Received: 30 July 2024 | Revised: 24 September 2024 | Accepted: 25 September 2024

DOI: 10.1002/alz.70059

Alzheimer's & Dementia®
THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION

RESEARCH ARTICLE

# The impact of arteriolosclerosis on cognitive impairment in decedents without severe dementia from the National Alzheimer's Coordinating Center

Cellas A. Hayes[1] | Christina B. Young[2] | Carla Abdelnour[2] | Alexis Reeves[1] | Michelle C. Odden[1] | Jeffrey Nirschl[3] | Paul K. Crane[4] | Kathleen L. Poston[2] | Elizabeth C. Mormino[2,5] | Kyan Younes[2]

[1]Department of Epidemiology and Population Health, Stanford University School of Medicine, Palo Alto, California, USA

[2]Department of Neurology and Neurological Sciences, Stanford University School of Medicine, Palo Alto, California, USA

[3]Department of Pathology, Stanford University, Stanford, California, USA

[4]School of Medicine, Department of Medicine, University of Washington, Seattle, Washington, USA

[5]Wu Tsai Neuroscience Institute, Stanford University, Stanford, California, USA

**Correspondence**
Cellas A. Hayes, Stanford University School of Medicine Department of Epidemiology and Population Health, 1701 Page Mill Rd, Palo Alto, CA 94304, USA.
Email: cahayes3@stanford.edu

**Funding information**
Burroughs Wellcome Fund Postdoctoral Diversity Enrichment Program, Grant/Award Number: 1267001; Alzheimer's Association, Grant/Award Number: AACSF-24-1307411; Iqbal Farrukh and Asad Jamal Fund; Society for Neuroscience, Grant/Award Number: Neuroscience Scholars Program; School of Medicine, Stanford University, Grant/Award Number: Propel Postdoctoral Fellowship; National Institute of Neurological Disorders and Stroke, Grant/Award Number: 5R25NS124528

## Abstract

**INTRODUCTION:** Alzheimer's disease neuropathologic change (ADNC), Lewy body disease (LBD), and vascular neuropathologies occur together. Previous studies have been limited by a large majority of participants with severe dementia or advanced stages of pathologies, which limits the detectability of cognitive effects from vascular neuropathologies.

**METHODS:** Using neuropathology data from the National Alzheimer's Coordinating Center, we examined the association of vascular neuropathologies with cognitive scores in participants without severe dementia ($N = 1526$) using multivariable linear regression.

**RESULTS:** Controlling for age, sex, education, LBD, and ADNC, arteriolosclerosis was associated with lower memory ($\beta = -0.16 \pm 0.06$, $p < 0.001$), executive function ($\beta = -0.25 \pm 0.05$, $p < 0.001$), and language scores ($\beta = -0.20 \pm 0.05$, $p < 0.001$). The effects of arteriolosclerosis remained when controlling for vascular risk factors.

**DISCUSSION:** Vascular neuropathologies exhibit distinct relationships with cognition. Arteriolosclerosis is an independent contributor to cognition. Further research should be conducted on whether arteriolosclerosis can serve as a surrogate marker for cognitive decline in early disease stages.

KEYWORDS
Alzheimer's pathology, arteriolosclerosis, cognition, Lewy body disease, mixed dementia, neuropathology, vascular

## Highlights

- In individuals who do not have severe dementia, vascular neuropathologies are common, and the combination of pathologies is heterogeneous in a convenience sample

from the Alzheimer's Disease Research Center that reported all the neuropathology data elements for this investigation.

- Arteriolosclerosis is associated with several cognitive domain scores, including memory, executive function, and language when controlling for the effects of Alzheimer's disease neuropathologic change and Lewy body disease.
- These results reinforce the importance of vascular pathology for cognition among people along the Alzheimer's disease spectrum.

## 1 | BACKGROUND

Alzheimer's disease (AD), Lewy body dementia, and vascular dementia are the three most common neurodegenerative diseases that result in cognitive impairment and subsequent dementia.[1] Neuropathologic studies have shown that co-pathology of AD neuropathologic change (ADNC), Lewy body disease (LBD), and vascular neuropathologies are common in late-onset neurodegenerative conditions.[2–5] The majority of neurodegenerative disease clinical trials target single ADNC and LBD pathologies, and more recent platform trials attempt to target multiple pathologies such as amyloid beta (A$\beta$) and neurofibrillary tau;[6,7] however, vascular pathologies have not been targeted in combinatorial therapeutics.

Neuropathologic studies have led to significant advances in understanding mixed pathologies' additive and synergistic effects on cognition.[8–12] It has been consistently found that the presence of LBD pathology, in addition to ADNC, is associated with more severe cognitive dysfunction compared to pure disease.[12–14] Thirty percent of individuals with ADNC and 70% of individuals with LBD pathology have been observed to also have vascular neuropathologies.[4,15–17] The co-occurrence of advanced ADNC and LBD can obscure subtler findings of greater relevance for people with earlier stages of pathology of dementia levels. Hence, our analyses focused on individuals who did not die with a global Clinical Dementia Rating (CDR) of 3 to determine the independent effects of vascular neuropathologies while accounting for ADNC and LBD.

It is well established that ADNC primarily induces memory deficits, while LBD significantly affects executive function and visuospatial abilities. Neurovascular pathologies, on the other hand, can have varied cognitive impacts depending on their type and location within the brain. Therefore, it is crucial to delineate which pathologies impact specific cognitive domains to enhance diagnostic accuracy, tailor treatments, and understand the concurrent influences of multiple pathologies over disease course. More specifically, Brenowitz et al. found that gross infarcts and cortical microinfarcts with ADNC were associated with worse memory compared to ADNC alone.[18] Also, microinfarcts were found to be associated with worse cognition and higher dementia risk when present with LBD pathology.[14] In a comprehensive neuropathology evaluation of participants from the Religious Orders Study and the Memory and Aging Project, Wilson et al. found that gross infarcts were associated with lower levels of episodic, semantic, working memory, and perceptual speed. In these community cohorts, they found that atherosclerosis, arteriolar sclerosis, microinfarcts, and cerebral amyloid angiopathy (CAA) were not associated with longitudinal cognitive change before death, contrary to what might be expected based on their physiological effects.[19]

The NACC neuropathology autopsy data are one of the major neurodegenerative disease pathology datasets, with a specific emphasis on AD, Lewy body dementia, and mixed dementia. The number of patients with dementia is greater than those who are normal or have mild cognitive impairment (MCI) in NACC.[20,21] Many analyses in NACC do not stratify results by disease severity. In NACC, severe dementia is accompanied by a large prevalence of intermediate and high levels of ADNC and/or limbic/neocortical LBD that can obscure the detection of milder neurovascular pathological impacts on cognitive performance.[22,23]

Our primary objective was to examine the independent association of vascular neuropathologies on harmonized cognitive domain scores (memory, executive function, and language) when considering ADNC and LBD pathology for those without severe dementia (i.e., CDR < 3). We conducted a cross-sectional investigation for participants with clinical observations within 2 years of death. In this study, the five vascular neuropathologies (arteriolosclerosis, atherosclerosis of the circle of Willis, CAA, gross infarcts/lacunes, and microinfarcts) have been harmonized across the Alzheimer's Disease Research Centers (ADRCs) for the National Alzheimer's Coordinating Center (NACC). The novelty in our approach lies in elucidating which vascular pathologies are associated with cognitive differences in participants that did not reach a CDR of 3 (severe dementia), independent of ADNC and LBD. This allows us to gain a clearer understanding of the relationship between vascular neuropathologies and cognitive changes among people in the earlier stages of their disease before developing severe dementia.

## 2 | METHODS

### 2.1 | Research participants selection

The current study used data acquired from the United States NACC Uniform Data Set (UDS) from the March 2023 data freeze.[24] The NACC is a data repository for participant information collected from the ADRC funded by the National Institute on Aging in the United States. Participants enrolled in ADRC were evaluated approximately

annually beginning in 2005. Most ADRCs enroll participants at all cognitive stages (normal, impaired not MCI, MCI, and dementia). All funded ADRCs were approved by their designated institutional review board. Data included in this analysis were obtained from 33 ADRCs.

## 2.2 | Exclusion criteria

The flowchart of the exclusion criteria and participant sample size is shown in Figure S1 in supporting information. The objective was to examine the independent association of vascular neuropathologies on harmonized cognitive domain scores for memory, executive function, and language when considering ADNC and LBD pathology for those without severe dementia (i.e., CDR < 3). The data received from the NACC included 47,772 participants, and the autopsied sample was 7476. Participants whose autopsy was > 2 years from their last clinical assessment were excluded ($N$ = 2056). First, we applied exclusion criteria based on confirmed neuropathology similar to a previous NACC investigation of co-occurring ADNC impact on domain-specific cognitive impairments at each pathologic stage of LBD.[12] The exclusion criteria, aligned with established NACC protocols,[12] were designed to minimize confounding from severe neurodegenerative disorders and vascular events, such as large territorial strokes and cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), which could independently drive cognitive impairments. Conditions like frontotemporal lobar degeneration (FTLD), prion diseases, and other rare neuropathologies were also excluded to reduce misattribution and enhance the homogeneity of the sample, thus improving the reliability of our findings in linking specific vascular neuropathologies with cognitive performance. The study initially included 5420 participants, and a systematic exclusion process was applied to refine the cohort based on specific neuropathological confirmation at autopsy. This process began with the exclusion of participants with primary vascular pathologies (e.g., individuals with large territorial strokes as their primary etiology), followed by the removal of cases associated with FTLD, prion diseases, and specific tauopathies.

We first excluded participants ($N$ = 154) with evidence of primary vascular pathology (NPPVASC) and CADASIL, a genetic variant linked to cerebral small vessel disease (NPPATH10). Next, we focused on FTLD pathologies. Participants with primary FTLD (NPPFTLD) or contributing FTLD (NPCFTLD) were also excluded ($N$ = 283). After the exclusions related to FTLD, cases of primary prion disease (NPPPRION), contributing prion disease (NPCPRION), and a NACC harmonized prion disease indicator (NACCPRIO) were removed ($N$ = 85).

Next, we excluded participants ($N$ = 486) with various FTLD tau subtypes (NPFTDTAU) and Pick's disease (NACCPICK). Then participants with other 3R tauopathies (NPFTDT2), corticobasal degeneration (NACCCBD), progressive supranuclear palsy (NACCPROG), argyrophilic grains (NPFTDT5), other 4R tauopathies (NPFTDT6), chronic traumatic encephalopathy (NPFTDT7), amyotrophic lateral sclerosis (ALS)/parkinsonism-dementia (NPFTDT8), tangle-dominant disease (NPFTDT9), and combined 3R and 4R tauopathies (NPFTDT10) were excluded ($N$ = 48).

We further excluded participants with other frontotemporal dementia (FTD) and tauopathy-related pathologies ($N$ = 374). The specific NACC variables were used: participants with FTD and parkinsonism associated with tau-positive or argyrophilic inclusions (NPFRONT), other tauopathies including tangle-only dementia or argyrophilic grain dementia (NPTAU), FTLD characterized by TAR DNA-binding protein 43 (TDP-43; NPFTDTDP), other types of FTLD (NPOFTD), atypical FTLD-U (NPOFTD1), neuronal intermediate filament inclusions disease (NPOFTD2), and basophilic inclusion body disease (NPOFTD3), FTLD-ubiquitin-proteasome system (NPOFTD4), FTLD not otherwise specified (NPOFTD5), no distinctive histopathology (NPFTDNO), FTD not otherwise specified (NPFTDSPC), FTD with ubiquitin-positive, tau-negative inclusions (NPFTD).

We excluded participants with other pathologies ($N$ = 144) including: pigment-spheroid degeneration (NPPDXA), multiple system atrophy (NPPDXB), trinucleotide repeat diseases such as Huntington's disease or spinocerebellar ataxias (NPPDXD), malformations of cortical development (NPPDXE), and metabolic or storage disorders of any type (NPPDXF), leukodystrophy (NPPDXG), multiple sclerosis, or

### RESEARCH IN CONTEXT

1. **Systematic review**: Neuropathologic studies reveal that co-pathology of Alzheimer's disease neuropathologic change (ADNC), Lewy body disorder (LBD), and vascular neuropathologies is frequent in late-onset neurodegenerative conditions. Studies show that mixed pathologies, including ADNC with LBD and vascular components, result in more severe cognitive dysfunction than single pathologies alone. Autopsy findings often reflect a combination of pathologies present at death and in late stages of cognitive impairment, which complicates the analysis of early-stage disease intervention relevance. The National Alzheimer's Coordinating Center (NACC) neuropathology data provides an opportunity to detect the impact of milder pathologies on cognitive function in those that did not die with severe dementia.
2. **Interpretation**: Among a sample of 1526 adults from the NACC with autopsy-confirmed neuropathology of five different vascular pathologies, arteriolosclerosis was associated with poor memory, executive function, and language scores after adjusting for Alzheimer's disease and Lewy body pathology.
3. **Future directions**: These findings highlight potentially modifiable vascular neuropathologies influencing cognitive scores. More studies are needed to understand the contribution of vascular neuropathologies in the context of ADNC and LBD on cognition.

other demyelinating diseases (NPPDXH), acute contusion or traumatic brain injury (NPPDXI), chronic contusion or traumatic brain injury (NPPDXJ), primary neoplasms (NPPDXK), metastatic neoplasms (NPPDXL), encephalitis or abscess (NPPDXM), and those with brain herniations at any site (NPPDXN).

We excluded participants with other pathologies indicated by NACC variables (NPPOTH1, NPCOTH1, NPPOTH2, NPCOTH2, NPOTH2X, NPPOTH3, NPCOTH3, NPOTH3X; $N = 298$). We further excluded participants with ALS and motor neuron disease (NPALSMND; $N = 1$). Next, we excluded participants with angiopathies other than CAA (NPOANG), which led to the removal of seven additional participants. We also excluded participants with chromosome abnormalities (NPCHROM) and (NACCDOWN; $N = 26$). Participants with TDP-43 pathology in any region (NPTDPA, NPTDPB, NPTDPC, NPTDPD, and NPTDPE) and hippocampal sclerosis (NPPHIPP/NPCHIPP) were excluded ($N = 538$). Participants with the presence of tauopathies other than tau (NACCBRAA = 7) were also excluded ($N = 2$).

In addition, we also excluded individuals with missing amyloid plaque indicators ($N = 7$), missing Braak score ($N = 6$), unknown or missing LBD pathology ($N = 109$), missing gross infarcts/lacunes ($N = 44$), missing CAA ($N = 23$), and missing arteriolosclerosis ($N = 269$) data; there were no individuals with missing data for atherosclerosis of circle of Willis or microinfarcts. These exclusion criteria result in a convenience sample with complete data for all of the neuropathology data elements needed for this investigation. The number of participants remaining in the sample post neuropathology exclusion criteria was 2502. Neuropathology exclusion criteria were adopted from previous NACC publications.[12] In summary, our study's exclusion criteria were carefully selected to support the research objective but may limit the applicability of the findings to populations with mixed or unclear etiologies of dementia.

## 2.3 | Justification for exclusion of individuals with severe dementia (i.e., CDR = 3)

In our analysis of the NACC neuropathology data, we excluded individuals with a CDR score of 3, indicating severe dementia. This decision is based on our overall objective and several key considerations that are critical for the integrity and interpretability of our findings. First, the use of NACC-specific harmonized cognitive scores ensures the rigor and reproducibility of our analysis. However, the high proportion of missing harmonized scores in individuals with CDR = 3 compromises the reliability of our cognitive assessments in this subgroup of individuals with CDR = 3: memory (missingness harmonized cognitive data = 86%), executive function (missingness = 94.5%), and language (missingness = 89.6%). These missing data introduce a significant limitation in the ability to assess cognitive function in these individuals.

Second, the majority of individuals with a CDR = 3 in the NACC neuropathology studies are clinically diagnosed with AD and exhibit high levels of ADNC at death. The high prevalence of advanced ADNC in individuals with CDR = 3 can confound our ability to detect more subtle but meaningful changes in cognition, particularly in relation to vascular neuropathologies, cross-sectionally. Our approach is further justified due to the participants with CDR = 3 predominantly exhibiting intermediate/high ADNC (55.4%), intermediate/high ADNC and limbic/cortical LBD (33.1%), or limbic/cortical LBD (5.3%). Only 6.1% of individuals with a CDR = 3 had no ADNC or LBD. This high prevalence of advanced ADNC with or without LBD and severe cognitive impairment supports our decision to exclude these individuals from our analysis, as they were likely preventatively impaired to visit clinical settings and/or may have the lowest cognitive scores. Excluding individuals with CDR = 3 from our analysis is a necessary step to minimize confounding factors and ensure the validity and interpretability of our findings.

Overall, this exclusion is justified by the high prevalence of advanced ADNC, the missing cognitive scores, and the likelihood of severe cognitive impairment in this subgroup. For interested readers, the supplementary materials include results of sensitivity analyses of the contribution of vascular pathology on cognition, including individuals with severe dementia (CDR = 3) (Supplementary Methods, Supplementary Results, and Tables S1–S9 in supporting information). The final number of participants included in the analysis was 1526. After applying the exclusion criteria from a previous neuropathology study focused on ADNC and LBD from Ryman et al.[12] and the addition of excluding participants with a CDR = 3, the sample represents a relatively homogenous data set to investigate vascular neuropathologies, LBD, and ADNC.

## 2.4 | Neuropathology characterization

Each ADRC conducted a neuropathologic assessment following consensus guidelines and uploaded data to NACC using neuropathology forms 9 and 10.[25,26] The consensus guidelines for LBD corresponded to the National Institute on Aging–Alzheimer's Association (NIA-AA) Lewy body score of 0 (none), 1 (brainstem), 2 (limbic/transitional), or 3 (neocortical diffuse).[12,25] No ADNC, low ADNC, intermediate ADNC, and high ADNC were determined per the NIA neuropathological defined criteria using Thal phase (NACC UDS variable NPTHAL), Braak stage (NACCBRAA), and Consortium to Establish a Registry for Alzheimer's Disease level (NACCNEUR).[12,25]

We used the following NACC variables relating to vascular pathology: arteriolosclerosis (NACCARTE), atherosclerosis of circle of Willis (NACCAVAS), CAA (NACCAMY), gross infarcts and lacunes (NACCINF), and microinfarcts (NACCMICR). Arteriolosclerosis refers to the histological changes commonly found in the small vessels of the brain in aging, including intimal deterioration, smooth muscle degeneration, and fibrohyalinotic thickening of arterioles with consequent narrowing of the vascular lumen.[27] Both arteriolosclerosis and the degree of intracranial atherosclerosis of the circle of Willis vessels were recorded on a semiquantitative scale, ranging from none (0) to severe (3).[28] CAA refers to the accumulation of amyloid within the leptomeninges and small/medium-sized cerebral blood vessels.[29] Gross infarcts are large artery or lacunar infarcts identified

macroscopically.[18] Lacunes are 3 to 15 mm cerebrospinal fluid (CSF)-filled cavities in the basal ganglia or white matter.[30] Microinfarcts are ischemic changes detected only on histological examination.[31] Microinfarcts and gross infarcts/lacunes were dichotomous-derived NACC variables, and arteriolosclerosis, atherosclerosis of circle of Willis, and CAA were modified to be dichotomous. All vascular pathologies were considered dichotomous variables in these analyses, similar to previous neuropathology investigations.[32]

## 2.5 | Harmonized cognitive domain measures

The detailed methods of the neuropsychological assessment developed for NACC are described elsewhere.[33] Briefly, an expert panel categorized items from neuropsychological cognitive exams as indicators of memory, executive function, language, visuospatial, or none of the domains. From the classifications, analyses used confirmatory factor analysis from a pooled sample of participants, and item parameters were derived for anchor items included in any of those studies. Anchor item parameters were used to obtain factor scores and corresponding standard errors for each domain other than visuospatial, when there were limited item data available at each NACC visit.

## 2.6 | Harmonized cardiovascular disease factors and risks

The cardiovascular harmonized workflow was created for harmonization of cardiovascular disease (CVD) risk factors and a risk score for several cohorts, including NACC. Participants' self-reported data on any heart disease, hypertension (HTN), and diabetes mellitus (DM) were recorded as binary variables (yes: ever had or no: never had). Body mass index (BMI) was measured as a continuous variable, based on data from the most recent visit. In brief, the cardiovascular harmonization workflow used participants' self-reported data on heart disease, HTN, and DM recorded as binary values. Any report of heart disease was considered sufficient for inclusion. BMI from the participants' most recent visit was also included as a quantitative variable. To create the risk score, the PCAMix package was used to compute principal components that combined both qualitative and quantitative data. The principal components were used to consolidate the CVD risk factors into a score. The first principal component was used because it accounted for the most variance across the four cardiovascular risk factors. The Cardiovascular Harmonization Workflow read me data file contains a reference for Lee et al.,[34] and the Alzheimer's Disease Sequencing Project Phenotype Harmonization Consortium (ADSP-PHC) is described elsewhere.[35]

## 2.7 | Statistical analyses

Demographic characteristics of the study participants were analyzed to assess differences across CDR groups. For continuous variables such as age, education, and cognitive scores (memory, executive function, and language), a one-way analysis of variance (ANOVA) was conducted to determine whether there were statistically significant differences between groups. After the ANOVA, a Tukey post hoc test was used to identify specific group differences. For categorical variables including sex, race, apolipoprotein E (*APOE*) genotype (categorized as 0 vs. $\geq 1$ $\varepsilon 4$ allele), and presence of each neuropathology finding (arteriolosclerosis, atherosclerosis of the circle of Willis, CAA, microinfarcts, and infarcts), chi-square tests were used to evaluate the associations between these categorical variables and the groups.

### 2.7.1 | Logistic regression for pathology associations

To understand which vascular neuropathologies were associated with ADNC and LBD in our selective analytical sample, we used logistic regression to evaluate the association between each vascular neuropathology and ADNC or LBD controlling for centered age at death (age at death – mean of sample), sex, education, and *APOE* $\varepsilon 4$ carrier (i.e., vascular pathology ~ centered age at death + sex + education + *APOE* $\varepsilon 4$ carrier + continuous levels of ADNC + LBD).

### 2.7.2 | Multivariable linear regression for cognition associations

Multivariable linear regression models were used to evaluate the relationship between individual vascular neuropathologies and cognitive domain scores. The base models included the cognitive domain measurement from a clinical observation within 2 years of death as an outcome with covariates including centered age at death, sex, education, and an individual vascular neuropathology (i.e., arteriolosclerosis, atherosclerosis of the circle of Willis, CAA, gross infarcts/lacunes, or microinfarcts). The fully adjusted model was further adjusted for *APOE* $\varepsilon 4$ carrier, continuous levels of LBD pathology severity, and ADNC pathology severity to quantify the independent effects of each vascular pathology. We also performed two sensitivity analyses: (1) to examine how grouping the presence of arteriolosclerosis, atherosclerosis, or both as a measure of perfusion/vessel disease was associated with cognitive scores; and (2) to examine how grouped tissue injury (presence of gross infarcts/lacunes, microinfarcts, or both) influences cognitive scores. The perfusion and damage pathologic categories were binarized based on the presence of the respective categories mentioned above. In addition, we also modeled LBD, ADNC, and CDR using dummy variables for the ordinal predictors. The results were almost identical, and we chose to present the models with these treated as linear here. In addition, we conducted an analysis to examine whether the inclusion of vascular risk factors—harmonized measurements for HTN, DM, and a CVD risk score—would attenuate the effects of vascular neuropathology on cognitive scores. These measurements were used and generated specifically for NACC participants.[35] All statistical analyses were conducted using R version 4.2.3. All $p$ values are two sided, and

**TABLE 1** Descriptive characteristics of the included sample stratified by global Clinical Dementia Rating.

| | Global Clinical Dementia Rating score | | | | | |
|---|---|---|---|---|---|---|
| | 0 (*N* = 342) | 0.5 (*N* = 358) | 1 (*N* = 358) | 2 (*N* = 468) | *p* value | Overall (*N* = 1526) |
| Age at death, years mean (SD) | 87.5 (7.8) | 87.8 (8.5) | 82.5 (11) | 80.2 (10.7) | <0.001* | 84.2 (10.2) |
| Male *n* (%) | 200 (59) | 156 (44) | 144 (40) | 188 (40) | <0.001 | 688 (45) |
| Education, years mean (SD) | 15.7 (2.8) | 15.8 (3.0) | 15.7 (3.0) | 15.3 (3.2) | 0.13 | 15.6 (3.0) |
| Missing *n* (%) | 1 (0.3) | 2 (0.6) | 2 (0.6) | 1 (0.2) | | 6 (0.4) |
| Hispanic Ethnicity *n* (%) | 4 (1.2) | 7 (2.0) | 5 (1.4) | 8 (1.7) | 0.77 | 24 (1.6) |
| Missing *n* (%) | 1 (0.3) | 0 (0) | 2 (0.6) | 3 (0.6) | | 6 (0.4) |
| Race *n* (%) | | | | | 0.53 | |
| White | 325 (95.0) | 336 (93.9) | 341 (95.3) | 453 (96.8) | | 1455 (95.3) |
| Black or African American | 14 (4.1) | 19 (5.3) | 12 (3.4) | 12 (2.6) | | 57 (3.7) |
| American Indian or Alaska Native | 1 (0.3) | 0 (0) | 0 (0) | 0 (0) | | 1 (0.1) |
| Native Hawaiian or Other Pacific Islander | 0 (0) | 0 (0) | 0 (0) | 1 (0.2) | | 1 (0.1) |
| Asian | 1 (0.3) | 2 (0.6) | 4 (1.1) | 1 (0.2) | | 8 (0.5) |
| Unknown | 1 (0.3) | 1 (0.3) | 1 (0.3) | 1 (0.2) | | 4 (0.3) |
| Hypertension *n* (%) | 271 (79.2) | 261 (72.9) | 228 (63.7) | 283 (60.5) | <0.001 | 1043 (68.3) |
| Missing *n* (%) | 18 (5.3) | 26 (7.3) | 27 (7.5) | 39 (8.3) | | 110 (7.2) |
| Diabetes *n* (%) | 50 (14.6) | 48 (13.4) | 55 (15.4) | 54 (11.5) | 0.45 | 207 (13.6) |
| Missing *n* (%) | 18 (5.3) | 26 (7.3) | 27 (7.5) | 39 (8.3) | | 110 (7.2) |
| CVD risk score mean (SD) | 0.4 (1.1) | 0.3 (1.0) | 0.1 (1.2) | 0.0 (1.1) | <0.001 | 0.2 (1.1) |
| Missing *n* (%) | 18 (5.3) | 26 (7.3%) | 27 (7.5%) | 39 (8.3%) | | 110 (7.2%) |
| AD and LBD status | | | | | <0.001 | |
| Neither | 268 (78.4) | 174 (48.6) | 78 (21.8) | 49 (10.5) | | 569 (37.3) |
| LBD | 19 (5.6) | 30 (8.4) | 44 (12.3) | 44 (9.4) | | 137 (9.0) |
| ADNC | 48 (14.0) | 119 (33.2) | 156 (43.6) | 259 (55.3) | | 582 (38.1) |
| ADNC/LBD | 7 (2.0) | 35 (9.8) | 80 (22.3) | 116 (24.8) | | 238 (15.6) |
| Arteriolosclerosis *n* (%) | 101 (29.5) | 159 (44.4) | 143 (39.9) | 205 (43.8) | <0.001 | 608 (39.8) |
| Atherosclerosis *n* (%) | 141 (41.2) | 154 (43.0) | 136 (38.0) | 167 (35.7) | 0.14 | 598 (39.2) |
| CAA *n* (%) | 38 (11.1) | 84 (23.5) | 104 (29.1) | 169 (36.1) | <0.001 | 395 (25.9) |
| Microinfarcts *n* (%) | 66 (19.3) | 83 (23.2) | 83 (23.2) | 104 (22.2) | 0.56 | 336 (22.0) |
| Gross infarcts/ lacunes n (%) | 48 (14.0) | 85 (23.7) | 58 (16.2) | 77 (16.5) | <0.01 | 268 (17.6) |
| *APOE* ε4 carrier status *n* (%) | 63 (18.4) | 106 (29.6) | 149 (41.6) | 205 (43.8) | <0.001 | 523 (34.3) |
| Missing *n* (%) | 15 (4.4) | 25 (7.0) | 38 (10.6) | 53 (11.3) | | 131 (8.6) |
| Memory mean (SD) | 0.9 (0.5) | 0.07 (0.7) | −0.8 (0.7) | −1.5 (0.6) | <0.001 | −0.307 (1.1) |
| Missing *n* (%) | 62 (18.1) | 63 (17.6) | 90 (25.1) | 203 (43.4) | | 418 (27.4) |
| Executive function mean (SD) | 0.3 (0.6) | −0.2 (0.7) | −0.7 (0.7) | −1.15 (1.0) | <0.001 | −0.3 (0.9) |
| Missing *n* (%) | 71 (20.8) | 92 (25.7) | 150 (41.9) | 316 (67.5) | | 629 (41.2) |
| Language mean (SD) | 0.5 (0.6) | −0.04 (0.6) | −0.6 (0.6) | −1.2 (0.6) | <0.001 | −0.3 (0.9) |
| Missing *n* (%) | 60 (17.5) | 67 (18.7) | 95 (26.5) | 247 (52.8) | | 469 (30.7) |

*Note*: Data were statistically compared across CDR groups using one-way ANOVA/Tukey post hoc for continuous variables or chi-square test for categorical variables.

Abbreviations: ADNC, Alzheimer's disease neuropathologic change; *APOE*, apolipoprotein E; CAA, cerebral amyloid angiopathy; CDR SUM, Clinical Dementia Rating Sum of Boxes; CERAD, Consortium to Establish a Registry for Alzheimer's Disease; CVD, cardiovascular disease; LBD, Lewy body disease; MCI, mild cognitive impairment; SD, standard deviation.

*Denotes all groups are different except for CDR 0 and CDR 0.5 in the Tukey post hoc.

the statistical significance was set at $p$ value < 0.05 for all demographic comparisons.

## 3 | RESULTS

### 3.1 | Sample characteristics

Table 1 contains an overview of the characteristics (demographics, clinical, *APOE* genotype, and neuropathology prevalence) of the included sample stratified by global CDR. We found significant differences in age at death, sex distribution, and several neuropathological factors across CDR groups. The mean age at death for all CDR stages was > 80 years old, with some variability as those having higher CDR scores were somewhat younger on average ($p < 0.001$). Males comprised 41.5% of the CDR 0 group, 56% of the CDR 0.5 group, and 60% in the CDR 1 and CDR 2 groups ($p < 0.001$). Education levels were similar across CDR groups ($p = 0.13$). The prevalence of ADNC only or ADNC/LBD varied significantly, with higher occurrences in groups with greater global CDR ($p < 0.001$). The presence of CAA and ≥ 1 *APOE* ε4 allele was more common with higher CDR scores ($p < 0.001$). Cognitive scores in memory, executive function, and language domains were lower on average among people with higher CDR scores ($p < 0.001$). In the post hoc analysis, all groups differed from each other, with CDR = 2 having the lowest scores for executive function and language domains ($p < 0.001$). However, in the post hoc analysis for the memory domain, all groups differed from each other except CDR = 0 and CDR = 0.5 ($p < 0.001$).

### 3.2 | Combination prevalence of neuropathology

Among the 1526 participants, the number of pathological findings ranged from 0 to 7 (Table 2). ADNC and LBD were binarized (i.e., low ADNC [none or low] vs. high ADNC [intermediate or high] and low LBD [no LBD or brainstem] vs. high LBD [limbic or neocortical]) to understand the heterogeneity of the possible combinations and prevalence of neuropathology in the sample. Notably, 166 individuals (11%) had no pathologies of interest, while 343 individuals (22%) had one pathology. The highest frequency was observed in those with two pathologies, encompassing 398 participants (26%). Participants with three pathologies comprised 22% of the sample ($n = 331$). The prevalence of individuals with four pathologies was 13% ($n = 193$), and those with five pathologies constituted 5% of the sample ($n = 75$). Fewer participants had six pathologies, accounting for 1% ($n = 19$), and only one individual (0.07%) had seven pathologies.

The heterogeneity of vascular pathologies with LBD and ADNC is shown in Figure 1. Figure S1 provides a visual representation of the heterogeneity between any ADNC, LBD, and all five vascular neuropathologies of the full sample. When visualizing the concomitance of pathologies, the five most prevalent pure or combinations of pathologies were participants with ADNC only ($n = 134$), atherosclerosis of the circle of Willis only ($n = 73$), both ADNC and LBD ($n = 56$), and both ADNC and atherosclerosis of the circle of Willis ($n = 51$). This detailed distribution highlights the varying burden of neuropathologies across the sample, with a notable proportion of participants exhibiting polypathology. Figure S2 in supporting information provides the visual depiction of the heterogeneity of the concomitance of pathologies in the full sample.

**TABLE 2** The frequency and percentage of participants with confirmed pathology.

| Frequency of polypathology | Number of participants | Overall percentage % in sample ($N = 1526$) |
|---|---|---|
| 0 | 166 | 10.88 |
| 1 | 343 | 22.48 |
| 2 | 398 | 26.08 |
| 3 | 331 | 21.69 |
| 4 | 193 | 12.65 |
| 5 | 75 | 4.91 |
| 6 | 19 | 1.25 |
| 7 | 1 | 0.07 |

*Note*: The overall frequency and percentages of pathologies included in the sample when all are treated as dichotomous to be used for an upset plot. All vascular neuropathologies were treated as dichotomous absent/present. Additionally, intermediate or high Alzheimer's disease neuropathologic change was treated as presence Alzheimer's disease versus none or low for absent. Lewy body disease was also dichotomized into none/brainstem (absent) versus limbic/neocortical (present).

### 3.3 | Association of vascular neuropathologies with LBD and ADNC

Controlling for demographics and *APOE* ε4 carrier, logistic regression models investigating the associations of individual vascular pathologies with ADNC and LBD showed that higher ADNC was independently associated with CAA (odds ratio [OR] = 1.93, 95% confidence interval [CI] [1.70–2.21], $p < 0.01$) and higher LBD was independently associated with a slightly lower prevalence of microinfarcts (OR = 0.88, 95% CI [0.77–1.00], $Pp = 0.05$). There were no associations between ADNC and arteriolosclerosis, atherosclerosis, infarcts/lacunes, or microinfarcts. There were no associations between LBD and arteriolosclerosis, atherosclerosis, infarcts/lacunes, or CAA (Table 3).

### 3.4 | Associations of vascular neuropathologies with cognitive scores

In the base multivariable linear regression models adjusting for demographics, arteriolosclerosis and CAA were significantly associated with lower memory, executive function, and language scores (Table 4). In the full multivariable linear regression adjusting for *APOE* genotype, ADNC, and LBD, arteriolosclerosis ($\beta = -0.16 \pm 0.06$, $p < 0.001$) and microinfarcts ($\beta = -0.14 \pm 0.07$, $p = 0.03$) were associated with lower memory scores. Arteriolosclerosis ($\beta = -0.25 \pm 0.05$,

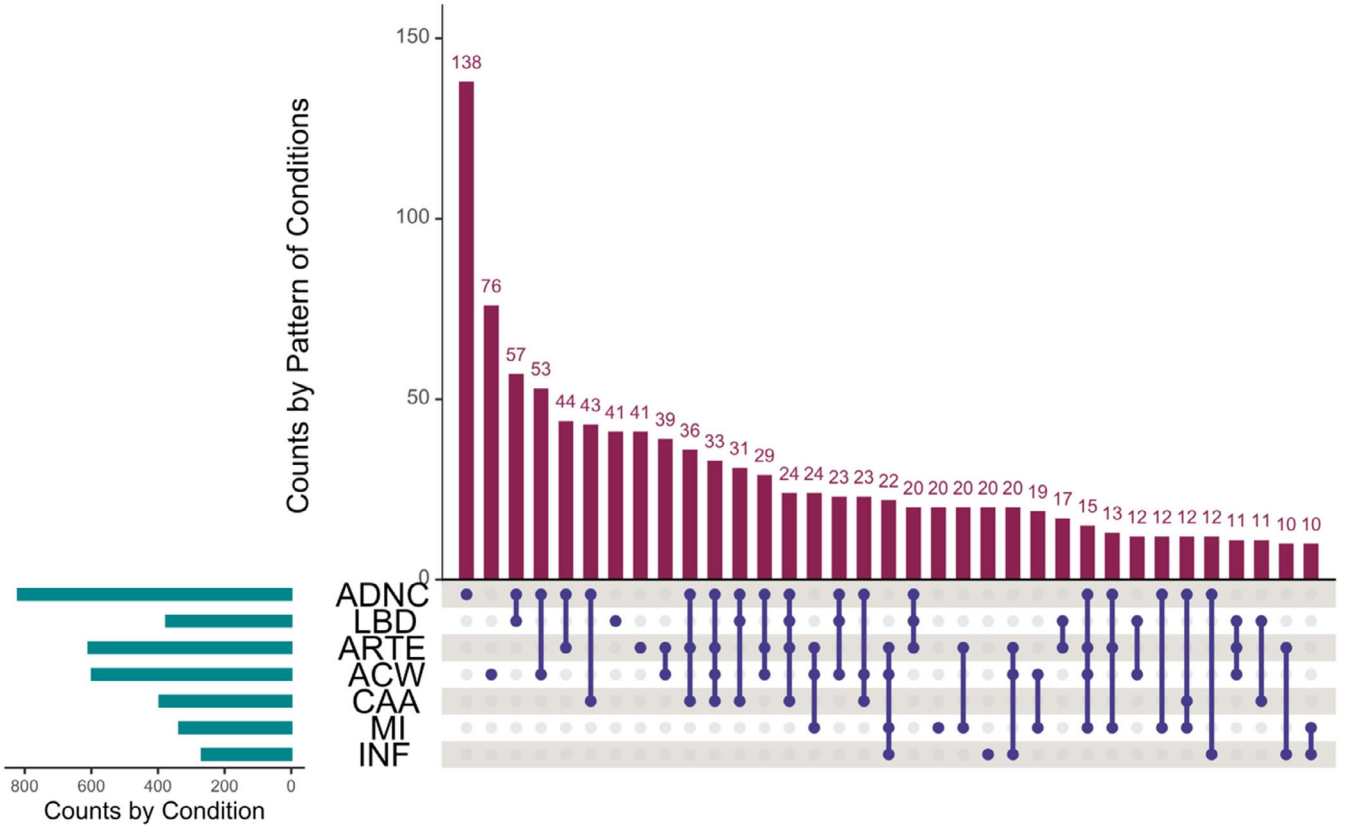


**FIGURE 1** Upset plot providing a visual representation of the heterogeneity between any ADNC, LBD, and all five vascular variables limited to a minimum of 10 participants exhibiting that characteristic. The horizontal bar graph with the *x* axis labeled counts by conditions refers to the total number of participants with that pathology present at autopsy. The figure has the number by pattern of conditions of each pathology present on the *y* axis, and the intersections that overlap on the *x* axis. The number above each bar indicates the number of participants with that combination of pathologies at autopsy. The dots in the figure indicate if a decedent had that specific pathology to the left. The lines connect the dots to indicate the overlap of the co/poly pathology. ACW, atherosclerosis of the Circle or Willis; ADNC, intermediate or high Alzheimer's disease neuropathologic change; ARTE, arteriolosclerosis; CAA, cerebral amyloid angiopathy; INF gross infarcts/lacunes; LBD, limbic or neocortical Lewy body disease stage; MI, microinfarcts.

**TABLE 3** Association of vascular pathologies with LBD and ADNC.

| | Arteriosclerosis | | Atherosclerosis | | Infarcts/lacunes | | Microinfarcts | | CAA | |
|---|---|---|---|---|---|---|---|---|---|---|
| Predictor | OR (95% CI) | *p* | OR (95% CI) | *p* | OR (95% CI) | *p* | OR (95% CI) | *p* | OR (95% CI) | *p* |
| LBD | 1.04 (0.94–1.15) | 0.47 | 0.92 (0.82–1.02) | 0.11 | 0.89 (0.77–1.02) | 0.10 | **0.88 (0.77–1.00)** | **0.05** | 1.09 (0.97–1.23) | 0.15 |
| ADNC | 1.09 (0.99–1.20) | 0.08 | 1.06 (0.96–1.17) | 0.28 | 0.91 (0.81–1.03) | 0.14 | 0.99 (0.88–1.11) | 0.82 | **1.93 (1.70–2.21)** | **<0.01** |

*Note*: Model: Individual logistic regression models (vascular pathology ~ demographics + *APOE ε4* carrier status + continuous levels of LBD (none, brainstem, limbic, and neocortical) + continuous levels of ADNC (none, low, intermediate, and high). Data are shown OR (95% confidence interval) and the *p* value. Bold indicates the groups within each model that demonstrated a significant association with LBD or ADNC ($p < 0.05$).
Abbreviations: ADNC, Alzheimer's disease neuropathic change; *APOE*, apolipoprotein E; CAA, cerebral amyloid angiopathy; CI, confidence interval; LBD, Lewy body disease; OR, odds ratio.

$p < 0.001$), CAA ($\beta = -0.15 \pm 0.07$, $p = 0.03$), and gross infarcts/lacunes ($\beta = -0.16 \pm 0.07$, $p = 0.02$) were associated with lower executive function scores. Last, arteriolosclerosis was associated with lower language scores ($\beta = -0.20 \pm 0.05$, $p < 0.001$; Table 4).

Out of the 1526 participants, 1043 individuals (73.7%) had HTN, and 207 individuals (14.6%) had DM. The cardiovascular risk score ranged from −2.30 to 3.93, with a mean of 0.2, indicating a slightly positive risk overall. The association of vascular neuropathologies with cognitive scores was evaluated using models adjusted for HTN and DM, as well as models adjusted for harmonized CVD risk scores (Table 5). In the models adjusting for HTN and DM, arteriolosclerosis was significantly associated with declines in all three cognitive

**TABLE 4** Association of vascular neuropathologies with cognitive scores.

| | Memory ($\beta \pm$ SE, $p$) | | Executive Function ($\beta \pm$ SE, $p$) | | Language ($\beta \pm$ SE, $p$) | |
|---|---|---|---|---|---|---|
| | Base models | Full models | Base models | Full models | Base models | Full models |
| **Predictor** | | | | | | |
| Arteriolosclerosis | **−0.25 ± 0.07, <0.001** | **−0.16 ± 0.06, 0.005** | **−0.31 ± 0.06, <0.001** | **−0.25 ± 0.05, <0.001** | **−0.24 ± 0.05, <0.001** | **−0.20 ± 0.05, <0.001** |
| Atherosclerosis | −0.03 ± 0.07, 0.63 | −0.01 ± 0.06, 0.89 | −0.08 ± 0.06, 0.16 | −0.07 ± 0.06, 0.20 | −0.08 ± 0.05, 0.15 | −0.07 ± 0.05, 0.16 |
| CAA | **−0.52 ± 0.07, <0.001** | −0.01 ± 0.07, 0.90 | **−0.41 ± 0.06, <0.001** | **−0.15 ± 0.07, 0.03** | **−0.37 ± 0.06, <0.001** | −0.05 ± 0.06, 0.35 |
| Gross infarcts/lacunes | −0.01 ± 0.09, 0.88 | −0.03 ± 0.07, 0.67 | −0.13 ± 0.07, 0.07 | **−0.16 ± 0.07, 0.02** | −0.09 ± 0.07, 0.17 | −0.10 ± 0.06, 0.08 |
| Microinfarcts | −0.09 ± 0.08, 0.26 | **−0.14 ± 0.07, 0.03** | −0.08 ± 0.07, 0.23 | −0.08 ± 0.06, 0.19 | 0.01 ± 0.06, 0.84 | −0.03 ± 0.06, 0.65 |

*Note*: Model: The base multivariable linear regression of individual models (Cognition ~ centered age at death + sex + education + 1 vascular variable) to quantify the effects of each vascular pathology. The full multivariable linear regression of individual models (Cognition ~ centered age at death + sex + education + *APOE ε4* carrier status + continuous levels of LBD + continuous levels of ADNC + 1 vascular variable) to quantify the independent effects of each vascular pathology. Data are presented as estimate ($\beta$) ± standard error (SE), $p$ value. Bold indicates significance.
Abbreviations: ADNC, Alzheimer's disease neuropathologic change; *APOE*, apolipoprotein E; CAA, cerebral amyloid angiopathy; LBD, Lewy body disease; SE, standard error.

**TABLE 5** Association of vascular neuropathologies with cognitive scores controlling for vascular risk factors.

| | Adjusting for HTN and DM | | | Adjusting for harmonized CVD risk | | |
|---|---|---|---|---|---|---|
| | Memory ($\beta \pm$ SE, $p$) | Executive function ($\beta \pm$ SE, $p$) | Language ($\beta \pm$ SE, $p$) | Memory ($\beta \pm$ SE, $p$) | Executive function ($\beta \pm$ SE, $p$) | Language ($\beta \pm$ SE, $p$) |
| **Predictor** | | | | | | |
| Arteriolosclerosis | **−0.15** ± 0.06, 0.01 | **−0.24 ± 0.06, <0.001** | **−0.21 ± 0.05, <0.001** | **−0.15** ± 0.06, 0.01 | **−0.25 ± 0.06, <0.001** | **−0.21 ± 0.05, <0.001** |
| Atherosclerosis | −0.02 ± 0.06, 0.78 | −0.07 ± 0.06, 0.23 | −0.07 ± 0.05, 0.20 | −0.02 ± 0.06, 0.78 | −0.07 ± 0.06, 0.24 | −0.07 ± 0.05, 0.18 |
| CAA | −0.01 ± 0.07, 0.90 | **−0.15 ± 0.07, 0.03** | −0.06 ± 0.06, 0.32 | −0.01 ± 0.07, 0.89 | **−0.15 ± 0.07, 0.03** | −0.06 ± 0.06, 0.34 |
| Gross infarcts/lacunes | −0.03 ± 0.07, 0.69 | **−0.15 ± 0.07, 0.03** | −0.11 ± 0.06, 0.09 | −0.04 ± 0.07, 0.62 | **−0.16 ± 0.07, 0.02** | −0.11 ± 0.06, 0.06 |
| Microinfarcts | **−0.15 ± 0.07, 0.02** | −0.08 ± 0.07, 0.24 | −0.03 ± 0.06, 0.56 | **−0.16 ± 0.07, 0.02** | −0.08 ± 0.07, 0.22 | −0.04 ± 0.06, 0.48 |

*Note*: HTN and DM Model: The multivariable linear regression of individual models (Cognition ~ centered age at death + sex + education + *APOE ε4* carrier status + hypertension + diabetes + continuous levels of LBD + continuous levels of ADNC + 1 vascular variable) to quantify the independent effects of each vascular pathology. CVD Risk Model: The multivariable linear regression of individual models (Cognition ~ centered age at death + sex + education + *APOE ε4* carrier status + harmonized CVD risk + continuous levels of LBD + continuous levels of ADNC + 1 vascular variable) to quantify the independent effects of each vascular pathology. Data are presented as estimate ($\beta$) ± standard error (SE), $p$ value. Bold indicates significance.
Abbreviations: ADNC, Alzheimer's disease neuropathologic change; *APOE*, apolipoprotein E; CAA, cerebral amyloid angiopathy; CVD, cardiovascular disease; DM, diabetes mellitus; HTN, hypertension; LBD, Lewy body disease; SE, standard error.

domains: memory scores ($\beta = -0.15 \pm 0.06$, $p = 0.01$), executive function ($\beta = -0.24 \pm 0.06$, $p < 0.001$), and language scores ($\beta = -0.21 \pm 0.05$, $p < 0.001$). Microinfarcts were significantly associated with lower memory scores ($\beta = -0.15 \pm 0.07$, $p = 0.02$), while gross infarcts/lacunes and CAA were associated with lower executive function scores ($\beta = -0.15 \pm 0.07$, $p = 0.03$ and $\beta = -0.15 \pm 0.07$, $p = 0.03$, respectively). These findings were replicated when adjusting for the harmonized CVD risk score (Table 5). In a supplementary analysis, when also controlling for cognitive impairment duration, arteriolosclerosis remained statistically significantly associated with executive function and language (Table S8). CAA and gross infarcts also remained significantly associated with poorer executive function (Table S8). In the sensitivity analyses, any perfusion dysfunction pathology (arteriolosclerosis, atherosclerosis, or both) was not associated with memory but was associated with lower executive function and language scores (Table S9). Similarly, CAA was also associated with executive function when included in the model with perfusion dysfunction (Table S9). Any tissue damage pathology (gross infarcts/lacunes, microinfarcts, or both) was not associated with cognitive outcomes independent of ADNC and LBD (Table S9).

## 4 | DISCUSSION

In this study, our objective was to investigate the influence of vascular neuropathologies on cognition. Even when accounting for the presence of ADNC and LBD pathologies, arteriolosclerosis was associated with cognitive functions across all three tested domains. These results highlight the impact of arteriolosclerosis on cognitive function, underscoring the need for attention to vascular neuropathologies in parallel to AD and LBD to comprehensively understand cognitive decline. For individuals in earlier stages of AD who qualify for amyloid monoclonal antibodies like Lecanemab, understanding the role of vascular neuropathologies is crucial, as it may influence the outcomes and the degree and rate of cognitive decline, further underscoring the importance of personalized treatment approaches. Like previous NACC neuropathology research,[36] our study underscores the critical need to consider arteriolosclerosis as an independent contributor to cognitive decline and accordingly calls for further investigation of therapeutic interventions for this cerebrovascular pathology.

This study emphasizes the importance of the comorbidities that influence cognition in older adults.[11] Neuropathological studies showed that arteriolosclerosis, atherosclerosis, CAA, microinfarcts, and LBD contribute to a higher risk of overall dementia and AD-type dementia.[10] As expected, we show that higher levels of ADNC were associated with CAA.[37] We also found that LBD was associated with slightly smaller rates for microinfarcts, but there were no other associations between LBD and other categories of vascular neuropathology.

Arteriolosclerosis and infarcts/lacunes have been previously found to be associated with the presence of mild AD, and in a subset of participants, arteriolosclerosis is associated with global cognition and language performance.[38] Lamar et al. found that individuals with mixed vascular neuropathology had a more rapid cognitive decline than those with a single cerebrovascular disease.[32] Consistent with our findings, they showed that mixed vascular neuropathology, including arteriolosclerosis, had the most profound effect on cognitive function compared to having little or no vascular neuropathology.[32] In a separate study that defined participants with and without cerebrovascular disease (moderate to severe arteriolosclerosis or atherosclerosis) plus having or not having AD, participants that had AD and cerebrovascular disease had a more rapid longitudinal decline in processing speed, working memory, verbal fluency, and CDR.[39] We did not observe a significant association between atherosclerosis of the circle of Willis and cognition, unlike Lamar et al.[32] This could be due to their community-based sample and the prevalence of dementia participants at autopsy.[32] In our sensitivity analysis, combining arteriolosclerosis and/or atherosclerosis of the circle of Willis, perfusion dysfunction was associated with lower executive function and language scores, but this finding was driven by arteriolosclerosis, not atherosclerosis of the circle of Willis.

In NACC, HTN and DM have been associated with dementia, along with those risk factors being > 50% prevalent in stratified conditions such as arteriolosclerosis and atherosclerosis of the circle of Willis.[40] Moreover, vascular risk factors based on the Framingham Stroke Risk Profile are associated with worse cognitive dysfunction in NACC participants.[41] Hence, we also controlled for risk factors for vascular neuropathologies such as HTN, DM, and a CVD risk score. Arteriolosclerosis remained a significant predictor across all cognitive domains. Further research is needed to understand the independence of arteriolosclerosis from its risk factors like HTN and other pathologies such as ADNC in diverse participant samples encompassing demographics, clinical factors, and community characteristics.[42]

Our results provide neuropathological evidence linking arteriolosclerosis to lower cognitive scores in people with up to moderate CDR stage, suggesting that altered arteriolar function may be particularly important across multiple cognitive domains. Studies using longitudinal cohorts have indicated that chronic low blood pressure is associated with dementia incidence, but these studies are nonspecific for diseases such as arteriolosclerosis.[43,44] Aligning with our findings for arteriolosclerosis, epidemiological and clinical studies have highlighted the role of pulsatile arterial hemodynamics in neurodegeneration and cognition.[45] Mean arterial pressure has been understudied and undervalued as a candidate for cognitive monitoring[46] despite being associated with cognitive impairment in individuals with MCI.[47] Pulse pressure amplification has also been associated with executive function and language cognitive domain deficits in MCI participants.[48] These results highlight the importance of vascular factors in the pathogenesis of cognitive decline and emphasize the need for further research to elucidate underlying mechanisms. Future directions could address how the presence and severity of arteriolosclerosis interact with neurodegeneration and cognitive impairment in the context of blood–brain barrier permeability changes,[49] deposition and aggregation of proteins,[50] increased neuroinflammation,[51] additional vascular changes,[52] and enlarged perivascular spaces[53,54] in early disease stages.

Recent studies indicate that CAA is a significant risk factor for amyloid-related imaging abnormalities (ARIAs), with advanced CAA—characterized by amyloid deposits in the tunica media, fibrinoid necrosis, and splitting of blood vessel walls—being prevalent in ≈ 25% of patients with AD.[55] This prevalence aligns closely with the incidence of ARIAs observed in immunotherapy trials.[56] Moreover, the high rate of ARIAs and related hemorrhagic complications raises concerns about the risk–benefit ratio of these therapies in patients with AD and concurrent CAA.[57] Notably, participants with more than four microhemorrhages were excluded from the Aducanumab and Lecanemab trials due to an increased risk for ARIAs.[58–60] Given that the proposed mechanism for ARIAs is hypothesized to involve vascular injury or leakiness, it is thought that uncontrolled HTN or other vascular risks such as DM, high cholesterol, and smoking could contribute to higher incidence rates of these conditions.[61] There is limited knowledge concerning the risk of ARIAs associated with other vascular neuropathologies such as arteriolosclerosis and atherosclerosis of the circle of Willis due to the lack of or the use of biomarkers for these diseases. This lack of data poses significant risks as more individuals begin receiving amyloid-targeting drugs in the near future. These adverse effects are likely to continue given the additional undefined criteria for vascular neuropathologies that might contribute to ARIAs. Therefore, there is an urgent need to investigate how these therapeutics perform in patients with a higher vascular burden than those included in the trials. This is particularly crucial for diverse populations like Native American/American Indian, Latino/Hispanic, and Black/African American communities, who are disproportionately affected by these vascular factors compared to their White counterparts.[62]

### 4.1 | Methodological considerations: strengths and limitations

Our study has several limitations that overlap with previous neuropathological studies using NACC data. First, participants included in the NACC data set are from memory clinics, which are biased toward predominantly AD.[24,63] Second, most NACC participants, including those in this study, are White, and have advanced levels of education.[24,63] Third, due to few items in the cognitive batteries, the harmonized cognitive scores did not include the visuospatial domain, which is important to ADNC and LBD-induced cognitive deficits.[12,33] Fourth, our study does not address the potential contribution of other neuropathological combinations on cognition, such as TDP-43 pathology in limbic-predominant age-related TDP-43 encephalopathy (LATE). LATE, which has been reported to be linked to memory loss in later life, has also been associated with vascular pathologies, albeit without a clear pathophysiological link. Given the more recent attention to LATE, large pathological data are not yet available to fully address its interaction and concomitance with other common neuropathologies.[64] In our study, 45% lacked quantitative data on TDP-43 and hence were excluded. Another limitation that aligns with LATE is that our study does not investigate age-related tau astrogliopathy, which has been found to be associated with arteriolosclerosis and gross infarcts in a subsample of NACC participants.[65] Future studies are needed to address our defined objective across clinical and community cohorts that have LATE and age-related tau astrogliopathy neuropathological data in addition to vascular, ADNC, and LBD.

Despite the limitations, our study has numerous notable strengths in maximizing the available neuropathology data from NACC. The lack of comprehensive vascular variable recording across all ADRC necessitated the use of derived variables for reproducibility. We focused on dichotomized vascular pathologies and did not delve into the possibility of dose–response relationships. Future research could explore finer gradients of vascular pathologies and their interactions, providing a more nuanced understanding of vascular predictors on neuropsychological measures. Our approach of removing those with severe dementia (CDR = 3) allowed us to detect subtler cognitive changes. A second strength is the inclusion of both LBD and ADNC in our analysis, which has not been thoroughly done in previous analyses of NACC neuropathology data. Our analyses offer a comprehensive view of different vascular neuropathologies and their heterogeneity and provide insight on their contributions to cognitive scores in decedents without severe dementia.

Our study underscores the significant potential impact of arteriolosclerosis on cognitive scores among the investigated vascular pathologies. Further research is needed to elucidate these complex interactions and their implications for disease progression. In essence, our study highlights the importance of addressing vascular pathologies in future research to better understand their effects on cognition at various stages of the disease. This research could ultimately lead to more targeted and effective interventions for individuals with dementia or at risk for cognitive impairment.

## ACKNOWLEDGMENTS

The NACC database is funded by NIA/NIH Grant U24 AG072122. NACC data are contributed by the NIA-funded ADRC: P30 AG062429 (PI James Brewer, MD, PhD), P30 AG066468 (PI Oscar Lopez, MD), P30 AG062421 (PI Bradley Hyman, MD, PhD), P30 AG066509 (PI Thomas Grabowski, MD), P30 AG066514 (PI Mary Sano, PhD), P30 AG066530 (PI Helena Chui, MD), P30 AG066507 (PI Marilyn Albert, PhD), P30 AG066444 (PI John Morris, MD), P30 AG066518 (PI Jeffrey Kaye, MD), P30 AG066512 (PI Thomas Wisniewski, MD), P30 AG066462 (PI Scott Small, MD), P30 AG072979 (PI David Wolk, MD), P30 AG072972 (PI Charles DeCarli, MD), P30 AG072976 (PI Andrew Saykin, PsyD), P30 AG072975 (PI David Bennett, MD), P30 AG072978 (PI Neil Kowall, MD), P30 AG072977 (PI Robert Vassar, PhD), P30 AG066519 (PI Frank LaFerla, PhD), P30 AG062677 (PI Ronald Petersen, MD, PhD), P30 AG079280 (PI Eric Reiman, MD), P30 AG062422 (PI Gil Rabinovici, MD), P30 AG066511 (PI Allan Levey, MD, PhD), P30 AG072946 (PI Linda Van Eldik, PhD), P30 AG062715 (PI Sanjay Asthana, MD, FRCP), P30 AG072973 (PI Russell Swerdlow, MD), P30 AG066506 (PI Todd Golde, MD, PhD), P30 AG066508 (PI Stephen Strittmatter, MD, PhD), P30 AG066515 (PI Victor Henderson, MD, MS), P30 AG072947 (PI Suzanne Craft, PhD), P30 AG072931 (PI Henry Paulson, MD, PhD), P30 AG066546 (PI

Sudha Seshadri, MD), P20 AG068024 (PI Erik Roberson, MD, PhD), P20 AG068053 (PI Justin Miller, PhD), P20 AG068077 (PI Gary Rosenberg, MD), P20 AG068082 (PI Angela Jefferson, PhD), P30 AG072958 (PI Heather Whitson, MD), P30 AG072959 (PI James Leverenz, MD). CAH is funded by internal Stanford Propel Postdoctoral Fellowship, Neuroscience Scholars Program sponsored by Society for Neuroscience, Pathways to Neuroscience 5R25NS124528, and the Burroughs Wellcome Fund Postdoctoral Diversity Enrichment Program (PDEP). This work was funded by the National Institutes of Health ADSP-PHC U24 AG074855, the Alzheimer's Association AACSF-24-1307411, and the Iqbal Farrukh and Asad Jamal Fund.

## CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest. Author disclosures are available in the supporting information.

## CONSENT STATEMENT

All human subjects provided informed consent in which they were enrolled at the respective Alzheimer's Disease Research Center.

## DATA AVAILABILITY STATEMENT

All data used in the current analyses is available for download from the NACC (https://www.alz.washington.edu/).

## ORCID

*Cellas A. Hayes* https://orcid.org/0000-0002-6259-9456

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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:** Hayes CA, Young CB, Abdelnour C, et al. The impact of arteriolosclerosis on cognitive impairment in decedents without severe dementia from the National Alzheimer's Coordinating Center. *Alzheimer's Dement*. 2025;21:e70059. doi:https://doi.org/10.1002/alz.70059