Received: 2 April 2023 | Revised: 4 August 2023 | Accepted: 13 August 2023

DOI: 10.1002/hipo.23573

RESEARCH ARTICLE

WILEY

The interaction of global small vessel disease burden and Alzheimer's disease pathologies do not change the independent association of amyloid-beta with hippocampal volume: A longitudinal study on mild cognitive impairment subjects

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Funding information
Alzheimer's Disease Neuroimaging Initiative (ADNI) (National Institutes of Health), Grant/Award Number: U01 AG024904; DOD ADNI, Grant/Award Number: W81XWH-12-2-0012; The Health Foundation for Creative Talents in Zhejiang Province, Grant/Award Number: 2016; The Wenzhou Municipal Science and Technology Bureau, Grant/Award Number: Y2020062

Abstract

The purpose of this study was to investigate whether the co-existence of global small vessel disease (SVD) burdens and Alzheimer's disease (AD) pathologies change hippocampal volume (HV) and cognitive function of mild cognitive impairment (MCI) subjects. We obtained MRI images, cerebrospinal fluid biomarkers ($A\beta_{1\text{-}42}$ and p-tau), and neuropsychological tests of 310 MCI subjects from ADNI. The global SVD score was assessed. We used linear regression and linear mixing effect to analyze the effects of global SVD burdens, AD pathologies, and their interactions (SVD*AD) on baseline and longitudinal HV and cognition respectively. We used simple mediation effect to analyze the influencing pathways. After adjusting for global SVD and SVD*AD, Aβ remained independently correlated with baseline and longitudinal HV (std $\beta = 0.294$, $p = .007$; std $\beta = 0.292$, $p < .001$), indicating that global SVD did not affect the correlation between Aβ and HV. Global SVD score was correlated with longitudinal but not baseline HV (std $\beta = 0.470$, $p = .050$), suggesting that global SVD may be more representative of long-term permanent impairment. Global SVD, AD pathologies, and SVD*AD were independently correlated with baseline and longitudinal cognitions, in which the association of Aβ (B = 0.005, 95% CI: 0.005; 0.024) and p-tau (B = −0.002, 95% CI: −0.004; −0.000) with cognition were mediated by HV, suggesting that HV is more likely to explain the progression caused by AD pathology than SVD. The co-existence of global SVD and AD pathologies did not affect the individual association of Aβ on HV; HV played a more important role in the influence of AD pathology on cognition than in SVD.

KEYWORDS
AD pathology, cognitive decline, hippocampal volume, interaction, MCI, small vessel disease

Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf

1 | INTRODUCTION

Mild cognitive impairment (MCI) refers to cognitive impairment that has no obvious impact on daily life (C. R. Jack Jr. et al., 2018). It is considered a middle state between normal aging and dementia, from which about 11%–33% of people may convert to dementia in 2 years (Tran et al., 2022). Alzheimer's disease (AD) and vascular dementia (VaD) are two main types of dementia. AD is characterized by amyloid beta (Aβ) peptide accumulation and hyperphosphorylation of tau (C. R. Jack et al., 2013), while small vessel disease (SVD) plays an important role in VaD (Kalaria, 2018). SVD includes enlarged perivascular space (EPVS), white matter hyperintensities (WMH), cerebral microbleeds (CMBs) and lacunes (Pasi & Cordonnier, 2020). SVD and AD pathology often co-exist in AD patients (Neuropathology Group. Medical Research Council Cognitive & Aging, 2001). Autopsy study (Kapasi et al., 2017) and some in-vivo studies (Saridin et al., 2020; Ye et al., 2015) also found that there was a possible synergistic effect between Aβ and SVD. Although the mechanism of the two is still uncertain, their common manifestations are cognitive impairment and significant changes in brain images.

Reduced hippocampal volume (HV) is considered the most sensitive MRI marker during AD progression (C. R. Jack Jr. et al., 1999), and it was observed in MCI subjects (Drago et al., 2011). HV reduction and cognitive impairment are the two main neurodegenerative manifestations of MCI progression, with HV reduction typically occurring before cognitive impairment. Currently, studies have confirmed the independent association of AD pathology and SVD burdens on hippocampal atrophy (Fiford et al., 2017; Guzman et al., 2013) or cognition (Li et al., 2021; Prosser et al., 2023; Wu et al., 2023; Z. Zhu et al., 2022). However, the interaction of AD pathology and SVD (SVD*AD) on neurodegenerative changes has been barely studied. Freeze et al. (Freeze et al., 2017) found no interactive effect of Aβ and WMH on HV reduction in AD patients. Soldan et al. (Soldan et al., 2020) also found no interactive effect of AD pathology and WMH on cognition in MCI. Nevertheless, these studies were limited to single SVD markers, and the role of global SVD has not been explored yet. The total SVD score is a comprehensive index incorporating the four biomarkers to reflect global burdens (Staals et al., 2014). Its description of SVD is more representative and explanatory than one or several biomarkers alone, since individual SVD biomarkers are often co-occurring and may affect each other. In addition, existed research about the role of HV were inconsistent and limited. Yatawara et al. (Yatawara et al., 2020) found that SVD indirectly contributed to cognitive impairment via HV in young onset dementia. Whereas Leijsen et al. (van Leijsen et al., 2019) drove to the conclusion that the effect of WMH on episodic memory decline was not mediated by HV in the elderly. There is a great need to clarify the role of HV in pathways that contribute to cognitive impairment through SVD and AD pathology.

Hence, the purpose of this study was to: (1) evaluate the correlation between global SVD, AD pathology, and their interactions with HV and cognitive decline; (2) explore the role of HV in the pathway of cognitive impairment predicted by different markers.

2 | MATERIALS AND METHODS

2.1 | Subjects

The Alzheimer's disease neuroimaging initiative (ADNI) is a public database intended to help researchers and clinicians to develop new treatments, monitor their effectiveness, and reduce the time and cost of clinical trials of Alzheimer's disease. Please see www.adni-info.org. for more information.

We obtained data from ADNI-2, including age, sex, baseline APOE, CSF biomarkers (Aβ and p-tau), T2-weighted fluid-attenuated inversion recovery (T2-FLAIR) images and T2*-weighted images, and baseline and follow-up T1-weighted (T1W) images and neuropsychological tests. We took the time of neuropsychological tests as the baseline time and selected the closest time for baseline images and CSF results. We selected the subjects with MCI (including early MCI and late MCI) at baseline. Diagnostic criteria for MCI were described elsewhere (Petersen et al., 2010). After screening, a total of 310 subjects were included in our dataset. We limited the follow-up time to 4 years, that is we obtained T1W images and neuropsychological tests of subjects for 4 years.

The ADNI study received written informed consent from all participants and/or their authorized representatives. This study was conducted in accordance with all the ethical standards established by the institutional and/or national research committees and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

2.2 | Image acquisition

All MRI (3.0 T) were downloaded from the ADNI database. Sequences were acquired as follows: (1) 3D T1W magnetization prepared rapid gradient echo sequence or 3D T1W Inversion Recovery prepared Spoiled Gradient Recalled echo sequence; (2) 2D T2-FLAIR sequence and (3) 2D T2*-weighted sequence. All the images were acquired following a standardized protocol validated across platforms (C. R. Jack Jr. et al., 2008). Detailed information is provided elsewhere (https://adni.loni.usc.edu/methods/documents/mri-protocols/).

2.3 | Image analysis

2.3.1 | White matter hyperintensity

WMH is hyperintense on T2-weighted (T2W) sequence and isointense or hypointense on T1W sequence (Wardlaw et al., 2013). The visual rating of deep and periventricular WMH was performed on T2-FLAIR images using the Fazekas scale. Specifically, periventricular and deep WMHs were graded from 0 to 4 respectively as described before (Fazekas et al., 1987; Figure 1).

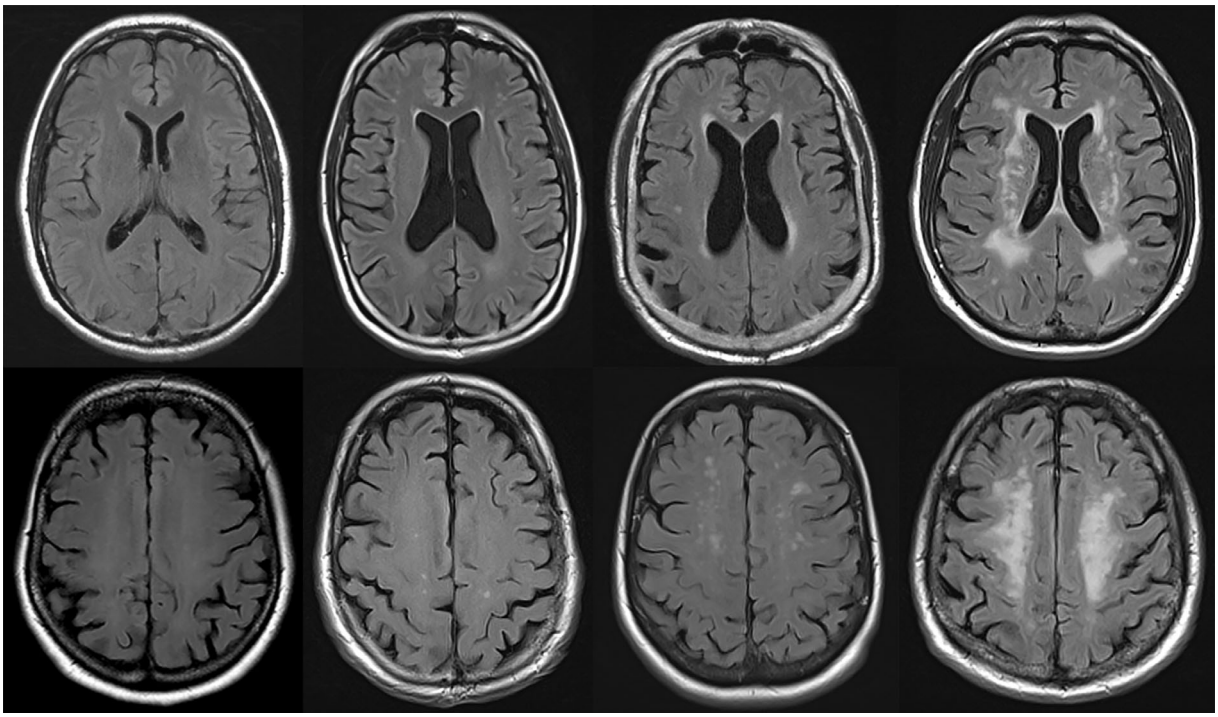

FIGURE 1 Illustration of Fazekas score of white matter hyperintensities (WMH). From left to right illustrate 0–3 points respectively. Upper line: periventricular WMH, lower line: deep WMH.

2.3.2 | Lacunes

We evaluated the presence of lacunes on T2-FLAIR images, which were defined as a round or ovoid, subcortical, fluid-filled cavity, 3–15 mm in diameter (Wardlaw et al., 2013).

2.3.3 | Cerebral microbleed

We evaluated the presence of CMB on T2*-weighted MRI, which was defined as a small area of signal void sized 2–5 mm or up to 10 mm, and are generally not seen on FLAIR, T1W, or T2W sequences (Wardlaw et al., 2013).

2.3.4 | Enlarged perivascular space

EPVS is a fluid-filled space that follows the path of a vessel through gray or white matter with a signal intensity similar to CSF, and it could appear linear, round, or ovoid, with a diameter generally smaller than 3 mm (Wardlaw et al., 2013). In the slice containing the greatest number of EPVS in basal ganglia, a 4-level severity score was applied on T1W image (Y. C. Zhu et al., 2010; Supplementary Material).

2.3.5 | Global SVD burden

The Staals' score, which combines WMH, lacunes, CMB, and EPVS, was used to evaluate the global SVD burden (Staals et al., 2014). The following items were given one point each: (1) Deep WMH scored 2–3 points or periventricular WMH scored 3 points; (2) Presence of lacunes; (3) Presence of CMB; (4) EPVS of grade 2–4 (more than 5 EPVS) (Figure 2). All imaging analyses were performed by a neuroradiologist without knowledge of clinical information. To evaluate the inter-observer consistency, another neuroradiologist performed assessments on randomly selected 1/3 cases. We used weighted kappa to evaluate the consistency between the two raters.

2.4 | CSF biomarker data

We downloaded CSF biomarker data from the ADNI database. For the current analysis, p-tau and $A\beta_{1\text{-}42}$ were selected. Other publication has provided complete instructions for biological assays (Shaw et al., 2011). $A\beta_{1\text{-}42}$ and p-tau were quantified using the multiple XMAP-Luminex platform (Luminex Corp, Austin, TX, USA) and the INNO-BIA AlzBio3 immunoassay kits (reagents on the Luminex analytical platform).

2.5 | Outcome variables

2.5.1 | Hippocampal volume

Baseline and longitudinal HV were automatically segmented on T1W sagittal images using FreeSurfer V.6.0.0 (http://surfer.nmr.mgh.harvard.edu/) on Linux system. We used the global HV rate adjusted for intracranial volume in the analysis. Out of 310 participants, 288 participants re-attended follow-up MRI scans.

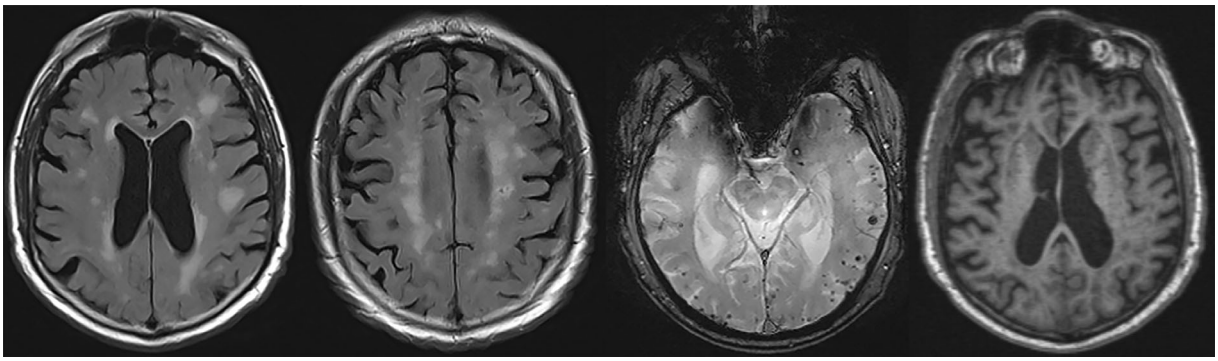

FIGURE 2 MRI illustration of cerebral small vessel diseases. From left to right: White matter hyperintensities (T2 Flair), lacunar infarct (T2 Flair), cerebral microbleeds (T2*), and periventricular spaces (T1).

2.5.2 | Neuropsychological test data

We obtained baseline and follow-up data of Mini-mental State Examination (MMSE) for global cognition, Trail Making Tests A and B (TMT-A, TMT-B) for executive function, Logical Memory-Delayed Recall, and Rey Auditory Verbal Learning Test (RAVLT)- 30 Minute Delayed Recall for memory function, and Category Fluency (Animals) and Boston Naming Test (BNT) for language function. Standard procedures of neuropsychological tests were published elsewhere (Petersen et al., 2010). Out of 310 participants, 287 participants re-attended follow-up neuropsychological tests.

2.6 | Statistical analysis

Categorical variables were summarized as percent (count) and continuous variables as mean ± *SD*. In all of the following models, we took gender, age, education, and APOE as covariates.

First, we used simple and multiple linear regression analyses on SPSS (v. 25.0; IBM, Armonk, NY, USA) to investigate the effect of SVD*AD (SVD*Aβ and SVD*p-tau), AD pathologies, and global SVD burdens on baseline HV and cognitive function. Each neuropsychological test score or HV was entered as the output variable, while age, sex, education, and APOE were input as independent variables (Model 1) (Supplementary Material). Then we added CSF biomarkers (Aβ and p-tau) or total SVD score into the baseline model separately (Model 2–3). In step 3, we added CSF biomarkers and total SVD score into the baseline model together (Model 4). Finally, SVD*Aβ and SVD*p-tau were added (Model 5). The explained variance (adjusted R^2), standardized betas (std β), and *p*-value were calculated for each model.

Next, to investigate the longitudinal association, we built linear mixing effect (LME) models using R software (v. 4.1.2, lme4 package v.1.1–28), incorporating the interactions between time and other variables (Aβ*Year, p-tau*Year, SVD*Year, SVD*Aβ*Year and SVD*p-tau*Year). The formulas of LME models were listed in Supplementary Material. All results with $p < .05$ were considered statistically significant. Multiple comparisons were corrected with the Bonferroni comparison ($p < .05/7$).

Furthermore, the single mediation analysis was run using the "Model 4" option of the SPSS macro process, with 5000 bootstrap samples (Bachl, 2017). Specifically, we used AD pathologies or global SVD as the independent variables, baseline neuropsychological test scores as dependent variables, and baseline HV as the intermediary variable. Sex, age, education, and APOE were included as covariables to adjust for potential confounders. Confidence intervals of BC bootstrap estimate that did not contain 0 were considered statistically significant.

3 | RESULTS

3.1 | Subjects characteristics

A total of 310 participants were included in this study, with 138 females (44.5%) and 172 males (55.5%). The mean (±*SD*) age was 71.71 ± 7.31, ranging from 55.1 to 91.5. The education years ranged from 9 to 20, with an average (±*SD*) of 16.39 ± 2.63. The mean HV ratio was 4.708 ± 0.770. The median total SVD score was 1. The weighted kappa of the total SVD score was 0.774 ($p < .001$), which was of good consistency. A summary can be found in Table 1.

3.2 | Relationship of global SVD and AD pathologies with baseline HV and cognitive performance

The results of simple and multiple linear regression analysis of baseline HV and cognitive performance were presented in Table 2. For HV, Aβ was independently related to HV in model 3 (std $\beta = 0.172$, $p = .005$) and model 4 (std $\beta = 0.176$, $p = .004$). For cognitive performance, in model 2, total SVD score was linked to MMSE (std $\beta = -0.116$, $p = .049$) and TMT-A (std $\beta = 0.149$, $p = .012$). In model 3, Aβ was related to MMSE (std $\beta = 0.134$, $p = .046$) and logical memory-delay test (std $\beta = 0.162$, $p = .015$), while p-tau was associated with MMSE (std $\beta = -0.142$, $p = .020$), TMT-B (std $\beta = 0.154$, $p = .009$), RAVLT (std $\beta = -0.211$, $p < .001$), logical memory-delay test (std $\beta = -0.153$, $p = .012$) and category fluency (animals) (std $\beta = -0.120$, $p = .047$). In model 4, total SVD score was correlated with MMSE (std $\beta = -0.119$, $p = .039$) and TMT-A (std $\beta = 0.151$,

TABLE 1 Subject characteristics.

Baseline variables	
Demographic factors	
Age, mean ± *SD*	71.71 ± 7.31
Sex (Female), *n* (%)	138 (44.5%)
Education (number of years), mean ± *SD*	16.39 ± 2.63
APOE, mean ± *SD*	0.52 ± 0.50
MRI marker	
HV ratio ($\times 10^3$), mean ± *SD*	4.708 ± 0.770
Total SVD score, *n* (%)	
0	47 (15.2%)
1	161 (51.9%)
2	77 (24.8%)
3	16 (5.2%)
4	9 (2.9%)
CSF biomarkers	
Aβ (pg/ml), mean ± *SD*	171.42 ± 51.61
P-tau (pg/ml), mean ± *SD*	43.34 ± 25.75
Neuropsychological tests	
MMSE, mean ± *SD*	27.99 ± 1.77
TMT-A, mean ± *SD*	39.41 ± 17.91
TMT-B, mean ± *SD*	110.66 ± 63.53
RAVLT, mean ± *SD*	4.26 ± 4.00
Logical memory-delayed recall, mean ± *SD*	6.71 ± 3.47
Category Fluency (Animals), mean ± *SD*	17.85 ± 5.16
BNT, mean ± *SD*	26.59 ± 3.41

Abbreviations: BNT, Boston Naming Test; HV, hippocampal volume; MMSE, mini mental state examination; RAVLT, Rey Auditory Verbal Learning Test-30 Minute Delayed; *SD*, standard deviation; SVD, small vessel disease; TMT-A, trail making test A; TMT-B, trail making test B.

$p = .010$); Aβ was linked to logical memory-delay test (std $\beta = 0.164$, $p = .014$); p-tau was associated with MMSE (std $\beta = -0.153$, $p = .012$), TMT-B (std $\beta = 0.162$, $p = .006$), RAVLT (std $\beta = -0.210$, $p < .001$), logical memory-delay test (std $\beta = -0.151$, $p = .013$) and category fluency (animals) (std $\beta = -0.129$, $p = .033$).

When adding SVD*Aβ and SVD*p-tau (Model 5), Aβ was associated with HV (std $\beta = 0.294$, $p = .007$) and RAVLT (std $\beta = 0.253$, $p = .030$); total SVD score was correlated with TMT-A (std $\beta = 0.659$, $p = .013$) and TMT-B (std $\beta = 0.543$, $p = .035$); p-tau was linked to MMSE (std $\beta = -0.217$, $p = 0.022$); Aβ*SVD was correlated with TMT-A (std $\beta = -0.687$, $p = 0.002$) and TMT-B (std $\beta = -0.547$, $p = .009$), while p-tau*SVD had no significant association with HV and all the seven neuropsychological tests (Table 2).

3.3 | Relationship of global SVD and AD pathologies with longitudinal HV and cognitive decline

The results of LME analysis were shown in Table 3. For HV, Aβ could predict the change of HV in model 3 (std $\beta = 0.159$, $p = .009$) and model 4 (std $\beta = 0.162$, $p = .007$). For cognitive decline, in model 2, total SVD score could predict the decline of MMSE (std $\beta = -0.066$, $p = .041$) and the prolongation of TMT-A (std $\beta = 0.103$, $p = .021$). In model 3, Aβ could predict the prolongation of RAVLT (std $\beta = 0.149$, $p = .012$) and Logical Memory-Delay Test (std $\beta = 0.106$, $p = 0.027$), while p-tau could predict the decline of RAVLT (std $\beta = -0.190$, $p < .001$), logical memory-delay test (std $\beta = -0.129$, $p = .003$) and category fluency (animals) (std $\beta = -0.123$, $p = .027$) and the prolongation of TMT-A (std $\beta = 0.102$, $p = .030$) and TMT-B (std $\beta = 0.138$, $p = .014$). In model 4, total SVD score predicted the decline of MMSE (std $\beta = -0.069$, $p = .032$) and the prolongation of TMT-A (std $\beta = 0.111$, $p = .012$); Aβ predicted the prolongation of RAVLT (std $\beta = 0.150$, $p = .012$) and logical memory-delay test (std $\beta = 0.107$, $p = .026$); p-tau predicted the decline of TMT-A (std $\beta = 0.112$, $p = .016$) and TMT-B (std $\beta = 0.146$, $p = .009$) and the prolongation of RAVLT (std $\beta = -0.191$, P = 0.001), logical memory-delay test (std $\beta = -0.128$, $p = .004$) and category fluency (animals) (std $\beta = -0.132$, $p = .018$).

When adding SVD*Aβ and SVD*p-tau (model 5), total SVD score predicted the change of HV (std $\beta = 0.470$, $p = .050$), and declined over time (SVD*Year, $p = .095$); Total SVD score predicted the prolongation of TMT-A (std $\beta = 0.557$, $p = .005$) and TMT-B (std $\beta = 0.567$, $p = .021$), and declined over time (SVD*Year, $p_{TMT\text{-}A} = .063$, $p_{TMT\text{-}B} = .066$). Aβ predicted the change of HV (std $\beta = 0.290$, $p = .008$) and remained consistent over time (Aβ*Year, std $\beta = 0.292$, $p < .001$); Aβ predicted the prolongation of TMT-A (std $\beta = 0.184$, $p = .041$) and RAVLT (std $\beta = 0.323$, $p = .003$), and remained consistent over time (Aβ*Year, $p_{TMT\text{-}A} = .004$, $p_{RAVLT} = .012$); Aβ*SVD predicted the decline of TMT-A (std $\beta = -0.500$, $p = .003$) and TMT-B (std $\beta = -0.574$, $p = .005$), and declined over time (Aβ*SVD*Year, $p_{TMT\text{-}A} = .135$, $p_{TMT\text{-}B} = .104$). While p-tau*SVD could not predict longitudinal HV and cognitive decline.

3.4 | Mediation analysis

Simple mediation analysis model showed that Aβ was indirectly associated with RAVLT via HV (B = 0.005, 95% CI: 0.005; 0.024), indicating that the effect of Aβ on memory function was mediated by HV (Figure 3). P-tau was indirectly associated with MMSE via HV (B = −0.002, 95% CI: −0.004; −0.000), indicating that the effect of p-tau on global cognition was mediated by HV (Figure 4). There were no mediation effects observed in SVD-related pathways, suggesting that the effects of SVD and SVD*AD on cognitive function were not mediated by HV (Supplementary Material).

4 | DISCUSSION

This study investigated the correlation of AD pathologies, global SVD, and their interaction with HV and cognition in MCI subjects. The main findings are as follows: (1) Aβ was associated with baseline and longitudinal HV, independent of global SVD and SVD*AD; (2) Global SVD,

TABLE 2 Results of linear regression analysis for baseline HV and cognition.

		Global cognitive function	Executive function		Memory function		Language function	
	HV	MMSE	TMT-A	TMT-B	Logical memory-delayed recall	RAVLT	Category fluency (animals)	BNT
Model 2								
	$R^2 = 0.259$	*$R^2 = 0.094$*	*$R^2 = 0.090$*	*$R^2 = 0.151$*	*$R^2 = 0.085$*	*$R^2 = 0.125$*	*$R^2 = 0.119$*	*$R^2 = 0.081$*
Total SVD score	0.029(0.588)	**−0.116(0.049)***	**0.149(0.012)***	0.088(0.122)	0.022(0.703)	0.019(0.735)	−0.092(0.111)	−0.054(0.363)
Model 3								
	$R^2 = 0.288$	*$R^2 = 0.121$*	*$R^2 = 0.090$*	*$R^2 = 0.175$*	*$R^2 = 0.136$*	*$R^2 = 0.183$*	*$R^2 = 0.131$*	*$R^2 = 0.082$*
Aβ	**0.172(0.005)***	**0.134(0.046)***	−0.100(0.142)	−0.086(0.186)	**0.162(0.015)***	0.111(0.087)	0.074(0.264)	0.069(0.314)
P-Tau	−0.062(0.258)	**−0.142(0.020)***	0.097(0.117)	**0.154(0.009)***	**−0.153(0.012)***	**−0.211(<0.001)****	**−0.120(0.047)***	−0.047(0.447)
Model 4								
	$R^2 = 0.268$	*$R^2 = 0.131$*	*$R^2 = 0.106$*	*$R^2 = 0.180$*	*$R^2 = 0.134$*	*$R^2 = 0.181$*	*$R^2 = 0.136$*	*$R^2 = 0.082$*
Total SVD score	0.034(0.513)	**−0.119(0.039)***	**0.151(0.010)***	0.094(0.093)	0.021(0.716)	0.012(0.833)	−0.097(0.092)	−0.054(0.364)
Aβ	**0.176(0.004)***	0.123(0.066)	−0.086(0.203)	−0.077(0.234)	**0.164(0.014)***	0.112(0.085)	0.065(0.326)	0.064(0.352)
P-Tau	−0.059(0.286)	**−0.153(0.012)***	0.111(0.073)	**0.162(0.006)****	**−0.151(0.013)***	**−0.210(<0.001)****	**−0.129(0.033)***	−0.052(0.403)
Model 5								
	$R^2 = 0.291$	*$R^2 = 0.128$*	*$R^2 = 0.147$*	*$R^2 = 0.200$*	*$R^2 = 0.130$*	*$R^2 = 0.181$*	*$R^2 = 0.134$*	*$R^2 = 0.082$*
Total SVD score	0.449(0.065)	−0.355(0.185)	**0.659(0.013)***	**0.543(0.035)***	0.117(0.661)	0.380(0.144)	−0.199(0.457)	−0.230(0.402)
Aβ	**0.294(0.007)***	0.052(0.665)	0.218(0.066)	0.167(0.146)	0.224(0.062)	**0.253(0.030)***	−0.009(0.941)	−0.047(0.700)
P-Tau	0.066(0.443)	**−0.217(0.022)***	0.049(0.600)	0.142(0.117)	−0.165(0.081)	−0.148(0.105)	−0.099(0.293)	−0.024(0.807)
Aβ*SVD	−0.251(0.204)	0.154(0.482)	**−0.687(0.002)****	**−0.547(0.009)***	−0.135(0.538)	−0.311(0.144)	0.169(0.439)	0.251(0.264)
P-Tau*SVD	−0.233(0.065)	0.120(0.390)	0.165(0.231)	0.075(0.576)	0.037(0.793)	−0.104(0.443)	−0.071(0.610)	−0.072(0.613)

Note: Values show standardized regression coefficients: standardized β (*p*-value) for predictor variables in regression models, adjusted for age, sex, education, and APOE. Bolded values denote statistical significance. Italic represents adjusted R^2.

Abbreviations: Aβ*SVD, the interaction of Aβ and small vessel disease; BNT, Boston Naming Test; HV, hippocampal volume; MMSE, mini mental state examination; p-Tau*SVD, the interaction of p-tau and small vessel disease; RAVLT, Rey Auditory Verbal Learning Test-30 Minute Delayed; SVD, small vessel disease; TMT-A, trail making test A; TMT-B, trail making test B.

*$p < .05$; **$p < .05/7$.

TABLE 3 Results of linear mixing effect analysis for longitudinal HV and cognition.

		Global cognitive function	Executive function		Memory function		Language function	
	HV	MMSE	TMT-A	TMT-B	Logical memory-delayed recall	RAVLT	Category fluency (animals)	BNT
Model 2								
	R^2 = 0.971	*R^2 = 0.780*	*R^2 = 0.757*	*R^2 = 0.844*	*R^2 = 0.806*	*R^2 = 0.785*	*R^2 = 0.756*	*R^2 = 0.810*
Total SVD score	0.026(0.616)	**−0.066(0.041)***	**0.103(0.021)***	0.067(0.222)	0.009(0.830)	−0.004(0.937)	−0.068(0.162)	−0.025(0.632)
SVD*year	0.013(0.552)	−0.036(0.605)	−0.057(0.390)	0.003(0.959)	−0.083(0.071)	−0.041(0.204)	0.023(0.614)	**−0.111(0.036)***
Model 3								
	R^2 = 0.970	*R^2 = 0.776*	*R^2 = 0.756*	*R^2 = 0.843*	*R^2 = 0.806*	*R^2 = 0.785*	*R^2 = 0.755*	*R^2 = 0.809*
Aβ	**0.159(0.009)***	0.117(0.237)	−0.054(0.293)	−0.063(0.315)	**0.106(0.027)***	**0.149(0.012)***	0.060(0.319)	0.028(0.640)
P-Tau	−0.056(0.322)	−0.063(0.146)	**0.102(0.030)***	**0.138(0.014)***	**−0.129(0.003)****	**−0.190(<0.001)****	**−0.123(0.027)***	−0.018(0.733)
Aβ*Year	**0.164(<0.001)****	**0.703(<0.001)****	**−0.354(0.005)****	**−0.400(<0.001)****	**0.451(<0.001)****	**0.157(0.011)***	**0.185(0.034)***	**0.379(<0.001)****
P-Tau*Year	**−0.062(0.009)***	**−0.145(<0.001)****	**0.153(0.039)***	**0.157(0.006)****	**−0.103(0.033)***	−0.009(0.803)	**−0.157(0.002)****	**−0.140(0.015)***
Model 4								
	R^2 = 0.970	*R^2 = 0.776*	*R^2 = 0.756*	*R^2 = 0.843*	*R^2 = 0.806*	*R^2 = 0.785*	*R^2 = 0.756*	*R^2 = 0.809*
Total SVD score	0.035(0.502)	**−0.069(0.032)***	**0.111(0.012)***	0.077(0.151)	0.010(0.812)	−0.013(0.799)	−0.084(0.109)	−0.027(0.595)
Aβ	**0.162(0.007)***	0.037(0.312)	−0.042(0.405)	−0.055(0.378)	**0.107(0.026)***	**0.150(0.012)***	0.051(0.401)	0.026(0.666)
P-Tau	−0.052(0.354)	−0.056(0.097)	**0.112(0.016)***	**0.146(0.009)***	**−0.128(0.004)****	**−0.191(0.001)****	**−0.132(0.018)***	−0.021(0.698)
SVD*Year	0.028(0.164)	0.001(0.992)	−0.091(0.165)	−0.032(0.535)	−0.039(0.365)	−0.025(0.441)	0.040(0.379)	−0.079(0.120)
Aβ*Year	**0.174(<0.001)****	**0.464(<0.001)****	**−0.390(0.003)****	**−0.413(<0.001)****	**0.437(<0.001)****	**0.147(0.019)***	**0.201(0.024)***	**0.348(<0.001)****
P-Tau*Year	**−0.057(0.014)***	**−0.287(<0.001)****	0.143(0.055)	**0.154(0.007)***	**−0.107(0.027)***	−0.012(0.746)	**−0.152(0.003)****	**−0.149(0.010)***
Model 5								
	R^2 = 0.971	*R^2 = 0.776*	*R^2 = 0.756*	*R^2 = 0.842*	*R^2 = 0.806*	*R^2 = 0.785*	*R^2 = 0.756*	*R^2 = 0.808*
Total SVD score	**0.470(0.050)***	−0.090(0.540)	**0.557(0.005)****	**0.567(0.021)***	0.142(0.458)	0.355(0.137)	−0.064(0.791)	−0.082(0.730)
Aβ	**0.290(0.008)***	0.043(0.522)	**0.184(0.041)***	0.204(0.066)	0.163(0.061)	**0.323(0.003)****	0.035(0.750)	−0.029(0.789)
P-Tau	0.076(0.378)	−0.076(0.144)	0.117(0.096)	0.137(0.106)	−0.111(0.102)	−0.163(0.054)	−0.093(0.274)	0.014(0.867)
Aβ*SVD	−0.277(0.161)	−0.011(0.927)	**−0.500(0.003)****	**−0.574(0.005)****	−0.121(0.446)	−0.376(0.058)	0.039(0.845)	0.122(0.532)
P-Tau*SVD	−0.235(0.060)	0.041(0.588)	0.016(0.875)	0.048(0.701)	−0.026(0.790)	−0.033(0.787)	−0.075(0.549)	−0.075(0.538)
SVD*Year	0.156(0.095)	0.488(0.116)	−0.587(0.063)	−0.453(0.066)	**0.485(0.018)***	0.198(0.204)	**0.514(0.019)***	0.165(0.500)
Aβ*Year	**0.292(<0.001)****	**0.708(0.003)****	**−0.700(0.004)****	**−0.678(0.001)****	**0.722(<0.001)****	**0.301(0.012)***	**0.546(0.001)****	**0.486(0.011)***
P-Tau*Year	−0.056(0.117)	−0.142(0.208)	0.046(0.685)	0.076(0.376)	0.030(0.690)	0.016(0.781)	−0.097(0.220)	−0.089(0.316)
Aβ*SVD*Year	−0.142(0.073)	−0.311(0.229)	0.393(0.135)	0.336(0.104)	**−0.365(0.033)***	−0.199(0.126)	**−0.440(0.016)***	−0.175(0.391)
P-Tau*SVD*Year	0.001(0.975)	−0.225(0.099)	0.151(0.275)	0.122(0.240)	**−0.211(0.019)***	−0.044(0.525)	−0.079(0.409)	−0.093(0.390)

Note: Values show standardized regression coefficients: standardized β (*p*-value) for predictor variables in regression models, adjusted for age, sex, education, and APOE. Bolded values denote statistical significance. Italic represents adjusted R^2.

Abbreviations: Aβ*SVD, the interaction of Aβ and small vessel disease; BNT, Boston Naming Test; MMSE, mini mental state examination; P-Tau*SVD, the interaction of p-tau and small vessel disease; SVD, small vessel disease; TMT-A, trail making test A; TMT-B, trail making test B; RAVLT, Rey Auditory Verbal Learning Test-30 Minute Delayed.

*p < .05; **p < .05/7.

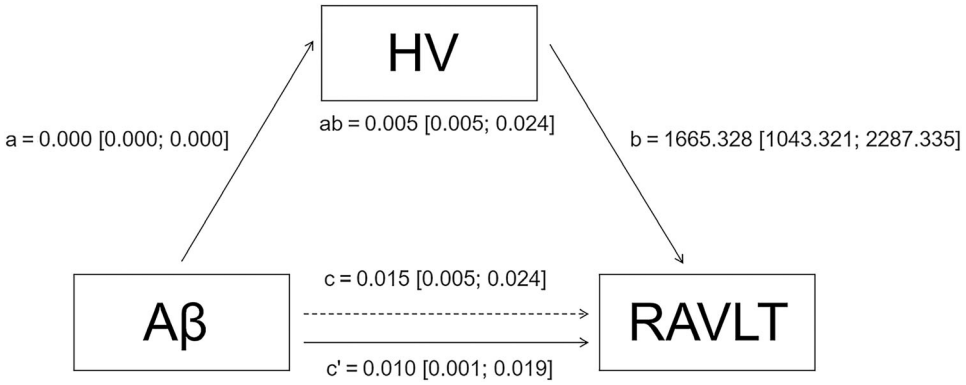

FIGURE 3 Graphical representation of the results of mediation analysis of pathway Aβ→ HV→ RAVLT. The diagram is presented with effect coefficients (a is the direct effect from X on M; b is the direct effect of M on Y; c is the total effect of X on Y; c' is the direct effect of X on Y and ab is the indirect effect of X on Y through M) and 95% CI. The diagram illustrates that Aβ (X) indirectly affects RAVLT score (Y) via the HV mediator (M). Aβ, amyloid-beta; HV, hippocampal volume; RAVLT, Rey Auditory Verbal Learning Test.

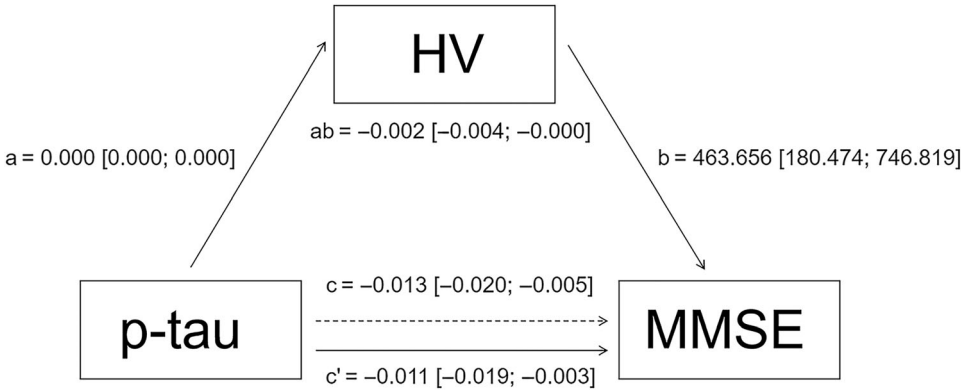

FIGURE 4 Graphical representation of the results of mediation analysis of pathway p-tau→ HV→ MMSE. The diagram is presented with effect coefficients (a is the direct effect from X on M; b is the direct effect of M on Y; c is the total effect of X on Y; c' is the direct effect of X on Y and ab is the indirect effect of X on Y through M) and 95% CI. The diagram illustrates that p-tau (X) indirectly affects MMSE score (Y) via the HV mediator (M). HV, hippocampal volume; MMSE, mini-mental state examination.

AD pathologies, and SVD*AD were independently correlated with cognitive function, in which the effect of AD pathologies on cognition was mediated by HV.

Hippocampal atrophy is one of the manifestations of AD progression, hence it was not surprising to find that Aβ was associated with HV. Despite that previous studies have already shown a correlation between the two (Guzman et al., 2013; Nosheny et al., 2015), in this work we notably found that this correlation was independent of global SVD and SVD*AD and remained consistent over time, suggesting that the presence of SVD does not change the effect of Aβ on HV. Accordingly, we found no independent association of global SVD or SVD*AD with baseline HV. One animal study suggested that the interactive effect of Aβ and SVD could lead to the degeneration of hippocampal cells (Amtul et al., 2014). However, Freeze et al. (Freeze et al., 2017) found that Aβ and WMH had an interactive effect on HV reduction in non-dementia individuals, but the effect disappeared when AD patients were added. Similarly, our study restricted the subjects to MCI and found no association. Nevertheless, we found that global SVD was independently associated with longitudinal HV, and this association decreased over time. The possible reason might be that global SVD is more representative of long-term chronic permanent damage, but in the progression of AD, the role of SVD gradually decreases. Given the inconsistencies of present findings, more research is needed to explore the underlying links.

Besides, we observed an independent association of global SVD and SVD*AD with baseline and follow-up cognitive function in MCI subjects, which differed by cognitive domains. In specific, global SVD was independently correlated with baseline and longitudinal executive function, and this correlation decreased over time. In the same time, global SVD was associated with longitudinal memory and language function, where the associations were enhanced over time. Previous studies on the correlation between global SVD and cognition have shown inconsistent results. Uiterwijk et al. (Uiterwijk et al., 2016) found that global SVD was associated with baseline executive function, but not with memory function in hypertension patients. However, another study found that higher global SVD was related both

with executive function and memory function in MCI (Li et al., 2021). Our study further confirms that global SVD was associated with longitudinal executive and memory decline regardless of AD pathology in MCI subjects, and showed how these associations changed over time. The reason why over time the association of SVD and executive function decreased, while the association of SVD with memory and language decline enhanced might be related to the regional progression of SVD. SVD first damages the frontal cortical tissues and the integrity of brain networks associated with executive function, then disrupts temporal lobe and hippocampus related to memory and language function. (Banerjee et al., 2018; Kalaria, 2018).

On the other hand, damaged blood vessels could lead to reduced clearance of Aβ, thus making pathological deposition of Aβ more severe; accumulation of Aβ in and around the cerebral vessels may lead to damage to small blood vessels (Liu et al., 2021). This may explain how SVD and AD pathology interact. A recent study showed that the interaction of Aβ and WMH can affect cognitive function (Saridin et al., 2020), while some other studies (Banerjee et al., 2017; Freeze et al., 2017) led to opposite results. Whereas previous studies only considered the interaction of individual SVD markers alone with Aβ, our study extended the results to global SVD burden, confirming that global SVD*Aβ can predict executive, memory and language decline in MCI subjects. This was in line with a previous study indicating that the combination of Aβ and global SVD burdens could meaningfully predict cognitive impairment (Liu et al., 2021). Nevertheless, that study only conducted a cross-sectional analysis, while our study included a 4-year longitudinal analysis, affirming the predictive value of it, and further revealed how these associations changed over time. The effect of SVD*Aβ on executive function decreased over time, and the effect on memory and language function increased over time, which corresponded to the trend of global SVD.

Furthermore, we found that the effect of AD pathology on cognition was mediated by HV. Based on prior studies, it was not hard to know that p-tau, Aβ (Pike et al., 2007), and hippocampal atrophy (Nathan et al., 2017; van Leijsen et al., 2019) were associated with cognitive impairment. However, there were few articles using mediation analysis method to detect the specific action path of HV. A previous study found that the association between plasma Aβ levels and cognition was explained through HV (Sapkota et al., 2022). In addition to confirming that HV mediated the correlation between CSF Aβ and cognition, our study also concluded that HV mediates the correlation between CSF p-tau and cognition. This provides potential evidence for future studies on the underlying pathological mechanism. Meanwhile, we drove to the conclusion that the pathway of SVD affecting cognitive function was not mediated by HV, suggesting that change in HV plays a less important role in the influence of SVD on cognition compared with the influence of AD pathology. Nevertheless, a previous study suggested that SVD was indirectly associated with cognition via HV (Yatawara et al., 2020). Future research is needed to clarify the relationship between HV and SVD.

We acknowledged some limitations. First, in the ADNI-2 data we used, there was a relatively low SVD burden and the sample was not balanced, which may cause selection bias. In addition, we did not consider vascular risk factors such as hypertension, which could affect SVD burdens. Second, ADNI is a highly selective database that may not generalize well to the broader population. Further studies are needed for diversity in cohorts to generalize these findings.

In conclusion, the presence of global SVD and SVD*AD do not affect the independent association between Aβ and HV in MCI subjects, and HV mediates the effect of AD pathology on cognitive impairment. Our study suggested that the effect of HV on AD is greater than that on SVD. This could provide potentially valuable insights into the studies of the mechanisms of different dementia types.

ACKNOWLEDGMENTS

Thanks to all the coworkers who made a contribution to this research and to all the subjects who made this research possible. Mengying Yu wrote the manuscript. Mengying Yu and Xuemiao Zhao interpreted the data and prepared the tables and figures. Zili Zhu and Yunjun Yang revised the manuscript for intellectual content. Mengying Yu, Qun Huang, and Nengzhi Xia acquired the data. Caiyun Wen, Meihao Wang, Zili Zhu, and Yunjun Yang contributed to the conception and design of the study. Lufei Feng made a contribution to the manuscript revision. All co-authors read and revised the article.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available in Alzheimer's Disease Neuroimaging Initiative (ADNI) database at https://adni.loni.usc.edu/data-samples/access-data/. These data were derived from the following resources available in the public domain: Alzheimer's Disease Neuroimaging Initiative (ADNI) database, https://adni.loni.usc.edu/.

COONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Yu, M., Feng, L., Zhao, X., Huang, Q., Xia, N., Xia, H., Wen, C., Wang, M., Zhu, Z., Yang, Y., & For the Alzheimer's Disease Neuroimaging Initiative (2023). The interaction of global small vessel disease burden and Alzheimer's disease pathologies do not change the independent association of amyloid-beta with hippocampal volume: A longitudinal study on mild cognitive impairment subjects. *Hippocampus*, *33*(11), 1197–1207. https://doi.org/10.1002/hipo.23573