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Associations between white matter hyperintensities, lacunes, entorhinal cortex thickness, declarative memory and leisure activity in cognitively healthy older adults: A 7-year study

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ABSTRACT

Introduction: Cerebral small vessel disease (cSVD) is a growing epidemic that affects brain health and cognition. Therefore, a more profound understanding of the interplay between cSVD, brain atrophy, and cognition in healthy aging is of great importance. In this study, we examined the association between white matter hyperintensities (WMH) volume, number of lacunes, entorhinal cortex (EC) thickness, and declarative memory in cognitively healthy older adults over a seven-year period, controlling for possible confounding factors. Because there is no cure for cSVD to date, the neuroprotective potential of an active lifestyle has been suggested. Supporting evidence, however, is scarce. Therefore, a second objective of this study is to examine the relationship between leisure activities, cSVD, EC thickness, and declarative memory.

Methods: We used a longitudinal dataset, which consisted of five measurement time points of structural MRI and psychometric cognitive ability and survey data, collected from a sample of healthy older adults (baseline N = 231, age range: 64–87 years, age M = 70.8 years), to investigate associations between cSVD MRI markers, EC thickness and verbal and figural memory performance. Further, we computed physical, social, and cognitive leisure activity scores from survey-based assessments and examined their associations with brain structure and declarative memory. To provide more accurate estimates of the trajectories and cross-domain correlations, we applied latent growth curve models controlling for potential confounders.

Results: Less age-related thinning of the right ($\beta = 0.92$, $p<.05$) and left EC ($\beta = 0.82$, $p<.05$) was related to less declarative memory decline; and a thicker EC at baseline predicted less declarative memory loss ($\beta = 0.54$, $p<.05$). Higher baseline levels of physical ($\beta = 0.24$, $p<.05$), and social leisure activity ($\beta = 0.27$, $p<.01$) predicted less thinning of right EC. No relation was found between WMH or lacunes and declarative memory or between leisure activity and declarative memory. Higher education was initially related to more physical activity ($\beta = 0.16$, $p<.05$) and better declarative memory ($\beta = 0.23$, $p<.001$), which, however, declined steeper in participants with higher education ($\beta = -.35$, $p<.05$). Obese participants were less physically ($\beta = -.18$, $p<.01$) and socially active ($\beta = -.13$, $p<.05$) and had thinner left EC ($\beta = -.14$, $p<.05$) at baseline. Antihypertensive medication use ($\beta = -.26$, $p<.05$), and light-to-moderate alcohol consumption ($\beta = -.40$, $p<.001$) were associated with a smaller increase in the number of lacunes whereas a larger increase in the number of lacunes was observed in current smokers ($\beta = 0.30$, $p<.05$).

Conclusions: Our results suggest complex relationships between cSVD MRI markers (total WMH, number of lacunes, right and left EC thickness), declarative memory, and confounding factors such as antihypertensive medication, obesity, and leisure activitiy. Thus, leisure activities and having good cognitive reserve counteracting this neurodegeneration. Several confounding factors seem to contribute to the extent or progression/decline of cSVD, which needs further investigation in the future. Since there is still no cure for cSVD, modifiable confounding factors should be studied more intensively in the future to maintain or promote brain health and thus cognitive abilities in older adults.

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1. Introduction

Against the background of demographic changes that currently take place in our society, cerebral small vessel disease (cSVD) is a growing age-associated epidemic that is linked to cognitive impairment. Given that cSVD compromises brain health, a more profound understanding of cSVD has become an increasing focus of scientific interest. CSVD is common in the elderly population and affects the arterioles, capillaries, and venules of the brain (Shi and Wardlaw, 2016). Further, there is increasing evidence that cSVD plays a role in Alzheimer's disease (AD) (Liu et al., 2018; Rizvi et al., 2021; Wardlaw et al., 2013). Therefore, the present paper focusses on cerebral small vessel disease and its relation to aging, lifestyle, and health status.

Following the "STandards for ReportIng Vascular changes on nEuroimaging" (STRIVE), cSVD magnetic resonance imaging (MRI) markers include recent small subcortical infarcts, white matter hyperintensities (WMH) of presumed vascular origin, lacunes of presumed vascular origin (lacunes), perivascular spaces, cerebral microbleeds, and brain atrophy (Wardlaw et al., 2013). In the current analysis, we included WMH, lacunes, and thinning of the entorhinal cortex (EC) as a focal atrophy measure. CSVD increases with age (Brickman et al., 2008; Chowdhury et al., 2011), and is related to traditional risk factors for vascular brain health, such as hypertension, obesity and the associated disease type-2 diabetes (Ling and Chabriat, 2020; van Harten, Oosterman, Potter van Loon, Scheltens, and Weinstein, 2007). Studies are demonstrating associations amongst cSVD markers (as WMH, lacunes, brain atrophy) (Appelman et al., 2009; Hotz et al., 2021; Kloppenborg et al., 2012; Rizvi et al., 2021), and between cSVD markers and cognitive decline (Bangen et al., 2018; Hamilton et al., 2021; Jokinen et al., 2011; Rizvi et al., 2018), but longitudinal studies with cognitively healthy older adults are scarce. From clinical research, we know that atrophy of the EC is thought to represent the earliest neuropathological changes in AD (Braak and Braak, 1991a, 1991b; Kaufman et al., 2018; Singh et al., 2006; Zhou et al., 2016), which in turn leads to poorer performance on declarative memory tasks that phenotypically resemble the most prominent symptom of AD (Brickman, 2013; Garnier-Crussard et al., 2022; YL. Wang et al., 2020). As EC atrophy precedes and predicts hippocampal atrophy (Pennanen et al., 2004), is measurable several years before clinical AD symptoms in cognitively healthy participants (Kulason et al., 2020; M. I. Miller et al., 2013; Pettigrew et al., 2016; Soldan et al., 2015) the interplay between cSVD, neurodegeneration (i.e., gray matter atrophy), and cognition is important for healthy aging. CSVD and AD also often coexist and share common vascular risk factors (Garnier-Crussard et al., 2022). Cross-sectional studies indicate that there is spatial overlap between cSVD MRI markers (i.e. WMH volume and areas of atrophy) in normal aging and AD (Rizvi et al., 2018; Tuladhar et al., 2015). It is therefore of interest to examine whether, in cognitively healthy older adults, an increase in WMH volume and/or number of lacunes is associated with thinning of the AD-prone region of the EC and with declarative memory loss.

Since no cure for cSVD exists to date (Zanon Zotin et al., 2021), treatment is aimed at controlling symptoms and preventing further damage. In addition to medication, modifiable healthy lifestyle factors such as being physically active can help control the symptoms of cSVD and reduce the risk of stroke (Hasbani et al., 2022). On the other hand, unhealthy lifestyle habits such as smoking (Gons et al., 2011; Jeerakathil et al., 2004; Moroni et al., 2018), excessive alcohol consumption (Livingston et al., 2020), and poor sleep quality (Gottesman and Seshadri, 2022) can negatively impact vascular brain health. However, comprehensive evidence including different leisure activities (physical, social, and cognitive), and their association with cSVD MRI markers and cognitive ability (i.e., memory performance) over the course of several years is missing.

Most studies are limited to a single leisure activity, mainly leisure physical activity (LPA), which has been associated with smaller WMH (Sexton et al., 2016), larger brain volume (Colcombe et al., 2003; Doi et al., 2015; Gu et al., 2020), thicker cortices (Gu et al., 2020), and a slower cognitive decline (Kraal et al., 2021; Palta et al., 2019). However, the findings are not fully consistent. For example, two recent longitudinal studies (Arild et al., 2022) showed no association between LPA and cSVD MRI markers, whereas a review suggests that LPA and/or leisure cognitive activity (LCA) may attenuate relations between different brain measurements and cognition (Song et al., 2022). However, most of the previous studies summarized in the reviews by Sexton et al. (2016) and Song et al. (2022) referred to cross-sectional study designs, and none of these studies examined all three leisure activities in healthy older adults. Given the lack of a standardized approach regarding the measurement and analysis of leisure activities, single activities have been treated and classified inconsistently, which could explain these large between-study differences. Some studies explicitly assign single activities to one activity dimension (e.g., leisure social activity (LSA) *or* LCA), others assess single activity items without categorizing them, and some combine activities into one construct (e.g., socio-intellectual activity). The different operationalizations have drawbacks. For example, a strict assignment of activity items into one superior activity dimension neglects the multidimensionality of a single activity (e.g., team sports involve physical, but also social and cognitive aspects), effects can be suppressed when activities are aggregated, and specificity is reduced when several activity dimensions are combined into one. To be able to examine the influence of physical, cognitive and social activity separately and to minimize the risk of attenuated effects, we consider the activity dimensions as distinct but related constructs. To the best of our knowledge, in the domain of brain and cognitive aging, no longitudinal study with more than two measurement occasions has yetconsidered the three dimensions (physical, social, and cognitive) of single leisure activities and explored their differential effects.

In the current seven-year study with five measurement time points including cognitively healthy older adults, we investigated how total WMH volume, number of lacunes, and thickness of the EC are related and whether these areas are associated with poorer declarative memory, including confounding factors (age, sex, education, antihypertensive medication, obesity, hazardous alcohol consumption, current smoking, poor sleep quality, leisure time activities). We hypothesized that WMH and lacunes would be associated with increasing EC thinning and that increasing EC thinning would be associated with poorer declarative memory.

Regarding the association between leisure activity, WMH, lacunes, EC thickness and declarative memory, we hypothesized that more LPA would be associated with less cSVD and a thicker EC and a more favorable development over time. For LCA and LSA, we chose an exploratory approach due to the small number of studies and inconsistent results.

2. Material and methods

2.1. Participants

Data from five measurement time points (i.e., baseline, 1-year follow- up, 2-year follow-up, 4-year follow-up, 7-year follow-up) were taken from the Longitudinal Healthy Aging Brain (LHAB) Database Project (Zöllig et al., 2011) – a prospective longitudinal community-based study describing the development of behavior and brain anatomy and function of cognitively healthy older adults. The project has been ongoing since 2011 and focuses on researching domain-overlapping links between measures of brain and behavior.

At each measurement time point, participants underwent brain imaging and completed an extensive battery of neuropsychological, psychometric, and motor tests. In addition to the behavioral and brain data, a broad range of additional information is available (e.g., self-report measures on leisure activity, lifestyle factors, well-being, health etc.). The brain imaging session was conducted in close temporal proximity to the behavioral assessments (difference between behavioral and MRI

assessments in days (M±SD): 2.2 (±5.2), at the 1-year follow-up: 2.6 (±5.2), at the 2-year follow-up: 4.3 (±13.0), at the 4-year follow-up: 4.6 (±9.3), and at the 7-year follow-up: 6.7 (±8.0)).

Inclusion criteria for study participation at baseline were age ≥ 64 years, right-handedness, fluent German language proficiency, a score of ≥ 26 on the Mini Mental State Examination (MMSE; (Folstein et al., 1975) no self-reported neurological disease of the central nervous system and no contraindications to MRI. Also on the basis of other cognitive domains analyzed in previous reports using this dataset, the sample can be regarded as cognitively healthy (Hotz et al., 2021; Jäncke et al., 2020; Malagurski et al., 2020a, 2020b; Oschwald et al., 2019). The study was approved by the ethical committee of the canton of Zurich. Participation was voluntary and all participants gave written informed consent in accordance with the declaration of Helsinki.

The LHAB baseline dataset included 232 participants (mean age at baseline: M = 70.85, range = 64 – 87, F:M = 114:118). Self-reported physical and mental health of the sample at baseline, as measured by the SF-12 (Ware et al., 1996) were 50.8 ± 7.4 ($M \pm SD$) and 54.8 ± 6.2, respectively, which indicates above-average health compared to a normative population (Ware et al., 1996). As expected, sample means for these general health indicators slightly declined over time, but still indicated above-average health at 7-year follow-up (physical health score: 48.4 ± 8.4, mental health score: 52.9 ± 7.7, MMSE: 28.2 ± 1.7). At 7-year follow-up, the dataset still comprised 53.88 % of the baseline sample (n = 125). As reported in other publications with this sample (Malagurski et al., 2020b; Oschwald et al., 2019), selectivity analyzes showed that the participants remaining in the study did not substantially differ from the baseline sample in terms of age, education or physical and mental health.

For the present analysis, participants were excluded if either structural MRI or cognition data were missing for all measurement time points. The MR images were reviewed by a neuroradiologist with over 30 years of experience to assure that they are free of intracranial hemorrhages, intracranial space occupying lesions, multiple sclerosis lesions or large chronic, subacute or acute infarcts. Five T1-weighted (T1w) images had to be excluded due to insufficient MRI data quality. Eight data points had to be excluded, due to WMH segmentation errors. The average educational attainment was higher than would be expected for a representative sample, with 51.4% holding a bachelor's, master's, or doctoral degree.

2.2. Brain imaging

2.2.1. MRI acquisition

Longitudinally structural MRI data were acquired at the University Hospital of Zurich on a Philips Ingenia 3.0T scanner (Philips Medical Systems, Best, The Netherlands) using the dsHead 15-channel head coil. The 2D fluid-attenuated inversion recovery (FLAIR) sequence, was used for WMH quantification, and acquired with the following parameters: Repetition time (TR): 11,000 ms, echo time (TE): 125 ms, inversion time (TI): 2800 ms, 180 × 240 × 159 mm^3 field of view (FOV), 32 transverse slices, in-plain resolution: 560 × 560, voxel size: 0.43 × 0.43 × 5.00 mm^3, interslice gap: 1 mm, scan time: ~5:08 min. 3D T1w images, used for WMH quantification and for the computation of EC thickness, were recorded with: 3D T1w turbo field echo (TFE) sequence, TR: 8.18 ms, TE: 3.799 ms, FA: 8°, 160 × 240 × 240 mm^3 FOV, 160 sagittal slices, in-plain resolution: 256 × 256, voxel size: 1.0 × 0.94 × 0.94 mm^3, scan time: ~7:30 min. The 3D FLAIR sequence was partially considered for the distinction between perivascular spaces and lacunes and recorded with the following parameters: TR: 4800 ms, TE: 281 ms, TI: 1650 ms, 250 × 250 mm FOV, 256 transverse slices, in-plain resolution: 326 × 256, voxel size: 0.56 × 0.98 × 0.98 mm^3, scan time: ~4:33 min.

2.2.2. Cerebrovascular small vessel disease MRI marker

WMH were automatitically segmented with UBO Detector (UBO: unidentified bright objects) (Jiang et al., 2018) using T1w and 2D FLAIR images. UBO Detector co-registers FLAIR images to T1w, extracts WMH-related intensity features mainly from FLAIR images (best WMH contrast) and requires T1w images for white matter, gray matter, and cerebrospinal fluid (CSF) segmentation. To distinguish between perivascular spaces and lacunes we used a combination of T1w, 2D and 3D FLAIR images. The detailed procedure for WMH volumetric quantification as well as the validation of the segmentation quality have been previously outlined (Hotz et al., 2021, 2022). In short, WMH volumes were automatically segmented with UBO Detector– a k-nearest neighbor (k-NN) algorithm. We employed a «Diffeomorphic Anatomical Registration through Exponentiated Lie» template (Ashburner, 2007) and a gray matter mask to reduce the possibility of false positive voxels. The customization of the WMH probability maps was done in our previous study (Hotz et al., 2022) evaluating different thresholds and nearest neighbors (k) between manually segmented WMH and the WMH outputted by UBO Detector using different accuracy measures. The best performance was achieved with a threshold of 0.9 and a NN of k = 3. According to Dadar et al. (2017), the Dice Similarity Coefficient (DSC) between manually and automatically segmented WMH was very good (DSC = 0.531) for the rather low WMH load of our participants. WMH volumes outputted by UBO Detector are in DARTEL space and therefore do not need to be adjusted for intracranial volume. To assure that all lacunes were correctly removed from the WMH segmentation, each WMH map was visually checked for false positives using FSLeyes (McCarthy, 2018).

Lacunes were manually segmented on T1w images, and the number of lacunes was extracted and outputted with Python (Van Rossum et al., 2009) (version 3.7.4) using pandas (The pandas development team, 2020). Based on the STRIVE (Wardlaw et al., 2013) we distinguished perivascular spaces from lacunes, assessing size (3–15 mm), signal intensity on MR images (similar to CSF on all sequences and usually a hyperintense rim), and orientation using a combination of FLAIR (2D and 3D) and T1w images. In addition, we examined inter-rater reliability in 13 randomly selected scans with lacunes and perivascular spaces as follows: Rater 1 marked 100 lesions that could be either a lacune or a perivascular spaces with a voxel on the axial T1w scan. Rater 2 and 3 independently divided the lacunes and perivascular spaces into two categories (0 = perivascular spaces; 1 = lacunes) (Cohen's kappa = 0.94). For more details on the assessment of the lacunes, see Hotz et al. (2021).

Right and left hemisphere EC thickness were derived applying FreeSurfer's *recon-all* pipeline to the individual T1w scans (FreeSurfer v6.0.1; Fischl 2012). To ensure unbiased registration between the measurement time points, FreeSurfer's longitudinal analysis stream was employed. For the parcellation of the right and left EC the Desikan-Killiany atlas (Desikan et al., 2006) was used. EC thickness was corrected for mean cortical thickness before analysis for each time point to determine a specific effect of EC thickness on the associations independent of total cortical thickness. We did not additionally correct for estimated total intracranial volume (eTIV), since cortical thickness measures generally do not correlate significantly with head size (Barnes et al., 2010; Jäncke et al., 2019; Schwarz et al., 2016; Westman et al., 2013), and this correction is therefore not recommended (Buckner et al., 2004; Schwarz et al., 2016).

The cSVD measurements were undertaken on a Supermicro X8QB6 workstation with 4 × Intel Xeon E57–4860 CPU (4 × 10 cores, 2.27 GHz) and 256 GB RAM. The computing host was a KVM virtualized guest instance with Ubuntu 18.04.4 LTS with 32 x Intel Xeon E7–4860 CPU (2.27 GHz) and 92 GB RAM.

2.3. Definition of predictors

The demographic factors we controlled for were age, sex, and education. Education was assessed according to the International Standard Classification for Education (ISCED) with a scale from 1 to 3 (1 = high school with or without vocational education, 2 = higher education

entrance qualification, business school or university of applied sciences, 3 = university degree). Antihypertensive medication was obtained from a medication questionnaire (self-reported physician prescription). Height and weight were used to calculate the body mass index (BMI) (weight-height-ratio in kg/m^2) to define obesity ($\geq 30\ kg/m^2$) according to the WHO (WHO, 2000). A hazardous alcohol consumption was determined by the Alcohol Use Disorders Identification Test (AUDIT) (Babor et al., 2001). According to the AUDIT, a score of 1 or more on question 2 or question 3 indicates consumption at a hazardous level. This refers to drinking three or more standard drinks per day, *or* consuming six or more standard drinks on one occasion even if this occurs less than monthly. Current smoking was defined as daily or non-daily use of cigarettes (Gmel et al., 2017). Poor sleep quality was assessed using the Pittsburgh Sleep Quality Index (PSQI; > 5 points = poor sleep quality) – a self-report questionnaire to assess sleep quality over the past month – was used (Buysse et al., 1989). It consists of items concerning subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication and daytime dysfunction. Age was the only metric variable; all other variables were dichotomous. Data on alcohol consumption and current smoking were only available for the baseline measurement, while the remaining data were assessed at each measurement time point and averaged to represent time-invariant predictors.

2.4. Definition of leisure activity

Leisure activity was assessed with the German Version of the «Expanded Victoria Longitudinal Study Activity Questionnaire» (Jopp and Hertzog, 2010). For information on data imputation, questionnaire adaptations, and correlations between dimensions of leisure activities, see Inline Supplementary Text 1. The questionnaire was used to collect current (e.g., in the last year) leisure activity in eight areas: *sports, craft, games, TV, cultural activity, social activity, knowledge gain*, and *various*. For each single leisure activity item (e.g., «reading the newspaper»), participants were asked to indicate the frequency of engagement (never, occasionally, once a month, once a week, several times a week, daily). To facilitate the summarizing across leisure activities, the original frequency of engagement (6-point-scale) was transformed into «activity per week», with «never» and «daily» being recoded to 0 and 7 activities per week, respectively (once a month = 0.25, once a week = 1, several times a week = 3.5). «Occasionally» was also recoded to 0 activities per week, since it corresponds to a very low frequency (less than once a month).

To reduce the dimension of the data and extract meaningful information, we chose an approach, in which we captured the physical, social and cognitive activity aspects of the single leisure activities. This approach was guided by the work of Karp et al. (2006) and Fratiglioni et al. (2004), who emphasized the multidimensional profile of a given leisure activity, qualified by specific combinations of mental, social and physical involvement. The single leisure activity items were rated by four psychologists. As proposed by Karp et al. (2006) and Fratiglioni et al. (2004) scores from «0» (no involvement) to «3» (high involvement) were assigned to indicate how physically, socially, or cognitively demanding a given leisure activity is. Accordingly, for each rater, this resulted in three scores per single leisure activity. The ratings were evaluated using Kendall's coefficient of concordance W (Kendall and Gibbons, 1990) and revealed high agreement for all three aspects (physical, social, cognitive) among the four raters: $W_{physical} = 0.888$ ($p < .001$), $W_{social} = 0.873$ ($p < .001$), $W_{cognitive} = 0.759$ ($p < .001$). Because of the good rater agreement, the four rater scores assigned to a given leisure activity were averaged, separately, for the three activity dimensions.

Subsequently, the individual activity frequencies (activity per week) were multiplied by the rating scores (i.e., «3.5 activity per week» multiplied by the physical aspect score «3» results in a weighted frequency value of «10.5»). Finally, physical (LPA), social (LSA) and cognitive (LCA) leisure activity scores were computed by adding up the weighted frequency values across all single leisure activities for each participant at each measurement time point. To facilitate comparison and interpretation, the three scores were converted to *T*-scores such that the values at baseline are scaled to $M = 50$ and $SD = 10$. A summary of the items and the ratings can be found in Inline Supplementary Table 1.

There are two major advantages of this analysis approach. On the one hand, the leisure activities are considered three-dimensional since several aspects can co-occur in a single leisure activity. For example, the leisure activity «ball games» comprises not only physical, but also social aspects (e. g., when carried out as a team sport). If we would only consider the dominant aspect of an activity, we would neglect the other activity aspects. On the other hand, the rating of physical, cognitive and social involvement from zero to three assures that the profiles reflect different levels of involvement. For example, the activity «use a calculator» is less cognitively demanding than «reading a job-specific book». Consequently, the profile for the latter activity contains a higher weighting score for «cognitive involvement».

2.5. Definition of declarative memory

Declarative memory was assessed with the Verbal Learning and Memory Test (VLMT) (Helmstaedter and Durwen, 1990), a German adaption of the Rey Auditory Verbal Learning Test (AVLT) (Rey, 1958; Schmidt, 1996), and the DCS figural memory test (Diagnosticum für Cerebralschädigung; Weidlich and Lamberti, 2001). The VLMT consists of five immediate recall trials (15 items / words of list A) and one immediate recall interference trial (15 items / words of list B) followed by another recall of the list A items. After a delay of 20–30 min, one delayed recall trial (list A) is conducted as well as a test of recognition. For the current analyzes, we used the delayed recall performance (number of correctly free recalled words). The DCS consists of six immediate recall trials (nine items / figures). The figures are visually presented and participants need to re-build the figures with five wooden sticks. The learning performance (number of correctly reproduced figures after five learning trials) was used for the current analysis.

The individual VLMT and DCS scores were standardized to *T* scores ($M = 50$, $SD = 10$) regarding baseline and averaged to calculate domain-average composite scores for declarative memory performance.

2.6. Statistical analysis

The statistical analysis was carried out in R version 4.1.0 (R Core Team, 2020). To obtain normally distributed volumes of WMH and lacunes, a natural log-transformation [$\log_e(x)$] was applied before implementing the statistical procedures. The threshold of the *p*-value was set to $p \leq 0.05$ for all statistical analyzes. The estimated effects of the predictors on the latent intercepts and slopes, as well as the correlations of the latent factors, were reported as standardized effect estimates (β) to provide comparable unit-independent effects.

2.6.1. Description of the subsample with lacunes

Since not all participants had lacunes, the subsample with lacunes ($n = 61$) was compared with the one without lacunes ($n = 170$). This was to determine whether the samples differed systematically. The continuous variables (age, brain measures, declarative memory, leisure activity) were compared using a Welch two-sample *t*-test. For categorical variables (sex, education, obesity, hazardous alcohol consumption, antihypertensive medication, current smoking, poor sleep quality) the Pearson's Chi-squared test (χ^2-test) with Yates' continuity correction was applied.

2.6.2. Latent growth curve modeling

We calculated univariate and bivariate latent growth curve (LGC) models in the structural equation modeling (SEM) framework using the *lavaan* package version 0.6–12 (Rosseel, 2012) to understand the complex relationships between different variables over time, see Fig. 1. The

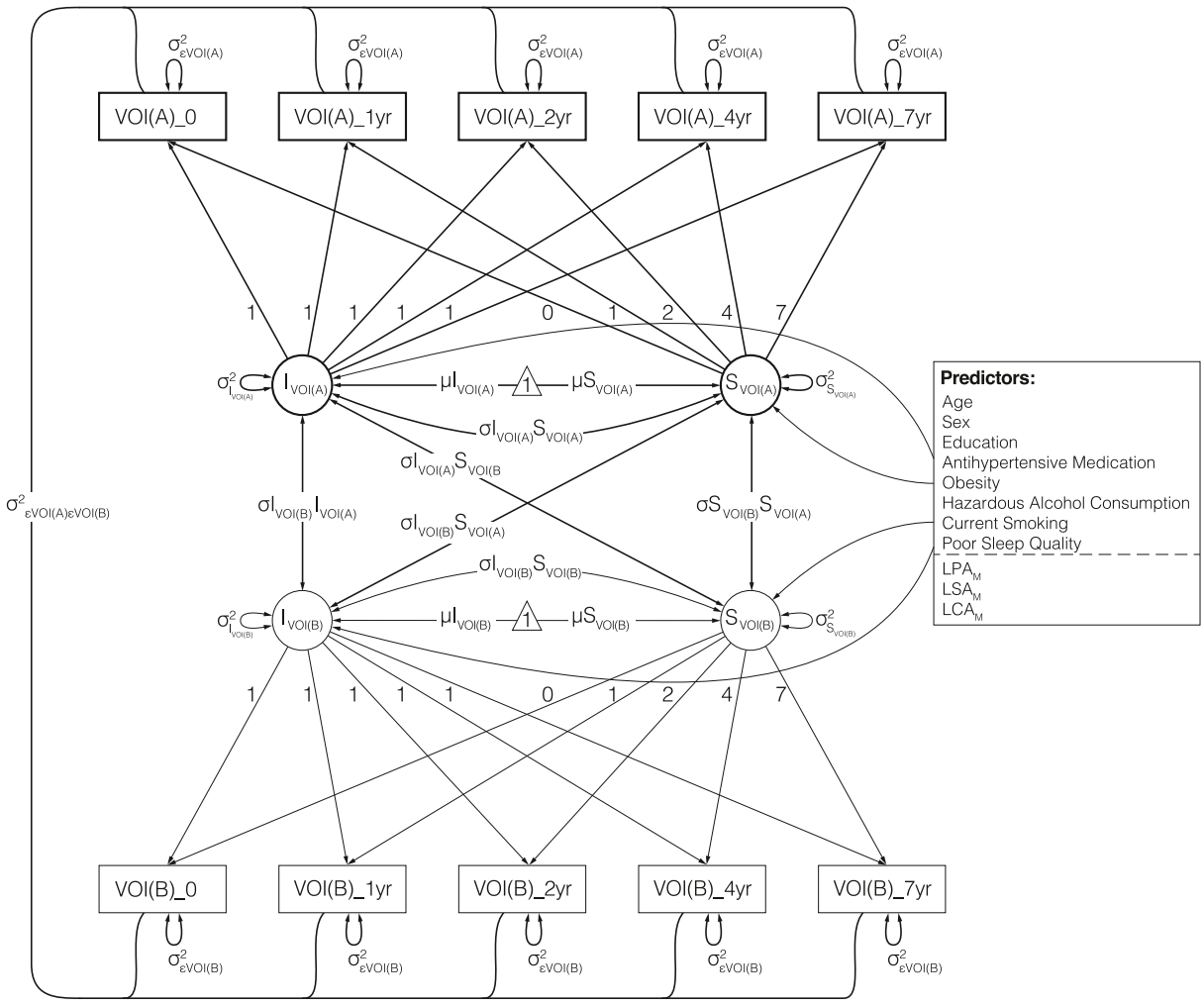

Fig. 1. Simplified path diagram of latent growth curve (LGC) models associating the trajectories of the variables of interest (VOI) A and B over five-time points (0 = baseline, 1 yr = 1-year follow-up, 2 yr = 2-year follow-up, 4 yr = 4-year follow-up, 7 yr = 7-year follow-up). Included VOI were: White matter hyperintensities (WMH), lacunes, right entorhinal cortical thickness (EC right), left entorhinal cortical thickness (EC left), declarative memory, leisure physical activity (LPA), leisure social activity (LSA), and leisure cognitive activity (LCA).

aim of the univariate models was to obtain an estimate of the intercept, the slope and the influences of the predictors on the variables of interest (e.g., do the predictors explain variance in the intercept or the slope?). The objective of the bivariate models was to estimate the interrelationships of the variables of interest (e.g., is the change in one variable related to the change of another variable?). Note that the predictors are also included in the bivariate models to control the relationships for these influences. Because the selectivity analysis did not indicate a systematic drop-out, we assumed missing values to be missing at random (MAR) (Little, 1995) and applied Full Information Maximum Likelihood Estimation (FIML) (Finkbeiner, 1979; Schafer and Graham, 2002) to preserve as much data as possible.

The univariate LGC models for WMH, number of lacunes, right and left EC thickness, and declarative memory each contained two latent factors: a latent intercept with factor loadings fixed to one (1,1,1,1,1) and a latent slope with factor loadings according to the time intervals (0,1,2,4,7). Both the intercept and the slope were allowed to vary between participants, allowing for an additional correlation estimation between the intercept and the slope. The means of the observed variables (residuals) at each time point were set to zero and the variance was held constant over time, assuming strict measurement invariance. We added regression paths to estimate the effects of demographic factors, antihypertensive medication, risk factors, and leisure activity on the intercepts and slopes of cSVD indicators, and declarative memory. The following regressors were added to the model: age entry (mean centered, 0 = 70.84 years), sex (0 = female, 1 = male), education (set to level 2 – medium level), antihypertensive medication (0 = no, 1 = yes), obesity (0 = no, 1 = yes), hazardous alcohol consumption (0 = no, 1 = yes), current smoking (0 = no, 1 = yes), poor sleep quality (0 = no, 1 = yes), and mean leisure activity score (LPA_M, LSA_M, LCA_M, $M = 50$). Note that LPA_M, LSA_M and LCA_M refer to manifest predictors (mean leisure activity scores).

Latent leisure activity scores – referred to as LPA, LSA, LCA – were estimated to better understand the effects of leisure activity, to examine the influence of the predictors and to assess bivariate relationships with cSVD markers and declarative memory. Again, two latent factors (intercept and slope) were estimated for all three leisure activity dimensions and the predictors mentioned above were included, except for the mean leisure activity score.

To assess the cross-sectional and longitudinal relationship between the above-mentioned variables, we combined two univariate models in each case. Thus, four latent factors were estimated (two intercepts and two slopes) per model, resulting in six correlations between the latent factors. The residual variances were kept constant for both variables studied in the models and the residual covariances were set to zero, implying that the residuals of the examined variables are uncorrelated.

To evaluate the adequacy of the models, we used the ratio of the χ^2-test to the respective degrees of freedom (χ^2/df) (Jöreskog and

Sörbom, 1993; Marsh and Hocevar, 1985), the Comparative Fit Index (CFI) (Bentler, 1990), and the root-mean-square error of approximation (RMSEA) (Browne and Cudeck, 1992; Steiger and Lind, 1984). Model fit was found to be good when: χ^2/ df ≤ 2, CFI > 0.97, RMSEA ≤ 0.05, and adequate fit was defined as: χ^2/df ≤ 3, CFI > 0.95, RMSEA 0.05 – 0.08 (Hu and Bentler, 1998; Jöreskog and Sörbom, 1993; Schermelleh-Engel et al., 2003).

We did not statistically control for multiple comparisons over the sequential tests and fitted models. To date, there is no consensus guidelines on how to best control for multiple comparisons in complex multivariate SEM models. Therefore, most researchers working with these models do not apply Type I error control, see Smith and Cribbie (2013). While there is one recommendation to control for the number of hypothesis tests within an SEM model (Cribbie, 2007) it is a subjective decision whether this number is based on the structural or measurement model.

On the one hand, leisure activities (LPA_M, LSA_M, LCA_M) were included as time-invariant predictors into the models to estimate the influence on intercept (I) and slope (S) (mu;μ) of brain measures and declarative memory. On the other hand, we modeled latent intercepts and slopes for each leisure activity dimension (LPA, LSA, LCA) to estimate more in-depth associations. Note that for these models LPA_M, LSA_M and LCA_M were not included as predictors (separated by dashed line).

The diagram shows the univariate models (thin lines), the bivariate models (thin + bold lines), and the predictors. Note that in the bivariate models, two VOI were modeled simultaneously, referred to as VOI1 and VOI2. Circles represent latent variables, and squares observed variables. One-headed arrows stand for regression paths, two-headed arrows show variances and covariances of latent variables (sigma; σ). Parameters with the same label are fixed to be equal. Intercept and slope of VOI are controlled for the predictors. Correlated residuals of the same manifest indicator over time were estimated. The residual variance (epsilon; ε) was held constant over time.

3. Results

3.1. Characteristics of the participants at baseline

Analyzes were performed on a dataset containing 231 participants. Characteristics of the participants at baseline are displayed in Table 1. The number of participants per measurement time point and variable can be taken from the Inline Supplementary Table 2.

According to the AUDIT evaluation, 33.3 % (77/231) of participants reported hazardous alcohol consumption at baseline. Because this percentage seemed very high, we conducted further tests to examine alcohol consumption using the standard classification into light, moderate, and heavy drinkers by "NHIS - Adult Alcohol Use," (2018), which accounts for differences between women and men. Using this definition, 53.3 % (41/77) of AUDIT-defined hazardous alcohol drinkers were assigned to the light-to-moderate drinkers group and the percentage of hazardous alcohol drinkers in our total sample dropped to 15.6 % (36/231), see Inline Supplementary Table 3. Within participants with lacunes, 61.6 % (16/26) are light-to-moderate drinkers when using the standard definition, see also Inline Supplementary Table 3.

According to the inferential statistical results, at baseline, participants with lacunes (n = 61; 72.9 years) were significantly older (t (90.88) = 3.443, p < .001) than participants without lacunes (n = 170; 70.1 years). Consequently, the sample with lacunes does not exactly represent the same population as the sample without lacunes. All other characteristics were not significantly different, see Inline Supplementary Table 4.

3.2. Univariate latent growth curve models

Using the univariate LGC models, we detected significant changes in all variables over the duration of the study; WMH volume and number of lacunes increased, while EC thickness and declarative memory decreased. Leisure activity tended to decrease, but not significantly. The right EC showed to be thicker on average than the left EC at baseline (t (230) = 4.130, p = < 0.001), and this difference remained significant over the seven years (t(119) = 2.511, p = .013). All variables revealed differences between participants at baseline (intercept); over the seven years (slope), only the cSVD MRI markers showed interindividual differences. For the estimates of intercepts, annual changes, and intercept and slope variance, see Table 2. Plots of individual trajectories of cSVD, EC thickness, declarative memory and leisure activity over the seven years, separately for women and men, are shown in Inline Supplementary Fig. 1. Model estimates and fit parameters for univariate LGC models are listed in Inline Supplementary Table 5, and Inline Supplementary Table 6.

Univariate analyzes showed that participants younger at baseline had lower WMH volume, fewer lacunes, larger right and left EC thickness, and a better declarative memory. In addition, participants younger at baseline showed a less steep increase in the number of lacunes, less thinning of the right and left EC, and less decline in declarative memory over the seven years. Women showed larger baseline WMH volumes, fewer lacunes, and a thinner right and left EC compared with men. Higher educated participants initially had larger WMH volumes and a thinner right EC, but showed fewer lacunes, which also increased less over the study course, better baseline declarative memory but also more declarative memory loss over the seven years, and more LPA. Participants taking antihypertensive medication had fewer lacunes at baseline and less increase over the study course and a thicker left EC at baseline. Obese participants demonstrated a less steep increase in the number of lacunes, a thinner left EC at baseline, and less baseline LPA and LSA. Alcohol consumers had fewer baseline lacunes, and a less steep increase in the number of lacunes. In contrast, current smokers showed more

Table 1
Characteristics of the participants (full sample, N = 231) at baseline.

Variable	Label	Baseline
Demographic Factors		
Age	Years, mean (*SD*)	70.8 (5.1)
Sex	Female, *n* (%)	113 (48.9)
Education	(1) Secondary with/without apprenticeship, *n* (%)	(1) 64 (28.4)
	(2) High schools, secondary technical schools, *n* (%)	(2) 46 (20.4)
	(3) Bachelor, Master, or Doctorate, *n* (%)	(3) 115 (51.1)
Antihypertensive Medication	Yes, *n* (%)	89 (40.6)
Risk Factors		
Obesity, BMI ≥ 30 kg/m^2	Yes, *n* (%)	21 (9.1)
Hazardous alcohol consumption	Yes, *n* (%)	77 (33.3)
Current smoking	Yes, *n* (%)	31 (13.4)
Poor sleep quality	Yes, *n* (%)	93 (40.3)
Cerebral Small Vessel Disease MRI Marker		
White matter hyperintensities	cm^3, mean (*SD*)	11.5 (11.9)
Number of participants with lacunes	Number, *n* (%)	61 (26.41)
Lacunes number	Mean number, [range]	4.11 [1–14]
Entorhinal cortical thickness (right)[a]	mm, mean (*SD*)	3.58 (0.34)
Entorhinal cortical thickness (left)[a]	mm, mean (*SD*)	3.50 (0.32)
Memory Performance	*T* scores (M = 50, SD = 10), mean (*SD*)	50 (10)
Leisure Activity (Physical, Social, Cognitive)	*T* scores (M = 50, SD = 10), mean (*SD*)	50 (10)

[a] Uncorrected thickness of the entorhinal cortex.

Table 2
Estimates of intercepts and annual changes with 95 % confidence intervals [CI], percentage change over the seven years and *p*-values interindividual differences in intercepts and slopes for cSVD MRI markers, and declarative memory.

Variable	Intercept	Slope Per Year	Slope Over 7 Years in%	Intercept Variance	Slope Variance
WMH					
Estimate	9.195	0.114	8.679	0.506	0.001
[CI]	[8.496; 9.895]	[0.072; 0.157]	[5.932; 11.107]	[0.415; 0.596]	[0.000; 0.001]
p-value	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001
LAC No.[a]					
Estimate	8.403	0.556	46.317	6.092	0.026
[CI]	[3.264; 13.542]	[0.205; 0.908]	[43.964; 46.935]	[2.889; 9.295]	[0.016; 0.035]
p-value	0.001	0.002	0.002	< 0.001	< 0.001
EC Right					
Estimate	3.542	–0.054	–13.621	0.085	0.001
[CI]	[3.184; 3.907]	[–0.097; –0.041]	[–21.325; –7.346]	[0.077; 0.116]	[0.000; 0.001]
p-value	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001
EC Left					
Estimate	3.451	–0.039	–10.542	0.076	0.001
[CI]	[3.125; 3.780]	[–0.087; –0.017]	[–19.488; –3.148]	[0.065; 0.103]	[0.000; 0.001]
p-value	< 0.001	0.004	0.004	< 0.001	< 0.001
Memory					
Estimate	48.922	–1.288	–18.429	42.613	0.063
[CI]	[42.112; 55.731]	[–2.190; –0.385]	[–36.403; –4.836]	[32.728; 52.498]	[−0.164; 0.290]
p-value	< 0.001	0.005	0.005	< 0.001	0.585

Abbreviations: WMH = white matter hyperintensities; LAC No. = number of lacunes; EC Right = right entorhinal cortex thickness; EC Left = left entorhinal cortex thickness, Memory = declarative memory.
Note: «Slope Over 7 Years in%» was calculated as follows: 7 times the slope divided by the intercept and multiplied by 100. «Intercept Variance » and «Slope Variance» list the significance of the variance in the intercept and the slope estimates. The estimates of intercept and slope are in the following units: WMH in cm^3_{log}, number of lacunes in number, entorhinal cortex thickness in mm, declarative memory and leisure activity in *T*-scores.
[a] Subgroup of participants with lacunes ($n = 61$).

baseline lacunes, and a steeper increase in the number of lacunes. Poor sleep quality, LPA_M, LSA_M and LCA_M showed no association with any other variable. For all results the standardized effect estimates, and *p*-values of univariate analysis are listed in Table 3.

3.3. Bivariate latent growth curve models

Bivariate analyzes showed that larger baseline WMH volumes were predictive of more lacunes (intercept-intercept) at baseline and over time (intercept-slope). The right and left EC were positively correlated cross-sectionally (intercept-intercept) and longitudinally (slope-slope), and a thicker right EC was predictive of less thinning of the left EC and vice versa (intercept-slope). A thicker right and left EC correlated with better declarative memory (intercept-intercept), a thicker right EC was predictive of a more favorable development of declarative memory over the 7 years (intercept-slope), and thinning of the right and left EC was associated with a greater decline in declarative memory (slope-slope). Better baseline declarative memory was predictive of less declarative memory loss.

Further bivariate analyzes were run to test associations between leisure activity scores, cSVD MRI markers, and declarative memory. Here, the analyzes show that higher baseline LPA, and LSA, scores correlated with less thinning of the right EC over time (intercept-slope).

For all results the standardized effect estimates, and *p*-values of bivariate cross-domain and univariate inner-domain correlations are listed in Table 4. Model estimates and fit parameters for bivariate LGC models are listed in Inline Supplementary Table 7.

4. Discussion

In this seven-year, five-wave longitudinal study of cognitively healthy community-dwelling participants, we examined how cSVD MRI markers (total WMH, number of lacunes), right and left EC thickness, and declarative memory were associated with different confounding factors (age, sex, education, antihypertensive medication, obesity, hazardous alcohol consumption, current smoking, poor sleep quality, leisure time activities). In addition, longitudinal relationships between cSVD MRI markers, declarative memory, and leisure activity were examined, controlling for potential confounders using LGC models. To our knowledge, this is the first multi-wave longitudinal study of cognitively healthy participants to relate physical, social, and cognitive leisure activity to brain health and declarative memory, considering risk and protective factors.

4.1. Declarative memory and cSVD

We found a significantly thicker right EC at baseline, which was maintained over the seven years. Reduced lateralization was observed in individuals with AD and mild cognitive impairment (MCI) (Long et al., 2013; Thompson et al., 2007). Hasan et al. (2016) and Wang et al. (2019) found a thicker right EC, larger right surface area of the EC (Simic et al., 2005; Wang et al., 2019), and larger right EC volume (Wang et al., 2019), but on the left EC more number of neurons (Simic et al., 2005). The exact reason for this right-left asymmetry is still elusive, but in the healthy aging brain genetic risk factors such as clinically silent apolipoprotein E (APOE) especially ε2 and ε4 allele might be involved (Corder et al., 1993; Donix et al., 2013; Shaw et al., 2007).

Thicker right and left ECs were related to each other and to declarative memory cross-sectionally and longitudinally, and that an initially thicker right EC was predictive for a more favorable development of declarative memory over the study course. The present study shows that, within participants, less thinning of the right and left EC is associated with less declarative memory decline over the seven-year study period, controlling for possible confounders. These results can be seen in context, as one of the first clinical symptoms in AD is the onset of declarative memory loss (Jahn, 2013), which is associated with very early aggregation of tau proteins and neuronal degeneration in the EC (Igarashi, 2023; Kaufman et al., 2018; Llorens-Martín et al., 2014). In the five-year study by Rodrigue and Raz (2004) with two measurement time points, a greater annual rate of atrophy in EC volume (but not

Table 3
Representation of the results of the univariate LGC models with the predictors. Listed are the standardized effect estimates (β) for intercept (I) and slope (S). To the left of the bold line are the effects of the predictors on the cSVD MRI markers and declarative memory. To the right of the bold line are the effects of the predictors on LPA, LSA, and LCA as latent factors.

	WMH	LAC No.[a]	EC Right	EC Left	Memory	LPA	LSA	LCA
Age								
I	0.426***	0.424***	–0.195**	–0.155*	–0.396***	–0.082	0.055	–0.017
S	0.085	0.537***	–0.406**	–0.320**	–0.556**	0.399	–0.020	0.044
Sex								
I	–0.178**	0.261**	0.135*	0.143*	–0.096	–0.069	–0.151	–0.146
S	–0.162	0.113	0.141	0.160	0.242	0.120	–0.157	–0.213
Education [b]								
I	0.146*	–0.339***	–0.140*	–0.101	0.231***	0.163*	–0.003	0.141
S	–0.172	–0.403***	0.021	0.047	–0.349*	0.172	0.039	0.024
AHM								
I	0.061	–0.391***	0.124	0.183**	–0.026	–0.055	–0.095	–0.000
S	–0.124	–0.257*	–0.113	0.006	0.006	–0.174	0.072	0.114
Obesity								
I	0.074	–0.024	–0.076	–0.152*	–0.082	–0.184**	–0.126*	0.005
S	–0.118	–0.208*	0.094	–0.081	0.157	–0.080	0.066	–0.230
Alcohol								
I	–0.024	–0.370***	0.046	0.050	0.005	–0.069	0.007	0.012
S	0.037	–0.398***	–0.094	0.071	0.156	–0.096	–0.232	0.016
Smoking								
I	0.037	0.254*	0.042	0.084	0.013	–0.046	0.099	–0.007
S	–0.186	0.286*	0.067	0.052	0.259	0.011	–0.262	–0.039
Sleep								
I	0.074	0.019	0.096	0.115	–0.095	–0.125	–0.107	–0.100
S	–0.048	0.156	0.103	0.041	–0.228	0.069	0.116	0.071
LPA_M								
I	0.015	–0.082	0.056	0.068	0.041			
S	0.057	–0.167	0.151	0.006	0.236			
LSA_M								
I	–0.011	–0.047	0.023	–0.085	0.052			
S	–0.087	–0.015	0.099	0.068	–0.045			
LCA_M								
I	–0.085	0.008	–0.093	0.002	–0.099			
S	–0.136	–0.070	0.048	0.051	0.047			

Abbreviations: AHM = antihypertensive medication; Alcohol = hazardous alcohol consumption; Smoking = current smoking; Sleep = poor sleep quality; LPA_M = mean leisure physical activity score; LSA_M = mean leisure social activity score; LCA_M = mean leisure cognitive activity score. WMH = white matter hyperintensities; LAC No. = number of lacunes; EC Right = right entorhinal cortex thickness; EC Left = left entorhinal cortex thickness, Memory = declarative memory; LPA = leisure physical activity; LSA = leisure social activity; LCA = leisure cognitive activity.
Note: Beta (β), 0.10 = weak effect, 0.30 = moderate effect, 0.50 = strong effect size (Cohen, 1992).
*$p < .05$; **$p < .01$; ***$p < .001$.
[a]Subgroup of participants with lacunes ($n = 61$).
[b]Because participants with higher educational levels showed a faster decline in declarative memory, it was evaluated whether the point of convergence (intersection of the different educational groups) occurred within seven years. Therefore, post-hoc *t*-tests were conducted at the seven-year follow-up. The results showed that the more highly educated still had better declarative memory at the seven-year follow-up. This indicates that the convergence point occurs after the observed 7 years. Education level 1 vs. level 2: $t(230) = -2.56$, education level 1 vs. level 3: $p = .012$; . education level 2 vs. level 3: $t(230) = -2.48$, $p = .015$; $t(230) = 0.77$, $p = .446$.

hippocampal or prefrontal volume) predicted a poorer memory in healthy adults controlling for age. They concluded that even mild age-related atrophy of EC volume is a sensitive predictor of memory loss in a healthy and educated population. Our finding that individuals with better declarative memory at baseline showed less memory decline over the 7 years, may indicate cognitive reserve. According to Stern et al. (2019), these initially better declarative memory skills – acquired before the onset of EC neurodegeneration – may serve as a protection against the loss of brain function and delay it. Other studies have further shown that higher premorbid IQ, education, or occupational level is related to a lower risk of developing dementia (Deary et al., 2004; Stern, 1994; Valenzuela and Sachdev, 2006), a later onset of dementia (Xu et al., 2020), and a slower age-related cognitive decline in general (Zahodne et al., 2015). Cognitive reserve as well as maintenance (Stern et al., 2019) may also be reflected in our above mentioned results of cross-sectional and longitudinal relationships between thicker right/left EG and better declarative memory.

In our analyzes, we did not find associations between WMH / lacunes and declarative memory, which is in line with recent studies showing that individuals with cSVD exhibit a typical pattern of cognitive decline, specifically showing impairments in attention, processing speed, and executive functions, while memory functions remain relatively

Table 4
Combined summary covariances between cSVD MRI markers, declarative memory, and leisure activity. All significant bivariate cross-domain correlations and the univariate inner-domain correlations between intercept and slope are described in standardized effect estimates (β).

Variables	WMH	LAC No.[a]	EC Right	EC Left	Memory
Intercept ~ ~ Intercept					
WMH		0.451**	–0.062	0.084	–0.107
LAC No.[a]			–0.040	–0.117	–0.010
EC Right				0.578**	0.198*
EC Left					0.288**
Memory					
LPA	–0.022	–0.081	0.059	0.078	0.079
LSA	–0.092	–0.140	0.035	–0.017	0.049
LCA	–0.060	–0.165	–0.041	–0.003	–0.072
Intercept ~ ~ Slope					
WMH	–0.247*	0.452**	–0.105	0.050	–0.102
LAC No.[a]	–0.463	0.506**	0.016	0.128	–0.273
EC Right	0.040	–0.078	0.222	0.391**	0.537*
EC Left	–0.193	0.095	0.106	0.504***	0.389
Memory	0.005	–0.024	0.204	0.110	0.930**
LPA	–0.096	–0.289	0.239*	0.190	0.576
LSA	–0.115	–0.051	0.270**	0.117	0.254
LCA	–0.169	0.028	0.182	0.078	0.295
Slope ~ ~ Slope					
WMH		–0.288	–0.132	–0.239	–0.005
LAC No.[a]			–0.080	0.229	–0.166
EC Right				0.577***	0.915*
EC Left					0.821*
Memory					
LPA	0.189	0.261	0.060	–0.093	–0.748
LSA	–0.251	–0.048	–0.162	–0.008	–0.321
LCA	–0.100	–0.294	0.164	0.230	–0.408

Abbreviations: WMH = white matter hyperintensities; LAC No. = number of lacunes; EC Right = thickness of right entorhinal cortex; EC Left = thickness of left entorhinal cortex, Memory = declarative memory; LPA = leisure physical activity; LSA = leisure social activity; LCA = leisure cognitive activity.
Note: Beta (β), 0.10 = weak effect, 0.30 = moderate effect, 0.50 = strong effect size (Cohen, 1992).
*$p < .05$; **$p < .01$; ***$p < .001$.
[a] Subgroup of participants with lacunes ($n = 61$).

unimpaired (Hamilton et al., 2021; Sachdev et al., 2014).

In contrast, the studies by Rizvi et al. (2018, 2021) reported a direct effect of WMH volume on memory performance in a sample that included cognitively healthy individuals and individuals with MCI. Interestingly, however, in their earlier publication the authors also reported indirect associations between WMH and memory performance mediated by averaged right and left EC thickness (using mediation analysis). Thus, it may well be that the lack of association between WMH (and number of lacunes) and declarative memory in this study is due to a mediation via cortical atrophy.

According to our analyzes, neither lacunes nor WMH were related to thinning of the EC in cognitively healthy older adults. However, both cSVD MRI markers – WMH and lacunes – were associated at baseline, and greater WMH volume predicted more lacunes over time. This finding is supported by other studies (Hotz et al., 2021; Xia et al., 2020) that reflect complex nesting and interaction of these two cSVD markers with a possible common underlying pathology.

4.2. Declarative memory and confounding factors

We demonstrated that higher education was associated with better declarative memory at baseline, but with a steeper declarative memory loss over time. Post-hoc *t*-tests of declarative memory scores at seven-year follow-up showed that participants with higher education still had better declarative memory after the seven years observation. However, these findings point to a convergence point outside this observed seven-year interval to which individuals converge regardless of education. This observation is in line with the neural compensation model of cognitive reserve (Stern, 2009), which assumes that there are differences between individuals in the ability to use alternative brain structures or networks when brain pathology is present that underlie specific task performance. That is, individuals with higher education may cope with normal age-related decline in memory by using other intact cognitive areas, effectively reducing the rate of memory decline until these secondary functions also begin to decline. However, the influence of education on change in cognition is not yet fully understood and alternative effects (e.g., no differences in change between different levels of education or slower decline for higher levels of education) have been reported (for a review, see Lenehan et al. 2015). Overall, the findings highlight the importance of education as a modifiable protective factor against memory loss and as a determinant of cognitive reserve, since education can improve cognitive reserve and postpone dementia (Gottesman et al., 2014).

4.3. Leisure activity, cSVD, and declarative memory

We found that higher engagement in physical and social leisure activity was linked to less thinning of the right EC over time. This indicates that especially sports, which in later life oftentimes also includes social aspects, and an active leisure time with friends and family are beneficial for brain health and thus may be protective against neurodegeneration of the EC later in life. Sport und CT (Bashir et al., 2021; Hillman et al., 2008; Rabin et al., 2019; Raffin et al., 2023; Walhovd et al., 2014). However, we found no associations for leisure activity with WMH, number of lacunes, left EC thickness, and memory. Previous research on this topic is mixed. Some studies have found associations between physical activity and brain health and/or cognition (Casaletto et al., 2020; Colcombe et al., 2003; Colcombe and Kramer, 2003; Doi et al., 2015; Erickson et al., 2011; Gu et al., 2020) whereas two recent longitudinal studies found no relation between either a five-year supervised

physical activity intervention and WMH growth (Arild et al., 2022) or between surveyed physical activity and executive functioning, progression of cSVD MRI markers, or microstructural integrity after correction for confounding factors over a nine-year follow-up (Landman et al., 2021). The review by Song et al. (2022) of 18 studies examining LPA and/or leisure cognitive activity (LCA) suggests emerging evidence for both LPA and LCA being protective for different brain markers and cognition (Colcombe and Kramer, 2003; Gu et al., 2020; Song et al., 2022). Similarly, Sexton et al. (2016) reported small positive effects of LPA on white matter volume and white matter lesions. However, most of the previous studies summarized in the reviews by Sexton et al. (2016) and Song et al. (2022) referred mostly to cross-sectional study designs, and none of these studies examined all three leisure activities in healthy older adults. In contrast to LPA and LCA, leisure social activity (LSA) is less investigated. A review and meta-analysis with mainly cross-sectional studies that combined LSA and LCA into a single construct reflecting socio-intellectual activity showed associations with total white matter (volume and lesions), hippocampal volume, and regional gray matter volume in the major brain lobes, but not with global gray matter volume (Anatürk et al., 2018; Colcombe and Kramer, 2003; Sexton et al., 2016). In addition, the meta-analysis by Brown et al. (2012) with older adults showed that change in social activity was related to memory performance in only two of four longitudinal studies, and they concluded that there is little evidence that social activity improves cognitive function (Brown et al., 2012).

To conclude, LPA is the most studied leisure activity compared to LCA and LSA, however, the effects of all leisure activities on brain or cognitive abilities seem to be rather small, and with a low overall certainty (Duffner et al., 2023). A fundamental challenge in inferring potential effects of leisure time activity is the large inter-study variability. This large inter-study variability can be seen in terms of the population studied (e.g., different demographic factors), the study design (longitudinal vs. cross-sectional), the outcome measures used (cognitive abilities or brain measurements), and the operationalization of leisure activity. To counter variability and better understand the effects of leisure activities, standardization in the operationalization of leisure activities would be particularly desirable (Song et al., 2022).

We would like to point out that the effectiveness of regular physical activity in primary and secondary prevention of various chronic diseases (e.g. cardiovascular diseases, diabetes, cancer, hypertension, obesity, depression, and osteoporosis) and premature death is considered undisputed (Anderson and Durstine, 2019; Warburton et al., 2006).

4.4. Leisure activity and confounding factors

Interestingly, leisure activity was the only age-independent predictor and did not change significantly over time. In addition, participants with a higher education initially engaged more in physical leisure activity, but not in cognitive or social leisure activity, than participants with a lower education. The association of physical activity and level of education in young to early old age has been reported previously (Blasko et al., 2014; Shaw and Spokane, 2008). Expectedly, our analysis showed that obese participants engage less in physical and social activity at baseline, which is in line with previous studies showing that overweight and obesity in adults are related to low levels of physical activity, high television viewing and poor sleep duration (Cassidy et al., 2017). In the study by Thedinga et al. (2021), obese participants reported staying away from sports and exercise due to traumatic experiences with stigma. These results underscore both the social component in sport and a possible pattern of avoidance due to self-discriminatory behaviors in sport, as well as in the amount of social activity.

4.5. CSVD and confounding factors

The larger initial WMH volumes in women found in this study, have also been reported in other studies (Alqarni et al., 2021; de Leeuw et al., 2001; Longstreth et al., 1996; Sachdev et al., 2009), and may reflect genetic and/or hormonal risk factors (V. M. Miller et al., 2013; Sachdev et al., 2016; Seo et al., 2013; Ten Kate et al., 2018). Men had thicker right and left EG than women at baseline, with no sex differences in the trajectories over the seven years of the study. This is in accordance with the result of the study by Wang et al. (2019). In return, men initially showed more lacunes than women, which is consistent with the study by Hao et al. (2021), in which the overall mortality rate for silent lacunar infarcts after five years was twice as high in men as in women.

Although participants with higher education had larger WMH volumes and a thinner right EC at baseline, there was a (non-significant) tendency for the WMH volumes to increase less over the seven years than in participants with a lower education. However, higher educated participants showed fewer initial lacunes with a smaller increase over time. Therefore a longitudinal protective effect of higher education on WMH and lacunes can be assumed.

Obesity was associated cross-sectionally with a thinner left EC in our study. Further, the initial thickness of the left EC as well as the number of lacunes at baseline and over time appeared to benefit from a possible protective effect of antihypertensive medication intake. Previous studies point to an association between antihypertensive medication intake and smaller declines of hippocampal volume (Korf et al., 2004), lower risk of dementia and AD (Ding et al., 2020; Ou et al., 2020), lower incidence of hemorrhagic and ischemic stroke (Perry et al., 2000), slowing of WMH, but inconsistent findings on total brain volume (van Middelaar et al., 2018). Considering that our participants with lacunes were on average older than the participants without lacunes, the possible longer intake of antihypertensive medication could explain the significant protective effect on the number of lacunes not found in the WMH. According to the standard definition by "NHIS - Adult Alcohol Use," (2018) our participants tend to a light (≤ 3 drinks per week) to moderate (women: > 3 and ≤ 7 drinks per week, men: > 3 and ≤ 14 drinks per week) alcohol consumption rather than a hazardous alcohol consumption as proposed when using the AUDIT. This is reflected by the beneficial effect of alcohol consumption on the number of lacunes at baseline and over time. This positive impact is consistent with numerous studies showing reduced risk of different cardiovascular disease outcomes with light-to-moderate alcohol consumption (Bell et al., 2017; O'Keefe et al., 2014; Ronksley et al., 2011; Scoccianti et al., 2016; Wood et al., 2018; Zhang et al., 2014). The association between moderate alcohol consumption and a lower risk of cardiovascular disease has also been observed in older individuals (Mukamal et al., 2006). It has been proposed that this is due to an increase in high-density lipoprotein (HDL) cholesterol that accompanies alcohol consumption, which has been associated with protection against heart disease and improvement in factors that influence blood clotting, which is the cause of many heart attacks and the most common strokes (Booyse et al., 2007). Another possible mechanism was suggested in a recent study by Mezue et al. (2023) that major cardiovascular events are reduced in individuals with light to moderate alcohol consumption compared with individuals with no or high alcohol consumption by lower activity of stress-associated brain areas. Although we showed that light to moderate alcohol consumption reduces lacunes in older healthy adults, adverse effects on noncardiovascular disease, particularly cancer, are observed in the population aged 50 years and older (GBD 2016 Alcohol Collaborators, 2018). In principle, there is no safe level of alcohol consumption (Anderson et al., 2023).

In contrast, current smoking resulted in more lacunes at baseline and over time, indicating a higher risk of cardiovascular disease in smokers. For example, smoking damages blood vessels with the risk that they thicken and narrow, causing the heart to beat faster, blood pressure to rise, and clots to form, which can lead to stroke (Centers for Disease Control and Prevention (US), National Center for Chronic Disease Prevention and Health Promotion (US), & Office on Smoking and Health (US), 2010; U.S. Department of Health and Human Services, 2014).

We found no association between poor sleep quality on cSVD MRI

markers or declarative memory controlled for all confounders. Although an association with brain health is assumed, the direction of the association between sleep disturbance and brain health is still unclear, with the possibility of reverse causality – such as longer sleep duration being an early marker of neurodegeneration (Gottesman and Seshadri, 2022).

5. Strength and limitations

An advantage of this longitudinal study is that due to the long observation period of seven years and the five measurement time points, statistical procedures using LGC models could be applied, which makes the error variance highly predictable. To minimize distortion of the true relationship, all associations were corrected for potential confounders. Another advantage is the quantification of WMH volumes with UBO Detector, an algorithm which we validated and customized in a previous work on the same sample (Hotz et al., 2022). Importantly, leisure activity was not handled one-dimensionally, allowing a weighted operationalization of physical, social, and/or cognitive aspects in one single activity, reducing overestimation and underestimation of effects. However, there are some limitations to consider. A long follow-up period carries the risk that older and less medically healthy participants are more likely to drop out of the study, which could lead to selection bias and obscure the strength and direction of the association between leisure activity, declarative memory, and brain health. However, previously conducted selectivity analyzes on our sample show that the dropout was not systematically biased in terms of physical and mental health. Although structured questionnaires are valid and commonly used methods to assess leisure activity, participants' responses may be biased and/or erroneous because social desirability may lead to overestimation and memory effects. Furthermore, the three leisure activity dimensions (LPA, LSA, LCA) are content-driven and correspond to previous research, but they are still arbitrary in number.

We did not control for multiple comparisons in the models, as there is little consensus on how to best control for multiple comparisons in complex multivariate structural equation models, and thus most researchers do not apply Type I error control (Smith and Cribbie, 2013). It should further be noted that the generalizability of the present study is limited by the selective sample of highly educated, cognitively healthy adults living in Switzerland with a high socioeconomic standard. Thus, our results reflect healthy and successful rather than typical aging. Due to the observational nature of this study, no causal relationships can be established, and therefore the associative results should be interpreted accordingly. To further investigate our findings, randomized controlled trials (RCTs) are recommended to test the effectiveness of leisure activity on brain health and memory.

6. Conclusion

The presented five-wave longitudinal analysis with cognitively healthy older participants explored the complex associations of cSVD MRI markers (total WMH volume, number of lacunes, right and left EC thickness), declarative memory, leisure activity, and confounding factors using LGC models. We found evidence of neuroprotective effects, with physical and social leisure activities being predictive of less thinning of the right EC over seven years. Further beneficial effects over time were shown for higher education, antihypertensive medication use and light-to-moderate alcohol consumption, while smoking and obesity were associated with disadvantageous outcomes. These findings have yet to be replicated. Given that there is no cure for cSVD, modifiable confounding factors should be intensively studied in the future to maintain and promote brain health in old age.

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Ethics statement

This study involving human participants was reviewed and approved by the Ethics Committee of the Canton of Zurich. The participants provided their written informed consent to participate in this study.

Data and code availability statement

The data supporting this manuscript are not publicly available because the used consent does not allow for the public sharing of the data.

Software availability statement

The following openly available software were used: FreeSurfer (https://surfer.nmr.mgh.harvard.edu). UBO Detector (https://cheba.unsw.edu.au/research-groups/neuroimaging/pipeline).

CRediT authorship contribution statement

Isabel Hotz: Conceptualization, Methodology, Validation, Data curation, Writing – original draft, Writing – review & editing, Visualization. **Pascal Frédéric Deschwanden:** Methodology, Validation, Formal analysis, Data curation, Writing – review & editing. **Susan Mérillat:** Investigation, Resources, Data curation, Writing – review & editing, Supervision, Project administration, Funding acquisition. **Lutz Jäncke:** Investigation, Resources, Writing – review & editing, Supervision, Project administration, Funding acquisition.

Declaration of Competing Interest

None.

Data availability

The data that has been used is confidential.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.neuroimage.2023.120461.

References

Alqarni, A., Jiang, J., Crawford, J.D., Koch, F., Brodaty, H., Sachdev, P., Wen, W., 2021. Sex differences in risk factors for white matter hyperintensities in non-demented older individuals. Neurobiol. Aging 98, 197–204. https://doi.org/10.1016/j.neurobiolaging.2020.11.001.

Anatürk, M., Demnitz, N., Ebmeier, K.P., Sexton, C.E., 2018. A systematic review and meta-analysis of structural magnetic resonance imaging studies investigating cognitive and social activity levels in older adults. Neurosci. Biobehav. Rev. 93, 71–84. https://doi.org/10.1016/j.neubiorev.2018.06.012.

Anderson, B.O., Berdzuli, N., Ilbawi, A., Kestel, D., Kluge, H.P., Krech, R., Ferreira-Borges, C., 2023. Health and cancer risks associated with low levels of alcohol

consumption. Lancet. Public Health 8 (1), e6–e7. https://doi.org/10.1016/S2468-2667(22)00317-6.
Anderson, E., Durstine, J.L., 2019. Physical activity, exercise, and chronic diseases: a brief review. Sports Med. Health Sci. 1 (1), 3–10. https://doi.org/10.1016/j.smhs.2019.08.006.
Appelman, A.P.A., Exalto, L.G., van der Graaf, Y., Biessels, G.J., Mali, W.P.T.M., Geerlings, M.I., 2009. White matter lesions and brain atrophy: more than shared risk factors? A systematic review. Cerebrovasc. Dis. 28 (3), 227–242. https://doi.org/10.1159/000226774.
Arild, A., Vangberg, T., Nikkels, H., Lydersen, S., Wisløff, U., Stensvold, D., Håberg, A.K., 2022. Five years of exercise intervention at different intensities and development of white matter hyperintensities in community dwelling older adults, a generation 100 sub-study. Aging 14 (2), 596–622. https://doi.org/10.18632/aging.203843.
Ashburner, J., 2007. A fast diffeomorphic image registration algorithm. NeuroImage 38 (1), 95–113. https://doi.org/10.1016/j.neuroimage.2007.07.007.
Babor, T.F., Higgins-Biddle, J.C., Saunders, J.B., Monteiro, M.G., 2001. AUDIT : The Alcohol Use Disorders Identification Test : Guidelines for Use in Primary Health Care (No. WHO/MSD/MSB/01.6a), 2nd ed. Department of Mental Health and Substance Dependence, World Health Organization, Geneva.
Bangen, K.J., Preis, S.R., Delano-Wood, L., Wolf, P.A., Libon, D.J., Bondi, M.W., Brickman, A.M., 2018. Baseline white matter hyperintensities and hippocampal volume are associated with conversion from normal cognition to mild cognitive impairment in the framingham offspring study. Alzheimer Dis. Assoc. Disord. 32 (1), 50–56. https://doi.org/10.1097/WAD.0000000000000215.
Barnes, J., Ridgway, G.R., Bartlett, J., Henley, S.M.D., Lehmann, M., Hobbs, N., Fox, N. C., 2010. Head size, age and gender adjustment in MRI studies: a necessary nuisance? NeuroImage 53 (4), 1244–1255. https://doi.org/10.1016/j.neuroimage.2010.06.025.
Bashir, S., Al-Sultan, F., Jamea, A.A., Almousa, A., Alzahrani, M.S., Alhargan, F.A., Abualait, T., Yoo, W.K., 2021. Physical exercise and cortical thickness in healthy controls: a pilot study. Eur. Rev. Med. Pharmacol. Sci. 25 (23), 7375–7379. https://doi.org/10.26355/eurrev_202112_27432.
Bell, S., Daskalopoulou, M., Rapsomaniki, E., George, J., Britton, A., Bobak, M., Hemingway, H., 2017. Association between clinically recorded alcohol consumption and initial presentation of 12 cardiovascular diseases: population based cohort study using linked health records. BMJ 356, j909. https://doi.org/10.1136/bmj.j909.
Bentler, P.M., 1990. Comparative fit indexes in structural models. Psychol. Bull. 107 (2), 238–246. https://doi.org/10.1037/0033-2909.107.2.238.
Blasko, I., Jungwirth, S., Kemmler, G., Weissgram, S., Tragl, K.H., Fischer, P., 2014. Leisure time activities and cognitive functioning in middle European population-based study. Eur. Geriatr. Med. 5 (3), 200–207. https://doi.org/10.1016/j.eurger.2013.09.003.
Booyse, F.M., Pan, W., Grenett, H.E., Parks, D.A., Darley-Usmar, V.M., Bradley, K.M., Tabengwa, E.M., 2007. Mechanism by which alcohol and wine polyphenols affect coronary heart disease risk. Ann. Epidemiol. 17 (5 Suppl), S24–S31. https://doi.org/10.1016/j.annepidem.2007.01.006.
Braak, H., Braak, E., 1991a. Demonstration of amyloid deposits and neurofibrillary changes in whole brain sections. Brain Pathol. 1 (3), 213–216.
Braak, H., Braak, E., 1991b. Neuropathological stageing of Alzheimer-related changes. Acta Neuropathol. 82 (4), 239–259. https://doi.org/10.1007/BF00308809.
Brickman, A.M., 2013. Contemplating Alzheimer's disease and the contribution of white matter hyperintensities. Curr. Neurol. Neurosci. Rep. 13 (12), 415. https://doi.org/10.1007/s11910-013-0415-7.
Brickman, A.M., Schupf, N., Manly, J.J., Luchsinger, J.A., Andrews, H., Tang, M.X., Brown, T.R., 2008. Brain morphology in older African Americans, Caribbean Hispanics, and whites from northern Manhattan. Arch. Neurol. 65 (8), 1053–1061. https://doi.org/10.1001/archneur.65.8.1053.
Brown, C.L., Gibbons, L.E., Kennison, R.F., Robitaille, A., Lindwall, M., Mitchell, M.B., Piccinin, A.M., 2012. Social activity and cognitive functioning over time: a coordinated analysis of four longitudinal studies. J. Aging Res. 2012, 287438 https://doi.org/10.1155/2012/287438.
Browne, M.W., Cudeck, R., 1992. Alternative ways of assessing model fit. Sociol. Methods Res. 21 (2), 230–258. https://doi.org/10.1177/0049124192021002005.
Buckner, R.L., Head, D., Parker, J., Fotenos, A.F., Marcus, D., Morris, J.C., Snyder, A.Z., 2004. A unified approach for morphometric and functional data analysis in young, old, and demented adults using automated atlas-based head size normalization: reliability and validation against manual measurement of total intracranial volume. NeuroImage 23 (2), 724–738. https://doi.org/10.1016/j.neuroimage.2004.06.018.
Buysse, D.J., Reynolds, C.F., Monk, T.H., Berman, S.R., Kupfer, D.J., 1989. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res. 28 (2), 193–213. https://doi.org/10.1016/0165-1781(89)90047-4.
Casaletto, K.B., Rentería, M.A., Pa, J., Tom, S.E., Harrati, A., Armstrong, N.M., Zahodne, L.B., 2020. Late-life physical and cognitive activities independently contribute to brain and cognitive resilience. J. Alzheimer Dis. 74 (1), 363–376. https://doi.org/10.3233/JAD-191114.
Cassidy, S., Chau, J.Y., Catt, M., Bauman, A., Trenell, M.I., 2017. Low physical activity, high television viewing and poor sleep duration cluster in overweight and obese adults; a cross-sectional study of 398,984 participants from the UK Biobank. Int. J. Behav. Nutr. Phys. Act. 14 (1), 57. https://doi.org/10.1186/s12966-017-0514-y.
Centers for Disease Control and Prevention (US), National Center for Chronic Disease Prevention and Health Promotion (US), & Office on Smoking and Health (US), 2010. How Tobacco Smoke Causes Disease: The Biology and Behavioral Basis For Smoking-Attributable Disease: A Report of the Surgeon General. Centers for Disease Control and Prevention (US), Atlanta (GA).
Chowdhury, M.H., Nagai, A., Bokura, H., Nakamura, E., Kobayashi, S., Yamaguchi, S., 2011. Age-related changes in white matter lesions, hippocampal atrophy, and cerebral microbleeds in healthy subjects without major cerebrovascular risk factors. J. Stroke Cerebrovasc. Dis. 20 (4), 302–309. https://doi.org/10.1016/j.jstrokecerebrovasdis.2009.12.010.
Cohen, J., 1992. A power primer. Psychol. Bull. 112 (1), 155–159. https://doi.org/10.1037/0033-2909.112.1.155.
Colcombe, S.J., Erickson, K.I., Raz, N., Webb, A.G., Cohen, N.J., McAuley, E., Kramer, A. F., 2003. Aerobic fitness reduces brain tissue loss in aging humans. J. Gerontol. A Biol. Sci. Med. Sci. 58 (2), 176–180. https://doi.org/10.1093/gerona/58.2.m176.
Colcombe, S.J., Kramer, A.F., 2003. Fitness effects on the cognitive function of older adults: a meta-analytic study. Psychol. Sci. 14 (2), 125–130. https://doi.org/10.1111/1467-9280.t01-1-01430.
Corder, E.H., Saunders, A.M., Strittmatter, W.J., Schmechel, D.E., Gaskell, P.C., Small, G. W., Pericak-Vance, M.A., 1993. Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. Science 261 (5123), 921–923. https://doi.org/10.1126/science.8346443.
Cribbie, R.A., 2007. Multiplicity control in structural equation modeling. Struct. Equ. Model. A Multidiscip. J. 14 (1), 98–112. https://doi.org/10.1207/s15328007sem1401_5.
Dadar, M., Maranzano, J., Misquitta, K., Anor, C.J., Fonov, V.S., Tartaglia, M.C., Alzheimer's Disease Neuroimaging Initiative, 2017. Performance comparison of 10 different classification techniques in segmenting white matter hyperintensities in aging. NeuroImage 157, 233–249. https://doi.org/10.1016/j.neuroimage.2017.06.009.
de Leeuw, F.E., de Groot, J.C., Achten, E., Oudkerk, M., Ramos, L.M., Heijboer, R., Breteler, M.M., 2001. Prevalence of cerebral white matter lesions in elderly people: a population based magnetic resonance imaging study. the Rotterdam scan study. J. Neurol. Neurosurg. Psychiatr. 70 (1), 9–14. https://doi.org/10.1136/jnnp.70.1.9.
Deary, I.J., Whiteman, M.C., Starr, J.M., Whalley, L.J., Fox, H.C., 2004. The impact of childhood intelligence on later life: following up the Scottish mental surveys of 1932 and 1947. J. Pers. Soc. Psychol. 86 (1), 130–147. https://doi.org/10.1037/0022-3514.86.1.130.
Desikan, R.S., Ségonne, F., Fischl, B., Quinn, B.T., Dickerson, B.C., Blacker, D., Killiany, R.J., 2006. An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. NeuroImage 31 (3), 968–980. https://doi.org/10.1016/j.neuroimage.2006.01.021.
Ding, J., Davis-Plourde, K.L., Sedaghat, S., Tully, P.J., Wang, W., Phillips, C., Launer, L.J., 2020. Antihypertensive medications and risk for incident dementia and Alzheimer's disease: a meta-analysis of individual participant data from prospective cohort studies. Lancet Neurol. 19 (1), 61–70. https://doi.org/10.1016/S1474-4422(19)30393-X.
Doi, T., Makizako, H., Shimada, H., Tsutsumimoto, K., Hotta, R., Nakakubo, S., Suzuki, T., 2015. Objectively measured physical activity, brain atrophy, and white matter lesions in older adults with mild cognitive impairment. Exp. Gerontol. 62, 1–6. https://doi.org/10.1016/j.exger.2014.12.011.
Donix, M., Burggren, A.C., Scharf, M., Marschner, K., Suthana, N.A., Siddarth, P., Bookheimer, S.Y., 2013. APOE associated hemispheric asymmetry of entorhinal cortical thickness in aging and Alzheimer's disease. Psychiatry Res. 214 (3), 212–220. https://doi.org/10.1016/j.pscychresns.2013.09.006.
Duffner, L.A., DeJong, N.R., Jansen, J.F.A., Backes, W.H., de Vugt, M., Deckers, K., Köhler, S., 2023. Associations between social health factors, cognitive activity and neurostructural markers for brain health - a systematic literature review and meta-analysis. Ageing Res. Rev. 89, 101986 https://doi.org/10.1016/j.arr.2023.101986.
Erickson, K.I., Voss, M.W., Prakash, R.S., Basak, C., Szabo, A., Chaddock, L., Kramer, A. F., 2011. Exercise training increases size of hippocampus and improves memory. Proc. Natl. Acad. Sci. U. S. A. 108 (7), 3017–3022. https://doi.org/10.1073/pnas.1015950108.
Finkbeiner, C., 1979. Estimation for the multiple factor model when data are missing. Psychometrika 44 (4), 409–420. https://doi.org/10.1007/BF02296204.
Fischl, B., 2012. FreeSurfer. NeuroImage 62 (2), 774–781. https://doi.org/10.1016/j.neuroimage.2012.01.021.
Folstein, M.F., Folstein, S.E., McHugh, P.R., 1975. Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J. Psychiatr. Res. 12 (3), 189–198. https://doi.org/10.1016/0022-3956(75)90026-6.
Fratiglioni, L., Paillard-Borg, S., Winblad, B., 2004. An active and socially integrated lifestyle in late life might protect against dementia. Lancet Neurol. 3 (6), 343–353. https://doi.org/10.1016/S1474-4422(04)00767-7.
Garnier-Crussard, A., Bougacha, S., Wirth, M., Dautricourt, S., Sherif, S., Landeau, B., Chételat, G., 2022. White matter hyperintensity topography in Alzheimer's disease and links to cognition. Alzheimer Dementia 18 (3), 422–433. https://doi.org/10.1002/alz.12410.
GBD 2016 Alcohol Collaborators, 2018. Alcohol use and burden for 195 countries and territories, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet 392 (10152), 1015–1035. https://doi.org/10.1016/S0140-6736(18)31310-2.
Gmel, G., Kuendig, H., Notari, L., & Gmel, C. (2017). Suchtmonitoring Schweiz: konsum von Alkohol, Tabak und illegalen Drogen in der Schweiz im Jahr 2016. Sucht Schweiz.
Gons, R.A.R., van Norden, A.G.W., de Laat, K.F., van Oudheusden, L.J.B., van Uden, I.W. M., Zwiers, M.P., de Leeuw, F.E., 2011. Cigarette smoking is associated with reduced microstructural integrity of cerebral white matter. Brain A J. Neurol. 134 (Pt 7), 2116–2124. https://doi.org/10.1093/brain/awr145.
Gottesman, R.F., Rawlings, A.M., Sharrett, A.R., Albert, M., Alonso, A., Bandeen-Roche, K., Mosley, T.H., 2014. Impact of differential attrition on the association of education with cognitive change over 20 years of follow-up: the ARIC

neurocognitive study. Am. J. Epidemiol. 179 (8), 956–966. https://doi.org/10.1093/aje/kwu020.
Gottesman, R.F., Seshadri, S., 2022. Risk factors, lifestyle behaviors, and vascular brain health. Stroke 53 (2), 394–403. https://doi.org/10.1161/STROKEAHA.121.032610.
Gu, Y., Beato, J.M., Amarante, E., Chesebro, A.G., Manly, J.J., Schupf, N., Brickman, A. M., 2020. Assessment of leisure time physical activity and brain health in a multiethnic cohort of older adults. JAMA Netw. Open 3 (11), e2026506. https://doi.org/10.1001/jamanetworkopen.2020.26506.
Hamilton, O.K.L., Backhouse, E.V., Janssen, E., Jochems, A.C.C., Maher, C., Ritakari, T. E., Wardlaw, J.M., 2021a. Cognitive impairment in sporadic cerebral small vessel disease: a systematic review and meta-analysis. Alzheimer Dementia 17 (4), 665–685. https://doi.org/10.1002/alz.12221.
Hamilton, O.K.L., Cox, S.R., Okely, J.A., Conte, F., Ballerini, L., Bastin, M.E., Deary, I.J., 2021b. Cerebral small vessel disease burden and longitudinal cognitive decline from age 73 to 82: the Lothian Birth Cohort 1936. Transl. Psychiatry 11 (1), 376. https://doi.org/10.1038/s41398-021-01495-4.
Hao, Z., Chen, Y., Wright, N., Qin, H., Turnbull, I., Guo, Y., Chen, Z., 2021. Natural history of silent lacunar infarction: 10-year follow-up of a community-based prospective study of 0.5 million Chinese adults. Lancet Reg. Health 17, 100309. https://doi.org/10.1016/j.lanwpc.2021.100309. Western Pacific.
Hasan, K.M., Mwangi, B., Cao, B., Keser, Z., Tustison, N.J., Kochunov, P., Soares, J., 2016. Entorhinal cortex thickness across the human lifespan. J. Neuroimaging 26 (3), 278–282. https://doi.org/10.1111/jon.12297.
Hasbani, N.R., Ligthart, S., Brown, M.R., Heath, A.S., Bebo, A., Ashley, K.E., de Vries, P. S., 2022. American heart association's life's simple 7: lifestyle recommendations, polygenic risk, and lifetime risk of coronary heart disease. Circulation 145 (11), 808–818. https://doi.org/10.1161/CIRCULATIONAHA.121.053730.
Helmstaedter, C., & Durwen, H.F. (1990). VLMT: verbaler Lern- und Merkfähigkeitstest: ein praktikables und differenziertes Instrumentarium zur Prüfung der verbalen Gedächtnisleistungen. [VLMT: a useful tool to assess and differentiate verbal memory performance.], 141, 21–30.
Hillman, C.H., Erickson, K.I., Kramer, A.F., 2008. Be smart, exercise your heart: exercise effects on brain and cognition. Nat. Rev. Neurosci. 9 (1), 58–65. https://doi.org/10.1038/nrn2298.
Hotz, I., Deschwanden, P.F., Liem, F., Mérillat, S., Malagurski, B., Kollias, S., Jäncke, L., 2022. Performance of three freely available methods for extracting white matter hyperintensities: freeSurfer, UBO Detector, and BIANCA. Hum. Brain Mapp. 43 (5), 1481–1500. https://doi.org/10.1002/hbm.25739.
Hotz, I., Deschwanden, P.F., Mérillat, S., Liem, F., Kollias, S., Jäncke, L., 2021. Associations of subclinical cerebral small vessel disease and processing speed in non-demented subjects: a 7-year study. NeuroImage Clin. 32, 102884 https://doi.org/10.1016/j.nicl.2021.102884.
Hu, L., Bentler, P.M., 1998. Fit indices in covariance structure modeling: sensitivity to underparameterized model misspecification. Psychol. Methods 3 (4), 424–453. https://doi.org/10.1037/1082-989X.3.4.424.
Igarashi, K.M., 2023. Entorhinal cortex dysfunction in Alzheimer's disease. Trends Neurosci. 46 (2), 124–136. https://doi.org/10.1016/j.tins.2022.11.006.
Jahn, H., 2013. Memory loss in Alzheimer's disease. Dialogues Clin. Neurosci. 15 (4), 445–454. https://doi.org/10.31887/DCNS.2013.15.4/hjahn.
Jäncke, L., Sele, S., Liem, F., Oschwald, J., Merillat, S., 2020. Brain aging and psychometric intelligence: a longitudinal study. Brain Struct. Funct. 225 (2), 519–536. https://doi.org/10.1007/s00429-019-02005-5.
Jäncke, Lutz, Liem, F., Merillat, S, 2019. Scaling of brain compartments to brain size. NeuroReport 30 (8), 573–579. https://doi.org/10.1097/WNR.0000000000001249.
Jeerakathil, T., Wolf, P.A., Beiser, A., Massaro, J., Seshadri, S., D'Agostino, R.B., DeCarli, C, 2004. Stroke risk profile predicts white matter hyperintensity volume: the Framingham study. Stroke 35 (8), 1857–1861. https://doi.org/10.1161/01.STR.0000135226.53499.85.
Jiang, J., Liu, T., Zhu, W., Koncz, R., Liu, H., Lee, T., Wen, W., 2018. UBO detector - a cluster-based, fully automated pipeline for extracting white matter hyperintensities. NeuroImage 174, 539–549. https://doi.org/10.1016/j.neuroimage.2018.03.050.
Jokinen, H., Gouw, A.A., Madureira, S., Ylikoski, R., van Straaten, E.C.W., van der Flier, W.M., LADIS Study Group, 2011. Incident lacunes influence cognitive decline: the LADIS study. Neurology 76 (22), 1872–1878. https://doi.org/10.1212/WNL.0b013e31821d752f.
Jopp, D.S., Hertzog, C., 2010. Assessing adult leisure activities: an extension of a self-report activity questionnaire. Psychol. Assess 22 (1), 108–120. https://doi.org/10.1037/a0017662.
Jöreskog, K.G., Sörbom, D., 1993. LISREL 8: Structural Equation Modeling with the SIMPLIS Command Language. (p. xvi, 202-xvi, 202). Lawrence Erlbaum Associates, Inc, Hillsdale, NJ, US.
Karp, A., Paillard-Borg, S., Wang, H.X., Silverstein, M., Winblad, B., Fratiglioni, L., 2006. Mental, physical and social components in leisure activities equally contribute to decrease dementia risk. Dement. Geriatr. Cogn. Disord. 21 (2), 65–73. https://doi.org/10.1159/000089919.
Kaufman, S.K., Del Tredici, K., Thomas, T.L., Braak, H., Diamond, M.I., 2018. Tau seeding activity begins in the transentorhinal/entorhinal regions and anticipates phospho-tau pathology in Alzheimer's disease and PART. Acta Neuropathol. 136 (1), 57–67. https://doi.org/10.1007/s00401-018-1855-6.
Kendall, M.G., Gibbons, J.D., 1990. Rank Correlation Methods, 5th ed. Oxford University Press, London New York NY: E. Arnold.
Kloppenborg, R.P., Nederkoorn, P.J., Grool, A.M., Vincken, K.L., Mali, W.P.T.M., Vermeulen, M., SMART Study Group, 2012. Cerebral small-vessel disease and progression of brain atrophy: the SMART-MR study. Neurology 79 (20), 2029–2036. https://doi.org/10.1212/WNL.0b013e3182749f02.
Korf, E.S.C., White, L.R., Scheltens, P., Launer, L.J., 2004. Midlife blood pressure and the risk of hippocampal atrophy: the honolulu Asia aging study. Hypertension 44 (1), 29–34. https://doi.org/10.1161/01.HYP.0000132475.32317.bb.
Kraal, A.Z., Dotterer, H.L., Sharifian, N., Morris, E.P., Sol, K., Zaheed, A.B., Zahodne, L. B., 2021. Physical activity in early- and mid-adulthood are independently associated with longitudinal memory trajectories in later life. J. Gerontol. A Biol. Sci. Med. Sci. 76 (8), 1495–1503. https://doi.org/10.1093/gerona/glaa252.
Kulason, S., Xu, E., Tward, D.J., Bakker, A., Albert, M., Younes, L., Miller, M.I., 2020. Entorhinal and transentorhinal atrophy in preclinical alzheimer's disease. Front. Neurosci. 14, 804. https://doi.org/10.3389/fnins.2020.00804.
Landman, T.R., Thijssen, D.H., Tuladhar, A.M., de Leeuw, F.E., 2021. Relation between physical activity and cerebral small vessel disease: a nine-year prospective cohort study. Int. J. Stroke Off. J. Int. Stroke Soc. 16 (8), 962–971. https://doi.org/10.1177/1747493020984090.
Lenehan, M.E., Summers, M.J., Saunders, N.L., Summers, J.J., Vickers, J.C., 2015. Relationship between education and age-related cognitive decline: a review of recent research. Psychogeriatr. Off. J. Jpn. Psychogeriatr. Soc. 15 (2), 154–162. https://doi.org/10.1111/psyg.12083.
Ling, Y., Chabriat, H., 2020. Incident cerebral lacunes: a review. J. Cereb. Blood Flow Metab. 40 (5), 909–921. https://doi.org/10.1177/0271678X20908361.
Little, R.J.A., 1995. Modeling the drop-out mechanism in repeated-measures studies. J. Am. Stat. Assoc. 90 (431), 1112. https://doi.org/10.2307/2291350.
Liu, Y., Braidy, N., Poljak, A., Chan, D.K.Y., Sachdev, P.S., 2018. Cerebral small vessel disease and the risk of Alzheimer's disease: a systematic review. Ageing Res. Rev. 47, 41–48. https://doi.org/10.1016/j.arr.2018.06.002.
Livingston, G., Huntley, J., Sommerlad, A., Ames, D., Ballard, C., Banerjee, S., Mukadam, N., 2020. Dementia prevention, intervention, and care: 2020 report of the lancet commission. Lancet 396 (10248), 413–446. https://doi.org/10.1016/S0140-6736(20)30367-6.
Llorens-Martín, M., Blazquez-Llorca, L., Benavides-Piccione, R., Rabano, A., Hernandez, F., Avila, J., DeFelipe, J., 2014. Selective alterations of neurons and circuits related to early memory loss in Alzheimer's disease. Front. Neuroanat. 8, 38. https://doi.org/10.3389/fnana.2014.00038.
Long, X., Zhang, L., Liao, W., Jiang, C., Qiu, B., Alzheimer's Disease Neuroimaging Initiative, 2013. Distinct laterality alterations distinguish mild cognitive impairment and Alzheimer's disease from healthy aging: statistical parametric mapping with high resolution MRI. Hum. Brain Mapp. 34 (12), 3400–3410. https://doi.org/10.1002/hbm.22157.
Longstreth, W.T., Manolio, T.A., Arnold, A., Burke, G.L., Bryan, N., Jungreis, C.A., Fried, L., 1996. Clinical correlates of white matter findings on cranial magnetic resonance imaging of 3301 elderly people. The cardiovascular health study. Stroke 27 (8), 1274–1282. https://doi.org/10.1161/01.STR.27.8.1274.
Malagurski, B., Liem, F., Oschwald, J., Mérillat, S., Jäncke, L., 2020a. Functional dedifferentiation of associative resting state networks in older adults - A longitudinal study. NeuroImage 214, 116680. https://doi.org/10.1016/j.neuroimage.2020.116680.
Malagurski, B., Liem, F., Oschwald, J., Mérillat, S., Jäncke, L., 2020b. Longitudinal functional brain network reconfiguration in healthy aging. Hum. Brain Mapp. 41 (17), 4829–4845. https://doi.org/10.1002/hbm.25161.
Marsh, H.W., Hocevar, D., 1985. Application of confirmatory factor analysis to the study of self-concept: first- and higher order factor models and their invariance across groups. Psychol. Bull. 97 (3), 562–582. https://doi.org/10.1037/0033-2909.97.3.562.
McCarthy, P. (2018). FSLeyes. Zenodo. doi:10.5281/zenodo.1887737.
Mezue, K., Osborne, M.T., Abohashem, S., Zureigat, H., Gharios, C., Grewal, S.S., Tawakol, A., 2023. Reduced stress-related neural network activity mediates the effect of alcohol on cardiovascular risk. J. Am. Coll. Cardiol. 81 (24), 2315–2325. https://doi.org/10.1016/j.jacc.2023.04.015.
Miller, M.I., Younes, L., Ratnanather, J.T., Brown, T., Trinh, H., Postell, E., BIOCARD Research Team, 2013a. The diffeomorphometry of temporal lobe structures in preclinical Alzheimer's disease. NeuroImage Clin. 3, 352–360. https://doi.org/10.1016/j.nicl.2013.09.001.
Miller, V.M., Garovic, V.D., Kantarci, K., Barnes, J.N., Jayachandran, M., Mielke, M.M., Rocca, W.A., 2013b. Sex-specific risk of cardiovascular disease and cognitive decline: pregnancy and menopause. Biol. Sex Differ. 4 (1), 6. https://doi.org/10.1186/2042-6410-4-6.
Moroni, F., Ammirati, E., Rocca, M.A., Filippi, M., Magnoni, M., Camici, P.G., 2018. Cardiovascular disease and brain health: focus on white matter hyperintensities. Int. J. Cardiol. Heart Vasc. 19, 63–69. https://doi.org/10.1016/j.ijcha.2018.04.006.
Mukamal, K.J., Chung, H., Jenny, N.S., Kuller, L.H., Longstreth, W.T., Mittleman, M.A., Siscovick, D.S., 2006. Alcohol consumption and risk of coronary heart disease in older adults: the cardiovascular health study. J. Am. Geriatr. Soc. 54 (1), 30–37. https://doi.org/10.1111/j.1532-5415.2005.00561.x.
NHIS - Adult Alcohol Use. (2018). Retrieved January 26, 2023, from https://www.cdc.gov/nchs/nhis/alcohol/alcohol_glossary.htm.
O'Keefe, J.H., Bhatti, S.K., Bajwa, A., DiNicolantonio, J.J., Lavie, C.J., 2014. Alcohol and cardiovascular health: the dose makes the poison…or the remedy. Mayo Clin. Proc. 89 (3), 382–393. https://doi.org/10.1016/j.mayocp.2013.11.005.
Oschwald, J., Mérillat, S., Liem, F., Röcke, C., Martin, M., Jäncke, L., 2019. Lagged coupled changes between white matter microstructure and processing speed in healthy aging: a longitudinal investigation. Front. Aging Neurosci. 11, 298. https://doi.org/10.3389/fnagi.2019.00298.
Ou, Y.N., Tan, C.C., Shen, X.N., Xu, W., Hou, X.H., Dong, Q., Yu, J.T., 2020. Blood pressure and risks of cognitive impairment and dementia: a systematic review and meta-analysis of 209 prospective studies. Hypertension 76 (1), 217–225. https://doi.org/10.1161/HYPERTENSIONAHA.120.14993.

Palta, P., Sharrett, A.R., Deal, J.A., Evenson, K.R., Gabriel, K.P., Folsom, A.R., Heiss, G., 2019. Leisure-time physical activity sustained since midlife and preservation of cognitive function: the Atherosclerosis Risk in Communities Study. Alzheimer Dementia 15 (2), 273–281. https://doi.org/10.1016/j.jalz.2018.08.008.

Pennanen, C., Kivipelto, M., Tuomainen, S., Hartikainen, P., Hänninen, T., Laakso, M.P., Soininen, H., 2004. Hippocampus and entorhinal cortex in mild cognitive impairment and early AD. Neurobiol. Aging 25 (3), 303–310. https://doi.org/10.1016/S0197-4580(03)00084-8.

Perry, H.M., Davis, B.R., Price, T.R., Applegate, W.B., Fields, W.S., Guralnik, J.M., Probstfield, J.L., 2000. Effect of treating isolated systolic hypertension on the risk of developing various types and subtypes of stroke: the systolic hypertension in the elderly program (SHEP). J. Am. Med. Assoc. 284 (4), 465–471. https://doi.org/10.1001/jama.284.4.465.

Pettigrew, C., Soldan, A., Zhu, Y., Wang, M.C., Moghekar, A., Brown, T., BIOCARD Research Team, 2016. Cortical thickness in relation to clinical symptom onset in preclinical AD. NeuroImage Clin. 12, 116–122. https://doi.org/10.1016/j.nicl.2016.06.010.

R Core Team, R. F. for S. C, 2020. R: A Language and Environment for Statistical Computing (4.0.4). Computer Software, Vienna: Austria.

Rabin, J.S., Klein, H., Kirn, D.R., Schultz, A.P., Yang, H.-S., Hampton, O., Jiang, S., Buckley, R.F., Viswanathan, A., Hedden, T., Pruzin, J., Yau, W.-Y.W., Guzmán-Vélez, E., Quiroz, Y.T., Properzi, M., Marshall, G.A., Rentz, D.M., Johnson, K.A., Sperling, R.A., Chhatwal, J.P., 2019. Associations of physical activity and β-amyloid with longitudinal cognition and neurodegeneration in clinically normal older adults. JAMA Neurology 76 (10), 1203–1210. https://doi.org/10.1001/jamaneurol.2019.1879.

Raffin, J., Rolland, Y., Fischer, C., Mangin, J.-F., Gabelle, A., Vellas, B., de Souto Barreto, P., 2023. Cross-sectional associations between cortical thickness and physical activity in older adults with spontaneous memory complaints: the MAPT Study. J. Sport Health Sci. 12 (3), 324–332. https://doi.org/10.1016/j.jshs.2021.01.011.

Rey, A., 1958. L'examen Clinique En psychologie. [The Clinical Examination in psychology.] (pp. 222–222). Presses Universitaries De France, Oxford, England.

Rizvi, B., Lao, P.J., Chesebro, A.G., Dworkin, J.D., Amarante, E., Beato, J.M., Brickman, A.M., 2021. Association of regional white matter hyperintensities with longitudinal Alzheimer-like pattern of neurodegeneration in older adults. JAMA Netw. Open 4 (10), e2125166. https://doi.org/10.1001/jamanetworkopen.2021.25166.

Rizvi, B., Narkhede, A., Last, B.S., Budge, M., Tosto, G., Manly, J.J., Brickman, A.M., 2018. The effect of white matter hyperintensities on cognition is mediated by cortical atrophy. Neurobiol. Aging 64, 25–32. https://doi.org/10.1016/j.neurobiolaging.2017.12.006.

Rodrigue, K.M., Raz, N., 2004. Shrinkage of the entorhinal cortex over five years predicts memory performance in healthy adults. J. Neurosci. 24 (4), 956–963. https://doi.org/10.1523/JNEUROSCI.4166-03.2004.

Ronksley, P.E., Brien, S.E., Turner, B.J., Mukamal, K.J., Ghali, W.A., 2011. Association of alcohol consumption with selected cardiovascular disease outcomes: a systematic review and meta-analysis. BMJ 342, d671. https://doi.org/10.1136/bmj.d671.

Rosseel, Y., 2012. lavaan: an R package for structural equation modeling. J. Stat Softw. 48 (2) https://doi.org/10.18637/jss.v048.i02.

Sachdev, P.S., Kalaria, R., O'Brien, J., Skoog, I., Alladi, S., Black, S.E., Internationlal Society for Vascular Behavioral and Cognitive Disorders, 2014. Diagnostic criteria for vascular cognitive disorders: a VASCOG statement. Alzheimer Dis. Assoc. Disord. 28 (3), 206–218. https://doi.org/10.1097/WAD.0000000000000034.

Sachdev, P.S., Parslow, R., Wen, W., Anstey, K.J., Easteal, S., 2009. Sex differences in the causes and consequences of white matter hyperintensities. Neurobiol. Aging 30 (6), 946–956. https://doi.org/10.1016/j.neurobiolaging.2007.08.023.

Sachdev, P.S., Thalamuthu, A., Mather, K.A., Ames, D., Wright, M.J., Wen, W., & OATS Collaborative Research Team, 2016. White matter hyperintensities are under strong genetic influence. Stroke 47 (6), 1422–1428. https://doi.org/10.1161/STROKEAHA.116.012532.

Schafer, J.L., Graham, J.W., 2002. Missing data: our view of the state of the art. Psychol. Methods 7 (2), 147–177. https://doi.org/10.1037/1082-989X.7.2.147.

Schermelleh-Engel, K., Moosbrugger, H., Müller, H., 2003. Evaluating the fit of structural equation models: tests of significance and descriptive goodness-of-fit measures. Methods Psychol. Res. 8 (2), 23–74.

Schmidt, M. (1996). Rey auditory verbal learning test: a handbook. Rey Auditory Verbal Learning Test: A Handbook, 17.

Schwarz, C.G., Gunter, J.L., Wiste, H.J., Przybelski, S.A., Weigand, S.D., Ward, C.P., Alzheimer's Disease Neuroimaging Initiative, 2016. A large-scale comparison of cortical thickness and volume methods for measuring Alzheimer's disease severity. NeuroImage Clin. 11, 802–812. https://doi.org/10.1016/j.nicl.2016.05.017.

Scoccianti, C., Cecchini, M., Anderson, A.S., Berrino, F., Boutron-Ruault, M.C., Espina, C., Romieu, I., 2016. European Code against Cancer 4th Edition: alcohol drinking and cancer. Cancer Epidemiol. 45, 181–188. https://doi.org/10.1016/j.canep.2016.09.011.

Seo, S.K., Jung, I., Lee, S.M., Cho, S., Choi, Y.S., Chung, T.S., Lee, B.S., 2013. Relationship between leukoaraiosis and menopause in healthy middle-aged women. Fertil. Steril. 100 (2), 500–504. https://doi.org/10.1016/j.fertnstert.2013.03.047.

Sexton, C.E., Betts, J.F., Demnitz, N., Dawes, H., Ebmeier, K.P., Johansen-Berg, H., 2016. A systematic review of MRI studies examining the relationship between physical fitness and activity and the white matter of the ageing brain. NeuroImage 131, 81–90. https://doi.org/10.1016/j.neuroimage.2015.09.071.

Shaw, B.A., Spokane, L.S., 2008. Examining the association between education level and physical activity changes during early old age. J Aging Health 20 (7), 767–787. https://doi.org/10.1177/0898264308321081.

Shaw, P., Lerch, J.P., Pruessner, J.C., Taylor, K.N., Rose, A.B., Greenstein, D., Giedd, J.N., 2007. Cortical morphology in children and adolescents with different apolipoprotein E gene polymorphisms: an observational study. Lancet Neurol. 6 (6), 494–500. https://doi.org/10.1016/S1474-4422(07)70106-0.

Shi, Y., Wardlaw, J.M., 2016. Update on cerebral small vessel disease: a dynamic whole-brain disease. Stroke Vasc. Neurol. 1 (3), 83–92. https://doi.org/10.1136/svn-2016-000035.

Simic, G., Bexheti, S., Kelovic, Z., Kos, M., Grbic, K., Hof, P.R., Kostovic, I., 2005. Hemispheric asymmetry, modular variability and age-related changes in the human entorhinal cortex. Neuroscience 130 (4), 911–925. https://doi.org/10.1016/j.neuroscience.2004.09.040.

Singh, V., Chertkow, H., Lerch, J.P., Evans, A.C., Dorr, A.E., Kabani, N.J., 2006. Spatial patterns of cortical thinning in mild cognitive impairment and Alzheimer's disease. Brain A J. Neurol. 129 (Pt 11), 2885–2893. https://doi.org/10.1093/brain/awl256.

Smith, C.E., Cribbie, R.A., 2013. Multiplicity control in structural equation modeling: incorporating parameter dependencies. Struct. Equ. Model. A Multidiscip. J. 20 (1), 79–85. https://doi.org/10.1080/10705511.2013.742385.

Soldan, A., Pettigrew, C., Lu, Y., Wang, M.C., Selnes, O., Albert, M., BIOCARD Research Team, 2015. Relationship of medial temporal lobe atrophy, APOE genotype, and cognitive reserve in preclinical Alzheimer's disease. Hum. Brain Mapp. 36 (7), 2826–2841. https://doi.org/10.1002/hbm.22810.

Song, S., Stern, Y., Gu, Y., 2022. Modifiable lifestyle factors and cognitive reserve: a systematic review of current evidence. Ageing Res. Rev. 74, 101551 https://doi.org/10.1016/j.arr.2021.101551.

Steiger, J.H., Lind, C., 1984. Statistically based tests for the number of common factors. Presented at the. In: Proceedings of the Annual Meeting of the Psychometric Society. Iowa City: IA.

Stern, Y., 1994. Influence of education and occupation on the incidence of alzheimer's disease. J. Am. Med. Assoc. 271 (13), 1004. https://doi.org/10.1001/jama.1994.03510370056032.

Stern, Y., 2009. Cognitive reserve. Neuropsychologia 47 (10), 2015–2028. https://doi.org/10.1016/j.neuropsychologia.2009.03.004.

Stern, Y., Barnes, C.A., Grady, C., Jones, R.N., Raz, N., 2019. Brain reserve, cognitive reserve, compensation, and maintenance: operationalization, validity, and mechanisms of cognitive resilience. Neurobiol. Aging 83, 124–129. https://doi.org/10.1016/j.neurobiolaging.2019.03.022.

Ten Kate, M., Sudre, C.H., den Braber, A., Konijnenberg, E., Nivard, M.G., Cardoso, M.J., Visser, P.J., 2018. White matter hyperintensities and vascular risk factors in monozygotic twins. Neurobiol. Aging 66, 40–48. https://doi.org/10.1016/j.neurobiolaging.2018.02.002.

The pandas development team, 2020. pandas-dev/pandas: Pandas (1.1.3). Computer Software, Zenodo. https://doi.org/10.5281/zenodo.3509134. Retrieved from.

Thedinga, H.K., Zehl, R., Thiel, A., 2021. Weight stigma experiences and self-exclusion from sport and exercise settings among people with obesity. BMC Public Health 21 (1), 565. https://doi.org/10.1186/s12889-021-10565-7.

Thompson, P.M., Hayashi, K.M., Dutton, R.A., Chiang, M.C., Leow, A.D., Sowell, E.R., Toga, A.W., 2007. Tracking Alzheimer's disease. Ann. N. Y. Acad. Sci. 1097, 183–214. https://doi.org/10.1196/annals.1379.017.

Tuladhar, A.M., Reid, A.T., Shumskaya, E., de Laat, K.F., van Norden, A.G.W., van Dijk, E.J., de Leeuw, F.E., 2015. Relationship between white matter hyperintensities, cortical thickness, and cognition. Stroke 46 (2), 425–432. https://doi.org/10.1161/STROKEAHA.114.007146.

U.S. Department of Health and Human Services. (2014). The health consequences of smoking—50 years of progress: a report of the surgeon general.

Valenzuela, M.J., Sachdev, P., 2006. Brain reserve and cognitive decline: a non-parametric systematic review. Psychol. Med. 36 (8), 1065–1073. https://doi.org/10.1017/S0033291706007744.

van Harten, B., Oosterman, J.M., Potter van Loon, B.J., Scheltens, P., Weinstein, H.C., 2007. Brain lesions on MRI in elderly patients with type 2 diabetes mellitus. Eur. Neurol. 57 (2), 70–74. https://doi.org/10.1159/000098054.

van Middelaar, T., Argillander, T.E., Schreuder, F.H.B.M., Deinum, J., Richard, E., Klijn, C.J.M., 2018. Effect of Antihypertensive Medication on Cerebral Small Vessel Disease: a Systematic Review and Meta-Analysis. Stroke 49 (6), 1531–1533. https://doi.org/10.1161/STROKEAHA.118.021160.

Van Rossum, Guido, Drake, Fred, L, 2009. Python 3 Reference Manual. CreateSpace, Scotts Valley, CA.

Wang, Y., Hao, L., Zhang, Y., Zuo, C., Wang, D., 2019. Entorhinal cortex volume, thickness, surface area and curvature trajectories over the adult lifespan. Psychiatry Research. Neuroimaging 292, 47–53. https://doi.org/10.1016/j.pscychresns.2019.09.002.

Walhovd, K.B., Storsve, A.B., Westlye, L.T., Drevon, C.A., Fjell, A.M., 2014. Blood markers of fatty acids and vitamin D, cardiovascular measures, body mass index, and physical activity relate to longitudinal cortical thinning in normal aging. Neurobiol. Aging 35 (5), 1055–1064. https://doi.org/10.1016/j.neurobiolaging.2013.11.011.

Wang, Y.L., Chen, W., Cai, W.J., Hu, H., Xu, W., Wang, Z.T., Alzheimer's Disease Neuroimaging Initiative, 2020. Associations of white matter hyperintensities with cognitive decline: a longitudinal study. J. Alzheimer Dis. 73 (2), 759–768. https://doi.org/10.3233/JAD-191005.

Warburton, D.E.R., Nicol, C.W., Bredin, S.S.D., 2006. Health benefits of physical activity: the evidence. Can. Med. Assoc. J. 174 (6), 801–809. https://doi.org/10.1503/cmaj.051351.

Wardlaw, J.M., Smith, E., Biessels, G.J., Cordonnier, C., Fazekas, F., Frayne, R., Dichgans, M., 2013. Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. Lancet Neurol. 12 (8), 822–838. https://doi.org/10.1016/S1474-4422(13)70124-8.

Ware, J., Kosinski, M., Keller, S.D., 1996. A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. Med. Care 34 (3), 220–233.

Weidlich, S., Lamberti, G., 2001. Diagnosticum Für Cebebralschädigung (DCS). Ein visueller Lern- und Gedächtnistestnach Nach F. Hiller. Hans Huber, Bern, Switzerland.

Westman, E., Aguilar, C., Muehlboeck, J.S., Simmons, A., 2013. Regional magnetic resonance imaging measures for multivariate analysis in Alzheimer's disease and mild cognitive impairment. Brain Topogr. 26 (1), 9–23. https://doi.org/10.1007/s10548-012-0246-x.

WHO, 2000. Obesity: preventing and managing the global epidemic. Report of a WHO consultation. World Health Organ. Tech. Rep. Ser. 894 i–xii, 1.

Wood, A.M., Kaptoge, S., Butterworth, A.S., Willeit, P., Warnakula, S., Bolton, T., Emerging Risk Factors Collaboration/EPIC-CVD/UK Biobank Alcohol Study Group, 2018. Risk thresholds for alcohol consumption: combined analysis of individual-participant data for 599 912 current drinkers in 83 prospective studies. Lancet 391 (10129), 1513–1523. https://doi.org/10.1016/S0140-6736(18)30134-X.

Xia, Y., Shen, Y., Wang, Y., Yang, L., Wang, Y., Li, Y., Dong, Q., 2020. White matter hyperintensities associated with progression of cerebral small vessel disease: a 7-year Chinese urban community study. Aging 12 (9), 8506–8522. https://doi.org/10.18632/aging.103154.

Xu, H., Yang, R., Dintica, C., Qi, X., Song, R., Bennett, D.A., Xu, W., 2020. Association of lifespan cognitive reserve indicator with the risk of mild cognitive impairment and its progression to dementia. Alzheimer Dementia 16 (6), 873–882. https://doi.org/10.1002/alz.12085.

Zahodne, L.B., Stern, Y., Manly, J.J., 2015. Differing effects of education on cognitive decline in diverse elders with low versus high educational attainment. Neuropsychol. 29 (4), 649–657. https://doi.org/10.1037/neu0000141.

Zanon Zotin, M.C., Sveikata, L., Viswanathan, A., Yilmaz, P., 2021. Cerebral small vessel disease and vascular cognitive impairment: from diagnosis to management. Curr. Opin. Neurol. 34 (2), 246–257. https://doi.org/10.1097/WCO.0000000000000913.

Zhang, C., Qin, Y.Y., Chen, Q., Jiang, H., Chen, X.Z., Xu, C.L., Zhou, Y.H., 2014. Alcohol intake and risk of stroke: a dose-response meta-analysis of prospective studies. Int. J. Cardiol. 174 (3), 669–677. https://doi.org/10.1016/j.ijcard.2014.04.225.

Zhou, M., Zhang, F., Zhao, L., Qian, J., Dong, C., 2016. Entorhinal cortex: a good biomarker of mild cognitive impairment and mild Alzheimer's disease. Rev. Neurosci. 27 (2), 185–195. https://doi.org/10.1515/revneuro-2015-0019.

Zöllig, J., Mérillat, S., Eschen, A., Röcke, C., Martin, M., Jäncke, L., 2011. Plasticity and imaging research in healthy aging: core ideas and profile of the international normal aging and plasticity imaging center (INAPIC). Gerontology 57 (2), 190–192. https://doi.org/10.1159/000324307.