist (SCL-90) (Derogatis et al., 1973)	Center for Epidemiological Studies Depression Score (CES-D), recalculated to exclude the item on loneliness (Item 14) (Radloff, 1991)
Education	Years of education	Years of education

Key: LISA, live active successful aging; MRI, magnetic resonance imaging.

^a Translation from: "Hvor tit sover du dårligt og uroligt?" Answers are on a Likert scale (1 = Every night or almost every night; 2 = Several times per week; 3 = Several times per month; 4 = Several times per year; 5 = Never).^b Translation from: "Sker det nogensinde, at du er alene, selvom du egentlig havde mest lyst til at være sammen med andre?". Answers are on a Likert scale (1 = Yes, often; 2 = Yes, sometimes; 3 = Only rarely; 4 = No) and were multiplied by -1 so that increasing scores indicated more frequent feelings of loneliness.^c Item 14 from the CES-D (Radloff, 1991). (Rarely or none of the time (less than 1 day); Some or a little of the time (1–2 days); Occasionally or a moderate amount of time (3–4 days); Most or all of the time (5–7 days).

measure was excluded from the analyses (see Appendix A for results in Whitehall only).

2.3. MRI acquisition and pre-processing

In the LISA study, MRI scans were acquired at the Danish Research Centre for Magnetic Resonance in Hvidovre, Denmark, using a 3T TX Philips Achieva MRI Scanner (Best, the Netherlands) with a 32-channel

head coil. T1-weighted images were acquired over 244 slices with isotropic voxels of 0.85 mm³ (TR = 9.3 ms, TE = 2.7 ms, 288 × 288 matrix, and flip angle = 8°). Diffusion weighted images (DWI) were acquired over 66 slices, with 2 mm³ isotropic voxels (echo-planar imaging with sensitivity encoding factor 2, repetition time (TR) = 9265 ms, echo time (TE) = 85 ms, 112 × 112 matrix, 62 uniformly distributed directions at $b = 1000$ s/mm² and 1 at $b = 0$ s/mm²). Two additional volumes were collected at $b = 0$ with reverse phase-encoding directions used to correct

Table 2

Sample characteristics for the test (LISA) and replication (Whitehall II) cohorts

Sample characteristics (Mean ± SD)	Cohort	
	LISA study (n = 251)	Whitehall II (n = 668)
Data collection period	2014–2017	2012–2016
Age (years)	66.5 ± 2.4	69.7 ± 5.1
Females (n, %)	148, 59%	129, 19%
<i>Lifestyle variables</i>		
Education (years)	14.44 ± 2.07	14.76 ± 3.32
BMI	25.71 ± 3.73	26.07 ± 4.16
Feelings of loneliness	Yes, often = 6, 2.4% Yes, sometimes = 39, 15.5% Only rarely = 99, 39.4% No = 107, 42.6%	Most or all of the time = 7, 1% Occasionally or a moderate amount of the time = 25, 3.7% Some or a little of the time = 69, 10.3% Rarely or none of the time = 567, 84.9%
Physical activity	134.45 ± 55.76 total score on PASE	2752 ± 1808.51 total score on CHAMPS
Systolic BP (mm/Hg)	143.45 ± 17.35	141 ± 17.54
Smoking	16.85 ± 16.87 years	20, 3% smokers
Alcohol consumption (units/wk)	10.69 ± 8.35	15.12 ± 14.74
Depressive symptoms (score)	0.36 ± 0.42	5.03 ± 5.93
Sleep quality	Every night/almost every night = 16, 6.3% Several times per week = 31, 12.4% Several times per month = 58, 23.1% Several times per year = 99, 39.4% Never = 47, 18.7%	4.84 ± 2.98 total score on PSQI
<i>Brain outcomes</i>		
Global MD	0.00074 ± 0.00002	0.00068 ± 0.00003
Global FA	0.49 ± 0.018	0.48 ± 0.018
Total GM volume (cm ³)	All: 590.13 ± 47.41 F: 570.58 ± 41.52 M: 618.22 ± 40.89	All: 622.49 ± 50.24 F: 573.21 ± 41.02 M: 634.28 ± 44.80
Right hippocampal volume (cm ³)	All: 3.77 ± 0.38 F: 3.69 ± 0.37 M: 3.88 ± 0.37	All: 3.94 ± 0.44 F: 3.77 ± 0.36 M: 3.99 ± 0.44
Left hippocampal volume (cm ³)	All: 3.66 ± 0.39 F: 3.57 ± 0.36 M: 3.79 ± 0.40	All: 3.79 ± 0.43 F: 3.58 ± 0.38 M: 3.84 ± 0.42
WMH volume (cm ³)	All: 4.46 ± 5.43 F: 4.39 ± 4.94 M: 4.55 ± 5.76	All: 6.52 ± 3.86 F: 6.52 ± 4.94 M: 6.51 ± 6.51
Mean cortical thickness (mm)	All: 2.34 ± 0.075 F: 2.35 ± 0.073 M: 2.33 ± 0.075	All: 2.32 ± 0.074 F: 2.32 ± 0.069 M: 2.32 ± 0.075

Key: F, female; FA, fractional anisotropy; LISA, live active successful aging; M, male; MD, mean diffusivity; PASE, physical activity scale for the elderly; WMH, white matter hyperintensity.

for susceptibility artefacts. 3D fluid-attenuated inversion recovery (FLAIR) images were acquired over 202 slices with 1 mm³ isotropic voxels (TR = 4800 ms, TE = 328 ms, 256 × 256 matrix).

In the Whitehall study, MRI scans were acquired at the Wellcome Centre for Integrative Neuroimaging (Centre for Functional Magnetic Resonance Imaging of the Brain, FMRIB) in Oxford, United Kingdom. Two 3T MRI scanners were used: Siemens Magnetom Verio with a 32-channel head coil and a Siemens Magnetom Prisma with a 64-channel head-neck coil (Erlangen, Germany). For acquisition details, please see [de Lange et al. \(2020\)](#).

For both cohorts, tools from the FMRIB Software Library ([Smith et al., 2004](#)) were applied to extract global FA and MD values from the diffusion weighted images. The diffusion tensor imaging (DTI) processing pipelines for LISA and Whitehall are detailed elsewhere ([Demnitz et al., 2021](#); [Zsoldos et al., 2018](#)). Total gray matter (GM) volume, right and left hippocampal volume (Hipp), cortical thickness and estimated Total Intracranial Volume (eTIV) were obtained from the T1 images using FreeSurfer v6.0 ([Fischl et al., 2002](#)). In LISA, white matter hyperintensity (WMH) volume was derived from masks manually drawn on the FLAIR image by a team of radiographers at Danish Research Centre for Magnetic Resonance. In Whitehall, global WMHs were obtained from FLAIR images using the Brain Intensity AbNormality Classification Algorithm tool, an automatic segmentation algorithm ([Griffanti et al., 2016](#)).

2.3.1. Covariates

Prior to statistical analysis, all variables were residualized with respect to age and sex using linear models (e.g., BMI ~ age + sex). Volumetric brain measures (WMH, GM, Hipp) were also residualized with respect to eTIV. In the Whitehall study, a further covariate of no interest was included for the identity of the MR scanner (Verio or Prisma). To illustrate the influence of age and sex on individual brain outcomes, additional models including these variables are presented in [Appendix B](#).

2.4. Statistical analyses

Statistical analyses were carried out in RStudio version 1.3.1056 ([RStudio Team, 2020](#)), running on R version 4.0.2 (R Core Team, 2020), with the CCA ([Gonzalez & Dejean, 2021](#)), candisc ([Friendly & Fox, 2021](#)), BayesFactor ([Morey & Rouder, 2018](#)) and ggplot2 ([Wickham, 2016](#)) packages.

2.4.1. Pre-registration

The hypotheses, methods, and analysis plan for this study were registered in a public repository (<https://osf.io/pfq4j>). Registration occurred after obtaining the results from the first cohort (LISA), but prior to the cross-study validation and replication analyses on the second cohort (Whitehall).

2.4.2. Canonical correlation analyses (CCA)

CCA was applied to derive a linear combination of latent constructs (or canonical variates) of lifestyle and brain structure measures. The obtained linear combination between canonical variates generates a canonical correlation coefficient, which is a Pearson's r statistic ([Sherry & Henson, 2005](#)). This method has previously been used in cognitive neuroscience to identify multivariate patterns between behaviour and neuroimaging datasets (for review, see [Zhuang et al. \[2020\]](#)). One of the challenges of CCA is overfitting, leading to overestimated correlations between the canonical variates. To overcome this, we tested the validity of the CCA model in a second independent dataset.

First, the full CCA model canonical model was evaluated using Wilk's λ , which are calculated from the eigenvalues and converted to F statistics using Rao's approximation ([Friendly & Fox, 2021](#)). The

squared canonical correlations (R_c^2), analogous to the R^2 in regressions, are reported to represent the proportion of variance shared by the pair of canonical variates. If a canonical correlation was significant (p -value ≤ 0.05), the following statistics were examined to interpret the contribution of each variable: (1) structure coefficients (r_s), which are comparable to bivariate correlations between the measured and canonical variates, and (2) squared structure coefficients (r_s^2), which represent the amount of variance the observed variables shares with its respective variate ([Sherry & Henson, 2005](#)). Squared structure coefficients can be interpreted as loadings, and $r_s \geq 0.3$ were interpreted as substantive loadings ([Dardas & Ahmad, 2014](#)). The validity of the canonical correlation analysis was tested by (1) performing a 5-fold cross-validation (with 1000 iterations) to estimate how much the correlation is expected to drop when tested on new data and then (2) bringing forward the coefficients from our main CCA for validation in a second independent dataset. Since canonical correlations tend to be overestimated, we expected that the canonical correlation observed in the replication set would resemble the average correlation from the 5-fold cross-validation (and reported in this article's pre-registration). Finally, in a complementary analysis, a separate CCA was conducted in the second dataset to examine whether similar covariance patterns emerged in the 2 datasets in a data-driven approach.

2.4.3. Bayesian regressions

A Bayesian framework was applied to test the strength of the evidence in favour of including each lifestyle factor in models of individual brain outcomes. Using default priors (Jeffrey-Zelner-Siow, r scale = 0.354), 8 multiple Bayesian regressions were conducted. Each model had the brain measure as a dependent variable and all lifestyle measures as independent variables (e.g., globalFA ~ depressive symptoms + sleep quality + physical activity + alcohol consumption + smoking years + education years + BMI + loneliness + systolic blood pressure). The inclusion Bayes factor (BF_{inc}) for each lifestyle measure was then used to depict their individual contributions in a heatmap. The BF_{inc} indicates the relative performance for models that include that particular factor, compared to all models that do not. In line with evidence categories proposed by [Wetzels and colleagues \(2011\)](#), BF_{inc} above 1, 3, or 10 were interpreted as anecdotal, moderate, or strong evidence in favour of the inclusion of the variable in explaining the data, respectively. Symmetrically, BF_{inc} values below 0.1 (1/10), 0.3 (1/3), or 1 (1/1) were interpreted as strong, moderate, or anecdotal evidence in favour of the exclusion of the variable in explaining the data, respectively.

In addition, univariate Bayesian regressions were conducted for each lifestyle factor and brain outcome pair (e.g., globalFA ~ depressive symptoms). Results from the univariate regressions are reported in the [Supplementary Information \(Appendix C\)](#).

3. Results

3.1. Canonical correlation analysis

Using CCA, we tested the lifestyle-brain relationship in two cohorts of older adults ([Table 2](#)). In the LISA cohort, the relationship between the 9 lifestyle variables and 7 age-related measures of brain structure was significant (Wilk's $\lambda = 0.68$, $F[63, 1329.6] = 1.5$, $p = 0.008$). While the full model explained ~38.5% of the variance shared between the lifestyle and brain datasets ([Appendix D.1](#)), only the first canonical pair explained a significant amount of shared variance between the 2 datasets ($R_c^2 = 0.136$; [Appendix D.2](#)). Therefore, only the first lifestyle-brain covariate pair was unpacked further.

A canonical correlation of 0.37 ($p < 0.001$) was observed between the lifestyle and brain variates in the first dimension ([Fig. 1C](#)). The

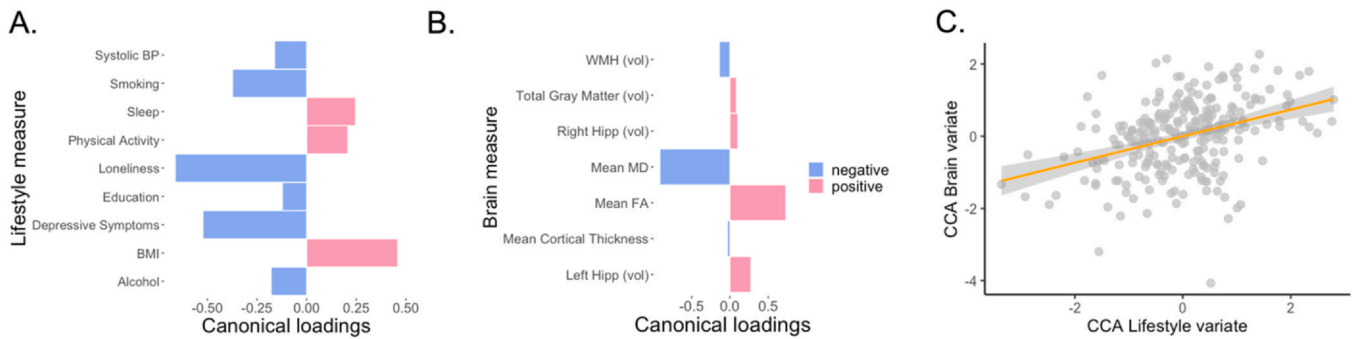


Fig. 1. Canonical loadings indicate the correlation between each (A) lifestyle or (B) brain measure and their respective canonical variates. The canonical correlation between the brain and lifestyle variates ($r_s = 0.37$) is shown in (C). Abbreviations: CCA, canonical correlation analysis; FA, fractional anisotropy; MD, mean diffusivity; WMH, white matter hyperintensity.

Table 3

Canonical solution for the lifestyle and brain variates in the first domain for the LISA cohort

	Coef	r_s	r_s^2 (%)	Cross-loadings (r_s)
<i>Lifestyle variate</i>				
Depressive symptoms	-0.392	-0.522	27.245	-0.192
Sleep quality	-0.077	0.246	6.041	0.090
Physical activity	0.189	0.207	4.303	0.076
Alcohol consumption	-0.139	-0.179	3.200	-0.066
Smoking (years)	-0.307	-0.373	13.920	-0.137
Education (years)	-0.176	-0.123	1.501	-0.045
BMI	0.536	0.458	20.963	0.169
Loneliness	-0.488	-0.662	43.814	-0.244
Systolic blood pressure	-0.281	-0.162	2.611	-0.059
<i>Brain variate</i>				
Global FA	-0.222	0.731	53.441	0.269
Global MD	-1.146	-0.916	83.968	-0.337
Right Hippocampal volume	-0.341	0.102	1.046	0.038
Left Hippocampal volume	0.519	0.274	7.501	0.101
WMH (volume)	0.073	-0.139	1.937	-0.051
Cortical thickness	-0.218	-0.034	0.114	-0.012
Total GM (volume)	0.087	0.086	0.743	0.032

Cross-loadings (r_s) represent a bivariate correlation between the measured variable and the opposite variate (e.g., physical activity-brain variate). $r_s \geq 0.3$ are highlighted in bold.

Key: Coef, standardised canonical coefficients; FA, fractional anisotropy; GM, gray matter; LISA, live active successful aging; MD, mean diffusivity; r_s , structure coefficient; r_s^2 , squared structure coefficient; WMH, white matter hyperintensity.

canonical loadings between each measured variable and their corresponding canonical variates are illustrated in Fig. 1. Feelings of loneliness, BMI, depressive symptoms, and years of smoking were the primary contributors to the lifestyle variate ($r_s \geq 0.3$). Better sleep quality and increased BMI were positively associated with the brain variate, which was indicative of increased brain health. Length of smoking history, more frequent feelings of loneliness and increased depressive symptoms were negatively associated with the brain variate (i.e., poorer brain health). Canonical loadings for the brain variate followed the expected direction, with negative contributions from white matter hyperintensity volume and mean global MD and positive contributions from volumetric measures of total gray matter, hippocampus and mean global FA. Mean cortical thickness had a negligible contribution to the brain variate, meaning that the bivariate correlation between cortical thickness and the brain latent was close to 0 ($r_s = -0.034$). Cross-loadings, also reported in Table 3, indicate the bivariate correlations between a particular measure and the opposing variate.

Bayesian multiple regressions were conducted to complement our interpretation of CCA results (Fig. 1D). Across all models of brain measures, only depressive symptoms, education, smoking, and

loneliness had inclusion Bayes factors greater than 3, suggesting at least moderate evidence for their inclusion into the respective models (Appendix E). There was strong and moderate evidence in favour of smoking being included in models of global FA ($BF_{inc} = 11.8$) and global MD ($BF_{inc} = 3.24$), respectively. Similarly, there was moderate and strong evidence in favour of depressive symptoms contributing to models with global DTI indices as outcomes (global FA: $BF_{inc} = 10.08$; global MD: $BF_{inc} = 3.17$). Loneliness showed moderate evidence for being included in a model with global MD as the outcome ($BF_{inc} = 3.72$). Further, the inclusion Bayes Factor indicated moderate evidence in favour of including education in models of total GM volume ($BF_{inc} = 4.86$) and right hippocampal volume ($BF_{inc} = 3.64$).

3.2. Cross-validation and replication

In the 5-fold cross-validation analysis, the average canonical correlation was reduced from 0.37 to 0.14 ± 0.09 SD. Since canonical correlations tend to be overestimated, we expected that the canonical correlation from this 5-fold cross-validation would be indicative of the canonical correlation observed in the cross-study validation. In the cross-study validation, the standardised canonical coefficients from the CCA model in the LISA study were taken across to a second independent sample of older adults, the Whitehall study. The resulting lifestyle-brain correlation in this cross-study validation was $r = 0.102$ ($p = 0.008$), resembling the average correlation from the 5-fold cross-validation (Appendix F).

3.3. Independent sample replication

A second CCA was conducted in the Whitehall study, to examine whether similar covariance patterns emerged in the two datasets in a data-driven approach. In the Whitehall study ($n = 668$), the relationship between the 9 lifestyle variables and seven measures of brain structure was significant (Wilks's $\lambda = 0.86$, $F[63, 3678] = 1.63$, $p = 0.001$; Appendix G.1). Since only the first canonical pair explained a significant amount of shared variance between lifestyle and brain measures ($R^2 = 0.072$; Appendix G.2), only the first lifestyle-brain covariate pair was further examined.

A canonical correlation of 0.27 ($p < 0.001$) was observed between lifestyle and brain variates in the first dimension. In the lifestyle variate, physical activity, alcohol consumption, education, systolic blood pressure, and BMI were the primary contributors ($r_s \geq 0.3$). Of these variables, BMI and blood pressure were negatively associated with the brain health variate. In contrast, increased education, physical activity and alcohol consumption were associated with better brain health, as indexed by the brain variate. The main



Fig. 2. Heatmap of the BF_{inc} obtained from multiple Bayesian regression analyses in the LISA (A) and Whitehall (B) studies, wherein each column represents a separate regression model. In the models where lifestyle factors showed at least moderate evidence (Inclusion $BF > 3$) in favour of being included, the direction of the relationship is indicated by blue or pink (negative or positive, respectively). BF_{inc} above 3 or 10 were interpreted as moderate or strong evidence, respectively, in favour of the inclusion of that variable in explaining the data. Abbreviations: BF_{inc} , inclusion Bayes factor; FA, fractional anisotropy; LISA, live active successful aging; MD, mean diffusivity; WMH, white matter hyperintensity. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

contributors to the brain variate were WMH and global FA ($r_s \geq 0.3$), with negative and positive canonical loadings, respectively (Table 4).

In the Bayesian multiple regressions, only systolic blood pressure, physical activity and BMI revealed moderate or strong evidence in favour of being substantive contributors to a model of WMH (Fig. 2; Appendix H). The evidence was of moderate strength for physical activity ($BF_{inc} = 9.52$) and BMI ($BF_{inc} = 3.46$), and strong for the inclusion of systolic blood pressure ($BF_{inc} = 40.26$).

3.4. Sensitivity analyses

Compared to Whitehall, participants in the LISA study were younger and more likely to be female. To explore the role of age and sex differences on the replicability of our findings, sensitivity analyses were conducted in sub-samples of the Whitehall cohort selected to match the age and sex distribution of the LISA study, respectively (Appendices I and J). In both cases, there was still no overlap between results regarding lifestyle factors with moderate or higher evidence strength in favour of being included in a model. Of note, these analyses were post-hoc and not planned for in the study's pre-registration.

4. Discussion

In this study, the relationship between latent lifestyle factors and MRI-derived metrics of brain structure from one cohort was validated on a second independent sample of older adults. In both cohorts, we found that latent lifestyle factors were positively associated with a latent measure of brain structure. This is in line with a body of literature indicating that modifiable lifestyle factors are associated with indices of preserved brain structure in old age (Bittner et al., 2021; Wassenaar et al., 2019). Although the lifestyle-brain relationship could be validated across studies, it was consistently weak ($r \approx 0.1$), corresponding to an explained variance of 1%. This means that if we knew all the latent lifestyle factors outlined in our analysis, it would explain only 1% of the variance in brain structure measured by MRI. However, this assumes that the covariance pattern between lifestyle and brain outcomes for the different cohorts is common across cohorts. Our study shows that the pattern of associations between lifestyle and brain outcomes differed substantively between the 2

Table 4

Canonical solution for the lifestyle and brain variates in the first domain for the Whitehall II MRI cohort

	Coef	r_s	r_s^2 (%)	Cross-loadings (r_s)
<i>Lifestyle variate</i>				
Depressive symptoms	-0.165	0.002	0	0.001
Sleep quality	-0.127	0.012	0.015	0.003
Physical activity	0.326	0.428	18.307	0.115
Alcohol consumption	0.307	0.336	11.303	0.090
Smoking	0.086	0.100	1.001	0.027
Education (years)	0.392	0.438	19.208	0.117
BMI	-0.615	-0.704	49.532	-0.188
Loneliness	0.267	0.204	4.142	0.054
Systolic blood pressure	-0.274	-0.334	11.221	-0.090
<i>Brain variate</i>				
Global FA	1.248	0.367	13.449	0.098
Global MD	1.293	-0.103	1.055	-0.027
Right Hippocampal volume	0.132	-0.134	1.791	-0.036
Left Hippocampal volume	-0.360	-0.202	4.086	-0.054
WMH (volume)	-0.787	-0.754	56.914	-0.202
Cortical thickness	0.162	-0.182	3.297	0.049
Total GM (volume)	-0.138	0.024	0.059	0.007

Cross-loadings (r_s) represent a bivariate correlation between the measured variable and the opposite variate (e.g. physical activity-brain variate). $r_s \geq 0.3$ are highlighted in bold.

Key: Coef, standardised canonical coefficients; FA, fractional anisotropy; GM, gray matter; MD, mean diffusivity; MRI, magnetic resonance imaging; r_s , structure coefficient; r_s^2 , squared structure coefficient; WMH, white matter hyperintensity.

cohorts – suggesting that the similar canonical correlation did not reflect shared mechanisms across cohorts.

Findings from observational studies of modifiable risk factors serve to inform interventions aimed at promoting healthy brain ageing (Ngandu et al., 2015; Yaffe & Hoang, 2013). Considering our analyses, we add a word of caution to this pipeline: future lifestyle interventions should be tailored to suit their target populations. If the lifestyle factors most associated with brain health can vary from sample to sample, then this should also be expected for intervention targets. For example, it could be argued that while the Danish sample might benefit from a smoking cessation programme, a physical activity intervention with particular attention to blood pressure management might be more suitable for the British sample. Others have further illustrated this with evidence that the estimated potential of dementia prevention through modifiable factors varies

across geographical regions. Compared to Europe and the US, there was a greater dementia prevention potential, as calculated by population attributable fractions, in Latin America, India, and China (Mukadam et al., 2019). Both studies included in our analyses stemmed from high-income countries and samples in northern Europe. This is in keeping with a geographical limitation of the field: almost 80% of studies on modifiable lifestyle factors and cognitive decline have emerged from the US or Europe (Beydoun et al., 2014). Differences in covariance patterns may, therefore, be even more marked in other geographical regions.

There is also pronounced individual variability in the benefits of lifestyle factors on the ageing brain within cohorts. This has been well documented in physical activity interventions, leading to the recommendation that thorough baseline characterisation may benefit the predictive power of physical activity interventions (von Cederwald et al., 2023). For example, baseline levels of white matter lesion load can limit the potential for brain plasticity following exercise (von Cederwald et al., 2023). A participant's sex, baseline physical activity levels and genotype (e.g., Apolipoprotein E4) are other potential moderators of the effect of physical activity on the ageing brain (Barha et al., 2021; Demnitz et al., 2023). These sources of individual variability may contribute to the weak signal of the observed lifestyle-brain associations, and further stress why characterising your sample is so important to make recommendations. Accordingly, baseline characterisation of participants in interventions is advisable for designing tailored interventions to promote healthy brain ageing.

To identify which lifestyle factors accounted for the most variance in brain structure measures, we complemented our analyses with Bayesian regressions. Across cohorts, there was no overlap in lifestyle factors with moderate-or-higher levels of evidence in favour of being associated with a particular brain outcome. One explanation is that the effect size of individual associations was simply too weak to generalise from one cohort to another. In LISA, there was moderate or strong evidence for loneliness, depressive symptoms, education and smoking to be included as independent variables in Bayesian regressions of individual brain outcomes. The direction of the relationships was in accordance with previously reported univariate brain-lifestyle relationships. In the Bayesian regression from the Whitehall study, the cardiovascular risk factors (blood pressure, physical activity, and BMI) prevailed. In line with the vascular aetiology of WMHs (Moroni et al., 2018), these lifestyle measures contributed to explaining the association with WMH volume, but no other brain outcome. Given that WMH volume was markedly higher in the British cohort ($t[349.23] = 5.51$, $p < 0.001$), it is plausible that cross-study differences in white matter lesion load contributed to the lack of generalisability in covariance patterns between the two studies. Nonetheless, the difference in WMH volume difference was no longer significant when adjusting for age, sex and estimated intracranial volume ($t[330.16] < 0.001$, $p = 1$). In the Whitehall study, contrary to expectations and previous findings (Topiwala et al., 2017), alcohol consumption loaded positively on the lifestyle factor in the CCA – suggesting that a higher consumption was associated with better brain health. However, it is important to stress that there was no evidence in favour of an association between alcohol and any brain outcome in the Bayesian regressions. It is likely, therefore, that the positive loading in the CCA is reflective of the collinearity between alcohol consumption and education or socio-economic status.

4.1. Methodological considerations

Strengths of our study included its multivariable nature, spanning most of the lifestyle measures focused on in the ageing literature, and the analysis of two large MRI cohorts from different countries. Lifestyle risk scores often apply cut-offs for recommended health behaviours, in

this way binarizing variables into “beneficial” or “harmful”. Here, whenever possible, we opted to use the continuous forms of the lifestyle variables, as this may be more sensitive to detect lifestyle-brain relationships (Anatürk et al., 2021). To generalise across samples, the most comparable items were selected from each study. Even so, there were differences in the acquisition and processing of both lifestyle and brain measures. For example, the WMH volumes in the LISA study were obtained from manual tracing by radiographers, while the same outcome stemmed from an automatic segmentation tool in the Whitehall study. Further, while sleep quality consisted of a single item measure in LISA, the total score from a standardised questionnaire was used in Whitehall. In one cohort, the use of “years of smoking” arguably reflected a more cumulative lifelong health behaviour than the binary measure (smoking vs not smoking) used in the other cohort. Accordingly, there are systematic differences between studies which may be overestimating their differences.

One difference between the 2 cohorts was the sex proportion. While the LISA sample was 59% female, this proportion was only 19% in the participants sampled from the Whitehall study. The male over-representation observed in the Whitehall study reflects the sex distribution of the British civil-service workforce in the 1980s, from which that cohort was recruited. Sex has been shown to moderate various lifestyle-brain relationships, such as the link between physical activity and parahippocampal volume (Casaletto et al., 2020). Although all measures included in our analyses were adjusted for sex, other non-linear or moderating effects may be unaccounted for. In a sensitivity analysis, we repeated our analyses on a sub-sample of the Whitehall study with 59% female participants to test whether this resulted in a covariance pattern more similar to the one in LISA (Appendix I). This was not found to be the case: matching the samples in terms of proportion of female participants did not produce more comparable findings between the two datasets. Similarly, restricting the Whitehall sample to match the slightly younger age range of the LISA study did not result in a more similar pattern of results between the two datasets (Appendix J).

Beyond the lifestyle factors included here, air pollution, hearing impairment and traumatic brain injury have also been shown to modify risk of reduced brain health (Livingston et al., 2020). Unfortunately, these variables were not available in the included datasets. Epidemiological studies have also examined the benefits of specific nutrients, whole diets, and individual foods (e.g., folate intake, Mediterranean diet, fruit and vegetable consumption) on brain health (for review, see Jensen et al. [2021]). It would be of interest to replicate our analyses with these additional modifiable lifestyle factors. Finally, given our focus on modifiable lifestyle factors, the current study does not account for the (undeniably important) role of non-modifiable factors such as genetics on brain structure (Satizabal et al., 2019), lifestyle factors (Topiwala et al., 2022) or their interactions (Barha et al., 2021).

4.2. Conclusion

Our CCA approach enabled us to identify a significant, albeit weak, correlation between latent lifestyle and brain factors that could be validated across studies of older adults. However, in multiple regressions, the pattern of observed associations between lifestyle and brain measures differed between samples. Baseline characterisation of participants in interventions may therefore be advisable for designing tailored and effective interventions to promote healthy brain ageing.

CRediT authorship contribution statement

Naiara Demnitz: Conceptualization, Methodology, Formal analysis, Writing – original draft, Funding acquisition. **Oliver Hulme:**

Methodology, Writing – review & editing. **Hartwig Siebner:** Resources, Supervision, Writing – review & editing. **Michael Kjaer:** Resources, Supervision, Writing – review & editing. **Klaus Ebmeier:** Conceptualisation, Funding acquisition, Resources, Supervision, Writing – review & editing. **Carl-Johan Boraxbekk:** Conceptualisation, Supervision, Writing – review & editing. **Claire Gillan:** Conceptualisation, Methodology, Funding acquisition, Writing – review & editing, Supervision.

Verification

The submission of this manuscript has been approved by all authors. This work has not been published previously and is not under consideration for publication elsewhere.

Disclosure statement

The authors report no conflicts of interest.

Acknowledgements

This work was supported by funding from the Global Brain Health Institute (GBHI), Alzheimer's Association and Alzheimer's Society (grant GBHI ALZ UK-21-723783). The LISA study was supported by the Nordea Foundation (grant from Center for Healthy Aging, University of Copenhagen, Denmark) and the Whitehall MRI Sub-study was funded by the UK Medical Research Council (G1001354). HRS holds a 5-year professorship in precision medicine at the Faculty of Health Sciences and Medicine, University of Copenhagen which is sponsored by the Lundbeck Foundation (grant R186-2015-2138). ND is supported by funding from the Lundbeck Foundation (grant R380-2021-1269). OJH was funded by a Novo Nordisk Foundation Exploratory Interdisciplinary Synergy grant (ref. NNF20OC0064869). KPE was supported by EU Horizon 2020 grant agreement number 732592 (Lifebrain). We are grateful to Dr. Athanasia Mowinckel for help with the processing of MR images from the Whitehall cohort.

Appendix A. Supporting material

Supplementary data associated with this article can be found in the online version at [doi:10.1016/j.neurobiolaging.2023.07.023](https://doi.org/10.1016/j.neurobiolaging.2023.07.023).

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