

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

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Abstract

Modifiable lifestyle factors have been shown to promote healthy brain ageing. However, most studies to date have focused on one factor at a time. Given that lifestyle factors do not occur in isolation, multivariable analyses may provide a more realistic model of the impact of modifiable lifestyle factors on brain ageing. We examined the relationship between nine lifestyle factors and seven MRI-derived indices of brain structure using canonical correlation analysis (CCA). The resulting covariance pattern was then explored with Bayesian regressions. CCA analyses were first completed in a Danish cohort of older adults ($n = 251$) and then replicated in an independent cohort from the United Kingdom ($n = 668$). In both cohorts, the latent lifestyle factors were positively associated with the latent structural brain measures (UK: $r = 0.37$, $p < 0.001$; Denmark: $r = 0.27$, $p < 0.001$). In the cross-validation study, the correlation between lifestyle-brain latent factors was $r = 0.10$, $p = 0.008$. However, the pattern of univariate associations differed between datasets. Taken together, these findings suggest that lifestyle interventions would benefit from baseline characterisation and tailoring towards the study sample.

Keywords: Old age; white matter hyperintensities; modifiable lifestyle factors; MRI

1. Introduction

The idea 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), and degree of social activity (Anaturk et al., 2018). These structural brain measures can be 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 predictors 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 additive risk factor is typically given a binary score (1 = risk, 0 = no risk). In a meta-analysis of six studies using composite risk factor scores, a dose-dependent relationship between modifiable risk factors and dementia incidence was observed (Peters et al., 2019). Yet while composite scores may

capture additive effects, they are blind to the clustering nature of risk factors (Peters et al., 2019) and 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 dementia risk. 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). Similarly, Norton and colleagues (2012) 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. 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 two 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 typically associated with age-related changes. 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 aims 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.

To test the individual covariation between modifiable lifestyle factors and MRI measures of brain structure sensitive to age-related changes (global grey matter, hippocampal volume, white matter hyperintensities and global FA and MD), we identified modes of covariation using canonical correlation analysis (CCA). CCA is a multivariate method used to investigate relationships between two 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 two vectors of random variables, lifestyle factors and MRI indices of brain structure in this case, CCAs find the linear combinations of these two 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/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 use that could influence the effect of training (e.g., androgens). We also excluded participants who reported a diagnosis of a neurological disorder, had no T1-weighted MRI brain scan, missing lifestyle data, or displayed significant artefacts on their MRI scan. The LISA study was registered on 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 & 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 on structural MRI scans (e.g., evidence of infarction), or had missing MRI or lifestyle measures. The Whitehall II MRI Sub-study has been registered on 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) (Table 1). A full overview of the measures collected in the LISA and Whitehall II studies is available in Ericksen 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 measure was excluded from the analyses.

Table 1. Overview of the lifestyle measures selected for analyses in each cohort.

Construct of interest	Selected variable	
	<i>LISA Study</i>	<i>Whitehall II MRI</i>
Sleep quality	“How often is your sleep poor or restless?”*	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)	CHAMPS Physical Activity Questionnaire for Older Adults (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?”**	“Please tell me how often you have felt this way during the past week: <i>I felt lonely.</i> ” ***
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

* 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).

** 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.

*** 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))

2. 3 MRI acquisition and pre-processing

In the LISA study, MRI scans were acquired at the Danish Research Centre for Magnetic

Resonance (DRCMR) in Hvidovre, Denmark, using a 3T TX Philips Achieva MRI Scanner

145 (Best, the Netherlands) with a 32-channel head coil. T1-weighted images were acquired over
146 244 slices with isotropic voxels of 0.85 mm³ (TR = 9.3 ms, TE = 2.7 ms, 288 × 288 matrix,
147 and flip angle = 8°). DWI scans were acquired over 66 slices, with 2mm³ isotropic voxels
148 (EPI with SENSE factor 2, TR = 9265 ms, TE = 85 ms, 112 × 112 matrix, 62 uniformly
149 distributed directions at $b = 1000$ s/mm² and 1 at $b = 0$ s/mm²). Two additional volumes were
150 collected at $b = 0$ with reverse phase-encoding directions used to correct for susceptibility
151 artefacts. 3D FLAIR images were acquired over 202 slices with 1mm³ isotropic voxels (TR=
152 4800ms, TE = 328ms, 256×256 matrix).

153
154 In the Whitehall study, MRI scans were acquired at the Wellcome Centre for Integrative
155 Neuroimaging (Centre for Functional Magnetic Resonance Imaging of the Brain, FMRIB) in
156 Oxford, United Kingdom. Two 3T MRI scanners were used: Siemens Magnetom Verio with
157 a 32-channel head coil and a Siemens Magnetom Prisma with a 64-channel head-neck coil
158 (Erlangen, Germany). For acquisition details, please see (de Lange et al., 2020).

159
160 For both cohorts, tools from the FMRIB Software Library (Smith et al., 2004) were applied to
161 extract global fractional anisotropy (FA) and mean diffusivity (MD) values from the diffusion
162 weighted images. The DTI processing pipelines for LISA and Whitehall are detailed
163 elsewhere (Demnitz et al., 2021; Zsoldos et al., 2018). Total gray matter (GM) volume, right
164 and left hippocampal volume (Hipp), cortical thickness and estimated Total Intracranial
165 Volume (eTIV) were obtained from the T1 images using FreeSurfer v6.0 (Fischl et al., 2002).
166 In LISA, white matter hyperintensity (WMH) volume was derived from masks manually
167 drawn on the FLAIR image by a team of radiographers at DRCMR. In Whitehall, global
168 WMHs were obtained from FLAIR images using the Brain Intensity AbNormality

Classification Algorithm (BIANCA) tool, an automatic segmentation algorithm (Griffanti et al., 2016).

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).

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 & Sievert, 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^2_c), 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 ($p\text{-value} \leq 0.05$), 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 (a) 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 (b) 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 two 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 as a predictor of individual brain outcomes. Using default priors (Jeffrey-Zelner-Siow, r scale = 0.354), univariate Bayesian regressions were conducted for each lifestyle factor and brain outcome pair (e.g., globalFA ~ depressive symptoms). 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 predictive 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, eight multiple Bayesian regressions were conducted. Each model had the brain measure as a dependent variable and all lifestyle measures as predictors (e.g., globalFA ~ depressive symptoms + sleep quality + physical activity + alcohol consumption + smoking years + education years + BMI + loneliness + systolic blood pressure). Results from the multiple regressions are reported in the Supplementary Information.

3. Results

3.1. CCA

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 A), only the first canonical pair explained a significant amount of shared variance between the two datasets ($R^2_c = 0.136$; Appendix B). Therefore, only the first lifestyle-brain covariate pair was unpacked further.

Table 2. Sample characteristics for the test (LISA) and replication (Whitehall II) cohorts.

Sample characteristics (Mean \pm SD)	Cohort	
	<i>LISA Study (n = 251)</i>	<i>Whitehall II (n = 668)</i>
Data collection period	2014 - 2017	2012 - 2016
Age (years)	66.5 \pm 2.4	69.7 \pm 5.1
Females (n, %)	148, 59%	129, 19%
<i>Lifestyle variables</i>		
Education (years)	14.44 \pm 2.07	14.76 \pm 3.32
BMI	25.71 \pm 3.73	26.07 \pm 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 \pm 55.76 total score on PASE	2752 \pm 1808.51 total score on CHAMPS
Systolic BP (mm/Hg)	143.45 \pm 17.35	141 \pm 17.54
Smoking	16.85 \pm 16.87 years	20, 3% smokers
Alcohol consumption (units/wk)	10.69 \pm 8.35	15.12 \pm 14.74
Depressive symptoms (score)	.36 \pm .42	5.03 \pm 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 \pm 2.98 total score on PSQI
<i>Brain outcomes</i>		

Global MD	.00074 ± .00002	.00068 ± .00003
Global FA	.49 ± .018	.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 ± .075 F: 2.35 ± 0.073 M: 2.33 ± 0.075	All: 2.32 ± .074 F: 2.32 ± 0.069 M: 2.32 ± 0.075

F, Female; M, Male.

A canonical correlation of 0.37 ($p < 0.001$) was observed between the lifestyle and brain variates in the first dimension (Figure 1C). The canonical loadings between each measured variable and their corresponding canonical variates are illustrated in Figure 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 grey 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 univariate regressions were conducted to complement our interpretation of CCA results (Figure 1D). Across all models predicting 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 C). The evidence in favour of including smoking as a predictor was strong for global FA ($BF_{inc} = 17.65$) and moderate for global MD ($BF_{inc} = 3.98$). There was strong evidence in favour of including depressive symptoms as a predictor of global FA ($BF_{inc} = 32.46$) and global MD ($BF_{inc} = 18.92$). Loneliness showed moderate and strong evidence for inclusion as a predictor of global FA ($BF_{inc} = 5.27$) and global MD ($BF_{inc} = 39.7$), respectively. Further, the inclusion Bayes Factor indicated moderate evidence in favour of education as a predictor of total GM volume ($BF_{inc} = 3.05$).

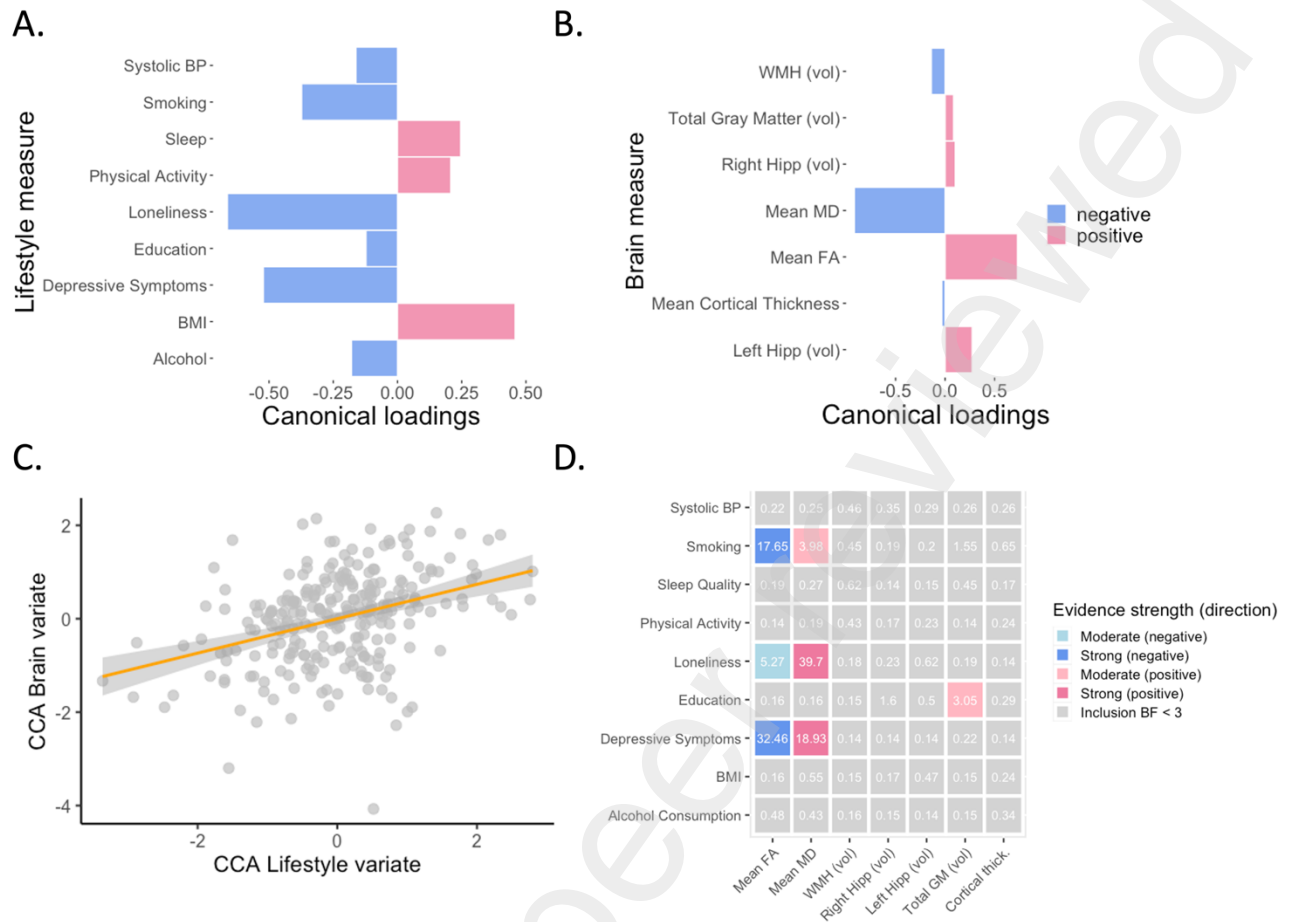


Figure 1. Canonical loadings indicate the correlation between each (A) lifestyle or (B) brain measure and their respective canonical variates. The canonical correlation between the brain and lifestyle variates ($r_s = 0.37$) is shown in C. Panel (D) presents a heatmap of the BF_{inc} obtained from univariate Bayesian regression analyses, wherein the BF_{inc} is indicative of the strength of the evidence in favour of including a given lifestyle measure as a parameter in the model explaining that measure of brain structure. 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.

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	-.522	27.245	-.192
Sleep quality	-0.077	.246	6.041	.090
Physical activity	0.189	.207	4.303	.076
Alcohol consumption	-0.139	-.179	3.200	-.066
Smoking (years)	-0.307	-.373	13.920	-.137
Education (years)	-0.176	-.123	1.501	-.045
BMI	0.536	.458	20.963	.169
Loneliness	-0.488	-.662	43.814	-.244
Systolic blood pressure	-0.281	-.162	2.611	-.059
<i>Brain variate</i>				
Global FA	-0.222	.731	53.441	.269
Global MD	-1.146	-.916	83.968	-.337
Right Hippocampus (volume)	-0.341	.102	1.046	.038
Left Hippocampus (volume)	0.519	.274	7.501	.101
WMH (volume)	0.073	-.139	1.937	-.051
Cortical thickness	-0.218	-.034	0.114	-.012
Total GM (volume)	0.087	.086	0.743	.032

Coef = standardised canonical coefficients; r_s = structure coefficient; r_s^2 = squared structure coefficient; 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.

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 D).

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 nine lifestyle variables and seven measures of brain structure was significant (Wilk's $\lambda = 0.86$, $F(63, 3678) = 1.63$, $p = 0.001$; Appendix E). Since only the first canonical pair explained a significant amount of shared variance between lifestyle and brain measures ($R^2_c = 0.072$; Appendix F), 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 contributors to the brain variate were WMH and global FA ($r_s \geq 0.3$), with negative and positive canonical loadings, respectively.

In the Bayesian univariate regressions, only systolic blood pressure, physical activity and BMI revealed moderate or strong evidence in favour of being substantive contributors to a model (Figure 2; Appendix G). There was strong evidence for including physical activity, BMI and systolic blood pressure as predictors of WMH (physical activity $BF_{inc} = 11.47$; BMI $BF_{inc} = 22.7$; systolic blood pressure $BF_{inc} = 45.51$), and moderate evidence for the inclusion of BMI as a predictor of global FA ($BF_{inc} = 3.05$).

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	.002	0	.001
Sleep quality	-0.127	.012	0.015	.003
Physical activity	0.326	.428	18.307	.115
Alcohol consumption	0.307	.336	11.303	.090
Smoking	0.086	.100	1.001	.027
Education (years)	.0392	.438	19.208	.117
BMI	-0.615	-.704	49.532	-.188
Loneliness	0.267	.204	4.142	.054
Systolic blood pressure	-0.274	-.334	11.221	-.090
<i>Brain variate</i>				
Global FA	1.248	.367	13.449	.098
Global MD	1.293	-.103	1.055	-.027
Right Hippocampus (volume)	0.132	-.134	1.791	-.036
Left Hippocampus (volume)	-0.360	-.202	4.086	-.054
WMH (volume)	-0.787	-.754	56.914	-.202
Cortical thickness	0.162	-.182	3.297	.049
Total GM (volume)	-0.138	.024	0.059	.007

Coef = standardized canonical coefficients; r_s = structure coefficient; r_s^2 = squared structure coefficient; 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.

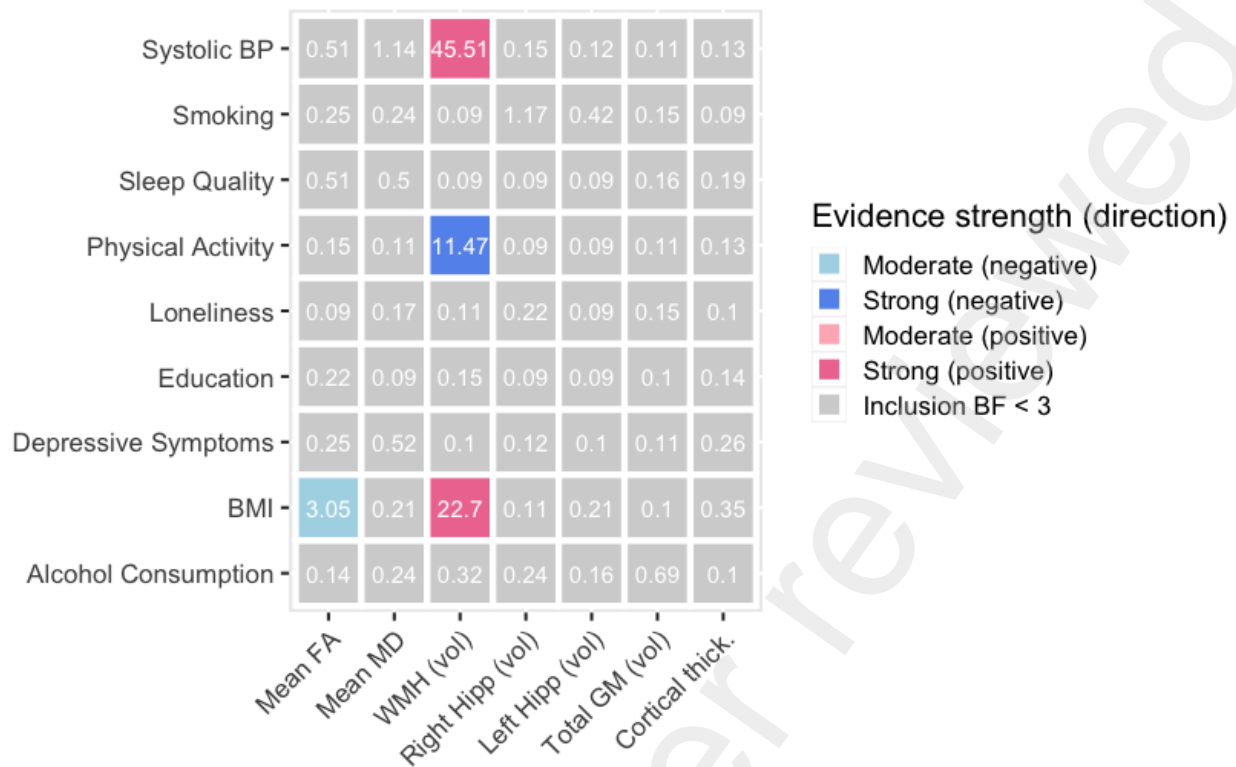


Figure 2. Heatmap of the BF_{inc} obtained from univariate Bayesian regression analyses in the Whitehall study, wherein each cell represents a separate regression model. The BF_{inc} is indicative of the strength of the evidence in favour of including a given lifestyle measure as a parameter in the model explaining that measure of brain structure. The direction of the association is indicated for factors which showed at least moderate evidence in favour of being included (Inclusion $BF > 3$).

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 two 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. 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. In Latin America, compared to Europe and the US, the estimated potential of dementia prevention rises from 33% to 56% (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.

385 There is also pronounced individual variability in the benefits of lifestyle factors on the
386 ageing brain within cohorts. This has been well documented in physical activity
387 interventions, leading to the recommendation that thorough baseline characterisation may
388 benefit the predictive power of physical activity interventions (von Cederwald et al., 2023).
389 For example, baseline levels of white matter lesion load can limit the potential for brain
390 plasticity following exercise (von Cederwald et al., 2023). A participant's sex, baseline
391 physical activity levels and genotype (e.g., APOE 4) are other potential moderators of the
392 effect of physical activity on the ageing brain (Barha et al., 2021). These sources of
393 individual variability may contribute to the weak signal of the observed lifestyle-brain
394 associations, and further stress why characterising your sample is so important to make
395 recommendations. Accordingly, baseline characterisation of participants in interventions is
396 advisable for designing tailored interventions to promote healthy brain ageing.

397 To identify which lifestyle factors accounted for the most variance in brain structure
398 measures, we complemented our analyses with Bayesian regressions. Across cohorts, there
399 was no overlap in lifestyle factors with moderate-or-higher levels of evidence in favour of
400 predicting a particular brain outcome. One explanation is that the effect size of univariate
401 associations was simply too weak to generalise from one cohort to another. In LISA, there
402 was moderate or strong evidence for loneliness, depressive symptoms, education and
403 smoking to be included as predictors in Bayesian regressions of individual brain outcomes.
404 The direction of the relationships was in accordance with previously reported univariate
405 brain-lifestyle relationships. In the Bayesian regression from the Whitehall study, the
406 cardiovascular risk factors (blood pressure, physical activity, and BMI) prevailed. In line with
407 the vascular aetiology of WMHs (Moroni et al., 2018), these lifestyle measures contributed to
408 the prediction of WMH volume, but no other brain outcome. Given that WMH volume was
409 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 a univariate 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.

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. 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. Accordingly, there are systematic differences between studies which may be overestimating their differences.

One difference between the two cohorts was the sex proportion. While the LISA sample was 59% female, this proportion dropped to 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 H). 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.

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. It would be of interest to replicate our findings with these additional modifiable lifestyle factors.

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 univariate 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.

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