HHS Public Access

Author manuscript

Neurobiol Aging. Author manuscript; available in PMC 2024 September 10.

Published in final edited form as:

Neurobiol Aging. 2024 April ; 136: 1–8. doi:10.1016/j.neurobiolaging.2024.01.002.

Perivascular space burden interacts with *APOE*-ε4 status on cognition in older adults

Marissa A. Gogniat[a,b], **Omair A. Khan**[a,c], **Corey W. Bown**[a], **Dandan Liu**[a,c], **Kimberly R. Pechman**[a,b], **L. Taylor Davis**[a,b,d], **Katherine A. Gifford**[a,b], **Bennett A. Landman**[a,d,e], **Timothy J. Hohman**[a,b,f], **Angela L. Jefferson**[a,b,g,*]

[a]Vanderbilt Memory and Alzheimer's Center, Vanderbilt University Medical Center, Nashville, TN, USA

[b]Department of Neurology, Vanderbilt University Medical Center, Nashville, TN, USA

[c]Department of Biostatistics, Vanderbilt University Medical Center, Nashville, TN, USA

[d]Department of Radiology and Radiological Sciences, Vanderbilt University Medical Center, Nashville, TN, USA

[e]Department of Electrical and Computer Engineering, Vanderbilt University, Nashville, TN, USA

[f]Vanderbilt Genetics Institute, Vanderbilt University Medical Center, Nashville, TN, USA

[g]Division of Cardiovascular Medicine, Department of Medicine, Vanderbilt University Medical Center, Nashville, TN, USA

Abstract

Enlarged perivascular spaces (ePVS) may adversely affect cognition. Little is known about how basal ganglia ePVS interact with apolipoprotein (*APOE*)-ε4 status. Vanderbilt Memory and Aging Project participants (n = 326 73 ± 7, 59% male) underwent 3 T brain MRI at baseline to assess ePVS and longitudinal neuropsychological assessments. The interaction between ePVS volume and *APOE*-ε4 carrier status was related to baseline outcomes using ordinary least squares regressions and longitudinal cognition using linear mixed-effects regressions. ePVS volume interacted with *APOE*-ε4 status on cross-sectional naming performance (β = −0.002, p = 0.002), and executive function excluding outliers (β = 0.001, p = 0.009). There were no significant

*Correspondence to: Vanderbilt Memory and Alzheimer's Center, 1207 17th Avenue South, Suite 204, Nashville, TN 37212, USA., angela.jefferson@vumc.org (A.L. Jefferson).

CRediT authorship contribution statement

Dandan Liu: Data curation, Formal analysis, Visualization. **Corey W. Bown:** Data curation, Methodology, Software, Validation, Writing – review & editing. **L. Taylor Davis:** Data curation, Methodology, Validation. **Kimberly R. Pechman:** Data curation, Project administration. **Marissa A. Gogniat:** Conceptualization, Methodology, Writing – original draft, Writing – review & editing. **Omair A. Khan:** Data curation, Formal analysis, Visualization. **Bennett A. Landman:** Methodology, Resources, Software. **Katherine A. Gifford:** Data curation, Project administration, Writing – review & editing. **Angela L. Jefferson:** Conceptualization, Funding acquisition, Methodology, Project administration, Supervision, Writing – review & editing. **Timothy J. Hohman:** Conceptualization, Data curation, Project administration, Writing – review & editing.

Declaration of Competing Interest

TJH serves on the Scientific Advisory Board for Vivid Genomics.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.neurobiolaging.2024.01.002.

longitudinal interactions (p-values>0.10) except for Coding excluding outliers (β = 0.002, p = 0.05). While cross-sectional models stratified by *APOE*-ε4 status indicated greater ePVS related to worse cognition mostly in *APOE*-ε4 carriers, longitudinal models stratified by *APOE*-ε4 status showed greater ePVS volume related to worse cognition among *APOE*-ε4 non-carriers only. Results indicated that greater ePVS volume interacts with *APOE*-ε4 status on cognition cross-sectionally. Longitudinally, the association of greater ePVS volume and worse cognition appears stronger in *APOE*-ε4 non-carriers, possibly due to the deleterious effects of *APOE*-ε4 on cognition across the lifespan.

Keywords

Aging; Perivascular space; Cognition; *APOE*-ε4

1. Introduction

Perivascular spaces (PVS) are fluid-filled compartments surrounding cerebral blood vessels that transport molecular debris from the brain to the cerebrospinal fluid (CSF) (Bown, Carare et al., 2022a). PVS can become enlarged (ePVS) in the basal ganglia, hypothesized to be due to arterial stiffening and protein aggregation, which greatly compromises functionality of important fluid and metabolic transport (Charidimou et al., 2015; Riba-Llena et al., 2018). In terms of arterial stiffening, it is hypothesized that greater stiffening leads to vessel wall damage and remodeling, resulting in ePVS around arteries (Bown, Carare et al., 2022; Mitchell, 2008). While there is extensive literature examining how small vessel disease (SVD) markers negatively affect cognitive aging, few studies have examined the impact of ePVS, and what literature does exist is mixed (Hilal et al., 2018; Paradise et al., 2021; Passiak et al., 2019). A meta-analysis of five population-based cross-sectional studies found total ePVS count is not associated with global cognition in aging (Hilal et al., 2018). By contrast, our group reported that ePVS counts in the basal ganglia are cross-sectionally associated with both worse information processing speed and executive function, and increased ePVS accounts for more variance in executive function performance compared to SVD markers (Passiak et al., 2019). Other groups have shown that greater ePVS count predicts greater global cognitive decline over a 4-year period, independent of SVD markers, (Paradise et al., 2021) and ePVS volume predicts a steeper longitudinal decline in information processing speed over a mean 5-year period (Ding et al., 2017). In addition, ePVS burden has been shown to be higher in Alzheimer's disease, which has been theorized to be due to the role ePVS plays in clearing abnormal protein accumulation (Bown, Carare et al., 2022; Chen et al., 2011). Therefore, ePVS may be an important SVD marker for cognitive decline and possible risk factor for Alzheimer's disease (AD).

Apolipoprotein E4 (*APOE*-ε4) is a well-known risk factor for AD (Lumsden et al., 2020) and cognitive decline in aging (Liu et al., 2013), with two copies of the allele conferring greater risk (Liu et al., 2013; Verghese et al., 2011). *APOE* regulates lipid homeostasis through cholesterol transport, and the ε4 allele is less efficient at this process, resulting in amyloid-β aggregation (Liu et al., 2013; Wildsmith et al., 2013). *APOE*-ε4 also confers vascular risk in aging, including breakdown of the blood brain barrier, which modifies

associations between SVD and cognition (Zlokovic, 2013). Furthermore, the impact of *APOE*-ε4 carrier status on ePVS over time is not well understood and may provide important information on how genetic risk for late onset AD interacts with SVD. *APOE*-ε4 carrier status is associated with greater ePVS in the basal ganglia (Luo et al., 2017), so the loss of cerebrovascular integrity associated with *APOE*-ε4 carrier status may interact with ePVS to adversely impact cognition.

This study is among the first to investigate the interaction between *APOE*-ε4 carrier status and basal ganglia ePVS on cognition. Using a semi-automated ePVS quantification method (Bown, Khan, et al., 2022), we hypothesize that associations between ePVS and cognition will be stronger among *APOE*-ε4 carriers both cross-sectionally and longitudinally. Based on prior literature (Ding et al., 2017; Paradise et al., 2021; Passiak et al., 2019), we expect executive functioning and information processing speed to be most strongly associated with the interaction between *APOE*-ε4 and ePVS in the basal ganglia. Since it is not known yet whether mechanisms that drive ePVS volume versus ePVS counts differ, we focus on ePVS volume but also report results for ePVS counts as supplemental information for the field.

2. Methods

2.1. Study Cohort

Participants were selected from the Vanderbilt Memory & Aging Project (VMAP), a longitudinal observational study of individuals without dementia (Jefferson et al., 2017). Inclusion for the legacy cohort required participants to be at least 60 years of age, have English proficiency, have adequate auditory and visual acuity, have a reliable study partner, and have normal cognition (NC) or meet diagnostic criteria for early MCI (eMCI; Aisen et al., 2010) or mild cognitive impairment (MCI; Albert et al., 2011). Participants were excluded for 3 T MRI contraindication, a history of other neurological disorders (e.g., dementia, stroke, or head injury with loss of consciousness greater than 5 min) major psychiatric illness, heart failure, or terminal illness.

The present study leveraged data collected at baseline (2012–2014), 18-month (2014–2016), 3-year (2015–2018), 5-year (2017–2019), 7-year (2019–2021), and 9-year (2021-ongoing) follow-up visits. Participants were excluded from this study if they were missing covariates, brain MRI, or neuropsychological testing data. Participants had at least one follow-up visit in the longitudinal analyses. See Figure 1 for more information on participant inclusion.

The protocol was approved by the Vanderbilt Institutional Review Board and written informed consent was obtained prior to data collection with participants. Due to participant consent restrictions in data sharing, a subset of data is available to others for purposes of reproducing the results or replicating procedures. These data, analytic methods, and study materials can be obtained by contacting the corresponding author.

2.2. APOE-ε4

As previously described (Cambronero et al., 2018), *APOE* genotyping was performed on blood samples using a TaqMan® single-nucleotide polymorphism (SNP) genotyping assay from Applied Biosystems (Foster City, California, USA). Polymerase chain reaction (PCR)

was completed on Life Technologies 7900HT real-time PCR machine and analysis was completed using Life Technologies SDS 2.4.1 software. *APOE*-ε4 status was defined as positive (ε2/ε4, ε3/ε4, ε4/ε4) or negative (ε2/ε2, ε2/ε3, ε3/ε3) and the number of ε4 alleles was calculated for each participant.

2.3. Neuropsychological Assessment

Participants completed the same comprehensive neuropsychological protocol at each time point (baseline, 18-month, 3-year, 5-year, 7-year, 9-year) assessing processing speed, executive function, language, memory, and visuospatial skills (Bown et al., 2020). Executive function and memory composites were created using latent variable models as previously described (Kresge et al., 2018) to minimize comparisons, as appropriate. These two composites were created for those domains that had the most input variables to provide a stable composite for the domain of interest. For the remainder of domains, we utilized one or two individual tests. See Table 1 for a full list of tests, including the tests that comprised the executive function and memory composites.

2.4. Multi-Modal Brain MRI

Participants underwent a brain MRI at study entry at the Vanderbilt University Institute of Imaging Science. Between 2014 and 2017, brain MRI was acquired on a 3 T Philips Achieva system (Best, the Netherlands) using an 8-channel phased-array SENSE receiver head coil. The system was upgraded to a 32-channel dStream head coil in 2017. T_1-weighted MPRAGE $1\times1\times1mm^3$) and T_2-weighted fluid-attenuated inversion recovery (FLAIR;$.45\times.45\times4mm^3$) images were acquired as part of a longer imaging protocol. Individual grey matter, white matter, and CSF volumes from T1-weighted MPRAGE images were used to calculate intracranial volume (ICV).

ePVS volumes in the basal ganglia were independently coded by two examiners (CWB and LTD). The T1 and FLAIR images were reviewed to ensure that lacunes were not mistakenly identified as ePVS. To standardize this process, lesions that had a signal on the T1 scan similar to CSF and were hypointense on FLAIR with a rim of hyperintensity were labeled lacunes.

A U-net deep learning model (Remedios et al., 2020) was used to quantify ePVS volume and count for the entire cohort (Bown, et al., 2022b). Briefly, full manual coding of ePVS in the basal ganglia was performed on a subset of 50 images. Next, 40 of these images were used to train and validate the network while the other 10 images were used to test the model. The remaining 276 T1-weighted images from the cohort were run through the model to generate ePVS maps. Output from the machine learning model was reviewed by a board-certified neuroradiologist (LTD). When discrepancies arose, the board-certified neuroradiologist's (LTD) expertise was followed. Inter-rater volume correlation in the basal ganglia was 0.77 and inter-rater mean symmetric surface distance in the basal ganglia was 1.36 mm. Inter-rater Dice coefficient on edits to model outputs was 0.67 and inter-rater volume correlation was 0.92 (for more details see Bown et al., 2022a).

2.5. Analytical Plan

Linear regression models with ordinary least-squares estimates cross-sectionally examined the interaction between ePVS volume and *APOE*-ε4 on baseline neuropsychological performance (one test per model). Models adjusted for baseline age, sex, race/ethnicity, years of education, baseline cognitive status, baseline Framingham Stroke Risk Profile (FSRP; minus age), and baseline intracranial volume (ICV). Models included lower order interaction terms as applicable. Follow-up models included stratifying by *APOE*-ε4 status to examine directionality of effects. Exploratory models were repeated stratifying by *APOE*-ε4 allele count in carriers (one ε4 allele vs two ε4 alleles) and using ePVS counts as the predictor.

Mixed effects models were used to analyze the interaction between ePVS volume and *APOE*-ε4 status on longitudinal neuropsychological performance (one test per model) using identical covariates. Exploratory models included a count stratification for *APOE*-ε4 carriers (one ε4 allele vs two ε4 alleles) and using ePVS counts as the predictor.

Significance testing was set a priori at $p < 0.05$. A false discovery rate (FDR) correction for multiple comparisons (for each set of analyses per hypothesis) was performed using the Benjamini-Hochberg procedure (Benjamini and Hochberg, 1995). Sensitivity analyses were performed on all models excluding participants with outliers above 4 standard deviations for both the predictor and outcome (Thabane et al., 2013). Outlier analyses were only interpreted when they significantly changed the results. All analyses were conducted using R 4.2.1 (R Core Team, 2021; www.r-project.org).

3. Results

3.1. Participant characteristics

Participants included 326 older adults (73 ± 7 years, 59% male, 87% White/non-Hispanic, 35% *APOE*-ε4 positive). In the current sample, 52% of participants were NC, 40% were MCI, and 8% were eMCI. Standardized basal ganglia ePVS volumes ranged from 43 to 1172 mm^3 and ePVS counts ranged from 11 to 268. ePVS volume and count were strongly correlated ($r = 0.82$, $p < 0.001$). Participants were followed an average of 5.3 years, with 87% of participants completing more than one visit. Please see Table 1 for additional details.

3.2. ePVS volume x APOE-ε4 cross-sectional neuropsychological outcomes

The ePVS volume x *APOE*-ε4 carrier status interacted only on Boston Naming Test performance ($\beta = -0.002$, $p = 0.002$) and survived FDR correction. When excluding outliers, this observation was attenuated ($p = 0.65$), and another observation between ePVS x *APOE*-ε4 carrier status and executive function performance emerged ($\beta = 0.001$, $p = 0.009$). See Figure 2 for details. Among *APOE*-ε4 carriers, greater ePVS volume was cross-sectionally associated with worse Boston Naming Test ($\beta = -0.004$, $p = 0.03$), Coding ($\beta = -0.012$, $p = 0.04$), Number Sequencing ($\beta = 0.026$, $p = 0.03$), executive function composite ($\beta = -0.001$, $p = 0.03$), and Hooper Visual Organization Test performances ($\beta = -0.004$, $p = 0.02$). All significant associations among *APOE*-ε4 carriers were attenuated when excluding outliers (p-values>0.11), and none survived FDR correction. Among *APOE*-ε4 non-carriers,

greater ePVS volume was cross-sectionally associated with worse Coding (β = −0.009, p = 0.04), Number Sequencing (β = 0.03, p = 0.04), executive function composite (β = −0.001, p = 0.04), and Hooper Visual Organization Test performances (β = −0.001, p < 0.00). All significant associations remained when excluding outliers; however, most models did not survive FDR correction. Log transformation of the Boston Naming Test total score did not alter results. These results can be viewed in Table 2.

In exploratory models examining *APOE*-ε4 allele count, ePVS volume in participants with one *APOE*-ε4 allele was associated with worse Boston Naming Test (β = −0.005, p = 0.03), Number Sequencing (β = 0.026, p = 0.03), executive function composite (β = −0.001, p = 0.03), and Hooper Visual Organization Test performances (β = −0.004, p = 0.02). When excluding outliers, all significant associations were attenuated (p-values>0.08) and models did not survive FDR correction. All models examining two *APOE*-ε4 alleles were null (p-values>0.39). See Supplemental Table 1 for details.

Models examining ePVS count x *APOE*-ε4 were comparable to ePVS volume. See Supplemental Table 3 for details.

3.3. ePVS volume x APOE-ε4 longitudinal neuropsychological outcomes

There were no significant longitudinal interactions between ePVS volume and *APOE*-ε4 status (p-values>0.10). When excluding outliers, the ePVS volume x *APOE*-ε4 status interaction term was associated with longitudinal Coding performance (β = 0.002, p = 0.05). In stratified models, greater ePVS volume was unrelated to all performances among *APOE*-ε4 carriers (p-values>0.30). Among *APOE*-ε4 non-carriers, greater ePVS volume was associated with worse Boston Naming Test (β = −0.001, p < 0.001), Coding (β = −0.002, p = 0.006), executive function composite (β = −0.0002, p = 0.001), and memory composite performances (β = −0.0001, p = 0.02). See Table 3 and Fig. 3 for details. Associations persisted when excluding outliers and with FDR correction.

In exploratory models examining *APOE*-ε4 allele count, ePVS volume was not associated with cognition in participants with one (p-values>0.40) or two *APOE*-ε4 alleles (p-values>0.46). See Supplemental Table 2 for details.

The ePVS count x *APOE*-ε4 interaction term was not associated with longitudinal cognition (p-values>0.23). See Supplemental Table 4 for details.

4. Discussion

This study aimed to better understand how *APOE*-ε4 status interacts with basal ganglia ePVS on cognition in aging adults free of dementia. We found ePVS volume interacted with *APOE*-ε4 status on cross-sectional naming performance (and executive function when outliers were excluded), and longitudinal coding performance when excluding outliers. Cross-sectionally, increased ePVS volume was associated with worse cognitive performance in both *APOE*-ε4 carriers and non-carriers, but findings were more robust in the *APOE*-ε4 carriers. By contrast, longitudinally, increased ePVS volume was associated with worse cognitive trajectory over a mean 5.4 year period in non-carriers only, perhaps reflecting the

masking of the cumulative, deleterious effects of *APOE*-ε4 over the lifespan. The integration of both cross-sectional and longitudinal models contributes to a better understanding of how genetic susceptibility for late onset AD interacts with ePVS and may impact cognitive functioning in older adulthood.

Our cross-sectional interaction results found that ePVS volume interacted with *APOE*-ε4 status on naming performance and (when outliers were excluded) executive function performance. While some studies have shown an association of ePVS on memory performance (Javierre-Petit et al., 2020), we did not find a significant interaction between ePVS volume and *APOE*-ε4 on memory. While cross-sectional results were seen in both *APOE*-ε4 carriers and non-carriers, the results appeared more robust in the carrier subgroup who showed greater ePVS volume was associated with worse naming, information processing speed, executive function, and visuospatial performances. This pattern of results aligns with previous work from our group (Bown, et al., 2022b) and others (Ding et al., 2017) showing greater basal ganglia ePVS burden is associated with worse processing speed, executive function, and visuospatial ability performance. These results reflect the cognitive domains we might expect basal ganglia dysfunction to impact the most given its importance within fronto-subcortical networks (Lanciego et al., 2012). In addition, these results align with our hypotheses that associations between ePVS and cognition would be stronger among *APOE*-ε4 carriers, particularly in processing speed and executive function, due to the damaging effects of *APOE*-ε4 on the vasculature. In our exploratory analyses, when stratifying models by allele count (instead of carrier status), among participants with two *APOE*-ε4 alleles, there was no association between ePVS and cognition. However, in those participants with one *APOE*-ε4 allele, greater ePVS was associated with worse naming, information processing speed, executive function, and visuospatial performance. Given the relatively small number of participants in this sample with two *APOE*-ε4 alleles (n = 21), post-hoc power analyses indicated that we would need many more participants with two *APOE*-ε4 alleles (n = 160) to detect a significant effect. These results may serve as preliminary evidence for future studies that are more adequately powered and should be interpreted with caution.

From a longitudinal perspective, ePVS volume and the *APOE*-ε4 status interaction term was not significantly associated with any cognitive outcomes. However, the ePVS volume and the *APOE*-ε4 status interaction term was significantly associated with longitudinal coding performance following outlier removal. These results complement previous work indicating that ePVS volume predicted a steeper decline in processing speed over a mean 5-year follow-up (Ding et al., 2017) and extend upon them with a longer follow-up time. Contrary to our hypotheses, greater ePVS volume was not associated with cognitive performance among *APOE*-ε4 carriers. Among *APOE*-ε4 non-carriers, ePVS volume was associated with worse naming, information processing speed, executive function, and episodic memory performance, indicating a relatively global association of ePVS on longitudinal cognition. These results were counter to our expectations and our cross-sectional results revealing associations between greater ePVS and worse cognition were more robust in *APOE*-ε4 carriers. It is possible that *APOE*-ε4 has a cumulative, detrimental effect on cognition throughout the lifespan leading up to study entry. *APOE*-ε4 carriers are thought to have worse cognition, starting possibly in middle age (Rawle et al., 2018). Therefore, while

greater ePVS may be associated with cognition among *APOE*-ε4 carriers, this effect may be masked by the cumulative effect of *APOE*-ε4 on cognition over the lifespan. Future studies might consider following participants over time, as early as middle age, to better elucidate these associations. In addition, there were no significant associations between ePVS and longitudinal cognition when stratified by number of *APOE*-ε4 alleles, suggesting that we were inadequately powered. Alternatively, there may not be a difference in cognition between heterozygotes and homozygotes in older age (Gharbi-Meliani et al., 2021), which could also reflect a masking of ePVS on cognition over time in *APOE*-ε4 carriers.

The current study has many notable strengths, including a community-based cohort free of clinical dementia, longitudinal follow-up over a mean 5.4 year period, a novel and robust method for detecting ePVS (Bown, et al., 2022b), and a comprehensive neuropsychological protocol. However, there are also several limitations that warrant discussion. The sample contained mostly White and highly educated participants, limiting generalizability. While the neuropsychological measures in this study are commonly used measures in both clinic and research, these tests have psychometric limitations. Additionally, attrition over the longitudinal follow-up period may have biased outcomes since cognitively impaired participants are more prone to withdrawing over time (data not shown). Similarly, practice effects from serial neuropsychological testing may have biased longitudinal outcomes. However, both limitations would favor the null hypothesis, making our study findings even more interesting. While the time of day in which each of our MRI scans were acquired could have influenced results due to fluctuations in circadian rhythm, we did not find that time of day had any statistically significant impact when included as a covariate in our models (results not shown). Finally, ePVS volume and counts were anatomically limited to the basal ganglia and there is inherent human error in ePVS quantification. Future studies may wish to consider examining other regions where ePVS appear, including the centrum semiovale, mesencephalon, and hippocampus (Hilal et al., 2018).

Despite these limitations, the present study provides modest evidence that genetic risk for AD interacts with an emerging marker of SVD on cognition. However, these results are preliminary and require replication. ePVS volume interacted with *APOE*-ε4 status on cross-sectional naming, but there were not significant interactions on longitudinal cognition. Cross-sectional results were driven by *APOE*-ε4 carriers, and when stratifying the longitudinal results, findings were only present in *APOE*-ε4 non-carriers. This latter observation may possibly be due to the deleterious effects of *APOE*-ε4 on cognition across the lifespan. Taken together, these results suggest an important mechanism by which *APOE*-ε4 status interacts with SVD markers on cognition in older adulthood.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

The authors would like to thank the dedicated Vanderbilt Memory and Aging Project participants, their loved ones, and our devoted staff and trainees who contributed to recruitment, screening, enrollment, and follow-up of the cohort.

Sources of Funding

This research was supported by F31-AG066358 (CWB), Alzheimer's Association IIRG-08–88733 (ALJ), R01-AG034962 (ALJ), R01-NS100980 (ALJ), K24-AG046373 (ALJ), Paul B. Beeson Career Development Award in Aging K23-AG045966 (KAG), UL1-TR000445 and UL1-TR002243 (Vanderbilt Clinical Translational Science Award), S10-OD023680 (Vanderbilt's High-Performance Computer Cluster for Biomedical Research), P20-AG068082 (Vanderbilt Alzheimer's Disease Research Center), T32-AG058524 (MAG), Richard Eugene Hickman Alzheimer's Disease Research Endowment, and the Vanderbilt Memory and Alzheimer's Center.

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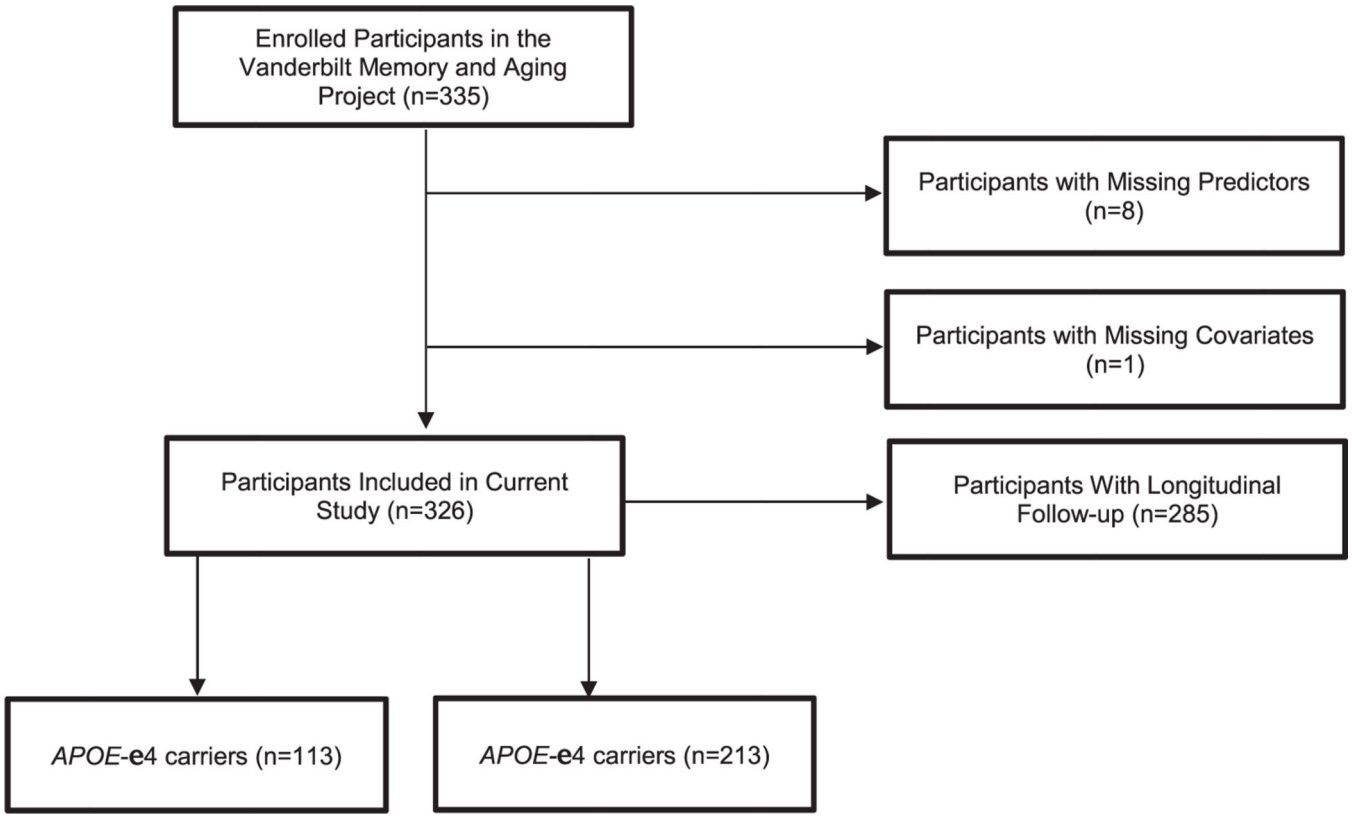

Fig. 1.
Current Study Inclusion Details.

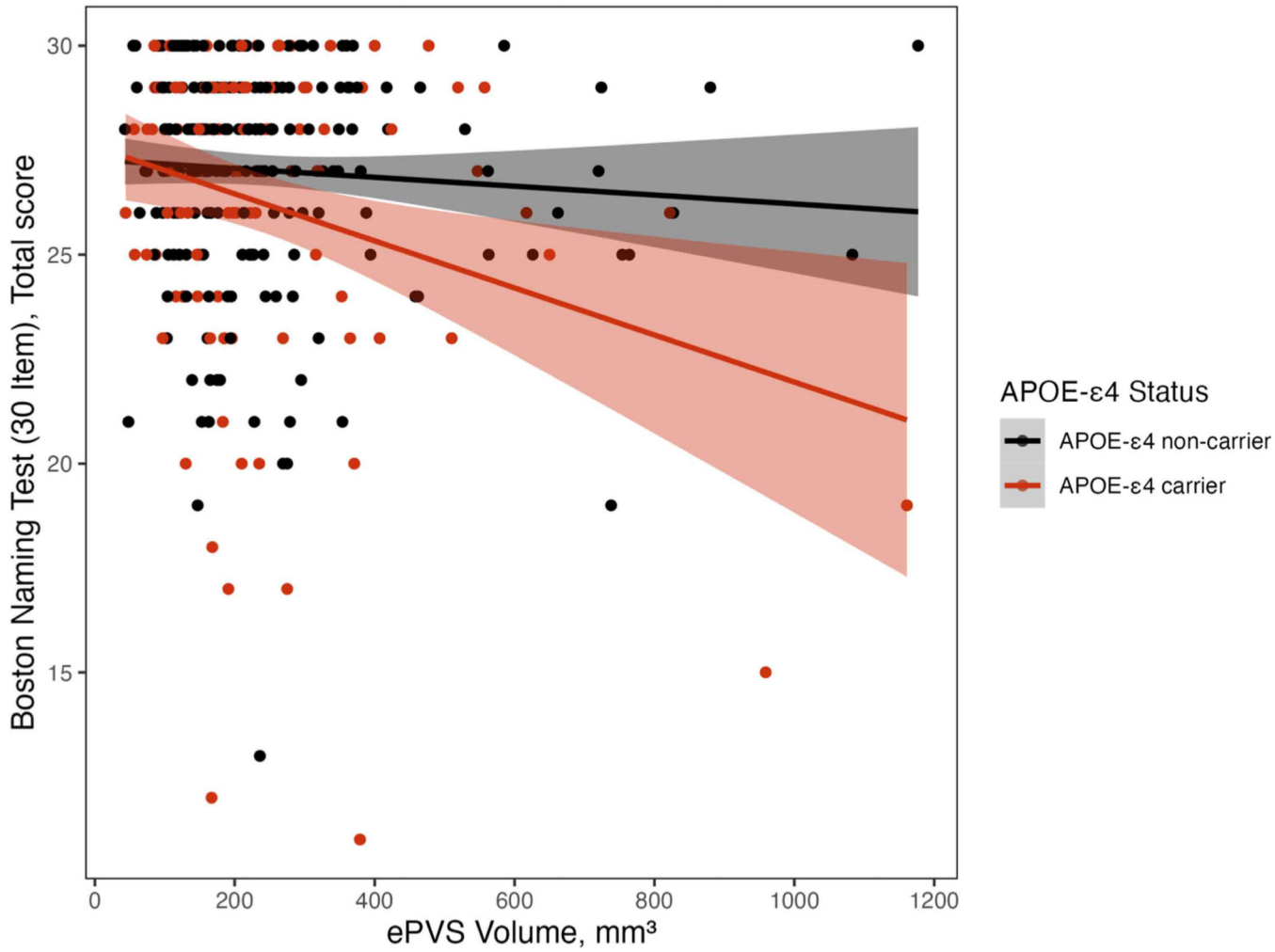

Fig. 2.

Cross-Sectional ePVS Volume x *APOE*-ε4 on Cognition. ePVS volume x *APOE*-ε4 associations on the Boston Naming Test. ePVS volume is shown in mm^3. Plot includes outliers. For the Boston Naming Test, higher values reflect better performance. ePVS volume x *APOE*-ε4 carrier status interacted on Boston Naming Test performance ($\beta = -0.002$, $p = 0.002$) and survived FDR correction. When excluding outliers, this observation was attenuated ($p = 0.65$).

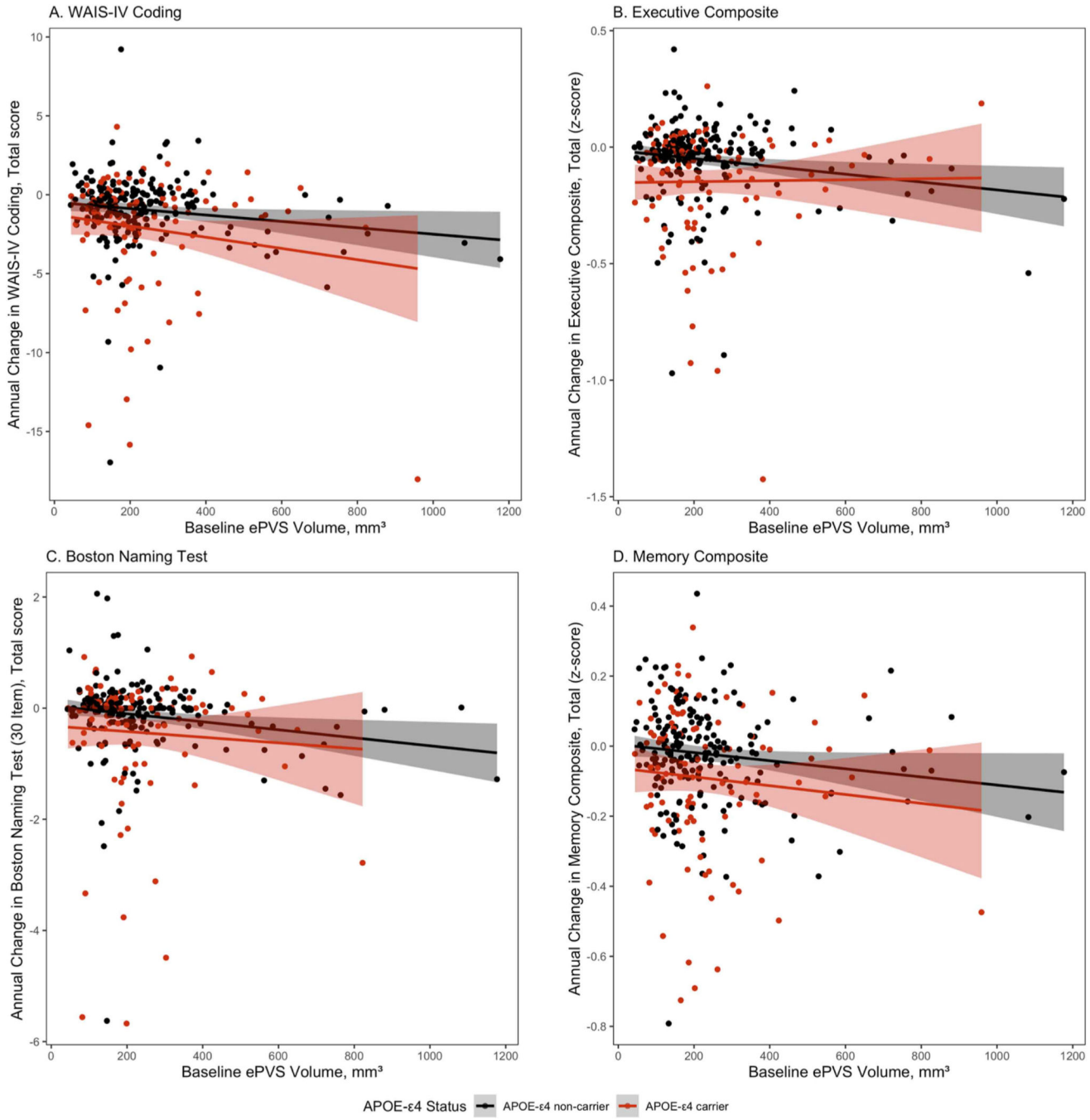

Fig. 3.

ePVS Volume x *APOE*-ε4 on Longitudinal Cognition. ePVS volume x *APOE*-ε4 associations with a) WAIS-IV Coding, b) Executive Composite, c) Boston Naming Test, and d) Memory Composite. Plots include outliers. For all cognitive domains listed, higher values reflect worse performance. There were no significant longitudinal interactions between ePVS volume and *APOE*-ε4 status (p-values>0.10). When excluding outliers, the

ePVS volume x *APOE*-ε4 status interaction term was associated with longitudinal Coding performance (β = 0.002, p = 0.05). WAIS, Wechsler Adult Intelligence Scale.

Table 1

Baseline Participant Characteristics.

	Total n= 326	*APOE*-ε4 Carrier n = 113	*APOE*-ε4 Non-Carrier n = 213	p-value
Demographic and Health Characteristics				
Age, years	73 ± 7.2	71 ± 6.2	74 ± 7.6	**0.01**
Sex, % male	59	64	56	0.20
Race, % non-Hispanic White	87	86	88	0.51
Education, years	16 ± 2.7	16 ± 2.5	16 ± 2.7	0.42
APOE-ε4 count	–	–	–	**< 0.001**
0 alleles, %	66	0	100	–
1 allele, %	28	81	0	–
2 alleles, %	6	19	0	–
Framingham Stroke Risk Profile, total *	12.5 ± 4.2	12.1 ± 4.3	12.7 ± 4.2	0.12
Systolic blood pressure	142 ± 18	141 ± 18	143 ± 18	0.17
Antihypertensive medication usage, %	54	56	54	0.70
Diabetes, %	18	25	15	**0.02**
Cigarette smoking, % current	2	2	2	0.73
Prevalent CVD, %	5	6	4	0.32
Atrial fibrillation, %	7	6	7	0.77
Left ventricular hypertrophy, %	4	5	4	0.51
Montreal Cognitive Assessment	25.3 ± 3.3	24.8 ± 3.6	25.7 ± 3.2	**0.03**
Intracranial volume, cm^3	1506 ± 151	1517 ± 151	1500 ± 150	0.28
Basal ganglia ePVS volume, mm^3	237 ± 173	235 ± 176	237 ± 172	0.76
Basal ganglia ePVS count	60 ± 36	59 ± 35	61 ± 37	0.51
Follow-up time, years	5.3 ± 1.8	5.1 ± 1.8	5.5 ± 1.7	**0.04**
Neuropsychological Outcomes				
Boston Naming Test	26.8 ± 3.2	26.3 ± 3.8	27.0 ± 2.7	0.28
Animal Naming	18.9 ± 5.3	18.4 ± 5.4	19.2 ± 5.3	0.11
WAIS-IV Coding	53.0 ± 13	51.0 ± 14	53.0 ± 12	0.09
DKEFS Number Sequencing	43.0 ± 21	46.0 ± 25	41.0 ± 17	0.10
Executive Function composite	0.02 ± 0.89	−0.11 ± 0.94	0.08 ± 0.85	0.09
DKEFS Tower Test	14.9 ± 4.7	15.3 ± 4.9	14.7 ± 4.6	0.31
DKEFS Letter-Number Switching	117 ± 93	128 ± 102	111 ± 88	0.06
DKEFS Color-Word Inhibition	69.0 ± 24	72.0 ± 23	68.0 ± 24	0.08
Letter Fluency (FAS)	39.0 ± 12	37.0 ± 11	40.0 ± 12	**0.01**
Hooper Visual Organization Test	24.4 ± 3.1	24.2 ± 3.6	24.5 ± 2.8	0.78
Episodic memory composite	−0.01 ± 0.96	−0.20 ± 1.0	0.08 ± 0.93	**0.02**
CVLT-II Total Learning	40.0 ± 12	38.0 ± 12	42.0 ± 12	**0.01**
CVLT-II Long Delay Free Recall	8.0 ± 4.3	7.3 ± 4.5	8.3 ± 4.2	0.09
CVLT-II Recognition	2.4 ± 1.0	2.2 ± 1.1	2.5 ± 0.93	**0.05**
BFLT Total Learning	112 ± 41	107 ± 43	115 ± 39	0.12

	Total n= 326	***APOE*-ε4 Carrier n = 113**	***APOE*-ε4 Non-Carrier n = 213**	**p-value**
BFLT Long Delay Free Recall	26.8 ± 11	24.9 ± 12	27.8 ± 10	**0.05**
BFLT Recognition	0.72 ± 0.21	0.68 ± 0.22	0.73 ± 0.21	**0.03**

Note. Values denoted as mean±SD or frequency. *APOE*-ε4, apolipoprotein E ε4 allele. BFLT, Biber Figure Learning Test. CVD, cardiovascular disease. CVLT-II, California Verbal Learning Test, Second Edition. DKEFS, Delis-Kaplan Executive Function System. ePVS, enlarged perivascular space. WAIS-IV, Wechsler Adult Intelligence Scale, Fourth Edition.

*A modified Framingham Stroke Risk Profile Score was included in statistical models, which excluded points assigned to age (*APOE*-ε4 Carriers=6.6 ± 3.3, *APOE*-ε4 Non-Carrier=6.5 ± 3.0). Neuropsychological outcomes represent baseline values.

Table 2

ePVS Volume x *APOE*-ε4 Associations with Cross-Sectional Cognition.

	β	95% Confidence Interval	*p*-value	FDR *p*-value
ePVS Volume x *APOE*-ε4 Interaction				
Boston Naming Test	−0.002	−0.009, −0.002	**0.002**	**0.03**
Animal Naming	−0.001	−0.007, 0.005	0.70	0.99
WAIS-IV Coding	−0.005	−0.019, 0.009	0.49	0.81
DKEFS Number Sequencing†	0.008	−0.014, 0.030	0.48	0.82
Executive Function Composite	0.0001	−0.001, 0.001	0.81	0.99
Hooper Visual Organization Test	−0.003	−0.007, 0.0004	0.07	0.58
Episodic Memory Composite	−0.0005	−0.001, 0.0004	0.28	0.72
***APOE*-ε4 Carriers**				
Boston Naming Test	−0.004	−0.008, −0.0004	**0.03**	0.12
Animal Naming	−0.002	−0.007, 0.002	0.33	0.59
WAIS-IV Coding	−0.012	−0.024, −0.0005	**0.04**	0.12
DKEFS Number Sequencing†	0.026	0.003, 0.049	**0.03**	0.12
Executive Function Composite	−0.001	−0.002, −0.00007	**0.03**	0.12
Hooper Visual Organization Test	−0.004	−0.008, −0.001	**0.02**	0.12
Episodic Memory Composite	−0.0003	−0.001, 0.001	0.52	0.73
***APOE*-ε4 Non-Carriers**				
Boston Naming Test	0.001	−0.001, 0.003	0.22	0.44
Animal Naming	−0.002	−0.006, 0.001	0.22	0.44
WAIS-IV Coding	−0.009	−0.018, −0.0004	**0.04**	0.12
DKEFS Number Sequencing†	0.014	0.003, 0.026	**0.02**	0.07
Executive Function Composite	−0.001	−0.001, −0.0004	< **0.001**	**0.01**
Hooper Visual Organization Test	−0.001	−0.003, 0.001	0.41	0.51
Episodic Memory Composite	0.0003	−0.0003, 0.001	0.28	0.44

Note. Bolded values represent significant findings. *APOE*-ε4: apolipoprotein E ε4 allele; DKEFS, Delis-Kaplan Executive Function System; WAIS-IV: Wechsler Adult Intelligence Scale, 4th edition.

†Higher values reflect worse performance.

Table 3

ePVS Volume x *APOE*-ε4 Associations with Longitudinal Cognition.

	β	95% Confidence Interval	*p*-value	FDR *p*-value
ePVS Volume x *APOE*-ε4 Interaction				
Boston Naming Test	0.001	−0.001, 0.002	0.46	0.75
Animal Naming	0.001	−0.001, 0.003	0.21	0.55
WAIS-IV Coding	0.002	−0.001, 0.005	0.12	0.55
DKEFS Number Sequencing†	−0.005	−0.013, 0.003	0.19	0.55
Executive Function Composite	0.0001	−0.0001, 0.0004	0.25	0.55
Hooper Visual Organization Test	−0.0001	−0.001, 0.001	0.80	0.95
Episodic Memory Composite	0.00005	−0.002, 0.0003	0.69	0.89
Stratified by *APOE*-ε4 Carriers				
Boston Naming Test	−0.0001	−0.002, 0.002	0.92	0.95
Animal Naming	0.0004	−0.001, 0.002	0.63	0.95
WAIS-IV Coding	0.0001	−0.003, 0.004	0.95	0.95
DKEFS Number Sequencing†	−0.004	−0.011, 0.003	0.30	0.95
Executive Function Composite	−0.00001	−0.0003, 0.0003	0.94	0.95
Hooper Visual Organization Test	−0.001	−0.002, 0.001	0.39	0.95
Episodic Memory Composite	−0.0001	−0.0003, 0.0002	0.52	0.95
Stratified by *APOE*-ε4 Non-carriers				
Boston Naming Test	−0.001	−0.0008, −0.001	**< 0.001**	**0.002**
Animal Naming	−0.001	−0.001, 0.0002	0.12	0.17
WAIS-IV Coding	−0.002	−0.003, −0.001	**0.002**	**0.006**
DKEFS Number Sequencing†	0.002	−0.002, 0.006	0.29	0.37
Executive Function Composite	−0.0002	−0.0002, 0.0001	**0.001**	**0.004**
Hooper Visual Organization Test	−0.0002	−0.001, 0.0002	0.44	0.49
Episodic Memory Composite	−0.0001	−0.0002, −0.00002	**0.02**	**0.04**

Note. Bolded values represent significant findings. *APOE*-ε4: apolipoprotein E ε4 allele; DKEFS, Delis-Kaplan Executive Function System; WAIS-IV: Wechsler Adult Intelligence Scale, 4th edition.

†Higher values reflect worse performance.