Research article

Journal of Alzheimer's Disease
1–18

DOI: 10.1177/13872877261467045
journals.sagepub.com/home/alz

Better cardiovascular health, measured by Life's Simple 7, is associated with lower white matter hyperintensity burden and greater cerebral blood flow over time

Diandra N. Denier-Fields[1,2], Ronald E. Gangnon[1], Leonardo A. Rivera-Rivera[3,4,5], Tobey J. Betthauser[3,6], Barbara B. Bendlin[3,5,6,7], Sterling C. Johnson[3,5,6,7] and Corinne D. Engelman[1,6,7]

Abstract

Background: Lifestyle factors have been studied for dementia risk, but few studies have comprehensively assessed both Alzheimer's disease (AD) and cerebrovascular disease (CBVD) pathologies.

Objective: Our research aims to determine the relationships between lifestyle and dementia pathologies.

Methods: We analyzed data from 1208 Wisconsin Registry for Alzheimer's Prevention (WRAP) participants. The cohort is enriched for participants with a family history of AD and a higher proportion of *APOE* ϵ4 carriers (n = 478); participants are primarily female (n = 827), non-Hispanic white (n = 1088), and highly educated (≥3 years professional or college education; n = 803), with an average baseline age of 64. Life's Simple Seven (LS7) scores were calculated from questionnaire data and clinical vitals. Brain health outcomes included CBVD biomarkers (white matter hyperintensities and arterial spin labeling [ASL] cerebral perfusion), AD biomarkers (amyloid Pittsburgh compound B index and tau standardized uptake value ratio Mayo meta-temporal composite), and cognitive outcomes (Preclinical Alzheimer Cognitive Composite Score 3 [PACC3], Delayed Recall, Immediate Learning, and Executive Function).

Results: Higher LS7 scores were significantly associated with lower white matter hyperintensity burden and higher ASL perfusion at the 6–8 year interval, with nominal associations observed at earlier time points and for global cognition (PACC3). No consistent associations were observed with amyloid or tau PET measures.

Conclusions: This study provides evidence that the beneficial effects of LS7 on cognition are primarily through cerebrovascular pathways rather than through AD pathology.

Keywords

Alzheimer's disease, amyloid, cerebrovascular diseases, cognition, lifestyle factors, tau protein

Received: 24 December 2025; accepted: 19 May 2026

[1]Department of Population Health Sciences, School of Medicine and Public Health, University of Wisconsin-Madison, Madison, WI, USA
[2]Department of Nutrition Science, University of Wisconsin-Madison, Madison, WI, USA
[3]Department of Medicine, School of Medicine and Public Health, University of Wisconsin-Madison, Madison, WI, USA
[4]Department of Medical Physics, School of Medicine and Public Health, University of Wisconsin-Madison, Madison, WI, USA
[5]Geriatric Research Education and Clinical Center, Wm. S. Middleton Memorial VA Hospital, Madison, WI, USA
[6]Wisconsin Alzheimer's Disease Research Center, School of Medicine and Public Health, University of Wisconsin-Madison, Madison, WI, USA
[7]Wisconsin Alzheimer's Institute, University of Wisconsin-Madison, School of Medicine and Public Health, Madison, WI, USA

Corresponding author:
Diandra N. Denier-Fields, University of Wisconsin-Madison, 610 Walnut Street, 1007 WARF, Madison, WI 53726-2397 USA.
Email: ddenier@wisc.edu

Handling Associate Editor: Ruth Peters

Introduction

While Alzheimer's disease (AD) is the most common form of dementia, accounting for 60–70% of cases, it has been estimated that up to half of AD cases include a vascular component, culminating in mixed pathology.[1] Based on neuropathology alone, approximately 26% of dementia cases have vascular dementia, but no AD pathology.[1]

Amyloid plaques and tau tangles are biomarkers of AD pathology that can be observed decades before a clinical diagnosis. Similarly, biomarkers of cerebrovascular disease (CBVD) appear long before the clinical diagnosis of vascular dementia and have been linked to cognitive decline.[2] In research settings, commonly used magnetic resonance imaging (MRI)-based proxies of CBVD include the volume of white matter hyperintensities (WMH), typically associated with ischemia or demyelination, and reduced cerebral blood flow (CBF), measured using arterial spin labeling (ASL) perfusion imaging. While these measures do not comprehensively capture all aspects of CBVD, and can also occur with normal aging, they reflect microvascular integrity and hypoperfusion and are widely recognized as relevant indicators of cerebrovascular contributions to cognitive impairment.[3–5] The utility of WMH and ASL perfusion imaging has also been highlighted in recent protocols, such as the Alzheimer's Disease Neuroimaging Initiative (ADNI) 4 study, for characterizing cerebrovascular mechanisms that may underlie or contribute to dementia pathology.[6] Recent updates to the AD research framework also further emphasize that neurodegeneration biomarkers are not specific to AD and may reflect processes such as vascular injury, and explicitly incorporate markers of non-AD co-pathology, including WMH and infarcts, highlighting the role of cerebrovascular disease in cognitive decline.[7]

In this study, we use CBVD to refer to imaging biomarkers of vascular brain health, including WMH burden and ASL perfusion. These biomarkers are commonly used in population studies to represent small vessel disease and reduced CBF, which are linked to cognitive decline and dementia risk.[8–11]

Cardiovascular health is a key modifiable factor that may influence both CBVD and cognitive outcomes. Poor cardiovascular health has been associated with cognitive decline, dementia, and WMH in late-life.[12,13] Cardiovascular disease risk can be estimated according to the American Heart Association's "Life's Simple 7 ideal cardiovascular health recommendations" (LS7), which include smoking status, dietary intake, physical activity, body mass index (BMI), fasting glucose, cholesterol, and blood pressure.[14] Cardiovascular disease risk has been associated with incident dementia, white matter hyperintensities, and cerebrospinal fluid biomarkers, but its relationship to AD-specific imaging is less clear, particularly in late life.[15–18] For example, Gottesman et al. (2017) found that midlife vascular risk was associated with greater amyloid deposition, but no significant association was observed for late-life risk factors, highlighting the importance of timing in understanding these relationships.

The Wisconsin Registry for Alzheimer's Prevention (WRAP) cohort offers a unique opportunity to assess the relationship between lifestyle and dementia pathology. As one of the largest and longest-running longitudinal studies focused on preclinical AD, WRAP is enriched for individuals with a parental history of AD. It includes detailed assessments of lifestyle, clinical vitals, neuroimaging for both AD and CBVD pathology, and repeated cognitive testing. This makes it particularly well-suited to evaluate both vascular and AD-related pathways within the same individuals over time.

Here, we utilized the WRAP cohort to test the association between the LS7 score and biomarkers of CBVD, cognition, and AD. A secondary aim was to determine the relevant time frame between the LS7 exposure and the imaging/cognitive outcomes. Evidence from the Whitehall 2 study that the impact of lifestyle factors on dementia can have a significant lag, with dementia incidence observed up to 25 years after the measured lifestyle factors.[13] To account for this, we tested associations at different time intervals (2–4 years, 4–6 years, and 6–8 years) between cardiovascular lifestyle factors and imaging/cognitive testing. Additionally, we sought to determine if the LS7 score is associated with cognition through one or both pathways (CBVD and/or AD) using mediation analysis. This mediation component offers a novel contribution by evaluating potential vascular pathways linking lifestyle to cognitive outcomes.

Methods

Study population

The WRAP cohort is enriched for individuals who have a parental history of AD and may be in the preclinical stages of the disease. The study consists of a longitudinal observational cohort started in 2001, with the initial follow-up beginning in 2005 and further visits performed on a biannual basis.[20] This study was approved by the Institutional Review Board (IRB) at the University of Wisconsin and conducted in accordance with the principles of the Helsinki Declaration. Written informed consent was obtained from all participants. Approximately 80% of the participants who were enrolled at baseline have remained active in the study.[21] In addition, continued recruitment and enrollment has occurred over the life of the study to increase the representation of minorities, including African Americans, Native Americans, Asians, and Hispanics. Participants were English speaking, age 40–65, and free of dementia at baseline. All participants in the study have undergone neuropsychological testing, clinical evaluation, behavioral risk factor assessment, and blood collection at each visit. A subset of participants underwent

brain imaging to monitor for signs of AD and CBVD as of May 2024. Imaging biomarker data were not collected uniformly across all participants due to factors such as staggered enrollment and limited funding for imaging at certain time intervals. However, due to the generally healthy nature of our cohort, only n = 32 have reached dementia, these missing data can be considered missing at random. Cognitive testing follow-up data were also subject to differences in availability due to staggered enrollment and ongoing recruitment of underrepresented participants who are more representative of the general population and who have not yet reached the later study intervals (4–6 or 6–8 years). As a result, some cognitive data are best described as not yet observed rather than missing due to attrition.

A total of 1805 participants were included in the WRAP May 2024 data freeze. Of these, 1208 participants had complete data for all variables required for analysis, including covariates such as demographic factors (age, sex, and years of education), genetic risk (*APOE* ϵ4 status), and clinical history (self-reported CBVD history), along with the predictor (all LS7 components) and at least one cognitive composite score (CCS) at the same visit. If there were multiple visits with complete LS7 data, the earliest visit was used.

Life's Simple 7

Measurements collected from clinical visits included BMI, blood pressure (BP), and blood-based assays. Height was measured in centimeters and weight was measured in kilograms; BMI was calculated as weight in kilograms divided by height in meters squared. Participants were asked to relax in a quiet room prior to BP readings; their BP was taken three times per arm and then averaged to ensure accurate readings. Blood assays included fasting plasma glucose and serum total cholesterol.

Self-reported lifestyle factors included physical activity, smoking status, and diet. Participants were asked about the following in a typical week: intensity of exercise (mild, moderate, and hard), duration of the exercise in minutes, and frequency of the exercise per week. Current smoking habits were assessed by answering "Have you ever smoked cigarettes?" and "If, yes, in the past month, have you smoked any cigarettes at all?" Participants completed a set of 15 questions about diet, corresponding to each of the Mediterranean-Dash Intervention for Neurological Delay (MIND) diet categories (Supplemental Table 1).[22]

Scoring LS7

Each LS7 component was assessed independently to provide a score of 0 (poor), 1 (intermediate), or 2 (optimal; Table 1) following the standard LS7 methodology, and these component scores were summed to

Table 1. Life's Simple 7 definition of cardiovascular health metrics.

	Smoking	Diet[a]	Physical activity intensity (min/week)	BMI	Fasting glucose	Blood cholesterol	Systolic & diastolic blood pressure
Optimal (Score = 2)	Never smoked **OR** Stopped >5 years ago	≥2 servings of fruits and ≥2 of vegetables, **PLUS** ≥1 serving of whole grains	≥150 moderate **OR** ≥75 hard **OR** ≥150 moderate and hard	<25	<100 mg/dL Untreated	<200 mg/dL Untreated	SBP <120 mm Hg and DBP <80 mm Hg Untreated
Intermediate (Score = 1)	Stopped in past 5 years	≥2 servings of fruits and ≥2 of vegetables, **OR** ≥1 serving of whole grains	1–149 moderate **OR** 1–74 hard **OR** 1–149 moderate and hard	25–29.9	<100 mg/dL Treated **OR** 100–125 mg/dL	<200 mg/dL Treated **OR** 200–239 mg/dL	SBP <120 mm Hg and DBP <80 mm Hg Treated **OR** SBP 120–139 **OR** DBP 80–89 mm Hg
Poor (Score = 0)	Current Smoker	<2 servings of fruits and <2 of vegetables, PLUS no whole grains	No moderate or hard	≥30	≥126 mg/dL	≥240 mg/dL	SBP ≥140 mm Hg **OR** DBP ≥90 mm Hg

[a]Scoring criteria for each participant were according to the original LS7 except diet was assessed using fruit, vegetable, and whole grain consumption. Adapted from: Sabia et al., 2019.[4]

create a total score ranging from 0 to 14.[13] The total LS7 score was modeled as a continuous variable in all regression analyses, with effect estimates interpreted per one-point increase in score.

The LS7 scoring criterion for diet was adjusted to reflect the data available in the WRAP cohort. In Sabia et al. (2019),[13] authors assessed diet based on fruit and vegetable consumption, plus high fiber bread. While the WRAP cohort contains data on fruit and vegetable consumption, high fiber bread was not included in the questionnaire and whole grains were used instead. Smoking history was determined by utilizing the longitudinal data of the WRAP study. At the biannual visits, each participant provides an update on their smoking status. We created a longitudinal smoking history measure that looked back at all previous visits to identify whether they were a never smoker, previous smoker who stopped less than or greater than 5 years ago, or current smoker. All other criteria were consistent with the LS7 scoring in Sabia et al.[13]

Health history and medications

Cardiovascular and cerebrovascular history were evaluated as potential covariates in regression models to account for underlying vascular risk. For CBVD outcomes (WMH and ASL perfusion), a composite "History of CBVD" variable was created that incorporated both participant-reported history of stroke or transient ischemic attack (TIA) and radiologist-confirmed presence of lacunar infarcts or microhemorrhages on MRI.[23,24] For cognitive and AD outcomes, a "Self-Reported CBVD" variable was used, reflecting only participant self-report of stroke or TIA. Coronary artery disease (CAD) status was determined based on a self-reported history of heart attack or cardiac surgery.

Medication use was also assessed as an indicator of disease management. Participants were classified as "on treatment" if they were prescribed any relevant medications for CAD (e.g., anticoagulants, antiplatelets, Angiotensin converting enzyme inhibitors, Angiotensin II receptor blockers, beta blockers, calcium channel blockers, cholesterol-lowering agents, diuretics, or vasodilators) or CBVD (e.g., medications for hypertension, diabetes, hyperlipidemia, or anticoagulation).[25,26] These variables were incorporated into expanded regression models and compared to base models using Bayesian Information Criterion (BIC), to determine the model with the best fit.

Cerebrovascular disease imaging biomarkers

Although MRI was introduced in the WRAP study as early as 2010, head coils capable of accurately measuring WMH and ASL perfusion were not implemented until 2019. At that time, WRAP updated its imaging protocols to include these assessments. A subset of participants who remained active and opted into imaging during this period were included in the present analysis. To ensure consistent signal sensitivity and uniform image quality, only scans acquired using the 48HAP, RM:Nova32channel, 8US TORSOPA, or 30AA + 60PA head coils were included.

MRI scans provided measurements of WMH, white matter, gray matter, cerebrospinal fluid (CSF) volume, and CBF using ASL perfusion. WMH volume was measured via MRI, using 3D T2-weighted FLAIR scans and calculated from the total volume of WMH (cubic cm).[27] WMH burden was calculated by dividing the total WMH volume by the total white matter volume, to account for varying white matter volume among participants, then multiplying by 100. Additionally, CBF was measured via ASL perfusion in both gray and white matter in ml/min/100 g. To address the known challenges of measuring CBF in white matter, due to its lower perfusion and longer transit times, a multi–post-labeling delay pseudo-continuous ASL (PCASL) technique with three post-labeling delays (1.0 s, 1.8 s, and 2.7 s) was employed. This approach enabled more accurate tissue perfusion estimates in both gray and white matter by correcting for arterial transit time.

While WMH and ASL perfusion can reflect disease-related ischemia and hypoperfusion, they are also influenced by normal aging and metabolic demand. To provide a broader context of cerebrovascular health, we also reported the presence or absence of lacunar infarcts and microhemorrhages, in "History of CBVD." Both of which are radiologist-interpreted indicators of small vessel disease and relevant to vascular contributions to cognitive impairment. These indicators were available for most participants and are included in the demographic summary and as covariates in the regression analyses.

For the CBVD imaging biomarkers, which included WMH burden and ASL perfusion, normality of the residuals was assessed using QQ plots, histograms, and the Shapiro-Wilk test. The WMH burden data showed skewness, and a cubic root transformation was applied to improve normality and stabilize variance, allowing the residuals to meet the assumptions of the regression model. In contrast, the ASL perfusion data were already normally distributed, so no transformations were applied, and the original data were used in the analysis.

Alzheimer's disease imaging biomarkers

A subset of the participants completed at least one positron emission tomography (PET) scan paired with a T1-weighted MRI for anatomical reference. Multiple tracers were used during imaging to measure AD pathology. Amyloid-β plaques were measured using ^{11}C-Pittsburgh compound B (PiB) as the tracer, and the distribution volume ratio (DVR) as the quantitative measure. The resulting imaging biomarker, PiB DVR, was calculated using an average of distribution volume ratios of cerebral amyloid

within eight selected cortical regions of interest: angular gyrus, anterior cingulate gyrus, posterior cingulate gyrus, frontal medial orbital gyrus, precuneus, supramarginal gyrus, middle temporal gyrus, and superior temporal gyrus, as detailed in Sprecher et al. (2015).[28–30] Tau neurofibrillary tangles were measured using ^{18}F-MK-6240 (MK6240) as the tracer, and the standardized uptake value ratio (SUVR) as the quantitative measure. The resulting imaging biomarker, Mayo meta-temporal composite (MTC) SUVR represents a bilateral volume-weighted composite of the parahippocampal gyrus, amygdala, temporal fusiform gyrus, inferior temporal gyrus, and the middle temporal gyrus.[27]

The distributions of PiB DVR and MTC SUVR measurements were right-skewed, which is expected given the inclusion of both amyloid and tau negative versus positive individuals within the study sample. Transformations did not substantially improve normality. Consequently, they were analyzed in their original continuous form. Non-normal residuals were acknowledged as a limitation of the analysis, and this limitation is considered in the interpretation of results.

Cognitive assessment

CCS, including Immediate Learning, Delayed Recall, Executive Function, and the Preclinical Alzheimer Cognitive Composite (PACC3), are widely used measures of cognitive function. Immediate Learning tests short-term memory, Delayed Recall tests long-term memory, Executive Function is a measure of cognitive processing, and PACC3 is indicative of global cognition.[31] Specific tests included in each CCS are shown in Supplemental Table 2.

All CCS were transformed into standardized z-scores with a mean of 0 and a standard deviation of 1, a commonly used technique in the field as detailed in Clark et al. (2016).[31] Visual inspection of residuals confirmed that, while slight deviations from normality were noted, the original z-score data was retained without further transformations. Repeated testing has been shown to improve participant CCS, therefore practice effects were accounted for by calculating the visit number minus one.[32] Participants were required to have completed at least one cognitive composite score (e.g., Delayed Recall or Immediate Learning) per visit to be included in the analysis.

Outcome timing

This study used longitudinal data from the WRAP cohort, with outcomes collected over time as new imaging and diagnostic methods became available. Cognitive testing began in 2005, PET imaging for AD biomarkers was available from 2009, and MRI imaging for CBVD biomarkers using the aforementioned head coils started in 2019. Each outcome: CCS, AD imaging biomarkers, and CBVD imaging biomarkers, were analyzed separately.

Predictor data (for all LS7 components) were collected between 2014 and 2023. To ensure temporal separation, outcomes were only included if they occurred at least two years after the predictor data. Time intervals between predictor and outcome were categorized into 2–4 years, 4–6 years, and 6–8 years. Each time interval was treated as a separate dataset, with the latest available outcome within each time window used for the analysis. The "Years to Outcome" variable was calculated as the difference between the participant's age at the outcome visit and their age at the predictor visit. Participant counts for each dataset (time interval) are shown in Figure 1. A minimum of 90 participants was required for analysis to avoid overfitting based on the maximum number of covariates included in the models ($n = 9$). All outcomes met this criterion. Overlap in available outcomes across modalities and time intervals is shown in Figure 2. Cognitive outcomes (CCS) were available for nearly all participants at each interval, while imaging data (WMH, ASL, PiB, and MTC) were available for overlapping but smaller subsets of participants, with similar patterns of data availability observed across 2–4, 4–6, and 6–8 year intervals.

CCS was the only outcome measured in all participants, whereas imaging outcomes (WMH, ASL perfusion, PiB DVR, and MTC SUVR) were measured in a subset of the participants. Figure 2 illustrates overlap in available imaging data at each time interval. Figure 2(a) shows the 2–4 year time interval which had 319 participants with at least one imaging measure at the 2–4 year time interval, 222 (70%) had data for both CBVD (WMH and/or ASL) and AD (PiB DVR and/or MTC SUVR) outcomes, 72 (23%) had CBVD only, and 25 (8%) had AD only. The UpSet plots in Figure 2(b) and 2(c) further depicts the distribution across CCS and all four imaging modalities (WMH, ASL, PiB DVR, and MTC SUVR) at 4–6 and 6–8 year time intervals.

Regression analysis

Generalized linear regression models were constructed using R studio package *lme4* (version 1.1–37.[33] Model selection was guided by the BIC, which allows comparison of alternative model specifications without relying on inspection of model output; lower BIC values indicate a better balance between model fit model complexity. Separate models were estimated for each outcome category: CBVD imaging biomarkers (WMH burden, GM and WM ASL perfusion), cognitive composite scores (Immediate Learning, Delayed Recall, Executive Function, PACC3), and Alzheimer's disease imaging biomarkers (PiB DVR and MTC SUVR). All models included sex (male as reference) and age (centered at 65 years).

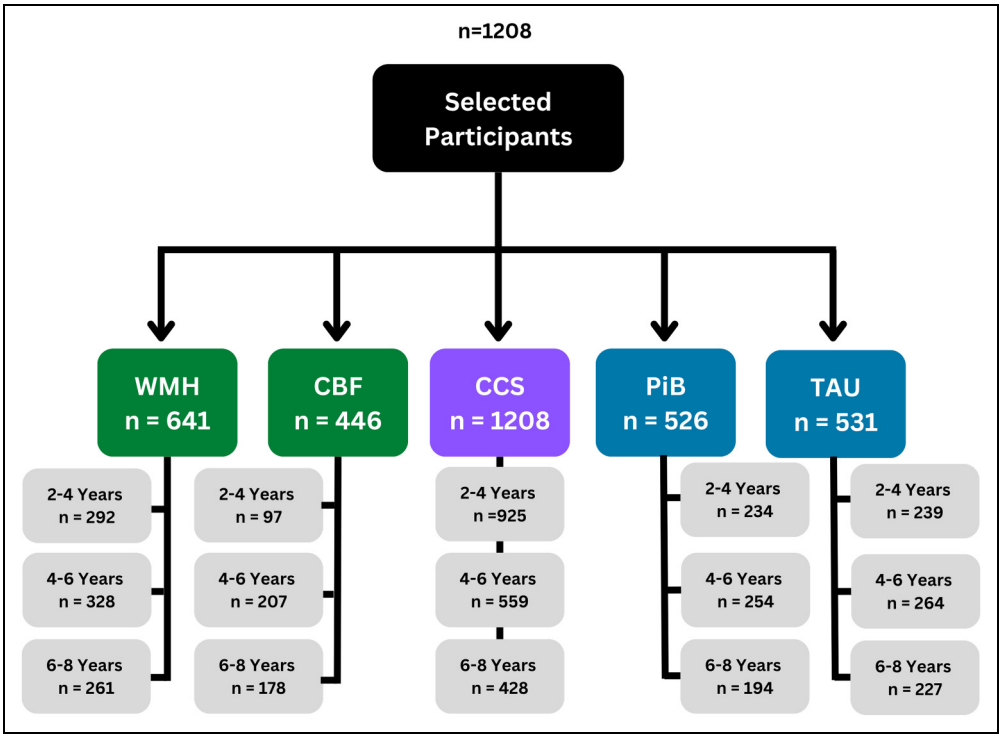

Figure 1. Sample sizes for the outcomes and time interval between the predictor and outcome.
A total of 1208 participants from the Wisconsin Registry for Alzheimer's Prevention study had data available for all seven of the Life's Simple 7 (LS7) components for at least one time interval. The number of participants with each outcome is shown, including white matter hyperintensities (WMH), arterial spin labeling (ASL) perfusion, cognitive composite scores (CCS), Pittsburgh compound B (PiB) distribution volume ratio (DVR), and Mayo meta-temporal composite (MTC) standardized uptake value ratio (SUVR). Time intervals were categorized based on the time between the predictor (LS7) and the outcome: 2–4 years, 4–6 years, and 6–8 years. Each outcome and time interval were analyzed as a unique dataset, with participant counts varying due to staggered enrollment, varying availability of outcome observations, and the structure of follow-up visits. Only the most recent observation for each participant within a given time interval was included.

Covariates were selected *a priori* based on established determinants of each outcome. For CBVD imaging biomarkers, the initial model included age, sex, and LS7 score. Cognitive models additionally included education, *APOE* ϵ4 allele count, and practice effects due to their known influence on cognitive performance. AD imaging biomarker models (PiB DVR and MTC SUVR) included *APOE* ϵ4 because of its strong association with amyloid and tau pathology.[34]

To evaluate whether additional covariates improved model performance for imaging biomarkers, we added each of the following separately to the *a priori* models and compared BIC values using the 4–6-year interval (the largest available sample): CBVD history, CAD history, CBVD/CAD medications, education, and *APOE* ϵ4. The original models consistently had the lowest BIC values. Adding CBVD history produced only a modest BIC increase ($\Delta BIC = 2–5$) while addressing a biologically relevant vascular risk factor; CBVD history or self-reported CBVD history was retained across all outcome domains for consistency. In contrast, adding CAD history, medications, education, or *APOE* ϵ4 resulted in substantially larger BIC increases ($\Delta BIC = 7–14$), indicating reduced model performance and increased risk of overfitting.

To determine whether LS7 effects varied by demographic factors or vascular burden, interaction terms (LS7×age, LS7×sex, LS7×CBVD history) were tested for CBVD imaging biomarkers. None of the interaction terms improved BIC, and likelihood ratio tests indicated no significant interactions (WMH $p > 0.21$; ASL $p = 0.09–0.07$). LS7 effect estimates remained unchanged; therefore, additive models were retained. The predictor variable of interest for all models was the LS7 score. We used a standard p-value threshold of 0.05 for primary analyses and additionally applied a conservative false discovery rate (FDR) correction within outcome families to account for multiple testing. FDR-adjusted results are presented in the Supplemental Material and were used to guide interpretation of findings.

Final model specifications:

CBVD imaging biomarkers (WMH burden, GM and WM ASL perfusion):

$$Outcome \sim Age + Sex + CBVD\ History + LS7$$

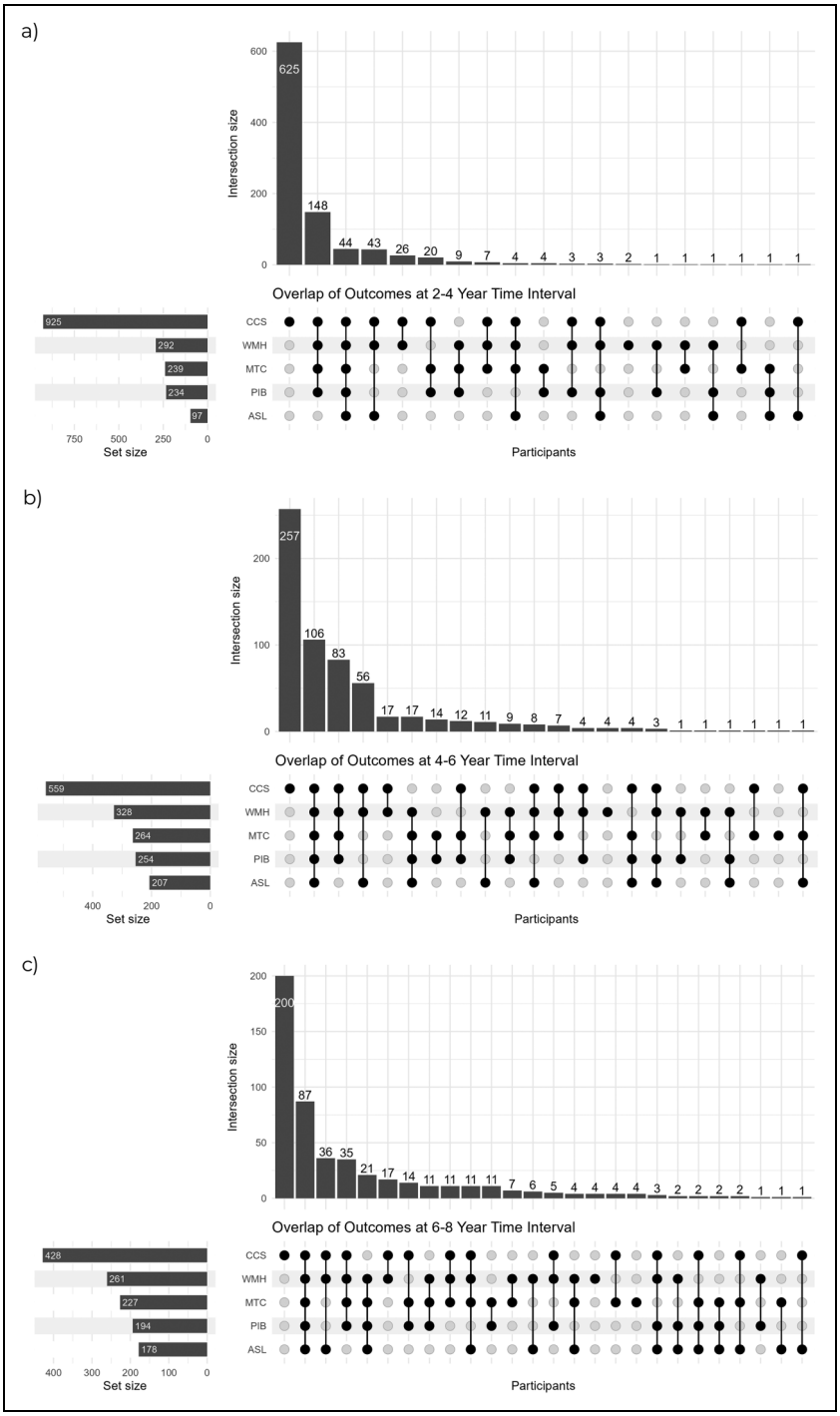

Figure 2. Participant overlap across outcomes at each follow-up interval.
UpSet plots illustrate the overlap in available outcome data—including cerebrovascular disease (CBVD; white matter hyperintensities [WMH] and arterial spin labeling [ASL] perfusion), Alzheimer's disease (AD; Pittsburgh compound B [PiB] distribution volume ratio [DVR] and Mayo meta-temporal composite [MTC] standardized uptake value ratio [SUVR]), and cognitive composite scores (CCS)—at the (a) 2–4 year, (b) 4–6 year, and (c) 6–8 year intervals. Each vertical bar represents the number of participants with data for the specific combination of outcomes indicated by the connected black dots below. Horizontal bars show the total number of participants with data available for each individual outcome. These plots demonstrate high data completeness for cognitive outcomes (CCS) and variable but overlapping coverage across imaging modalities, with similar patterns observed across time intervals.

CCS (Immediate Learning, Delayed Recall, Executive Function, PACC3):

$$Outcome \sim Age + Sex + Education + APOE\ \varepsilon4 + Practice\ Effects + Self - Reported\ CBVD\ History + LS7$$

AD imaging biomarkers (PiB DVR and MTC SUVR):

$$Outcome \sim Age + Sex + APOE\ \varepsilon4 + Self - Reported\ CBVD\ History + LS7$$

A key assumption of generalized linear models is that the residuals are approximately normally distributed to ensure the accuracy of parameter estimates and hypothesis testing. To assess this assumption, we conducted visual inspections of residuals using QQ plots and histograms; and performed statistical tests such as the Shapiro-Wilk test. When significant deviations from normality were detected, transformations (cubic root and log) were considered to stabilize variance and improve normality. Decisions regarding specific transformations and the handling of non-normal residuals are detailed in the Methods outcome-specific sections above.

Exploratory post-hoc mediation analysis

We conducted mediation analyses to explore whether CBVD imaging biomarkers mediated the relationship between cardiovascular health, as measured by LS7, and cognition. Candidate models were identified based on results from our primary regression analyses. Specifically, we selected mediation pathways where both the LS7 score (predictor) was significantly associated with the imaging biomarker (mediator), and the LS7 score was also significantly associated with a CCS (outcome) at the same follow-up time interval. This exploratory analysis was designed to complement the primary regression models by examining whether imaging biomarkers of CBVD and/or AD might explain the observed associations between LS7 and cognition.

Mediation analyses were performed using the mediate() function from the "mediation" package in R (v4.5.0), with 1000 nonparametric bootstrap simulations to estimate indirect effects.[35] The LS7 score was treated as the independent variable, and models included covariates described above. Analyses were restricted to participants with complete data for the relevant predictor, mediator, and outcome variables. Sample sizes for the mediation models were n = 207 for WMH at the 6–8 year interval and n = 145 for both gray and white matter ASL perfusion at the 6–8 year interval.

Results

Participant characteristics

The participant characteristics at baseline and at the 2–4 time interval are shown in Table 2. Most of the WRAP cohort participants were female (68–77%) and non-Hispanic white (90–95%). The cohort is highly educated with most participants having some college education (13 or more years). Due to the nature of recruitment, the WRAP cohort has been enriched for a parental history of AD and 38–40% had at least one *APOE* ϵ4 allele, notably higher than the estimated 26% prevalence in the general U.S. population.[36] Approximately half of the participants were taking at least one medication related to cardiovascular or cerebrovascular disease prevention, including antihypertensives, cholesterol-lowering drugs, diabetes medications, or anticoagulants. Self-reported history of cardiovascular conditions was also captured, with 2–7% of participants reporting a history of coronary artery disease (heart attack or cardiac surgery) and 2–3% reporting a history of cerebrovascular events (stroke or TIA), while 5–7% had a confirmed history of CBVD after the addition of lacunar infarcts and microhemorrhages from MRI imaging. These data provide important context regarding the cardiometabolic health of the cohort. The total LS7 score ranged from 3–14, with the mean and median being a score of 9 to 10 out of 14. In general, the cohort had a moderately healthy lifestyle. At the 2–4 year time interval between predictor and outcome, the average age of participants at the outcome measurement was 67.1 for WMH, 66.0. for ASL perfusion, 66.6 for cognitive testing, 67.3 for PiB DVR, and 67.4 for MTC SUVR.

Additionally, to address loss to follow-up, we evaluated potential survival bias by comparing characteristics at the initial imaging visit (2–4 years) between participants who had follow-up imaging data at 4–6 or 6–8 years and those who did not. As shown in Supplemental Table 3, the two groups were well balanced in terms of age, sex, race, education, and *APOE* ϵ4 carrier status. However, LS7 scores were slightly higher (between 0.5 and 1 point) in participants with follow-up across all biomarker imaging outcomes (WMH p = 0.022, ASL p = 0.150, PIB p = 0.003, MTC p = 0.002, CCS p = 0.012), indicating that individuals with better cardiovascular health were more likely to have repeat imaging. Importantly, 2–4 year values for WMH burden, ASL perfusion, amyloid PiB DVR, and tau MTC SUVR did not differ by follow-up status, suggesting that missingness is unlikely to bias imaging outcome estimates. In contrast, differences were more pronounced in the cognitive testing subset. As shown in Supplemental Table 4, participants with follow-up cognitive data tended to have had higher education, LS7 scores, and cognitive performance across all domains, and were less likely to be from underrepresented racial/ethnic groups. These differences likely, at least in part, reflect staggered enrollment in WRAP, with more recent recruitment efforts aimed at increasing cohort diversity. Consequently, a higher proportion of underrepresented participants have not yet reached their later follow-up

Table 2. Characteristics of the participants at baseline and in each outcome dataset at the 2–4 year time interval.

Variables	Baseline Full sample n = 1208	By outcome at 2–4 year time interval				
		WMHa,b—MRI n = 292	CBFc—MRI n = 104	CCSd—Cognitive testing n = 936	Amyloide–PETf n = 235	Taug—PET n = 241
Age	64 ± 7, 39 to 82	67 ± 7, 50 to 81	66 ± 7, 51 to 81	67 ± 7, 42 to 85	67 ± 7, 50 to 83	67 ± 7, 50 to 83
Sex	69% Female	72% Female	77% Female	68% Female	69% Female	69% Female
Race/ Ethnicity	90% NHWh 8% AAi 2% Other	93% NHW 6% AA 1% Other	96% NHW 4% AA	94% NHW 4% AA 2% Other	91% NHW 6% AA 3% Other	92% NHW 5% AA 3% Other
Educationj	10% ≤ 12 21% 13–14 25% 15–16 27% 17–18 17% ≥ 19	9% ≤ 12 18% 13–14 22% 15–16 32% 17–18 19% ≥ 19	6% ≤ 12 26% 13–14 26% 15–16 26% 17–18 16% ≥ 19	9% ≤ 12 20% 13–14 25% 15–16 26% 17–18 20% ≥ 19	9% ≤ 12 16% 13–14 25% 15–16 33% 17–18 17% ≥ 19	9% ≤ 12 18% 13–14 24% 15–16 34% 17–18 15% ≥ 19
APOE ϵ4[k]	60% 0 ϵ4 36% 1 ϵ4 4% 2 ϵ4	60% 0 ϵ4 37% 1 ϵ4 3% 2 ϵ4	62% 0 ϵ4 36% 1 ϵ4 2% 2 ϵ4	62% 0 ϵ4 35% 1 ϵ4 3% 2 ϵ4	61% 0 ϵ4 37% 1 ϵ4 2% 2 ϵ4	60% 0 ϵ4 38% 1 ϵ4 2% 2 ϵ4
CAD Statusl	*Self Reported* 4% Yes 96% No *On Treatment* 48% Yes 31% No 21% N/A	*Self Reported* 4% Yes 96% No *On Treatment* 48% Yes 33% No 19% N/A	*Self Reported* 6% Yes 94% No *On Treatment* 47% Yes 32% No 21% N/A	*Self Reported* 4% Yes 96% No *On Treatment* 47% Yes 32% No 21% N/A	*Self Reported* 2% Yes 98% No *On Treatment* 45% Yes 35% No 20% N/A	*Self Reported* 2% Yes 98% No *On Treatment* 46% Yes 34% No 20% N/A
CBVD Statusm	*Self Reported* 3% Yes 97% No *On Treatment* 52% Yes 27% No 21% N/A	*History* 5% Yes 95% No *On Treatment* 53% Yes 27% No 20% N/A	*History* 7% Yes 93% No *On Treatment* 54% Yes 26% No 20% N/A	*Self Reported* 2% Yes 98% No *On Treatment* 51% Yes 28% No 21% N/A	*Self Reported* 2% Yes 98% No *On Treatment* 50% Yes 30% No 20% N/A	*Self Reported* 2% Yes 98% No *On Treatment* 51% Yes 30% No 19% N/A
LS7 Scoren	9 ± 2, 3 to 14	9 ± 2, 3 to 14	10 ± 2, 4 to 13	10 ± 2, 3 to 14	10 ± 2, 3 to 13	10 ± 2, 3 to 14
Outcome	*N/A*	*WMH Burdeno* 0.57 ± 0.36, 0.00 to 2.28	*Gray Matter* 44.7 ± 13.0, 15.7 to 82.6; *White Matter* 29.6 ± 8.6, 10.5 to 53.5	*Immediate Learning* 0.2 ± 1.1, −4.3 to 3.1; *Delayed Recall* 0.2 ± 1.1, −4.4 to 2.4; *Executive Function* −0.1 ± 1.1, −6.5 to 4.9; *PACC3p* 0.1 ± 1.2, −4.4 to 5.3	*PiB DVRq* 1.16 ± 0.21, 0.86 to 2.10	*MTC SUVR* 1.12 ± 0.21, 0.79 to 2.59

[a]White matter hyperintensities
[b]Magnetic resonance imaging
[c]Cerebral blood flow as measured by arterial spin labeling perfusion
[d]Cognitive composite score
[e]Amyloid measured as PiB DVR
[f]Positron emission tomography
[g]Tau as measured by Mayo meta-temporal composite standardized uptake value ratio (MTC SUVR)
[h]Non-Hispanic White
[i]African American
[j]Education in years
[k]*APOE* ϵ4 allele count
[l]Coronary artery disease
[m]Cerebrovascular disease
[n]Life's Simple 7
[o]Total WMH volume divided by the total white matter volume, multiplied by 100
[p]Preclinical Alzheimer's Cognitive Composite score, global cognition
[q]Pittsburgh compound B distribution volume ratio

visits. This pattern, at least partially, reflects *data not yet observed* due to study design rather than attrition and aligns with WRAP's goal of improving representativeness of the general population. Additionally, FDR–adjusted results for all analyses are provided in the Supplement and are referenced where relevant below.

LS7 and CBVD

For all outcomes, we compared the magnitude of the beta coefficients for a one-point increase in the LS7 score to a one-year increase in age. This comparison was used to contextualize the impact of lifestyle as measured by the LS7 score against the well-established risk factor of age. This approach provides a clearer interpretation of how lifestyle improvements relate to age-associated risk.

WMH burden. Higher LS7 scores were significantly associated with lower WMH burden at the 2–4 year ($\beta = -0.02$, 95% CI: −0.03 to −0.02, $p = 0.0035$) and 6–8 year ($\beta = -0.03$, 95% CI: −0.05 to −0.001, $p = 0.012$) intervals (Figure 3(a), Supplemental Table 5). No significant association was observed at the 4–6 year interval ($\beta = -0.01$, 95% CI: −0.03 to 0.01, $p = 0.285$). The effect size for one point increase in the LS7 score was comparable to one-year increase in age at 2–4 and 6–8 years intervals. Notably, only the association at the 6–8 year time interval remained statistically significant after FDR correction ($q = 0.036$; Supplemental Table 6). These findings suggest that better cardiovascular health, as measured by LS7, is associated with lower WMH burden over time.

ASL perfusion. As expected, at all time intervals, an increase in age was associated with lower blood flow in both the gray matter (Figure 3(b)) and white matter (Figure 3(c), Supplemental Table 5). Higher LS7 scores were significantly associated with greater cerebral perfusion at the 6–8 year interval, observed in both gray matter ($\beta = 1.71$, 95% CI: 0.66 to 2.77, $p = 0.001$) and white matter ($\beta = 1.18$, 95% CI: 0.42 to 1.94, $p = 0.002$), but not at earlier intervals (2–4 or 4–6 years; all $p > 0.10$). Associations at the 6–8 year interval remained statistically significant after FDR correction ($q = 0.013$ for both; Supplemental Table 6). These findings suggest that better cardiovascular health is linked to higher perfusion over the longer term.

LS7 and cognition

PACC3. Higher LS7 scores were significantly associated with better global cognition, as measured by the PACC3 z-score, at both the 2–4 year ($\beta = 0.04$, 95% CI: 0.00 to 0.07, $p = 0.038$) and 6–8 year ($\beta = 0.07$, 95% CI: 0.03 to 0.13, $p = 0.021$) intervals (Figure 4(a), Supplemental Table 7). No significant association was observed at the 4–6 year interval ($\beta = 0.03$, 95% CI: −0.02 to 0.07, $p = 0.259$). However, these associations did not remain statistically significant after FDR correction and should be interpreted with caution ($q = 0.222$; Supplement Table 6). Despite this, the consistency in direction and magnitude of the effect supported inclusion of PACC3 in exploratory mediation analyses. These findings suggest that better cardiovascular health may be associated with cognitive performance over time, although the evidence is less robust after correction for multiple testing.

Delayed recall, immediate learning, and executive function. No significant associations were observed between LS7 score and Delayed Recall (Figure 4(b)), Immediate Learning (Figure 4(c)), or Executive Function (Figure 4(d)) composite z-scores at any of the three time intervals (Supplemental Table 7).

LS7 and AD biomarkers

PiB DVR. The PiB DVR is a biomarker of amyloid accumulation as plaques in between the neurons; higher values indicate more amyloid accumulation and more AD pathology. LS7 score was not significantly associated with amyloid burden, as measured by the PiB DVR, at any time interval: 2–4 years ($\beta = 0.01$, 95% CI: −0.00 to 0.02, $p = 0.060$), 4–6 years ($\beta = 0.00$, 95% CI: −0.01 to 0.02, $p = 0.623$), or 6–8 years ($\beta = -0.01$, 95% CI: −0.03 to 0.01, $p = 0.301$) (Figure 5(a), Supplemental Table 8). These findings suggest that while LS7 may influence cerebrovascular and cognitive outcomes, it does not appear to affect amyloid accumulation over time in this cohort.

MTC SUVR. MTC SUVR is an imaging biomarker of tau aggregation as tau tangles in four critical regions of the brain; higher values indicate more tau aggregation and more AD pathology. LS7 score was not significantly associated with tau deposition, as measured by the SUVR for the MTC, at 2–4 years ($\beta = 0.01$, 95% CI: −0.00 to 0.02, $p = 0.227$) or 6–8 years ($\beta = 0.01$, 95% CI: −0.01 to 0.03, $p = 0.178$) (Figure 5(b), Supplemental Table 8). At the 4–6 year interval, there was a small but statistically significant association between higher LS7 score and greater MTC SUVR ($\beta = 0.02$, 95% CI: 0.00 to 0.03, $p = 0.026$); however, the direction of the effect was contrary to expectations, limiting its interpretability. This association did not remain statistically significant after FDR correction ($q = 0.160$; Supplemental Table 6).

Mediation analysis

We conducted mediation analyses to determine whether CBVD imaging biomarkers mediated the association between LS7 and global cognitive function (PACC3). Three models met criteria for inclusion based on our primary regression results showing significant relationships between LS7 and imaging outcomes, and nominally significant association between LS7 and cognition ($p < 0.05$) within the same time interval (Figure 6). Although associations with PACC3 did not survive correction for multiple comparisons, these models were retained for exploratory mediation analyses given the consistency in effect direction and their relevance to the study aims.

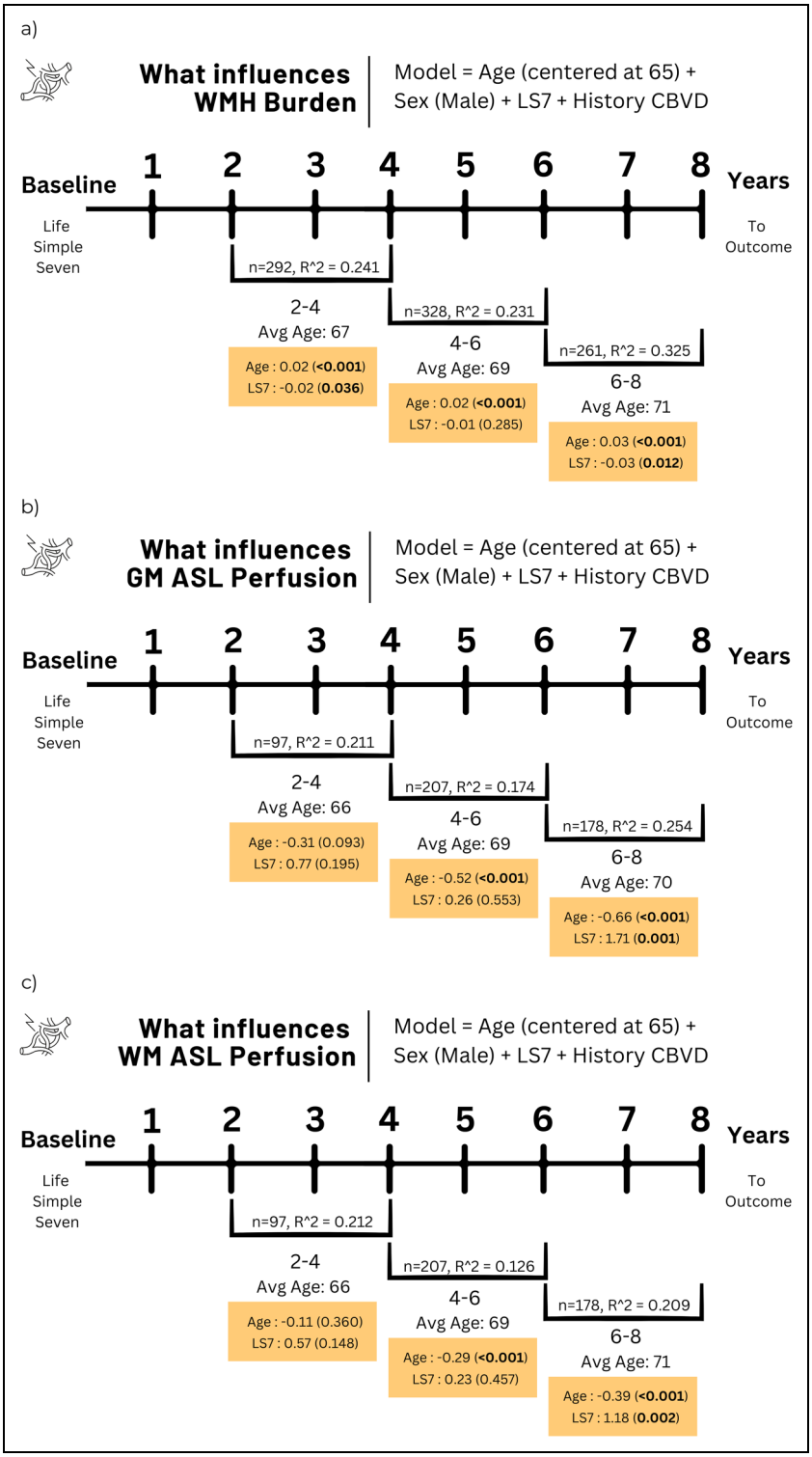

Figure 3. Cerebrovascular disease associations with Life's Simple 7 (LS7) score.
Generalized linear model results for (a) cubic root transformed white matter hyperintensity burden (WHM burden), (b, c) arterial spin labeling (ASL) perfusion measuring cerebral blood flow in ml/min/100 g for (b) white matter and (c) gray matter. All models controlled for age (centered at 65 years), sex, and history of CBVD, with the LS7 score as the primary variable of interest. The sample size (n), variance (R^2), and average age are provided for each time interval (2–4 years, 4–6 years, and 6–8 years between predictor and outcome). Beta estimates (β) and p-values are presented for LS7 and age, which is displayed to provide a benchmark for understanding the magnitude of LS7's beta estimate; all other variables are shown in Supplemental Table 5. For WMH burden was calculated as (WMH lesion volume / total white matter volume) × 100 and cube root transformed to stabilize variance.

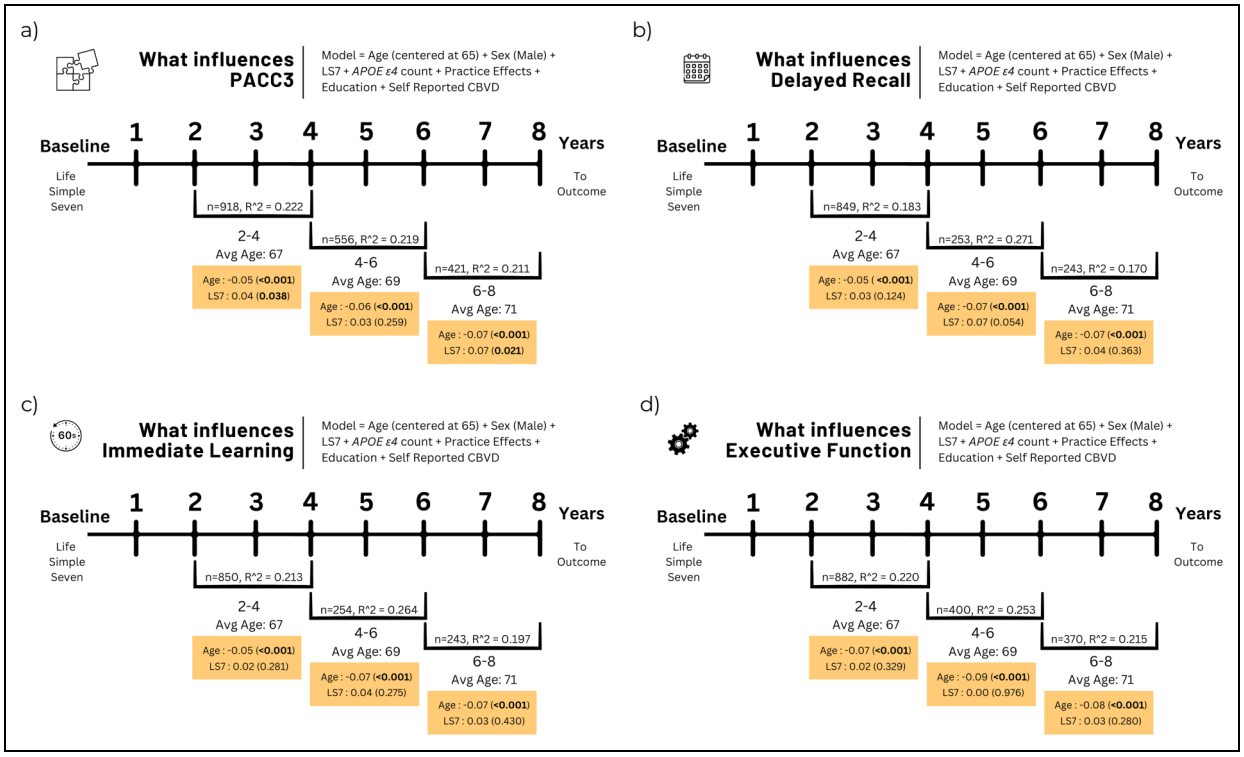

Figure 4. Cognitive composite score associations with Life's Simple 7 (LS7) score. Generalized linear model results for z-scores of a) Pre-Clinical Alzheimer's Cognitive Composite score 3 (PACC3), b) Delayed Recall, c) Immediate Learning, and d) Executive Function. All models controlled for age (centered at 65 years), sex, race/ethnicity, APOE ϵ4 allele count, practice effects, education in years, with the LS7 score as the primary variable of interest. The sample size (n), variance (R^2) and average age are provided for each time interval (2–4 years, 4–6 years, and 6–8 years between predictor and outcome). Beta estimates (β) and p-values are presented for LS7 and age, which is displayed to provide a benchmark for understanding the magnitude of LS7's beta estimate; all other variables are shown in Supplemental Table 7.

At the 6–8 year interval, WMH burden demonstrated a significant indirect effect ($\beta = 0.017$, $p = 0.018$; Figure 6(a)), indicating that WMH significantly mediated the relationship between LS7 and PACC3. This indirect pathway reflects that higher LS7 scores were associated with lower WMH burden ($\beta = -0.028$, $p = 0.022$), which in turn was associated with better cognitive performance ($\beta = -0.588$, $p = 0.017$). The direct effect of LS7 on PACC3 was not statistically significant ($\beta = 0.050$, $p = 0.320$), and the total effect was also non-significant ($\beta = 0.067$, $p = 0.186$). Approximately 25% of the total effect was estimated to be mediated through WMH burden.

In contrast, ASL perfusion in both gray (Figure 6(b)) and white matter (Figure 6(c)) did not demonstrate significant mediation effects at the 6–8 year interval, despite significant associations between LS7 and perfusion. While LS7 was significantly associated with both gray matter ($\beta = 1.529$, $p = 0.015$) and white matter perfusion ($\beta = 1.084$, $p = 0.017$), neither the indirect effects (GM: $\beta = 0.007$, $p = 0.472$; WM: $\beta = 0.008$, $p = 0.491$) nor the paths from perfusion to cognition (GM: $\beta = 0.005$, $p = 0.498$; WM: $\beta = 0.008$, $p = 0.376$) were statistically significant. The direct and total effects for both ASL models were also non-significant.

Together, these findings suggest that WMH burden may represent a cerebrovascular pathway linking cardiovascular health to cognitive performance over longer follow-up periods in this cohort. Mediation analyses involving ASL perfusion did not demonstrate significant indirect effects, although these results should be interpreted cautiously given the smaller sample size and exploratory nature of these analyses.

Discussion

Principal findings

In this longitudinal study involving 1208 WRAP participants, we examined the association between cardiovascular health, as measured by the LS7, and cognitive outcomes, as well as CBVD and AD imaging biomarkers, across multiple follow-up intervals. Higher LS7 scores were associated with more favorable cerebrovascular outcomes, including lower WMH burden and higher ASL perfusion, as well as better PACC3 performance over time. Notably, only the associations with cerebrovascular measures at the 6–8 year interval remained significant after correction for

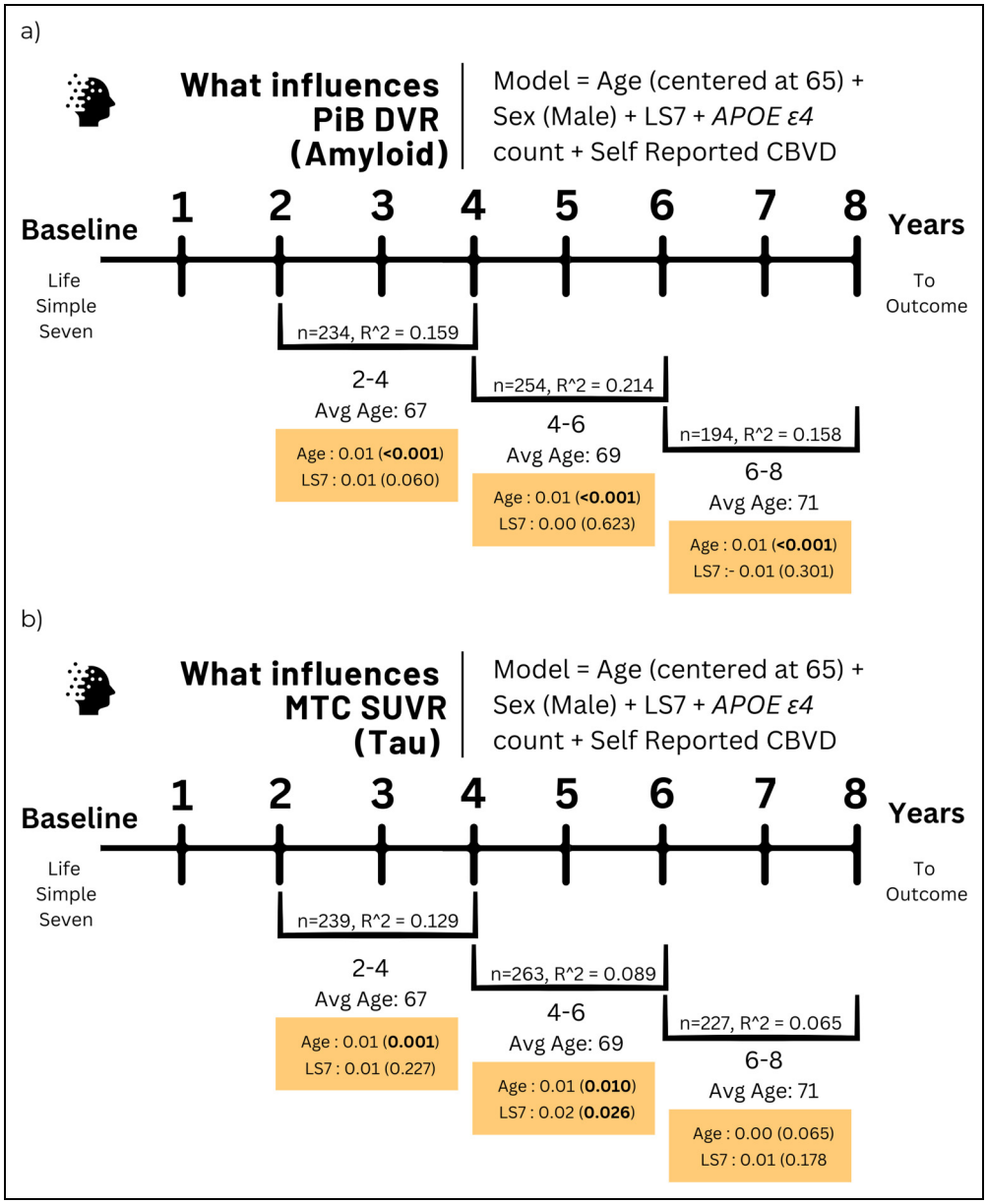

Figure 5. Alzheimer's disease imaging associations with Life's Simple 7 (LS7) score. Generalized linear model results for a) PiB DVR (amyloid) and b) standardized uptake value ratio (SUVR) Mayo meta-temporal composite (MTC). All models controlled for age (centered at 65 years), sex, and APOE ϵ4 allele count, with the Life's Simple 7 (LS7) score as the primary variable of interest. The sample size (n), variance (R^2) and average age are provided for each time interval (2–4 years, 4–6 years, and 6–8 years between predictor and outcome). Beta estimates (β) and p-values are presented for LS7 and age, which is displayed to provide a benchmark for understanding the magnitude of LS7's beta estimate; all other variables are shown in Supplemental Table 8.

multiple comparisons, indicating that the most robust relationships between cardiovascular health and brain outcomes emerge over longer follow-up periods under a more stringent significance threshold.

While associations with PACC3 did not survive FDR correction, they were retained for exploratory mediation analyses given their consistency in direction and relevance to the study aims. In contrast, LS7 scores were not significantly associated with PiB DVR (amyloid burden) or tau MTC SUVR (tau deposition) at any time interval after FDR correction.

The lack of association with amyloid and tau imaging, alongside consistent associations with cerebrovascular measures, suggests that lifestyle-related risk may operate primarily through vascular mechanisms in this preclinical population. This reinforces emerging models of dementia in which vascular dysfunction represents an early and potentially modifiable contributor to cognitive decline,

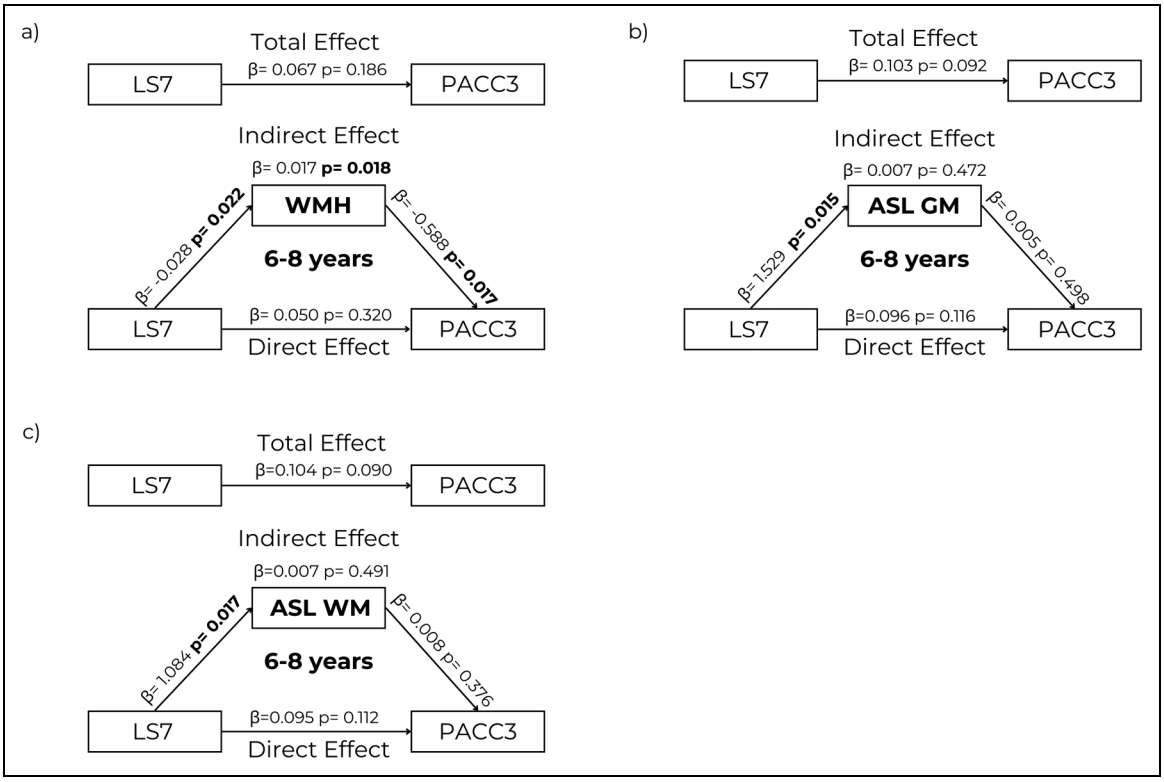

Figure 6. Mediation analysis results for significant outcomes.
Post-hoc mediation analysis models testing whether cerebrovascular disease (CBVD) imaging biomarkers mediate the association between Life's Simple 7 (LS7) cardiovascular health scores and global cognition (PACC3). Imaging biomarkers were assessed 6–8 years after the LS7 predictor, with PACC3 measured at the same time interval. Panels depict total, direct, and indirect (mediation) effects for each pathway: (a) White matter hyperintensities (WMH burden n = 207), (b) ASL perfusion in gray matter (ASL GM, n = 145), and (c) ASL perfusion in white matter (ASL WM, n = 145). Bolded paths indicate statistically significant effects ($p < 0.05$).

preceding or acting independently of classical AD pathology.[37] These findings highlight cardiovascular health as a practical and modifiable target for early intervention to preserve brain health in at-risk populations.

Context and mechanistic interpretation

To contextualize these findings, we examined CBVD imaging biomarkers, CCS, and AD imaging biomarkers. CBVD imaging biomarkers such as white matter hyperintensities and reduced cerebral blood flow are established indicators of small vessel disease and vascular dysregulation, both of which are linked to later cognitive decline and dementia.[9,37] Cognitive composites such as PACC3 capture subtle early changes in memory and executive function and are validated predictors of preclinical AD.[38] Amyloid (PiB DVR) and tau (MTC SUVR) PET biomarkers reflect the core pathological processes of Alzheimer's disease and are central to current research frameworks for identifying preclinical disease.[39] Together, these imaging and cognitive outcomes allow us to evaluate the impact of lifestyle and vascular health on brain aging across multiple complementary pathways.

Cognition and exploratory mediation

To further explore potential mechanisms linking cardiovascular health and cognition, we conducted exploratory post hoc mediation analyses for outcomes with significant associations. These analyses suggested that WMH and ASL perfusion partially mediated the association between LS7 and cognition, consistent with the hypothesis that lifestyle influences cognitive aging through vascular pathways.

Although limited by modest sample size, this analysis provides preliminary evidence that cerebrovascular integrity may be a key pathway through which modifiable lifestyle factors protect cognitive health. Together these findings reinforce the importance of vascular health in preserving cognitive function and suggest that modifiable lifestyle factors may exert their cognitive benefits primarily through cerebrovascular, rather than amyloid or tau-related, pathways.

Comparison with prior literature (CBVD and cognition)

Our findings align with previous research, reinforcing the role of cardiovascular health in maintaining cognitive

function and reducing cerebrovascular disease risk. Wei et al. (2022) reported higher LS7 scores were associated with better scores on cognitive function tests in the NHANES (National Health and Nutrition Examination Survey) study,[40] supporting our results of better cognitive outcomes with higher LS7 scores. Similarly, Liu et al. (2022), found that lower LS7 scores were associated with greater odds of cerebral small vessel disease in the PRECISE (Polyvascular Evaluation for Cognitive Impairment and Vascular Events) study.[41]

These results align with our findings that higher LS7 scores were associated with lower WMH burden and better ASL perfusion, indicating healthier cerebrovascular function. Importantly, this suggests that cardiovascular health, captured through simple, routinely measured clinical metrics, may represent a modifiable pathway to preserve cerebrovascular integrity before irreversible structural damage occurs.

In clinical settings, LS7 may serve as a practical tool to identify individuals at elevated risk for vascular contributions to cognitive decline and to guide early, targeted lifestyle interventions. From a research perspective, these findings support prioritizing vascular pathways as early and potentially actionable targets in dementia prevention frameworks.

Alzheimer's disease imaging biomarkers

In regard to AD imaging, Gottesman et al. (2017) reported that midlife modifiable risk factors, such as smoking, diabetes, prehypertension, and hypertension, were associated with an increased risk of amyloid deposition and dementia, emphasizing the importance of addressing vascular health in midlife to mitigate long-term risks.[19] While there are currently no publications focusing on the LS7 and AD imaging, Zhao et al. (2022) found that higher LS7 scores were associated with more favorable CSF AD biomarkers in the CABLE (Chinese Alzheimer's Biomarker and LifestylE) study, particularly among *APOE* ϵ4 non-carriers, reporting higher (healthier) $A\beta_{42/40}$ ratios and lower (healthier) pTau-181 associated with an increase in the LS7 score.[17]

These mixed findings highlight the complexity of the lifestyle—biomarker relationship and suggest that associations may differ by biomarker type (CSF versus PET), *APOE* genotype, and cohort composition. The null results in WRAP may reflect both the high proportion of *APOE* ϵ4 carriers and the relatively young, preclinical sample, where vascular pathways may be the earliest detectable link between lifestyle and brain health.

Clinical relevance and lifestyle context

A unique aspect of this study is the inclusion of a wide range of imaging biomarkers and cognitive outcomes within the same cohort. Cardiovascular health, as captured by the LS7, is not only associated with brain health but represents a clinically actionable, modifiable pathway to reduce risk for cerebrovascular dysfunction and cognitive decline.

Unlike many biomarkers used in dementia research, LS7 components are routinely collected in clinical care and directly translatable into lifestyle or medical interventions. This positions LS7 as a practical framework for early identification and risk reduction, particularly in midlife populations at elevated risk for AD and vascular dementia.

The LS7 includes seven easily assessable lifestyle metrics including diet, physical activity, smoking status, blood pressure, blood sugar, cholesterol, and BMI, which makes it ideal for implementation in a clinical setting. Other dementia risk scores, including CAIDE, LIBRA, ANU-ADRI, and CogDrisk, incorporate overlapping but broader domains such as cognitive and social activity, depression, and sleep.[42–46] While these approaches offer expanded risk profiling, LS7 provides a streamlined and widely accessible framework. Future research will consider the recently updated Life's Essential 8 (LE8), which incorporates sleep and refines the LS7 components.[47]

Age effects and interpretation of timing

Age remains one of the strongest predictors of CBVD, cognitive decline, and AD, and our findings are consistent with this established risk. Each year of age over 65 was associated with poorer outcomes across all domains.[48–50] Notably, a one-unit increase in LS7 score was associated with an effect similar to being one year younger for WMH at 6–8 years, and 2.5–3 years younger for CBF at 6–8 years. This suggests that even modest improvements in cardiovascular health may meaningfully offset age-related cerebrovascular decline. These estimates provide a clinically meaningful benchmark for the potential impact of lifestyle interventions and algins with results see in wide scale lifestyle intervention trials such as the US POINTER study.[51]

Differences between WMH and CBF may be attributed to the nature of the two measures. WMH typically form due to ischemia, stroke, or microbleeds, meaning that they occur at a given point in time due to a specific event or as a result of chronically reduced blood flow, whereas CBF is more of a gradient where there can be a gradual reduction overtime, even among healthy adults.[24,50,52]

Cohort context and generalizability

WRAP is a deeply phenotyped, midlife-to-older adult cohort, with participants in the present analyses ranging from approximately 67–71 years. This places the WRAP imaging sample close in age to the UK Biobank imaging

subset (mean age ~64) and younger than biomarker-intensive cohorts such as ADNI-3 (mean age ~75).[53,54]

WRAP is predominantly female (~69%), a pattern common in volunteer aging research cohorts. In contrast, large multi-ethnic cardiovascular studies such as Multi-Ethnic Study of Atherosclerosis (MESA) report more balanced sex distributions (~47% male) and Atherosclerosis Risk in Communities (ARIC) includes ~45% male participants.[19,55]

The racial composition of WRAP (~94% non-Hispanic White) reflects regional enrollment patterns but contrasts with the greater diversity of MESA, where over 50% of participants are individuals traditionally underrepresented in research, and with the design of ARIC, which intentionally sampled both Black and White adults across U.S. communities.[19,55]

APOE ϵ4 carrier frequency in WRAP (~38–40%) is higher than in population-based cohorts such as the UK Biobank (~26%) and similar to ADNI-3 (~32% among cognitively unimpaired adults).[53,54]

Collectively, these demographic characteristics enhance WRAP's sensitivity to detecting preclinical changes in a genetically at-risk population but may limit generalizability to broader and more diverse groups.

Strengths and limitations

Strengths of this study include a comprehensive set of outcomes with relatively large sample sizes. Few studies incorporate both CBVD and AD biomarkers alongside cognition within the same cohort. Here we include both imaging biomarkers of vascular dementia and AD pathology along with cognition within the same cohort.

Limitations include modest sample sizes at some intervals and non-overlapping subsets of participants across outcomes and intervals. Differences in enrollment timing, imaging availability, and protocols may contribute to variability in effect magnitude.

Although multiple comparisons increase the risk of Type I error, we applied FDR correction within predefined outcome families. Following correction, only cerebrovascular associations at the 6–8 year interval remained statistically significant, while cognitive and AD biomarker findings should be interpreted with caution. Despite this, the consistent direction and alignment with existing literature suggest that these findings may reflect meaningful relationships that warrant further investigation.

Generalizability is limited by cohort composition, and CBVD imaging measures (WMH, ASL perfusion, and history of CBVD including lacunar infarcts and microhemorrhages) serve as proxies of small vessel disease rather than diagnostic indicators of vascular cognitive impairment and dementia, though they are included in recent VCID research frameworks.

Although education and *APOE* ϵ4 were excluded from some imaging models based on *a priori* hypotheses, expanded models including these covariates did not improve model fit or significance of associations. These considerations support the validity of our original model structure while highlighting the need for replication in larger, more diverse, and harmonized longitudinal cohorts.

Conclusion

In summary, this study demonstrates that better cardiovascular health, as measured by LS7, is associated with favorable CBVD imaging biomarkers and cognitive outcomes, but not with AD-specific imaging biomarkers. Higher (healthier) LS7 scores were associated with lower WMH burden, greater CBF, and better cognitive performance, suggesting that cardiovascular health influences dementia risk primarily through the vascular pathway. Given that more than half of dementia cases include a vascular component, these findings highlight the clinical importance of targeting cardiovascular health through diet and lifestyle modifications as a promising strategy for dementia prevention.

Acknowledgements

The authors especially thank the WRAP participants and staff for their contributions to the studies. Without their efforts, this research would not be possible.

ORCID iDs

Diandra N. Denier-Fields https://orcid.org/0000-0001-5954-5062

Ronald E. Gangnon https://orcid.org/0000-0003-2587-6714

Corinne D. Engelman https://orcid.org/0000-0003-4750-5607

Ethical considerations

All ethical guidelines were met, and IRB approvals have been obtained.

Consent to participate

All participants provided signed informed consent before participation.

Consent for publication

Not applicable

Author contribution(s)

Diandra N. Denier-Fields: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Visualization; Writing – original draft; Writing – review & editing.

Ronald E. Gangnon: Conceptualization; Methodology; Writing – review & editing.

Leonardo A. Rivera-Rivera: Data curation; Investigation; Writing – review & editing.

Tobey J. Betthauser: Data curation; Resources; Writing – review & editing.

Barbara B. Bendlin: Methodology; Writing – review & editing.

Sterling C. Johnson: Funding acquisition; Writing – review & editing.
Corinne D. Engelman: Conceptualization; Funding acquisition; Methodology; Project administration; Writing – review & editing.

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This study was supported by the National Institutes of Health (NIH) grants [grant number R01AG27161] (Wisconsin Registry for Alzheimer Prevention: Biomarkers of Preclinical AD) and [grant number R01/RF1AG054047] (Genomic and Metabolomic Data Integration in a Longitudinal Cohort at Risk for Alzheimer's Disease). Computational resources were supported by core grants to the Center for Demography and Ecology [grant number P2CHD047873] and the Center for Demography of Health and Aging [grant number P30AG017266].

Declaration of conflicting interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Data availability statement

The data supporting the findings of this study are available on request from the Wisconsin Registry for Alzheimer's Prevention (https://wrap.wisc.edu/data-requests-2/). The data is not publicly available due to privacy restrictions.

Supplemental material

Supplemental material for this article is available online.

References

1. Santisteban MM and Iadecola C. Hypertension, dietary salt and cognitive impairment. *J Cereb Blood Flow Metab* 2018; 38: 2112–2128.
2. Kloppenborg RP, Nederkoorn PJ, Geerlings MI, et al. Presence and progression of white matter hyperintensities and cognition: a meta-analysis. *Neurology* 2014; 82: 2127–2138.
3. Wardlaw JM, Smith EE, Biessels GJ, et al. Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. *Lancet Neurol* 2013; 12: 822–838.
4. Gorelick PB, Scuteri A, Black SE, et al. Vascular contributions to cognitive impairment and dementia: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2011; 42: 2672–2713.
5. Iadecola C. The pathobiology of vascular dementia. *Neuron* 2013; 80: 844–866.
6. Arani A, Borowski B, Felmlee J, et al. Design and validation of the ADNI MR protocol. *Alzheimers Dement* 2024; 20: 6615–6621.
7. Jack CR, Andrews JS, Beach TG, et al. Revised criteria for diagnosis and staging of Alzheimer's disease: alzheimer's Association Workgroup. *Alzheimers Dement* 2024; 20: 5143–5169.
8. Debette S and Markus HS. The clinical importance of white matter hyperintensities on brain magnetic resonance imaging: systematic review and meta-analysis. *Br Med J* 2010; 341: c3666–c3666.
9. Duering M, Biessels GJ, Brodtmann A, et al. Neuroimaging standards for research into small vessel disease—advances since 2013. *Lancet Neurol* 2023; 22: 602–618.
10. Alsop DC, Dai W, Grossman M, et al. Arterial spin labeling blood flow MRI: its role in the early characterization of Alzheimer's disease. *J Alzheimers Dis* 2010; 20: 871–880.
11. Wierenga CE, Hays CC and Zlatar ZZ. Cerebral blood flow measured by arterial spin labeling MRI as a preclinical marker of Alzheimer's disease. *J Alzheimers Dis* 2014; 42: S411–S419.
12. Samieri C, Perier M-C, Gaye B, et al. Association of cardiovascular health level in older age with cognitive decline and incident dementia. *JAMA* 2018; 320: 657.
13. Sabia S, Fayosse A, Dumurgier J, et al. Association of ideal cardiovascular health at age 50 with incidence of dementia: 25 year follow-up of Whitehall II cohort study. *Br Med J* 2019; 366: l4414.
14. Lloyd-Jones DM, Hong Y, Labarthe D, et al. Defining and setting national goals for cardiovascular health promotion and disease reduction: the American Heart Association's strategic impact goal through 2020 and beyond. *Circulation* 2010; 121: 586–613.
15. Wu J, Xiong Y, Xia X, et al. Can dementia risk be reduced by following the American Heart Association's Life's Simple 7? A systematic review and dose-response meta-analysis. *Ageing Res Rev* 2023; 83: 101788.
16. Fu Y, Sun Y, Wang Z, et al. Associations of Life's Simple 7 with cerebral white matter hyperintensities and microstructural integrity: uK Biobank cohort study. *Eur J Neurol* 2023; 30: 1200–1208.
17. Zhao Y-L, Ou Y-N, Ma Y-H, et al. Association between Life's Simple 7 and cerebrospinal fluid biomarkers of Alzheimer's disease pathology in cognitively intact adults: the CABLE study. *Alzheimers Res Ther* 2022; 14: 74.
18. Alber J, Alladi S, Bae H, et al. White matter hyperintensities in vascular contributions to cognitive impairment and dementia (VCID): knowledge gaps and opportunities. *Alzheimers Dement (N Y)* 2019; 5: 107–117.
19. Gottesman RF, Albert MS, Alonso A, et al. Associations between midlife vascular risk factors and 25-year incident dementia in the Atherosclerosis Risk in Communities (ARIC) cohort. *JAMA Neurol* 2017; 74: 1246.
20. Rue AL, Hermann B, Jones JE, et al. Effect of parental family history of Alzheimer's disease on serial position profiles. *Alzheimers Dement* 2008; 4: 285–290.
21. Johnson SC, Koscik RL, Jonaitis EM, et al. The Wisconsin Registry for Alzheimer's Prevention: a review of findings and current directions. *Alzheimers Dement (Amst)* 2018; 10: 130–142.

22. Morris MC, Tangney CC, Wang Y, et al. MIND Diet slows cognitive decline with aging. *Alzheimers Dement* 2015; 11: 1015–1022.
23. American Stroke Association. *Transient ischemic attack (TIA). Types of Stroke*, https://www.stroke.org/en/about-stroke/types-of-stroke/tia-transient-ischemic-attack (2025, accessed 6 May 2025).
24. Li Q, Yang Y, Reis C, et al. Cerebral small vessel disease. *Cell Transplant* 2018; 27: 1711–1722.
25. Types of Heart Medications. www.heart.org, https://www.heart.org/en/health-topics/heart-attack/treatment-of-a-heart-attack/cardiac-medications (accessed 6 May 2025).
26. CDC. *Stroke*. https://www.cdc.gov/stroke/prevention/index.html (2025, accessed 6 May 2025). Preventing stroke.
27. Du L, Hermann BP, Jonaitis EM, et al. Harnessing cognitive trajectory clusterings to examine subclinical decline risk factors. *Brain Commun* 2023; 5: fcad333.
28. Reed BR, Marchant NL, Jagust WJ, et al. Coronary risk correlates with cerebral amyloid deposition. *Neurobiol Aging* 2012; 33: 1979–1987.
29. Levin F, Jelistratova I, Betthauser TJ, et al. In vivo staging of regional amyloid progression in healthy middle-aged to older people at risk of Alzheimer's disease. *Alzheimers Res Ther* 2021; 13: 178.
30. Sprecher KE, Bendlin BB, Racine AM, et al. Amyloid burden is associated with self-reported sleep in nondemented late middle-aged adults. *Neurobiol Aging* 2015; 36: 2568–2576.
31. Clark LR, Racine AM, Koscik RL, et al. Beta-amyloid and cognitive decline in late middle age: findings from the Wisconsin Registry for Alzheimer's Prevention study. *Alzheimers Dement* 2016; 12: 805–814.
32. Goldberg TE, Harvey PD, Wesnes KA, et al. Practice effects due to serial cognitive assessment: implications for preclinical Alzheimer's disease randomized controlled trials. *Alzheimers Dement (Amst)* 2015; 1: 103–111.
33. Bates D, Mächler M, Bolker B, et al. Fitting linear mixed-effects models using lme4. *J Stat Softw* 2015; 67: 1–48.
34. Noguchi S, Murakami K and Yamada N. Apolipoprotein E genotype and Alzheimer's disease. *Lancet* 1993; 342: 737.
35. Tingley D, Yamamoto T, Hirose K, et al. mediation: R Package for Causal Mediation Analysis, http://www.jstatsoft.org/v59/i05/ (2019).
36. Jansen WJ, Ossenkoppele R, Knol DL, et al. Prevalence of cerebral amyloid pathology in persons without dementia: a meta-analysis. *JAMA* 2015; 313: 1924.
37. Iturria-Medina Y, Sotero RC, Toussaint PJ, et al. Early role of vascular dysregulation on late-onset Alzheimer's disease based on multifactorial data-driven analysis. *Nat Commun* 2016; 7: 11934.
38. Donohue MC, Sperling RA, Salmon DP, et al. The Preclinical Alzheimer Cognitive Composite: measuring amyloid-related decline. *JAMA Neurol* 2014; 71: 961.
39. Jack CR, Bennett DA, Blennow K, et al. NIA-AA Research Framework: toward a biological definition of Alzheimer's disease. *Alzheimers Dement* 2018; 14: 535–562.
40. Wei J, Wang L, Kulshreshtha A, et al. Adherence to Life's Simple 7 and cognitive function among older adults: the National Health and Nutrition Examination Survey 2011 to 2014. *J Am Heart Assoc* 2022; 11: e022959.
41. Liu D, Cai X, Yang Y, et al. Associations of Life's Simple 7 with cerebral small vessel disease. *Stroke* 2022; 53: 2859–2867.
42. Huque MH, Kootar S, Eramudugolla R, et al. Cogdrisk, ANU-ADRI, CAIDE, and LIBRA risk scores for estimating dementia risk. *JAMA Netw Open* 2023; 6: e2331460.
43. Kivipelto M, Ngandu T, Laatikainen T, et al. Risk score for the prediction of dementia risk in 20 years among middle aged people: a longitudinal, population-based study. *Lancet Neurol* 2006; 5: 735–741.
44. Schiepers OJG, Köhler S, Deckers K, et al. Lifestyle for Brain Health (LIBRA): a new model for dementia prevention. *Int J Geriatr Psychiatry* 2018; 33: 167–175.
45. Anstey KJ, Cherbuin N and Herath PM. Development of a new method for assessing global risk of Alzheimer's disease for use in population health approaches to prevention. *Prev Sci* 2013; 14: 411–421.
46. Anstey KJ, Kootar S, Huque MH, et al. Development of the CogDrisk tool to assess risk factors for dementia. *Alzheimers Dement (Amst)* 2022; 14: e12336.
47. Lloyd-Jones DM, Allen NB, Anderson CAM, et al. Life's Essential 8: updating and enhancing the American Heart Association's Construct of Cardiovascular Health: a presidential advisory from the American Heart Association. *Circulation* 2022; 146: e18–e43.
48. Breijyeh Z and Karaman R. Comprehensive review on Alzheimer's disease: causes and treatment. *Molecules* 2020; 25: 5789.
49. Deary IJ, Corley J, Gow AJ, et al. Age-associated cognitive decline. *Br Med Bull* 2009; 92: 135–152.
50. Silva D, Faraci TM and M F. Contributions of aging to cerebral small vessel disease. *Annu Rev Physiol* 2020; 82: 275–295.
51. Baker LD, Espeland MA, Whitmer RA, et al. Structured vs self-guided multidomain lifestyle interventions for global cognitive function: the US POINTER randomized clinical trial. *JAMA* 2025; 334: 681–691.
52. Merino JG. White matter hyperintensities on magnetic resonance imaging: what is a clinician to do? *Mayo Clin Proc* 2019; 94: 380–382.
53. Weber C, Carrillo MC, Jagust W, et al. The Worldwide Alzheimer's Disease Neuroimaging Initiative: ADNI-3 updates and global perspectives. *Alzheimers Dement (N Y)* 2021; 7: e12226.
54. Heise V, Offer A, Whiteley W, et al. A comprehensive analysis of APOE genotype effects on human brain structure in the UK Biobank. *Transl Psychiatry* 2024; 14: 143.
55. Ostovaneh MR, Hughes TM, Wu CO, et al. Deep phenotyping of dementia in a multi-ethnic cardiovascular cohort: the Multi-Ethnic Study of Atherosclerosis (MESA). *PLoS One* 2024; 19: e0298952.