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The Interaction Between Vascular Risk Factors, Cerebral Small Vessel Disease, and Amyloid Burden in Older Adults

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Abstract.
Background: Cerebral small vessel disease (SVD) and Alzheimer's disease pathology, namely amyloid-β (Aβ) deposition, commonly co-occur. Exactly how they interact remains uncertain.
Objective: Using participants from the Alzheimer's Disease Neuroimaging Initiative ($n = 216$; mean age 73.29 ± 7.08 years, 91 (42.1%) females), we examined whether the presence of vascular risk factors and/or baseline cerebral SVD was related to a greater burden of Aβ cross-sectionally, and at 24 months follow-up.
Method: Amyloid burden, assessed using ^{18}F-florbetapir PET, was quantified as the global standardized uptake value ratio (SUVR). Multimodal imaging was used to strengthen the quantification of baseline SVD as a composite variable, which included white matter hyperintensity volume using MRI, and peak width of skeletonized mean diffusivity using diffusion tensor imaging. Structural equation modeling was used to analyze the associations between demographic factors, *Apolipoprotein E ε4* carrier status, vascular risk factors, SVD burden and cerebral amyloid.
Results: SVD burden had a direct association with Aβ burden cross-sectionally (coeff. = 0.229, $p = 0.004$), and an indirect effect over time (indirect coeff. = 0.235, $p = 0.004$). Of the vascular risk factors, a history of hypertension (coeff. = 0.094, $p = 0.032$) and a lower fasting glucose at baseline (coeff. = –0.027, $p = 0.014$) had a direct effect on Aβ burden at 24 months, but only the direct effect of glucose persisted after regularization.
Conclusion: While Aβ and SVD burden have an association cross-sectionally, SVD does not appear to directly influence the accumulation of Aβ longitudinally. Glucose regulation may be an important modifiable risk factor for Aβ accrual over time.

Keywords: Amyloid, cerebral small vessel disease, hypertension, peak width of skeletonized mean diffusivity, positron emission tomography, white matter hyperintensities

[1]Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (http://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).

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INTRODUCTION

The overlap between vascular risk factors, cerebral small vessel disease (SVD), and Alzheimer's disease (AD) pathology, namely cerebral amyloid-β (Aβ), is a vexed issue. Despite epidemiological evidence to suggest that vascular risk factors such as hypertension, dyslipidemia, obesity, and type 2 diabetes mellitus are modifiable risk factors for the development of AD [1–3], the literature on the association between these risk factors and SVD with Aβ burden is inconsistent.

A number of cohort studies across the AD spectrum have utilized composite scores of vascular burden to assess the relationship with Aβ, with mixed results. While there is some evidence to support an association between longitudinal Aβ accumulation and midlife vascular risk factor burden [4], as well as the metabolic syndrome [5], other studies have demonstrated no significant association [6–8]. Some of this discrepancy is explained by variations in the study populations, as well as methodological differences in quantifying vascular burden. Importantly, individual vascular risk factors may each have differential effects on Aβ burden [9–12]. There is a need to more precisely understand which vascular risk factors, if any, are potentially modifiable contributors to Aβ load. Whether the impact of these vascular risk factors is mediated by its effect on SVD pathology, or from a direct effect on Aβ, also requires clarification.

Moreover, while cerebral SVD and Aβ commonly co-occur in the brains of older people, whether the presence of SVD has a direct effect on the progression of Aβ accumulation is unclear. White matter hyperintensity (WMH) volume, obtained from structural magnetic resonance imaging (MRI), is a commonly used quantifiable marker of SVD. A systematic review [13] of the association between Aβ and WMH demonstrated that most studies found no relationship between WMH and Aβ, whether examined in a state of disease or in cognitively healthy controls. However, it is recognized that the assessment of SVD in the ageing brain using WMH volume alone has limitations [14, 15].

Diffusion tensor imaging (DTI) offers an alternative method by which SVD can be quantified, typically as measured by an increase in mean diffusivity (MD), or a reduction in the directionality and coherence of white matter fibers within a bundle, as measured by a decrease in fractional anisotropy (FA) [16]. Peak width of skeletonized mean diffusivity (PSMD) is an alternative, fully automated imaging marker of SVD based on DTI. It is the calculated difference between the 5th and 95th percentile of the skeletonized MD values (to eliminate cerebrospinal fluid contamination). PSMD has been validated in sporadic and genetically determined SVD, as well as people with AD and healthy controls, and is potentially a more robust marker of SVD than WMH load [17]. PSMD is significantly negatively correlated with processing speed and memory [18]. It has been shown to outperform other conventional markers of SVD in predicting cognition, including WMH volume, enlarged perivascular spaces, lacunes, microbleeds, and average MD [19].

To date, most studies have examined the relationship between SVD and Aβ pathologies based on diagnostic classification, such as in healthy controls, mild cognitive impairment (MCI) or AD. However, neither pathology is consistently synonymous with the degree of clinical impairment; for example, approximately 30% of healthy older adults without cognitive decline have high levels of Aβ binding on PET imaging [20], and Aβ begins to accumulate decades prior to the onset of cognitive symptoms [21]. There is arguably significant variability and possibility of error in clinical diagnoses, and 14% of individuals diagnosed with mild or moderate AD have sparse or no Aβ plaques at postmortem [22]. While Aβ is typically considered an early pathological feature of AD, it is important to acknowledge that it alone does not represent the AD clinical syndrome. Thus, using a sample from the Alzheimer's Disease Neuroimaging Initiative, we examined the relationship between cerebral SVD and Aβ pathology independent of diagnostic category, cross-sectionally and at 24 months' follow-up, using quantifiable biomarkers across multiple imaging modalities: WMH volume on cerebral MRI and PSMD on DTI as markers of SVD, and standardized uptake value ratio quantified on amyloid PET as a measure of Aβ burden. We asked the questions:

(1) Do baseline vascular risk factors and/or SVD burden have a direct effect on Aβ burden, cross-sectionally and over time?
(2) Does the presence of SVD mediate the effect of vascular risk factors on Aβ burden?

MATERIALS AND METHODS

Participants

Participants were drawn from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database

(http://www.adni.loni.usc.edu). The ADNI was launched in 2003 as a public-private collaboration lead by Principal Investigator, Dr Michael W. Weiner. It is a multisite, longitudinal investigation to assess biomarkers throughout the ageing process, from normal ageing, early MCI, late MCI, to dementia. The primary goal of ADNI has been to test whether serial MRI, PET, other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of MCI and early AD. Participants with baseline DTI, MRI, and amyloid PET scans (that is, from the ADNI2 and ADNIGO cohorts) by July 2017 were included ($n = 216$). Those with follow-up MRI and amyloid PET scans at 24 months were also included as part of the longitudinal analysis. All ADNI participants provided written informed consent approved by each sites' Institutional Review Board.

Clinical and biomarker assessment

Clinical and biomarker assessments are standardized across sites, and available in the ADNI2 and ADNIGO procedures manuals (http://adni.loni.usc.edu/methods/documents/). In addition to demographic features, this included data on relevant cardiovascular risk factors including a history of hypertension, cardiovascular disease, atrial fibrillation, smoking and stroke, body mass index (BMI), as well as fasting cholesterol and fasting blood glucose levels at baseline.

Imaging acquisition

Amyloid PET scans were acquired on multiple scanners but all with an F^{18}-AV-45 (Florbetapir) radiotracer (8.0–10 mCi). Scanning commenced at 50 min post-injection and was 20-min duration (four × 5 min frames). To standardize data acquisition across protocols, all scans underwent clearly outlined pre-processing procedures. MRI and DTI scans were also acquired across multiple sites on multiple 3T MRI scanners, according to standardized protocols. All imaging protocols and pre-processing procedures are publicly available on the ADNI website (http://adni.loni.usc.edu/methods/).

Amyloid PET data processing

Data for amyloid PET were processed by ADNI core laboratories in accordance with detailed "Florbetapir processing methods" (available via the https://ida.loni.usc.edu portal). Cortical amyloid burden was quantified as the standardized uptake value ratio (SUVR) using a composite reference region comprised of the whole cerebellum, brainstem/pons and eroded subcortical white matter, as per the ADNI recommendations for longitudinal florbetapir analyses [23]. For this study we used the data file current at the time of analysis, "UCBERKELEYAV45_10_17_16".

DTI data processing and PSMD calculation

DTI data processing was completed at the Centre for Healthy Brain Ageing, UNSW Sydney. Diffusion weighted images (DWI) were pre-processed using the FMRIB's Diffusion Toolbox of the FMRIB Software Library (FSL) [24]. Raw DTI data were visually inspected to exclude any severe artefacts. A binary brain mask was created to remove the non-brain tissue and Eddy-current correction was applied. Diffusion tensor was reconstructed using the DTIfit program included in FSL. For skeletonization from FA images, we followed the ENIGMA-TBSS protocols (http://enigma.ini.usc.edu/wp-content/uploads/2014/01/ENIGMA_TBSS_protocol_USC.pdf). Using the FA-derived projection parameters, MD images were projected onto the skeleton. The final MD skeletons were further masked with the template skeleton threshold at an FA value of 0.3 to avoid contamination of the skeleton through cerebrospinal fluid partial volume effects. Regions of the skeleton directly adjacent to the ventricles, such as the fornix, were removed from further analysis by a custom-made mask [17].

Statistical analysis

Data cleaning and descriptive analyses were completed using SPSS version 25 [25], and the remaining analyses were conducted using R, version 4.0.2 [26]. Variables were explored to examine if they were normally distributed. WMH volumes were right skewed, and therefore logarithmically transformed (by base 10). PSMD was multiplied by 1000 because values were extremely small. All continuous variables were standardized to place them on a common metric. Descriptive statistics for the study sample characteristics at baseline were presented using means and standard deviations for continuous variables, and frequencies and percentages for categorical variables.

Structural equation modeling (SEM) was conducted using the lavaan package [27] to investigate the hypothesized relationships between sociodemo-

graphic variables and vascular risk factors with SVD pathology and Aβ load on imaging, at baseline and at 24 months follow-up. Results of analyses with p-values < 0.05 were regarded as statistically significant. The variables used in SEM can either be observed (also known as indicators), or latent (unobserved variables or factors formed from multiple observed indicators). Latent variables tap the underlying construct (e.g., SVD pathology) of observed indicators with measurement error modelled and removed and hence may produce less biased parameter estimates [28]. Moreover, SEM uses Full Information Maximum Likelihood (FIML) to handle missing data which has been shown to be more efficient than other methods such as listwise deletion [29].

The hypothesized model is displayed in Fig. 1. In Fig. 1, circles represent latent variables, and rectangles represent observed variables/indicators, and the presence of arrows connecting variables implies a hypothesized relationship between them. The sociodemographic and vascular risk factors examined included age, sex, education, *APOE* ε4 carrier, having a history of hypertension, cardiovascular disease, atrial fibrillation, or smoking, as well as BMI, fasting total cholesterol, and fasting blood glucose. Only two participants had a history of stroke and therefore stroke was excluded from the model. The primary outcomes were 1) global SUVR at baseline, 2) global SUVR at 24 months follow-up, and 3) SVD at baseline, a latent variable, indicated by PSMD and WMH volume. Although WMHs are a widely accepted neuroimaging marker of SVD, not all WMHs are solely vascular in origin [30]. Moreover, normal appearing white matter on T2-FLAIR images has been associated with abnormalities on other modalities such as DTI [31]. Thus, in addition to the statistical benefits as described above, PSMD and WMH volume were modelled as a latent variable to provide a more robust marker of SVD. Because FIML was used to handle missing data, all participants with available baseline data (including covariates) were retained in the analysis. PSMD measures at 24 months were not available. The mean and variance of the SVD factor were constrained to 0 and 1, respectively, to ensure model identification [32]. Because all continuous variables were standardized, the model coefficients could be interpreted as standardized regression coefficients (for example, a standard deviation change in SVD for every standard deviation change in age). Indirect effects could be interpreted as change in the outcome in standard deviation for every standard deviation change in a continuous predictor via the mediator(s). For categorical variables, the model coefficients could be interpreted as differences in standardized unit across groups.

The direction of effect (that is, from SVD to SUVR1) was chosen *a priori* based on clinical, pathological, and animal model studies that demonstrate that early vascular dysfunction predates and contributes to the pathogenesis of AD biomarker accumulation, including Aβ [33]. AD is a complex neurodegenerative disorder with multiple biological components; although understanding the temporal sequencing of pathological events remains a challenge, large data-driven analysis of the ADNI cohort has shown that vascular dysregulation may be the earliest and most robust process associated with the AD cascade, followed next by Aβ accumulation [34]. A non-recursive model with reciprocal paths between SVD and SUVR1 was explored and tested but did not converge due to model non-identification.

Given the potential for model overfitting with the number of factors for our sample size, regularized SEM was conducted using the regsem package [35] as a sensitivity analysis to assess the robustness of the original FIML model. Regularized SEM penalizes specific model parameters such that fewer parameters are retained in the model, hence reducing model complexity [36]. The lasso (least-absolute-shrinkage-and-selection operator) method was used in the current analysis, and because lasso parameter estimates tend to be biased toward zero [37], the model was refitted without any penalty using the chosen parameters based on the best regularized SEM solution [38].

Data availability

ADNI data are shared through the LONI Image and Data archive, contingent on adherence to the Data Use Agreement and publication policies (http://adni.loni.usc.edu/data-samples/access-data/) and were downloaded from https://ida.loni.usc.edu.

RESULTS

Sample characteristics

A total of 216 participants met criteria for having florbetapir PET, DTI, and MRI scans at baseline (mean age 73.29 ± 7.08, 91 (42.1%) females). Participants' baseline demographic and clinical char-

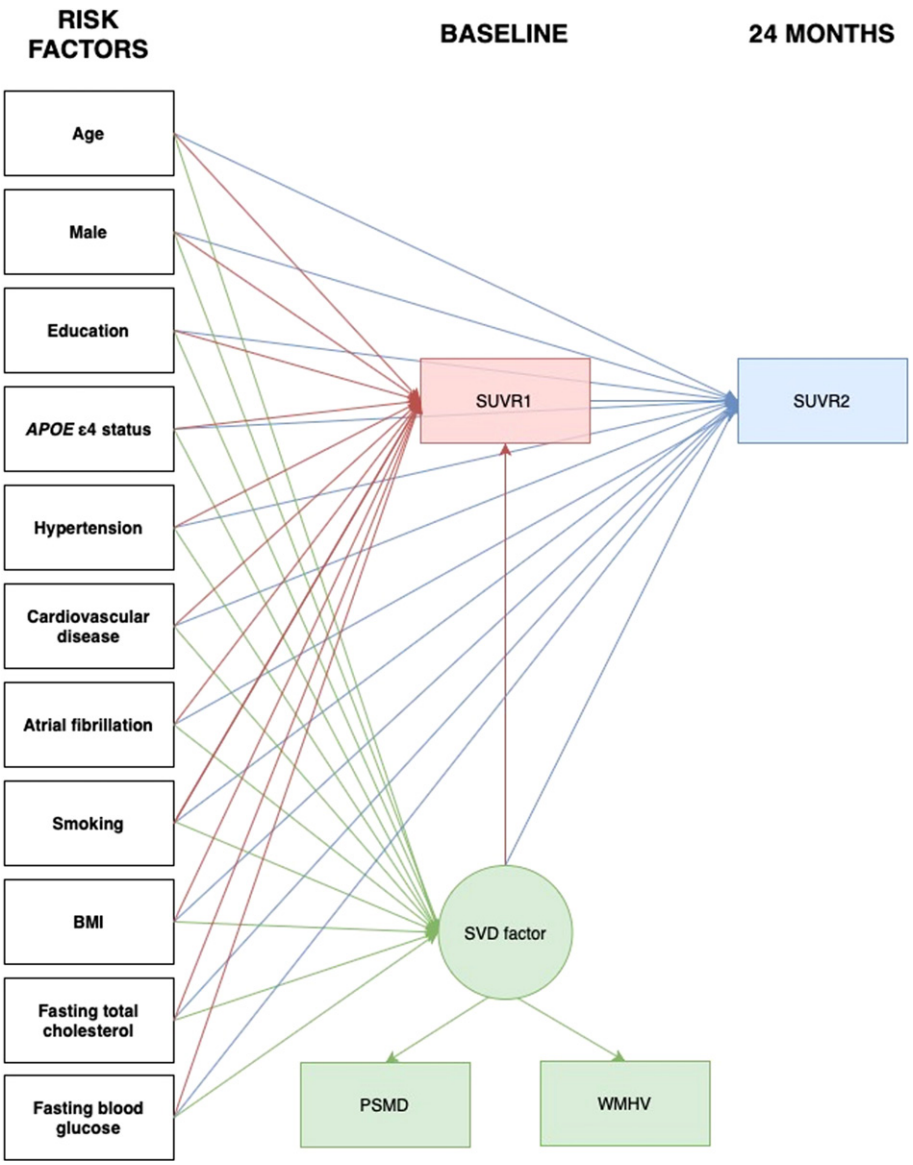

Fig. 1. Hypothesized model for testing. Age, sex, education, *APOE* ε4 carrier status, as well as vascular risk factors (history of hypertension, cardiovascular disease, atrial fibrillation, smoking, body mass index as well as fasting total cholesterol and fasting glucose levels) were always included. The primary outcomes were 1) cortical SUVR at baseline (SUVR1), 2) cortical SUVR at 24 months follow-up (SUVR2), and 3) SVD at baseline, comprised of PSMD and WMH volume. *APOE* ε4, *Apolipoprotein E* ε4; BMI, body mass index; PSMD, peak width of skeletonized mean diffusivity; SUVR, standardized uptake value ratio; SVD, small vessel disease; WMHV, white matter hyperintensity volume.

acteristics are outlined in Table 1. Table 2 summarizes the longitudinal imaging characteristics of the sample, at baseline and 24 months' follow-up.

Statistically significant direct effects of the mediation model are summarized in Fig. 2. The statistically significant indirect and direct effects for predictors of SVD and Aβ burden are summarized below. Details of all effects on SVD and Aβ, at baseline and 24 months follow-up, can be found in Supplementary Tables 1 and 2, respectively.

Associations with baseline amyloid burden and SVD

Based on the model fit indices, the model had an adequate fit with the data ($\chi^2(df = 12) = 17.154$, $p =$

0.144; CFI = 0.994; TLI = 0.950; RMSEA = 0.045, 90% CI [0.000, 0.089]; SRMR = 0.019). The factor loadings from the latent SVD factor to both baseline PSMD ($\lambda = 0.517$, standard error (SE) = 0.067, $p < 0.001$) and WMH volume ($\lambda = 0.593$, SE = 0.075, $p < 0.001$) were statistically significant.

Table 1
Participant characteristics at baseline ($n = 216$)

	Baseline n (%) or mean ± SD
Demographics	
Mean age (y)	73.29 ± 7.08
Female	91 (42.1)
Education (y)	15.97 ± 2.75
Married	169 (78.2)
MMSE score (out of 30)	27.20 ± 2.63
Diagnosis	
Alzheimer's disease	47 (21.8)
MCI (including SMC/EMCI/LMCI)	30 / 61 / 32 (56.9)
Healthy controls	46 (21.3)
History of vascular risk factors	
Hypertension	116 (53.7)
Stroke/TIA	2 (0.9)
Cardiovascular disease	146 (67.6)
Atrial fibrillation	7 (3.2)
Smoking	91 (42.1)
Current vascular risk factors	
BMI (kg/m^2)[a]	27.59 ± 5.15
Fasting blood glucose (mg/dL)[b]	102.25 ± 27.36
Fasting total cholesterol (mg/dL)[b]	189.33 ± 35.40
APOE genotype[c]	
APOE ε4/ε4	18 (8.4)
APOE ε2/ε4 or ε3/ε4	91 (42.3)
APOE ε2/ε2 or ε2/ε3 or ε3/ε3	106 (49.3)

SD, standard deviation; MMSE, Mini-Mental State Examination; BMI, body mass index, SMC, significant memory concern; EMCI, early mild cognitive impairment; LMCI, late mild cognitive impairment; TIA, transient ischemic attack; *APOE*, *Apolipoprotein E*. '[a]' indicates 3 missing values, $n = 213$; '[b]' indicates 29 missing values, $n = 187$; '[c]' indicates one missing value, $n = 215$.

Firstly, SVD burden was significantly associated with a higher baseline Aβ burden (coefficient = 0.229, SE = 0.079, $p = 0.004$) (Fig. 2).

Age (coeff. = 0.737, SE = 0.124, $p < 0.001$), *APOE* ε4 status (coeff. = 0.455, SE = 0.166, $p = 0.006$), a history of CVD (coeff. = 0.698, SE = 0.266, $p = 0.009$), and fasting total cholesterol level (coeff. = –0.232, SE = 0.107, $p = 0.031$) were significantly associated with SVD (Fig. 2). Baseline SVD significantly mediated the associations of age (coeff. = 0.168, SE = 0.070, $p = 0.015$), and CVD (coeff. = 0.160, SE = 0.080, $p = 0.045$) with baseline Aβ burden (Supplementary Table 1).

Further, sex (coded female = 0, male = 1) (coeff. = –0.295, SE = 0.135, $p = 0.029$) and *APOE* ε4 status (coeff. = 0.632, SE = 0.116, $p < 0.001$) showed significant direct associations with baseline Aβ burden (Fig. 2).

The remaining risk factors (i.e., education, history of hypertension, atrial fibrillation, smoking, BMI, as well as fasting total cholesterol and glucose levels) were unrelated to baseline amyloid burden, either directly, or via SVD (see Supplementary Table 1 for detailed results).

Effects on 24-month amyloid burden

Aβ burden at 24 months was predicted by higher baseline Aβ levels (coeff. = 1.028, SE = 0.021, $p < 0.001$) (Fig. 2). While baseline SVD burden did not significantly predict 24-month Aβ levels after controlling for baseline Aβ levels, its indirect effect via baseline Aβ levels were significant (coeff. = 0.235, SE = 0.081, $p = 0.004$).

Table 2
Longitudinal imaging characteristics

	Baseline mean ± SD	24 months mean ± SD	Statistical comparison
MRI, *n*	*216*	*118*	
WMH volume (cm^3)	9.06 ± 11.18	10.49 ± 13.37	Z = –3.49, $p < 0.001$
Log_{10} WMH volume	0.74 ± 0.44	0.79 ± 0.45	0.03 (0.00, 0.05) t(117) = 2.01, $p = 0.047$
DTI, *n*	216	–	
PSMD (mm^2/s)	$3.37 \times 10^{-4} \pm (7.82 \times 10^{-5})$	–	NA
Amyloid PET, *n*	*216*	*137*	
Global $SUVR_{cerebel.}$	1.23 ± 0.24	1.21 ± 0.23	0.01 (–0.00, 0.03), t(136) = 1.90, $p = 0.06$
Global $SUVR_{comp.}$	0.89 ± 0.16	0.88 ± 0.15	0.01 (0.01, 0.02), t(136) = 5.29, $p < 0.001$

WMH volumes were non-normally distributed and so a Wilcoxon Signed Rank Test was used to statistically compare baseline and follow-up WMH volume. The other statistical comparisons were completed using paired samples *t*-tests, and results include the mean difference (95% CI), test result (*df*), and *p*-value. MRI, magnetic resonance imaging; WMH, white matter hyperintensity; DTI, diffusion tensor imaging; PSMD, peak width of skeletonized mean diffusivity; PET, positron emission tomography; SUVR, standardized uptake value ratio; cerebel., referenced to the cerebellum; comp., referenced to a composite reference region.

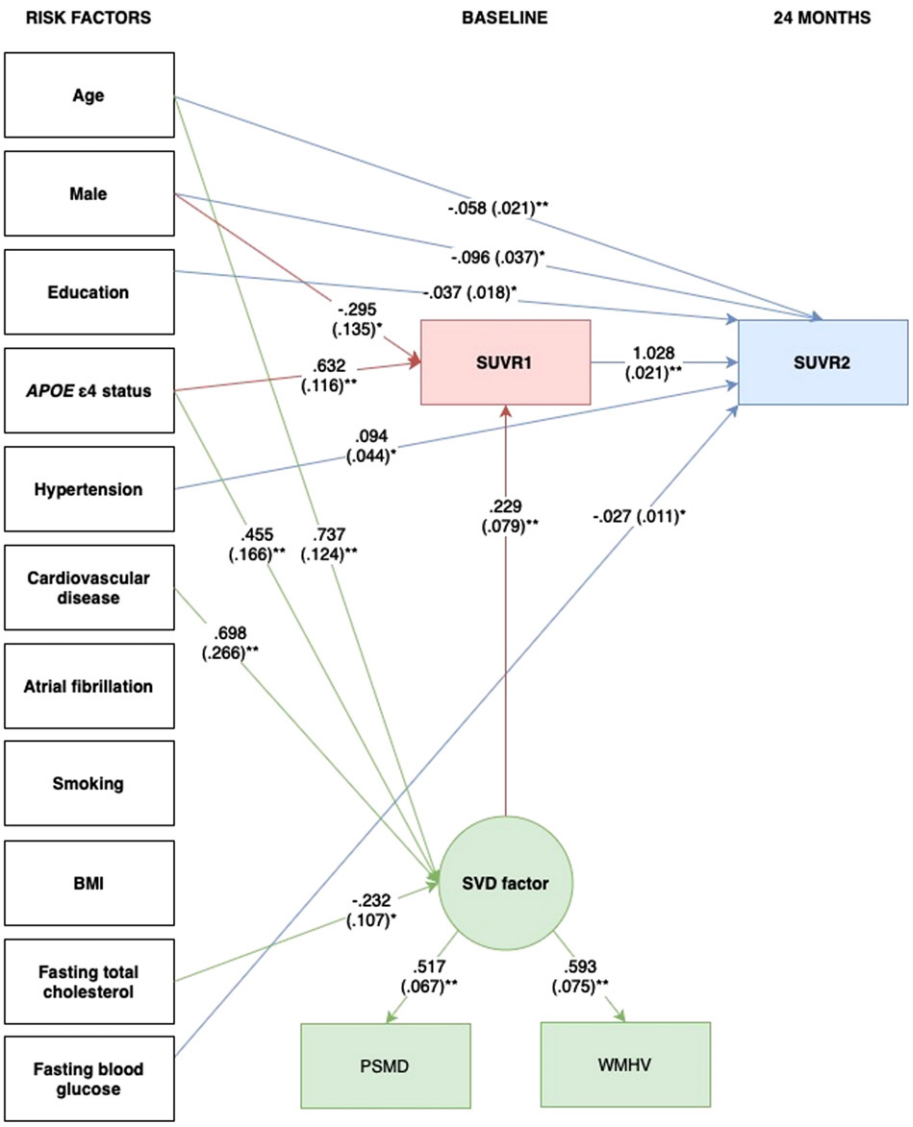

Fig. 2. Significant direct associations between demographic and vascular risk factors, small vessel disease and amyloid burden, at baseline and 24 months follow-up. The numbers indicate the estimate of effect size (standard error). * denotes $p < 0.05$; ** denotes $p < 0.01$. Sex was coded female = 0, male = 1. *APOE ε4*, *Apolipoprotein E ε4*; BMI, body mass index; PSMD, peak width of skeletonized mean diffusivity; SUVR1, standardized uptake value ratio at baseline; SUVR2, standardized uptake value ratio at 24 months; SVD, small vessel disease; WMHV, white matter hyperintensity volume.

The direct effect of sex (coeff. = –0.096, SE = 0.037, $p = 0.010$) and education (coeff. = –0.037, SE = 0.018, $p = 0.041$) were significant, indicating that being female and having fewer years education predicted greater 24-month Aβ burden (Fig. 2).

Age had a significant indirect effect on 24-month Aβ burden (coeff. = 0.197, SE = 0.073, $p = 0.007$), and this was predominantly driven via its effect on baseline SVD and Aβ (coeff. = 0.173, SE = 0.071, $p = 0.015$). However, a small negative direct effect of age was also observed (coeff. = –0.058, SE = 0.021, $p = 0.006$).

A previous diagnosis of hypertension had a direct effect on higher Aβ levels at 24 months (coeff. = 0.094, SE = 0.044, $p = 0.032$). Similarly, baseline fasting glucose level (coeff. = –0.027, SE = 0.011, $p = 0.014$) directly predicted Aβ levels at 24 months (Fig. 2). The negative direction of effect indicates that a lower fasting blood glucose at baseline predicted higher Aβ levels at 24 months. A history of

CVD (coeff. = 0.164, SE = 0.082, $p = 0.045$) had a significant indirect effect via baseline SVD and Aβ. Finally, *APOE* ε4 status (coeff. = 0.141, SE = 0.062, $p = 0.023$) had a total indirect effect on longitudinal Aβ burden.

The remaining factors (a history of atrial fibrillation, smoking, BMI, and fasting total cholesterol level) were unrelated to 24-month Aβ burden, by total, direct nor indirect effects (see Supplementary Table 2 for details).

Sensitivity analysis

The regularized SEM model was tested with 33 penalty values on the structural parameters involving demographic and cardiovascular risk factors. The optimal solution with the smallest BIC had a penalty value of 0.1, with fourteen parameters regularized to zero. This solution was used to refit a model without any penalty which showed an adequate fit with the data ($\chi^2(df = 24) = 33.852$, $p = 0.087$; CFI = 0.989; TLI = 0.953; RMSEA = 0.044, 90% CI [0.000, 0.076]; SRMR = 0.029).

The significant findings on baseline amyloid burden and SVD were replicated, with the exception of *APOE* ε4 status and cholesterol no longer having a significant association with SVD. The detailed results of effects on baseline amyloid burden and SVD based on regularized SEM are summarized in Supplementary Table 3.

The significant findings on 24-month amyloid burden were also replicated, except for education and hypertension, which no longer had a significant direct effect on 24-month Aβ burden. The detailed results of effects on the 24-month amyloid burden based on regularized SEM are available in Supplementary Table 4.

DISCUSSION

This study, using structural equation modeling, examined the complex relationship between Aβ and vascular pathologies, in conjunction with demographic and vascular risk factors. To our knowledge, this is the first study to assess the relationship between cerebral Aβ and SVD whereby SVD was treated as a latent variable indicated by PSMD and WMH volume. Moreover, the relationship was examined regardless of diagnosis and across imaging modalities, to mitigate the uncertainty associated with clinical phenotypes.

Our findings indicate that SVD is directly associated with concurrent cerebral Aβ burden but does not appear to have a direct effect on Aβ over time. There is some evidence to support this finding in the existing literature, which to date has most commonly used WMH volume as a proxy for SVD. While some studies have described an association between WMH load and SUVR [39–42], many report no significant relationship between Aβ and WMH burden across diagnostic groups, and over time (see Roseborough et al. [13] for a systematic review). To our knowledge, there is no comparable literature assessing the relationship between PSMD and Aβ. However, our results are in keeping with previous studies utilizing related DTI measures which indicated altered white matter tract structural integrity in Aβ positive individuals, such as changes to mean diffusivity [43, 44] and fractional anisotropy [45]. Taken together, our findings suggest that while SVD and Aβ commonly co-occur, the presence of one pathology does not necessarily directly propagate the progression of the other pathology over time.

Our study demonstrated direct effects of select cardiovascular risk factors on Aβ burden longitudinally—namely, a history of hypertension and baseline fasting blood glucose level. However, it should be noted that the direct effect of hypertension was relatively small and was not replicated using the regularized SEM approach, and so this result should be interpreted with caution. The existing evidence on the interaction between blood pressure and Aβ to date is varied. Some studies have demonstrated an association between Aβ accumulation on PET imaging and hypertension both as previously diagnosed hypertension [9, 46], and as measured at the time of assessment [5, 12, 47]. This also echoes previous neuropathological findings [48]. However, conflictual literature also exists which has not supported this association [4, 6, 10]. A particular issue in understanding the relationship between hypertension and Aβ is the variable definitions of abnormal blood pressure utilized across studies; this includes a previous diagnosis of hypertension, systolic or diastolic readings outside of the normal reference range, or the use of antihypertensive treatment. Regardless, chronic arterial hypertension has been shown to drive parenchymal Aβ accumulation in animal models [49] and may impair efficient clearance of Aβ plaques [50], which provides a possible pathophysiological mechanism for a direct effect of hypertension in the accumulation of Aβ. Further investigation is required to clarify the role of hypertension in the pathophysiology of AD,

including whether adequate treatment or prevention of hypertension may confer some benefit in the delay or reduced development of Aβ aggregates.

The findings regarding fasting blood glucose level and Aβ burden are challenging to explain, that is, a lower fasting blood glucose at baseline was predictive of greater Aβ at 24 months. While this was contrary to our expectation, the published literature on this topic is conflictual. The Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability ('FINGER') study supported a negative association, in which PiB-PET positive participants had better glucose homeostasis [10]. Similarly, type 2 diabetes was associated with lower cerebral cortical Aβ in certain brain regions in another ADNI cohort [51]. However, a number of studies have found no significant association between Aβ and other markers of glucose control, including HbA1c [52], impaired fasting glucose (that is, fasting glucose level > 100 mg/dL) [12], or a clinical diagnosis of type 2 diabetes [6, 53]. Thus, while there is more robust epidemiological evidence of an association between diabetes and AD [3], at a biomarker level there remains significant inconsistency in the literature which requires further clarification.

We also note a small but significant negative direct effect of age on Aβ at 24 months, suggesting that younger age was associated with greater longitudinal Aβ levels. The most likely explanation for this is the fact that Aβ accumulation over time observes sigmoidal kinetics and slows in established AD [21]. Moreover, Aβ accumulation appears to plateau with age in those without concurrent neurodegeneration [54]. The differential rates of amyloid accumulation in relation to age may therefore be explained by the inclusion of participants across the AD spectrum in our cohort, with younger participants being more likely to be to the left on the sigmoidal curve and therefore likely to show more change. This result is not inconsistent with the overall (total) effect of age in predicting Aβ burden being positive—that is, being older predicted a higher Aβ at 24 months—in keeping with existing literature on the natural history of Aβ accumulation with age [20, 55].

Several limitations of the study should be recognized, including aspects of the statistical methodology. Firstly, the inclusion of multiple predictive factors may risk model overfitting. We attempted to verify the robustness of the model using regularized SEM, and it is reassuring that this sensitivity analysis afforded comparable results at both baseline and follow-up. Secondly, our sample size was limited to $n = 216$, and approximately half of that at 24 months follow-up. We used FIML, a statistical methodology widely available and accepted to handle missing data which is preferable to other traditional methods [29] and comparable with advanced methods such as multiple imputation when the model is correctly specified [56]. Nevertheless, some caution should be taken in interpreting these results, and future studies would ideally include a larger sample to cross-validate the proposed model and further investigate predictors of neuropathology in the aging brain.

Next, further limitations in our study reflect the challenges in quantifying SVD. Firstly, SVD was unable to be quantified at 24 months as PSMD data was not available, and we were therefore unable to test the inverse direction of effect over time, i.e., whether the presence of amyloid promotes SVD. However, our method was chosen *a priori* based on the vascular hypothesis of AD which purports that vascular dysfunction precedes and promotes Aβ accumulation [33], and so this was able to be tested even in the absence of follow-up SVD data. Furthermore, while WMH are commonly used as a proxy for SVD burden, not all WMH are vascular in origin; WMH are heterogenous and it is not clear what proportion of WMH seen are of vascular etiology or due to axonal injury, inflammation, or neurodegeneration [30]. We attempted to address this by using PSMD as an alternative marker of SVD. There are other markers of SVD such as lacunar infarcts, cerebral microbleeds and perivascular spaces which were not included in this study, some of which are associated with cerebral amyloid [57]. The acquisition of scans across multiple sites could also render the imaging data susceptible to slight variations. However, ADNI is a well-established trial with detailed protocols and subsequent quality review checks to assist with the standardization of procedures across sites (http://adni.loni.usc.edu/methods/documents/). Moreover, it is important to acknowledge that the ADNI cohort is selected to be free of extensive cerebrovascular disease; participants were included if their Hachinski ischemic scale score was < 4, and were excluded if the screening MRI demonstrated multiple lacunar infarcts or a single large infarct (http://adni.loni.usc.edu/wp-content/uploads/2008/07/adni2-procedures-manual.pdf). As such, one must be cautious in interpreting the results in relation to cerebral SVD due to the relatively low burden in this cohort. Future studies could consider examination in cohorts with a higher cerebrovascular using a more comprehensive composite marker of SVD.

Furthermore, given the need to constrain the number of predictors in the statistical model, we did not examine medication usage as a potential confound, which would be pertinent to consider in future work. The study also did not investigate Aβ and SVD biomarkers in relation to cognitive function, which limits its application in understanding the clinical implications of our findings. However, ADNI does incorporate participants across a spectrum of cognitive capabilities, from healthy controls to AD. Our study attempted to remove the uncertainty often associated with clinical diagnostic categories, to examine imaging biomarkers as quantifiable endophenotypes.

Conclusion

There is growing evidence that both SVD and Aβ accumulation are important in the development of AD; our findings suggest that at a pathological level, they have both direct and indirect associations. Glucose regulation may be an important modifiable risk factor for Aβ accrual. Longitudinal studies incorporating cognitive performance, as well as additional biomarkers, are needed to further clarify whether vascular burden contributes to the development of AD-related pathology and determine its relevance to clinical outcomes.

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SUPPLEMENTARY MATERIAL

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