


## RESEARCH ARTICLE

## Utility of cerebrovascular imaging biomarkers to detect cerebral amyloidosis

Matthew D. Howe<sup>1,2</sup>  | Megan R. Caruso<sup>1</sup> | Masood Manoochehri<sup>1</sup> | Zachary J. Kunicki<sup>2</sup> | Sheina Emrani<sup>3</sup> | James L. Rudolph<sup>4,5</sup> | Edward D. Huey<sup>1,2</sup> | Stephen P. Salloway<sup>1,2</sup> | Hwamee Oh<sup>2</sup> | for the Alzheimer's Disease Neuroimaging Initiative

<sup>1</sup>Butler Hospital Memory & Aging Program, Providence, Rhode Island, USA

<sup>2</sup>Department of Psychiatry and Human Behavior, Brown University, Providence, Rhode Island, USA

<sup>3</sup>University of Pennsylvania Perelman School of Medicine, Philadelphia, Pennsylvania, USA

<sup>4</sup>Center of Innovation in Long-Term Services and Supports, Providence VA Medical Center, Providence, Rhode Island, USA

<sup>5</sup>Department of Medicine, The Warren Alpert Medical School of Brown University, Providence, Rhode Island, USA

## Correspondence

Matthew Howe, Butler Hospital Memory & Aging Program, 345 Blackstone Boulevard, Providence, RI 02906, USA.

Email: [matthew\\_howe@brown.edu](mailto:matthew_howe@brown.edu)

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

## Funding information

NIMH, Grant/Award Number: 2R25MH101076-06A1; NIA, Grant/Award Numbers: 2P01AG051449-06, R01AG068990; National Institutes of Health, Grant/Award Number: U01 AG024904; Department of Defense, Grant/Award Number: W81XWH-12-2-0012; National Institute of Biomedical Imaging and Bioengineering; Alzheimer's Association; Alzheimer's Drug Discovery Foundation; Araclon Biotech; BioClinica, Inc.; Biogen;

## Abstract

**INTRODUCTION:** The relationship between cerebrovascular disease (CVD) and amyloid beta ( $A\beta$ ) in Alzheimer's disease (AD) is understudied. We hypothesized that magnetic resonance imaging (MRI)-based CVD biomarkers—including cerebral microbleeds (CMBs), lacunar infarction, and white matter hyperintensities (WMHs)—would correlate with  $A\beta$  positivity on positron emission tomography ( $A\beta$ -PET).

**METHODS:** We cross-sectionally analyzed data from the Alzheimer's Disease Neuroimaging Initiative (ADNI,  $N = 1352$ ). Logistic regression was used to calculate odds ratios (ORs), with  $A\beta$ -PET positivity as the standard-of-truth.

**RESULTS:** Following adjustment, WMHs (OR = 1.25) and superficial CMBs (OR = 1.45) remained positively associated with  $A\beta$ -PET positivity ( $p < 0.001$ ). Deep CMBs and lacunes exhibited a varied relationship with  $A\beta$ -PET in cognitive subgroups. The combined diagnostic model, which included CVD biomarkers and other accessible measures, significantly predicted  $A\beta$ -PET (pseudo- $R^2 = 0.41$ ).

**DISCUSSION:** The study highlights the translational value of CVD biomarkers in diagnosing AD, and underscores the need for more research on their inclusion in diagnostic criteria. **ClinicalTrials.gov:** ADNI-2 (NCT01231971), ADNI-3 (NCT02854033).

## KEYWORDS

ADNI, Alzheimer's disease, amyloid beta, cerebrovascular disease, magnetic resonance imaging, positron emission tomography, small vessel disease

This is an open access article under the terms of the [Creative Commons Attribution](https://creativecommons.org/licenses/by/4.0/) License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.

© 2024 The Author(s). *Alzheimer's & Dementia* published by Wiley Periodicals LLC on behalf of Alzheimer's Association.

Bristol-Myers Squibb Company; CereSpir, Inc.; Cogstate; Eisai Inc.; Elan Pharmaceuticals, Inc.; Eli Lilly and Company; EuroImmun; F. Hoffmann-La Roche Ltd; Genentech, Inc.; Fujirebio; GE Healthcare; IXICO Ltd.; Janssen Alzheimer Immunotherapy Research & Development, LLC.; Johnson & Johnson Pharmaceutical Research & Development LLC.; Lumosity; Lundbeck; Merck & Co., Inc.; Meso Scale Diagnostics, LLC.; NeuroRx Research; Neurotrack Technologies; Novartis Pharmaceuticals Corporation; Piramal Imaging; Servier; Takeda Pharmaceutical Company; Transition Therapeutics; Canadian Institutes of Health Research

## Highlights

- Cerebrovascular biomarkers linked to amyloid beta ( $A\beta$ ) in Alzheimer's disease (AD).
- White matter hyperintensities and cerebral microbleeds reliably predict  $A\beta$ -PET positivity.
- Relationships with  $A\beta$ -PET vary by cognitive stage.
- Novel accessible model predicts  $A\beta$ -PET status.
- Study supports multimodal diagnostic approaches.

## 1 | BACKGROUND

Alzheimer's disease (AD), the leading cause of dementia worldwide, is biologically defined by the presence of amyloid beta ( $A\beta$ ) plaques and tau neurofibrillary tangles.<sup>1,2</sup> Although understudied, neuropathological and neuroimaging studies indicate that cerebrovascular disease (CVD) is a common finding in patients with AD, with AD and CVD co-pathology accounting for  $\approx 20\%$ – $30\%$  of cases in some cohorts.<sup>3–5</sup> The rising incidence of AD, attributed partly to increased life expectancy, is also driven by modifiable CVD risk factors, including hypertension, diabetes mellitus, and hyperlipidemia.<sup>6–8</sup> These modifiable CVD risk factors have been shown to interact with age, sex, and apolipoprotein E (APOE)  $\epsilon 4$  genotype, potentially influencing susceptibility to AD via actions on glial cells, changes in blood–brain barrier structure/function, and decreased perivascular clearance of  $A\beta$  peptides in animal models.<sup>7,9–11</sup> Furthermore, CVD may promote perivascular  $A\beta$  deposition that exerts downstream effects on the neurovascular unit (NVU), including basement membrane fibrosis, perivascular inflammation, and  $A\beta$ -mediated vasoconstriction—with potential additive and synergistic effects on cognitive decline in AD.<sup>11–14</sup> Therefore, the relationship between CVD and AD may be bidirectional along the progression of pathology and clinical severity.

Much interest has been paid to using structural neuroimaging to identify small vessel disease and vascular dementia *in vivo*, with radiopathologic studies indicating that structural magnetic resonance imaging (MRI) features of CVD, including cerebral microbleeds (CMBs) and white matter hyperintensities (WMHs), are predictive of perivascular  $A\beta$  plaques and cerebral amyloid angiopathy (CAA) on autopsy.<sup>2,7,15–17</sup> The use of CVD measures to aid in detecting total  $A\beta$  burden in AD (i.e., parenchymal and vascular plaques) is understudied,<sup>13</sup> but could be applied clinically to aid in selecting patients for testing with positron emission tomography ( $A\beta$ -PET) or interpreting the results of novel blood biomarkers. However, prior to clinical use, there is a need to characterize the potential utility of CVD biomarkers in identifying  $A\beta$  pathology and estimating AD risk in various stages of cognitive decline, which may vary given the potential additive burden of CVD and AD pathology on cognition.<sup>5,7</sup>

Seeking to identify a cerebrovascular “signature” of  $A\beta$  pathology in AD, we investigated the degree to which CVD neuroimag-

ing biomarkers—including CMBs, lacunar infarction, and WMHs—correlate with  $A\beta$ -PET positivity, a core biomarker of AD under the Amyloid/Tau/Neurodegeneration framework.<sup>2</sup> We selected these CVD biomarkers due to: (1) high-quality neuropathological evidence linking them to relevant age-related cerebral small vessel diseases and/or neuropathology of AD (i.e., Thal, Braak, or Consortium to Establish a Registry for Alzheimer's Disease [CERAD] staging)<sup>16</sup>; (2) the utility of incorporating these biomarkers into existing algorithms for small vessel disease detection, such as the Boston Neuroimaging Criteria 2.0 or the Cerebral Small Vessel Disease Score<sup>4,15,17</sup>; as well as (3) relative ease of assessment with clinical MRI protocols that are already used in health care settings.<sup>18</sup> Based on the existing literature, we hypothesized that these CVD biomarkers would exhibit independent, positive correlations with  $A\beta$ -PET positivity, and further sought to explore how their inclusion, alongside other accessible clinical, genetic, and neuroimaging measures, might improve prediction of  $A\beta$ -PET positivity in AD cases and controls.<sup>19–24</sup>

To test these hypotheses, we used participant data from the Alzheimer's Disease Neuroimaging Initiative (ADNI), a well-described observational cohort study of older adults with AD.<sup>25,26</sup> Taking advantage of this cohort enriched for AD, we primarily sought to characterize the associations between commonly identified MRI-visible CVD measures and  $A\beta$ -PET positivity. We further explored the diagnostic performance of an accessible algorithm, which includes demographic (age, sex), genetic (apolipoprotein E [APOE]  $\epsilon 4$  status), cognitive (Montreal Cognitive Assessment [MoCA]), and MRI-visible CVD measures.<sup>25,26</sup> To inform future studies in specific clinical populations, we additionally stratified participants into cognitively unimpaired (CU), mild cognitive impairment (MCI), and dementia cohorts for further analyses.

## 2 | METHODS

### 2.1 | Participants

The ADNI was launched in 2003 as a public-private partnership, led by Principal Investigator Michael W. Weiner. This study utilizes data obtained from ADNI-2 (NCT01231971) and ADNI-3 (NCT02854033), two recent phases of this landmark study that has collected data at

over 50 sites in North America and has been used to develop clinical, imaging, genetic, and biochemical biomarkers for the early detection and tracking of AD over the past 20 years ([adni.loni.usc.edu](http://adni.loni.usc.edu)).<sup>25,26</sup> The primary goal of ADNI has been to test whether serial MRI, PET, other biological markers, as well as clinical and neuropsychological assessments can be combined to measure the progression of MCI and early AD.

Participants in ADNI are 55–90 years of age, and either English or Spanish speaking. Exclusions include inability to tolerate a blood draw, contraindication to neuroimaging, evidence of infarction or other focal brain lesion (those with multiple lacunes or lacunes in a critical memory structure are excluded), any significant neurologic disease, major recent psychiatric disorders, or significant systemic illness or medical conditions. Baseline diagnoses were determined using a combination of cutoff scores from several instruments including the Mini-Mental Status Examination (MMSE), Cognitive Change Index (CCI), Weschler Logical Memory Test, and Clinical Dementia Rating (CDR) Staging Instrument. Based on these assessments, participants were assigned a diagnostic category according to expert consensus of cognitively normal (CN), subjective memory complaint (SMC), mild cognitive impairment (MCI), and AD dementia. Written informed consent was obtained from all participants or authorized representatives prior to the start of study procedures, with local institutional review boards and research ethics boards providing oversight for the study. The authors certify that the study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments.

## 2.2 | ADNI data set

For the current analysis, we downloaded demographic, neuroimaging, and genetic data from the Laboratory of Neuro-Imaging (LONI) site where ADNI data is housed, including A $\beta$ -PET, structural MRI, and APOE genotype determined by the Illumina Human BeadChip panel.<sup>27</sup> Due to differences in imaging protocols and PET tracers in ADNI-1, we limited our analysis to participants who screened for ADNI-2 and ADNI-3 ( $N = 1430$ ). After a review of screening and baseline visit data, 78 individuals with unknown A $\beta$ -PET status ( $N = 76$ ) or absent clinical diagnosis ( $N = 2$ ) were excluded to yield our final sample ( $N = 1352$ ).

Data frames were downloaded from LONI using the *adnimerge* R package (version 0.1.1). We obtained up-to-date demographic, cognitive, and APOE genotypes from the Alzheimer's Disease Cooperative Study (ADNIMERGE). In addition, we obtained imaging data including whole and regional brain volumes from University of California at San Francisco (ADNIMERGE), WMH and infarct data from the Center for Neuroscience at University of California at Davis (UCD\_WMH\_05\_02\_22, MRI\_INFARCTS\_01\_29\_21), region-specific CMB counts from the Mayo Clinic Aging and Dementia Imaging Research Laboratory (MAYOADIRL\_MRI\_MCH\_09\_07\_22), and florbetapir and florbetaben standardized uptake value ratio (SUVR) summary data from the University of California at Berkeley (UCBERKELEYAV45\_04\_26\_22, UCBERKELEYFBB\_04\_26\_22). For a detailed

## RESEARCH IN CONTEXT

- **Systematic review:** Our comprehensive review of the Alzheimer's disease (AD) radiopathologic literature underscored that although cerebrovascular biomarkers are well documented in small vessel disease, their individual and potentially additive effects in detecting amyloidosis are understudied. This highlighted the need for a focused study on how these biomarkers operate across different stages of AD, particularly as part of a multimodal diagnostic strategy.
- **Interpretation:** Our research newly demonstrates the unique and independent effects of cerebrovascular biomarkers in detecting amyloidosis in various cognitive stages of AD. This contribution improves the current understanding of specific cerebrovascular biomarkers across the AD spectrum, revealing nuanced relationships between these biomarkers and the disease.
- **Future directions:** Future studies should seek to examine how location-specific cerebrovascular factors affect cognitive and functional decline over time, explore integration with blood biomarkers to enhance diagnostic accuracy, and establish their validity across diverse populations in cohorts with vascular and other non-AD dementias.

summary of the standard imaging acquisition and analysis pipelines used in ADNI, see [Supplementary Methods](#). We last accessed the ADNI database on December 27, 2023.

## 2.3 | Determination of A $\beta$ positivity

Participants were classified as A $\beta$  positive or A $\beta$  negative based on A $\beta$ -PET SUVRs according to the standard analysis pipeline at the University of California at Berkeley (see [Supplementary Methods](#)). A $\beta$ -PET positivity was defined as SUVR >1.11 and SUVR >1.08 for florbetapir and florbetaben, respectively.<sup>28,29</sup> For quantitative comparisons, SUVR was transformed to a standardized Centiloid scale as described previously by Roysse et al.<sup>30</sup>

## 2.4 | Quantification of medial temporal lobe and white matter volumes

Using T1 and T2-weighted MRI images, WMH and medial temporal lobe (MTL) volumes were quantified by the Center for Neuroscience at University of California at Davis and the University of California at San Francisco, respectively, according to the standard FreeSurfer analysis pipeline (See [Supplementary Methods](#)). To control for inter-individual and disease stage-related variability in global atrophy, mean MTL and

total WMH volumes (WMHv) were normalized to whole brain volumes, and then log transformed.

## 2.5 | Quantification and localization of CMBs

“Definite” or “probable” CMBs were identified and reported by the Mayo Clinic Aging and Dementia Imaging Research Laboratory by review of T2\* gradient recall echo images according to the standard analysis pipeline (see [Supplementary Methods](#)). We divided CMBs into lobar (cortical and cerebellar) or deep (subcortical, periventricular white matter, and brainstem regions) as described previously by Charidimou et al.<sup>15</sup> We then classified participants by the presence or absence of superficial and deep CMBs, respectively.

## 2.6 | Quantification of lacunar infarcts

Lacunar infarcts were identified by a physician specifically trained in interpretation of MRI, with infarct size, location, and other imaging characteristics recorded according to the standard analysis pipeline at the Center for Neuroscience at University of California Davis (see [Supplementary Methods](#)). For this analysis, we considered only lesions equal to or greater than 3 mm in size as cerebral infarcts. We then classified participants based on the presence or absence of infarcts.<sup>31</sup>

## 2.7 | Covariates

We adjusted all models for demographics (age, sex), cognition (MoCA score), and APOE genotype (number of  $\epsilon 4$  alleles).

## 2.8 | Statistics

Data cleaning, analysis, and plotting were conducted in R using the *mice*, *psfmi*, *pROC*, and *ggplot2* packages. Missing data comprised no more than 5% of the overall sample and were handled by multiple imputation by chained equations (Table S1). Descriptive statistics were calculated for each group and reported as mean (SD), median (IQR), and N (%) according to Rubin's rules.<sup>32</sup> Adjusted odds ratios (ORs) were calculated by logistic regression with dichotomized A $\beta$ -PET status as the outcome and reported with a 95% confidence interval (CI), with statistical significance determined by the Wald test. For evaluation of regression model goodness-of-fit and parsimony, we used prediction model pooling, selection, and performance evaluation across multiply imputed data sets to calculate the Nagelkerke Pseudo-R<sup>2</sup> and Akaike information criterion (AIC). The Hosmer-Lemeshow test was used to test goodness-of-fit compared to the null model, with  $p > 0.05$  denoting acceptable model fit to the observed data.

Exploratory receiver-operating characteristic (ROC) analysis was performed to calculate area under the curve (AUC) as well as diagnostic sensitivity, specificity, and accuracy at Youden's optimal cutoff.

Nested models were created using forward variable selection: Step 1: Base (age, sex, APOE  $\epsilon 4$  genotype), Step 2: Base + MTLv, and Step 3: Base + MTLv + CVD (see Table S2 for further details on model components). Nested models with forced forward selection were compared using the likelihood ratio test for multiply imputed data, reported as the  $d_3$  statistic with degrees of freedom (df) corresponding to difference in number of predictors between model steps. Statistical significance was defined by a threshold of  $p < 0.05$ .

## 3 | RESULTS

### 3.1 | Participant characteristics

To assess the relationships between CVD biomarkers and the outcome (A $\beta$ -PET positivity), we analyzed cross-sectional screening visit data for ADNI-2 and ADNI-3 ( $N = 1352$ ), and then subdivided participants based on cognitive stage at screening (Table 1). For the purposes of our analysis, participants categorized at their screening visit as cognitively normal or experiencing SMCs were classified as cognitively unimpaired (CU,  $N = 611$ ), encompassing 198 (32.4%) A $\beta$ -PET positive and 413 (67.6%) A $\beta$ -PET negative participants. The MCI cohort ( $N = 531$ ) contained 294 (55.4%) A $\beta$ -PET positive and 237 (44.6%) A $\beta$ -PET negative participants. Finally, the dementia cohort (DEM,  $N = 210$ ) was predominantly A $\beta$ -PET positive ( $N = 181$  [86.2%]), with a smaller proportion A $\beta$ -PET negative participants ( $N = 29$  [13.8%]) (Table 1, Table S1).

### 3.2 | Development of the adjusted model for prediction of A $\beta$ -PET positivity

We next sought to gauge the relationship between specific MRI markers of CVD neuropathology and A $\beta$ -PET positivity in the overall cohort using a model that was adjusted by accessible measures of vascular risk (age, sex, APOE  $\epsilon 4$ ), cognitive impairment (MoCA), and AD-related atrophy (MTL volume [MTLv]) (Table 2). After adjustment for these covariates, we identified statistically significant effects of MRI-based CVD biomarkers. We found that increased WMHv (OR = 1.25 [95% CI: 1.20–1.29],  $p < 0.001$ ) and presence of one or more superficial CMBs (OR = 1.45 [95% CI: 1.31–1.61],  $p < 0.001$ ) as being associated with A $\beta$ -PET positivity in the overall cohort (Table 2). We did not identify any statistically significant relationships between deep CMBs (OR = 0.88 [95% CI: 0.74–1.04],  $p = 0.12$ ) or lacunar infarction (OR = 1.01 [95% CI: 0.89–1.15],  $p = 0.40$ ) and A $\beta$ -PET positivity in the overall cohort (Table 2). The adjusted model exhibited a pseudo-R<sup>2</sup> = 0.41, consistent with a large effect size for goodness-of-fit.

Based on these findings, we next sought to use this model to understand how the relationships between CVD biomarkers and A $\beta$ -PET positivity may differ across different cognitive stages. Thus we repeated this regression analysis in the CU, MCI, and DEM cohorts described in the following sections, which are organized by CVD biomarker of interest.

**TABLE 1** Baseline demographic and clinical characteristics.

Characteristic <sup>a</sup>	Cognitively unimpaired		Mild cognitive impairment		Dementia	
	Aβ- (N = 413)	Aβ+ (N = 198)	Aβ- (N = 237)	Aβ+ (N = 294)	Aβ- (N = 29)	Aβ+ (N = 181)
Age, years	70 (6)	73 (7)	70 (8)	73 (7)	76 (8)	74 (8)
Sex, male	184 (45%)	72 (36%)	134 (57%)	160 (54%)	24 (83%)	100 (55%)
Education, years	16.78 (2.34)	16.53 (2.48)	16.35 (2.46)	16.29 (2.61)	16.62 (2.24)	15.51 (2.61)
APOE ε4, alleles						
0	313 (77%)	97 (49%)	180 (78%)	91 (31%)	23 (79%)	47 (26%)
1	87 (21%)	89 (45%)	46 (20%)	151 (52%)	6 (21%)	88 (49%)
2	6 (1.5%)	11 (5.6%)	5 (2.2%)	51 (17%)	0 (0%)	43 (24%)
MoCA, score	26.05 (2.58)	25.65 (2.51)	23.7 (3.0)	22.5 (3.3)	18.2 (4.0)	16.9 (4.6)
MTLv, normalized (log)	-4.21 (0.10)	-4.22 (0.10)	-4.23 (0.10)	-4.28 (0.11)	-4.31 (0.13)	-4.38 (0.12)
WMHv, normalized (log)	-6.84 (1.33)	-6.24 (1.42)	-6.47 (1.40)	-6.03 (1.36)	-6.02 (1.01)	-5.69 (1.13)
CMBs, any location (1+)	84 (21%)	47 (24%)	58 (25%)	95 (32%)	6 (21%)	73 (41%)
CMBs, superficial (1+)	61 (15%)	42 (21%)	45 (19%)	82 (28%)	5 (18%)	66 (37%)
CMBs, deep (1+)	27 (6.6%)	10 (5.1%)	12 (5.1%)	27 (9.2%)	1 (3.6%)	18 (10%)
Infarct (1+)	24 (6.8%)	22 (12%)	17 (8.7%)	23 (9.1%)	1 (4.3%)	7 (4.5%)
Aβ-PET burden, cl <sup>b</sup>	4 (9)	55 (31)	1 (10)	73 (33)	-3 (14)	88 (30)

Abbreviations: APOE, Apolipoprotein E; CMBs, Cerebral Microbleeds; MoCA, Montreal Cognitive Assessment; MTLv, Medial temporal Lobe Volume; WMHv, White Matter Hyperintensity Volume.

Note: See Table S1 for missing values.

<sup>a</sup>Mean (SD); n (%); Median (IQR).

<sup>b</sup>CL, centiloids.

**TABLE 2** Prediction of Aβ-PET positivity in the overall cohort.

Characteristic	OR <sup>a</sup>	95% CI <sup>b</sup>	p-value
Age, years	1.05	1.04, 1.06	<0.001
Sex, male	0.66	0.60, 0.71	<0.001
APOE ε4, alleles	5.66	5.24, 6.11	<0.001
MoCA, score	0.89	0.88, 0.90	<0.001
MTLv, normalized (log)	0.12	0.08, 0.17	<0.001
WMHv, normalized (log)	1.25	1.20, 1.29	<0.001
CMBs, superficial (1+)	1.45	1.31, 1.61	<0.001
CMBs, deep (1+)	0.88	0.74, 1.04	0.12
Infarction (1+)	1.01	0.89, 1.15	0.90

Abbreviations: APOE, Apolipoprotein E; CMBs, Cerebral Microbleeds; MoCA, Montreal Cognitive Assessment; MTLv, Medial temporal Lobe Volume; PET, Positron Emission Tomography; WMHv, White Matter Hyperintensity Volume.

<sup>a</sup>OR = Odds ratio.

<sup>b</sup>CI, Confidence interval.

N = 1352.

### 3.3 | Cerebral microbleeds

We hypothesized that the presence of superficial CMBs would be associated with Aβ-PET positivity across all cognitive stages. Examining each cohort separately, we identified a consistent and statistically significant relationship between superficial CMBs and Aβ-PET positivity, as observed in the CU (OR = 1.38 [95% CI: 1.18–1.62], *p* < 0.001),

MCI (OR = 1.37 [95% CI: 1.17–1.61], *p* < 0.001), and DEM cohorts (OR = 2.17 [95% CI: 1.46–3.29], *p* < 0.001; Table 3; Figure 1, panel 1).

Conversely, when examining deep CMBs, we hypothesized that they would not significantly predict Aβ-PET status for any cognitive stage. However, our analysis revealed differences in these relationships depending on cognitive stage: a negative association in the CU cohort (OR = 0.51 [95% CI: 0.39–0.66], *p* < 0.001) contrasted with a positive association in the MCI (OR = 1.32 [95% CI: 1.02–1.72], *p* = 0.037) and DEM cohorts (OR = 2.99 [95% CI: 1.36–7.33], *p* = 0.011; Table 3; Figure 1, panel 2). These data indicate a potential complex relationship between deep CMBs and Aβ-PET that appears to be dependent on cognitive stage.

### 3.4 | Lacunar infarction

We next sought to characterize how lacunar infarction might correlate with Aβ-PET positivity. Given the relatively low frequency of lacunar infarcts identified in our sample, we were unable to separately analyze infarct location or size-dependent effects. Regardless, analyzing each cognitive stage separately revealed a significant association of one or more infarcts in the CU cohort (OR = 1.31 [95% CI: 1.09–1.58], *p* = 0.005), but not in the MCI (OR = 0.89 [95% CI: 0.73–1.08], *p* = 0.200) or DEM cohorts (OR = 1.28 [95% CI: 0.74–2.28], *p* = 0.400; Table 3; Figure 1, panel 3). There was significant variability, highlighting a heterogeneous relationship between these lesions and Aβ-PET.

**TABLE 3** Adjusted cerebrovascular predictors of A $\beta$ -PET positivity by cohort.

Characteristic	OR <sup>a</sup>	95% CI <sup>b</sup>	p-value
<b>CU cohort (N = 611)</b>			
CMBs, superficial (1+)	1.38	1.18, 1.62	<0.001
Infarction (1+)	1.31	1.09, 1.58	0.005
WMHv, normalized (log)	1.25	1.19, 1.31	<0.001
CMBs, deep (1+)	0.51	0.39, 0.66	<0.001
<b>MCI cohort (N = 531)</b>			
CMBs, superficial (1+)	1.37	1.17, 1.61	<0.001
CMBs, deep (1+)	1.32	1.02, 1.72	0.037
WMHv, normalized (log)	1.15	1.09, 1.21	<0.001
Infarction (1+)	0.89	0.73, 1.08	0.20
<b>Dementia cohort (N = 210)</b>			
CMBs, deep (1+)	2.99	1.36, 7.33	0.011
CMBs, superficial (1+)	2.17	1.46, 3.29	<0.001
WMHv, normalized (log)	1.54	1.33, 1.79	<0.001
Infarction (1+)	1.28	0.74, 2.28	0.40

Note: See Table S3 for the full model with covariates.

<sup>a</sup>Adjusted odds ratios (OR) were adjusted for age, sex, APOE genotype, cognition (MoCA), and MTL volume.

<sup>b</sup>CI, confidence interval; CMBs, Cerebral Microbleeds; WMHv, White Matter Hyperintensity Volume.

### 3.5 | White matter hyperintensities

We next investigated the predictive value of WMHv (normalized to whole brain volume) for A $\beta$ -PET positivity, postulating that the effects would be consistent across the disease course. We found that increased WMHv was a significant predictor of A $\beta$ -PET positivity across all disease stages: CU (OR = 1.25 [95% CI: 1.19–1.31],  $p < 0.001$ ), MCI (OR = 1.15 [95% CI: 1.09–1.21],  $p < 0.001$ ), and DEM (OR = 1.54 [95% CI: 1.33–1.79],  $p < 0.001$ ; Table 3; Figure 1, panel 4). These results remained significant after adjustment for other CVD measures, and additional covariates, indicating a consistent and strong relationship between WMHv and A $\beta$ -PET positivity across the cognitive spectrum, irrespective of MTL atrophy or whole brain volume.

### 3.6 | Added benefit to assessing CVD biomarkers to predict A $\beta$ -PET positivity

To evaluate the influence of cumulative CVD burden on the likelihood of A $\beta$ -PET positivity, and to model how these biomarkers might be used in the context of a clinical workup, we next employed nested logistic regression models in our analysis of the overall cohort. Step 1 (Base) included participant demographics (age, sex), genetic screening (APOE  $\epsilon$ 4), and cognition (MoCA). Step 2 (Base + MTLv) included the same variables, with the addition of MTLv as a clinically relevant surrogate for AD-related atrophy. Finally, Step 3 (Base + MTLv + CVD) incorporated our CVD biomarkers of interest (superficial and deep CMBs, lacunar infarcts, and WMHv). To compare the “added benefit”

for each model step, we examined the change in AIC ( $\Delta$  AIC) values between nested model steps, with negative values indicating improved parsimony in model prediction of A $\beta$ -PET positivity (i.e., improved goodness-of-fit without substantially increasing model complexity). For a list of these variables for each model step in tabular format, see Table S2.

In the overall cohort, our base model included age, sex, APOE  $\epsilon$ 4 genotype, and cognition (MoCA) as covariates (Step 1: pseudo- $R^2 = 0.38$ ; Table 4). As expected, we found that assessing MTL volume (MTLv), a commonly used measure of atrophy, enhanced model fit (Step 2: pseudo- $R^2 = 0.39$ ,  $\Delta$  AIC =  $-11.43$ ,  $d_3[1] = 11.33$ ,  $p = 0.001$ ; Table 4). It is notable that further improvements in fit and parsimony were observed upon adding CVD biomarkers to the model, even when MTL atrophy had already been included (Step 3: pseudo- $R^2 = 0.41$ ,  $\Delta$  AIC =  $-15.78$ ,  $d_3[4] = 5.30$ ,  $p < 0.001$ ). These findings indicate that for the overall cohort, inclusion of CVD biomarkers produced additional benefits to model fit without increasing complexity (i.e., the model became more parsimonious).

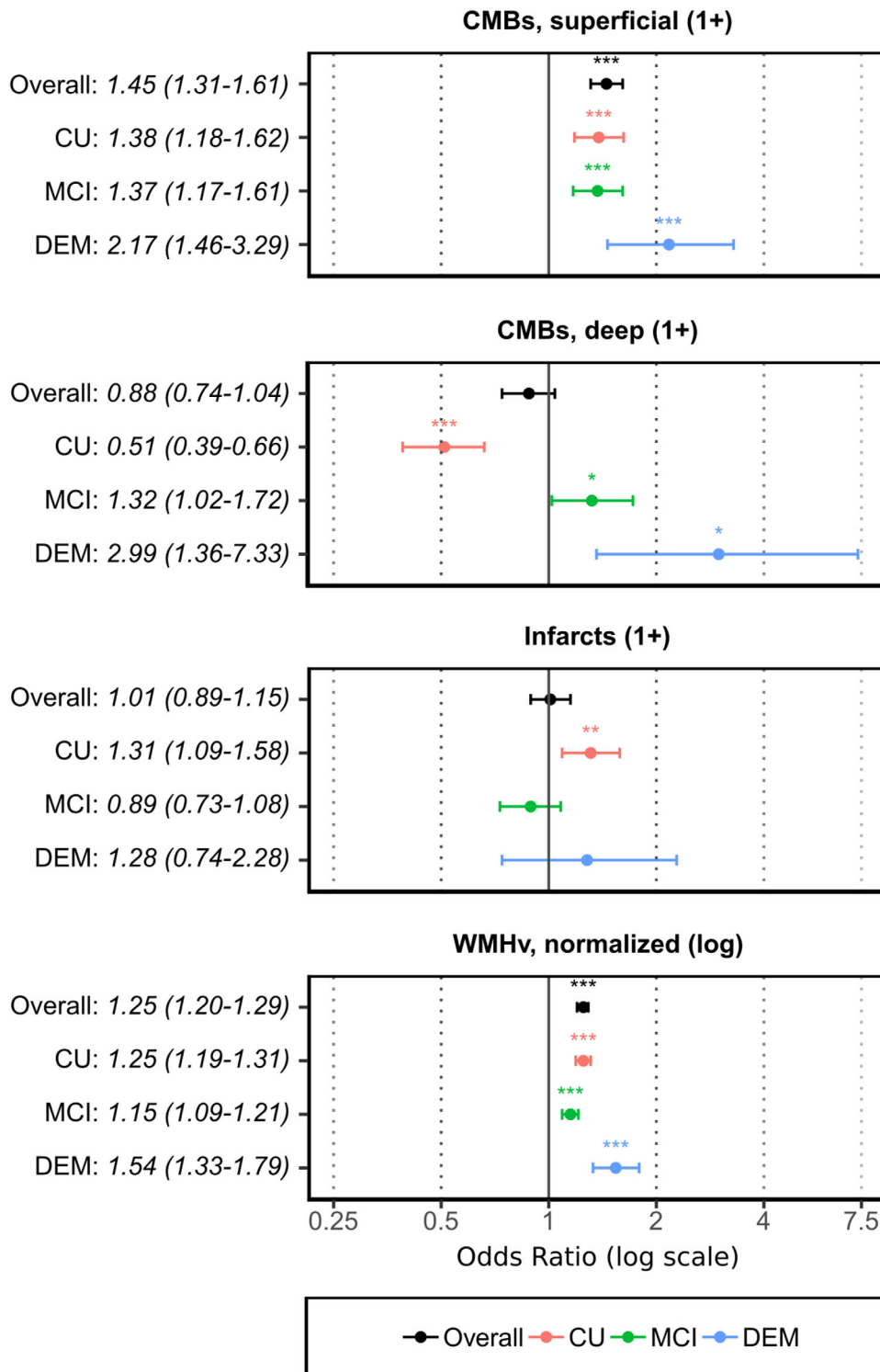
Repeating this stepwise analysis across cognitive stages, model parsimony improved when CVD biomarkers, but not MTLv, were added to the workup of preclinical AD in the CU cohort ( $\Delta$  AIC =  $-5.53$ ,  $d_3[4] = 3.22$ ,  $p = 0.012$ ). However, there was no consistent further benefit to prediction of A $\beta$ -PET positivity for the later disease stages when either MTLv or CVD biomarkers were added (Tables S3 and S4). Regardless, for the combined accessible model (i.e., ‘Step 3’: Base + MTLv + CVD), we observed moderate to large effect sizes for the prediction of A $\beta$ -PET positivity across all cohorts, with pseudo- $R^2$  values of 0.24, 0.37, and 0.45 in the CU, MCI, and DEM cohorts, respectively (Figure S1).

### 3.7 | Exploratory analysis of diagnostic performance by cohort

We finally sought to explore the diagnostic performance of our combined accessible model in discriminating between A $\beta$ -positive and A $\beta$ -negative individuals with ROC analysis, using A $\beta$ -PET as the standard-of-truth. In the CU cohort, we identified a model AUC of 0.77 (95% CI: 0.75–0.78), consistent with moderate discriminatory ability between A $\beta$ -PET positives and negatives using the predicted probabilities estimated by the model. In the MCI cohort, we identified slightly improved discrimination between A $\beta$ -PET positives and negatives (AUC = 0.81 [95% CI: 0.80–0.83]); in the DEM cohort, the model exhibited the highest discriminatory ability between A $\beta$ -PET positives and negatives (AUC = 0.90 [95% CI: 0.88–0.91]). Additional data exploring the diagnostic performance of the combined accessible model, including ROC curves and histograms with fitted probability values, are displayed in Figure S2 and Table S5.

## 4 | DISCUSSION

In recent years there has been a growing emphasis on integrating multimodal biomarkers (genetic, fluid, and neuroimaging measures) to inform further workup of AD and to enhance the specificity of cognitive



**FIGURE 1** Differential prediction of Aβ-PET positivity by CVD-related MRI findings. Forest plots show the adjusted odds ratios (ORs) with 95% confidence intervals (CIs) for each cohort: Cognitively unimpaired (CU, N = 611, red), mild cognitive impairment (MCI, N = 531, green), and dementia (DEM, N = 210, blue), compared to the overall effect (black). ORs were derived from logistic regression models adjusted for relevant covariates. Cerebral microbleeds (CMBs) and white matter hyperintensity volume (WMHv) are shown to be significant predictors in varying degrees across cohorts. Lacunar infarcts were significant predictors in the CU cohort, only. Statistical significance determined by the Wald test is denoted as follows: \*p < 0.05, \*\*p < 0.01, \*\*\*p < 0.001.

**TABLE 4** Prediction of A $\beta$ -PET positivity with nested models in the overall cohort.

Characteristic	Model 1: Base (Pseudo-R <sup>2</sup> = 0.38)			Model 2: Base + MTLv <sup>1</sup> (Pseudo-R <sup>2</sup> = 0.39)			Model 3: Base + MTLv <sup>1</sup> + CVD <sup>2</sup> (Pseudo-R <sup>2</sup> = 0.41)		
	OR <sup>a</sup>	95% CI <sup>b</sup>	p-value	OR <sup>a</sup>	95% CI <sup>b</sup>	p-value	OR <sup>a</sup>	95% CI <sup>b</sup>	p-value
Age, years	1.08	1.07, 1.08	<0.001	1.07	1.06, 1.08	<0.001	1.05	1.04, 1.06	<0.001
Sex, male	0.67	0.62, 0.73	<0.001	0.66	0.60, 0.71	<0.001	0.66	0.60, 0.71	<0.001
APOE $\epsilon$ 4, alleles	5.70	5.29, 6.15	<0.001	5.63	5.22, 6.08	<0.001	5.66	5.24, 6.11	<0.001
MoCA, score	0.86	0.85, 0.87	<0.001	0.89	0.88, 0.90	<0.001	0.89	0.88, 0.90	<0.001
MTLv, normalized (log)	-	-	-	0.10	0.07, 0.15	<0.001	0.12	0.08, 0.17	<0.001
WMHv, normalized (log)	-	-	-	-	-	-	1.25	1.20, 1.29	<0.001
CMBs, superficial (1+)	-	-	-	-	-	-	1.45	1.31, 1.61	<0.001
CMBs, deep (1+)	-	-	-	-	-	-	0.88	0.74, 1.04	0.120
Infarction (1+)	-	-	-	-	-	-	1.01	0.89, 1.15	0.900

Note: See Table S2 for description of nested model steps.

See Table S3 for nested models by cohort.

<sup>a</sup>OR = odds ratio.

<sup>b</sup>CI, confidence interval.

N = 1352.

testing.<sup>2,33</sup> Our study extends this paradigm by incorporating accessible biomarkers of CVD into a model that already includes baseline demographics (age, sex), cognitive screening (MoCA), genetic information (APOE genotyping), along with clinically accessible neuroimaging measures of brain atrophy (MTL volume). These findings emphasize the underappreciated role of CVD biomarkers in AD diagnostics, and highlight their potential to provide a more holistic evaluation of AD and mixed pathologies.

Our findings underscore the need to consider each CVD biomarker distinctly in AD diagnostics and progression, a significant gap in the literature. For example, prior work indicates that the presence superficial “lobar” CMBs are highly specific to CAA.<sup>15</sup> Our finding of superficial CMBs’ uniformly positive association with A $\beta$ -PET across cognitive stages aligns with prior studies and the Boston Neuroimaging Criteria 2.0, a widely accepted diagnostic strategy for CAA.<sup>15,34</sup> Deep CMBs (subcortical, periventricular, or brainstem) are less well characterized and may relate to mixed small vessel pathologies, including hypertensive vasculopathy.<sup>35,36</sup> However, we also found that deep CMBs displayed a biphasic relationship with A $\beta$ -PET positivity, marked by a negative association in the CU cohort, and a positive one in later stages of MCI and dementia due to AD. Although this requires further study, it is possible that mixed small vessel disease etiologies, affecting deeper brain regions, may explain the paradoxical positive association in MCI and dementia due to higher overall CVD burden contributing to clinically overt cognitive impairment.<sup>5,36–38</sup>

In addition, WMH has been increasingly recognized as a marker of small vessel disease and is posited to contribute to cognitive decline in AD. Although mounting evidence links increased WMHv to A $\beta$ , tau, and small vessel neuropathology, other studies suggest it may reflect AD-related Wallerian degeneration in later disease stages.<sup>24,39–41</sup> Our findings of a consistent association between WMH and A $\beta$ -PET positivity across all cognitive stages suggest a stable and independent relationship with A $\beta$  neuropathology. The reproducibility across

cognitive stages, even after adjusting for other variables (including normalization of WMH to whole brain volume), further emphasizes WMH as a promising structural biomarker of A $\beta$  pathology. This result echoes findings of longitudinal studies that link WMH to upstream A $\beta$  accumulation and further progression of disease,<sup>42,43</sup> rather than a downstream side-effect of Wallerian degeneration secondary to neurodegeneration associated with later disease stages. More work is needed to examine the performance of WMH alongside other CVD biomarkers in prediction of future disease progression.

Asymptomatic infarction is an understudied biomarker in AD and small vessel disease, due in part to challenges inherent in the variable size/distribution of pathology (cortical vs sub-cortical/lacunar), unclear timing of injury (“silent” injury), as well as the underlying etiology (thrombotic, micro-embolic, or watershed infarction).<sup>16,22,44,45</sup> Although we were not sufficiently powered to analyze these subtypes of stroke, or able to determine timing given the cross-sectional design, taken together as a whole, we found that the presence of lacunar infarction was significantly associated with A $\beta$ -PET positivity in preclinical AD, but not in MCI or dementia groups. Whereas longitudinal analysis in a stroke cohort would be required to assess temporal relationships to A $\beta$  positivity, our findings in preclinical AD are in line with basic science research linking stroke to A $\beta$  deposition and impairment in perivascular A $\beta$  clearance pathways as a potential driver of AD, rather than an incidental finding.<sup>11,46,47</sup>

Taken together, these results may facilitate the development of new CVD-based assessments to aid in detection of A $\beta$  neuropathology during preclinical and symptomatic stages, potentially increasing diagnostic confidence, especially important given the gravity of a dementia diagnosis.<sup>3–5</sup> Because MRI is already used widely in the clinical workup of cognitive complaints,<sup>18</sup> pending further validation and development of specific cutoffs for each measure, these CVD biomarkers could be translated to inform workup with blood biomarkers, A $\beta$ -PET, or cerebrospinal fluid analysis in a stage-specific manner.<sup>48–50</sup> Prior to

translation to clinical use, more work is needed to validate this model in a data set that includes cases of vascular dementia alongside cases of “mixed” pathology and “pure” AD. This could enable development of AD-specific cutoffs for each CVD biomarker; for example, milder CVD biomarker changes may be more consistent with AD, whereas more severe increases in CV burden could be more consistent with a primary diagnosis of vascular cognitive impairment. Based on our analysis, these optimal cutoffs may differ according to cognitive stage. Although additional studies are needed to address differentiation from vascular and other non-AD dementias in clinical populations, our findings demonstrate the potential value of considering CVD biomarkers alongside established research criteria such as the National Institute on Aging–Alzheimer’s Association Amyloid/Tau/Neurodegeneration Framework.<sup>2</sup>

Our cross-sectional analysis has some important limitations, including potential ascertainment bias in the ADNI data set due to a high prevalence of A $\beta$  positivity, which does not fully represent the spectrum of vascular or other non-AD pathologies seen in clinical populations.<sup>4,44</sup> While excluding individuals with clear non-AD pathology likely increases the specificity of our analysis, it may limit its generalizability to clinical populations with mixed pathologies. Survival bias may also be at play, given that cerebral and systemic vascular diseases are a leading cause of morbidity and mortality in older populations, potentially contributing to underestimation of the impacts of ischemic stroke in later disease stages.<sup>51,52</sup> Furthermore, the ADNI data set’s relative lack of racial or ethnic diversity limits our findings, as neuropathological studies show a higher vascular co-pathology burden in minoritized or traditionally underrepresented racial and ethnic groups.<sup>3</sup> Taken together, these limitations may lead to an underestimation of the relationship between these CVD biomarkers and A $\beta$  positivity.

Future research should focus on several key areas to build upon our findings. More work is needed to longitudinally assess these relationships, to better establish causality, and to develop and validate specific cutoffs that are tuned to clinical populations. Inclusion of additional CVD biomarkers, such as enlarged perivascular spaces and cortical/cerebellar microinfarction, may further improve diagnostic performance and potential specificity for AD.<sup>53–58</sup> Additional longitudinal studies are warranted to observe the progression of A $\beta$ /tau pathology, neurodegeneration, and cognitive/functional decline over time in patients stratified by CVD biomarker status. These approaches could help define the bounds of AD, mixed vascular-AD dementia, and primary vascular cognitive impairment. By gaining deeper insights into the trajectory of AD, it may also lead to improved prediction of outcomes with novel amyloid-lowering immunotherapies, including risk of amyloid-related imaging abnormalities (ARIA), a vascular consequence of treatment that underscores the need to better understand the relationship between CVD and AD. Implementation and standardization of CVD biomarkers could increase the efficacy and safety of these treatments via improved patient selection and monitoring protocols.<sup>13,59–61</sup>

In summary, our study highlights the complex interplay between CVD and AD, pointing toward a more nuanced understanding of AD

progression that incorporates accessible neuroimaging measures of CVD pathology. Although more work is needed prior to clinical use, this comprehensive analysis in a large observational cohort may help to refine diagnostic criteria for AD and informs future validation studies in more racially diverse and diagnostically complex cohorts. If successful, this integrative approach could lead to more personalized and effective treatment strategies, improving outcomes for individuals with AD.

## ACKNOWLEDGMENTS

M.D.H. designed the analysis, wrote the initial drafts of the manuscript, assisted with the statistical analysis, and created all tables and figures. M.R.C. and M.M. reviewed the ADNI study procedures, assisted with writing the Methods and Supplementary Methods sections, and reviewed the manuscript. Z.J.K. performed all data cleaning, analyzed data, and reviewed the manuscript. S.E. assisted with designing the analysis, assisted with the literature review, and revised the manuscript. J.L.R., E.D.H., and S.P.S. reviewed all results, revised the initial drafts, and assisted with writing the final drafts of the manuscript. H.O. provided input on designing the analysis, reviewed the ADNI neuroimaging analysis pipeline, provided input on the statistical analysis, and assisted with writing the final drafts of the manuscript.

The authors would like to thank the ADNI leadership, investigators and participants, the staff at the Laboratory of NeuroImaging (LONI), and the faculty and staff of the Center for Neuroscience at University of California Davis, the University of California San Francisco, and the Mayo Clinic Aging and Dementia Imaging Research Laboratory for sharing their neuroimaging analysis to make our study possible. Salary support to M.D.H. is provided by the National Institute of Mental Health (NIMH 2R25MH101076-06A1, Audrey Tyrka, PI). S.P.S. is supported by the National Institute on Aging (NIA 2P01AG051449-06, John Sedivy, PI). H.O. is supported by NIA R01AG068990 (Hwamee Oh, PI). Data collection and sharing for this project was funded by ADNI (National Institutes of Health Grant U01 AG024904) and DOD ADNI (Department of Defense award number W81XWH-12-2-0012). ADNI is funded by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, and through generous contributions from the following: AbbVie, Alzheimer’s Association; Alzheimer’s Drug Discovery Foundation; Araclon Biotech; BioClinica, Inc.; Biogen; Bristol-Myers Squibb Company; CereSpir, Inc.; Cogstate; Eisai Inc.; Elan Pharmaceuticals, Inc.; Eli Lilly and Company; EuroImmun; F. Hoffmann-La Roche Ltd and its affiliated company Genentech, Inc.; Fujirebio; GE Healthcare; IXICO Ltd.; Janssen Alzheimer Immunotherapy Research & Development, LLC.; Johnson & Johnson Pharmaceutical Research & Development LLC.; Lumosity; Lundbeck; Merck & Co., Inc.; Meso Scale Diagnostics, LLC.; NeuroRx Research; Neurotrack Technologies; Novartis Pharmaceuticals Corporation; Pfizer Inc.; Piramal Imaging; Servier; Takeda Pharmaceutical Company; and Transition Therapeutics. The Canadian Institutes of Health Research is providing funds to support ADNI clinical sites in Canada. Private sector contributions are facilitated by the Foundation for the National Institutes of Health ([www.fnih.org](http://www.fnih.org)). The grantee organization is the Northern California Institute for Research and

Education, and the study is coordinated by the Alzheimer's Therapeutic Research Institute at the University of Southern California. ADNI data are disseminated by the Laboratory for Neuro-Imaging at the University of Southern California.

### CONFLICT OF INTEREST STATEMENT

M. Howe: None to disclose. M. Caruso: None to disclose. M. Manoochchri: None to disclose. Z. Kunicki: None to disclose. S. Emrani: None to disclose. J. Rudolph: None to disclose. E. Huey: None to disclose. S. Salloway: Dr. Salloway has provided consultation to Biogen, Eisai, Avid, Lilly, Genentech, and Roche. H. Oh: None to disclose. Butler Hospital has received research grants from Biogen, Eisai, Avid, Roche, Genentech, Janssen, and Lilly. Author disclosures are available in the [supporting information](#).

### CONSENT STATEMENT

Written informed consent was obtained from all participants or authorized representatives prior to the start of study procedures, with local institutional review boards and research ethics boards providing oversight for the study. The authors certify that the study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments. For more information, see [adni.loni.usc.edu](mailto:adni.loni.usc.edu)

### ORCID

Matthew D. Howe  <https://orcid.org/0000-0002-6373-1535>

### REFERENCES

- Alzheimer's Association. 2024 Alzheimer's disease facts and figures. *Alzheimers Dement*. 2024;20(5):3708-3821.
- Jack CR, Bennett DA, Blennow K, et al. NIA-AA research framework: toward a biological definition of Alzheimer's disease. *Alzheimer's & Dementia*. 2018;14(4):535-562. doi:10.1016/j.jalz.2018.02.018
- Filshtein TJ, Dugger BN, Jin LW, et al. Neuropathological diagnoses of demented hispanic, black, and non-hispanic white decedents seen at an Alzheimer's disease center. *JAD*. 2019;68(1):145-158. doi:10.3233/JAD-180992
- Jäkel L, De Kort AM, Klijn CJM, Schreuder FHBM, Verbeek MM. Prevalence of cerebral amyloid angiopathy: a systematic review and meta-analysis. *Alzheimers Dement*. 2022;18(1):10-28. doi:10.1002/alz.12366
- Kapasi A, DeCarli C, Schneider JA. Impact of multiple pathologies on the threshold for clinically overt dementia. *Acta Neuropathol*. 2017;134(2):171-186. doi:10.1007/s00401-017-1717-7
- Ahtiluoto S, Polvikoski T, Peltonen M, et al. Diabetes, Alzheimer disease, and vascular dementia: a population-based neuropathologic study. *Neurology*. 2010;75(13):1195-1202. doi:10.1212/WNL.0b013e3181f4d7f8
- Santos CY, Snyder PJ, Wu W, Zhang M, Echeverria A, Alber J. Pathophysiological relationship between Alzheimer's disease, cerebrovascular disease, and cardiovascular risk: a review and synthesis. *Alz & Dem Diag Ass & Dis Mo*. 2017;7(1):69-87. doi:10.1016/j.dadm.2017.01.005
- Shah NS, Vidal JS, Masaki K, et al. Midlife blood pressure, plasma  $\beta$ -amyloid, and the risk for alzheimer disease: the honolulu asia aging study. *Hypertension*. 2012;59(4):780-786. doi:10.1161/HYPERTENSIONAHA.111.178962
- Blanchard JW, Akay LA, Davila-Velderrain J, et al. APOE4 impairs myelination via cholesterol dysregulation in oligodendrocytes. *Nature*. 2022;611(7937):769-779. doi:10.1038/s41586-022-05439-w
- Carnevale D, Mascio G, D'Andrea I, et al. Hypertension induces brain amyloid accumulation, cognitive impairment, and memory deterioration through activation of receptor for advanced glycation end products in brain vasculature. *Hypertension*. 2012;60(1):188-197. doi:10.1161/HYPERTENSIONAHA.112.195511
- Howe MD, McCullough LD, Urayama A. The role of basement membranes in cerebral amyloid angiopathy. *Front Physiol*. 2020;11:601320. doi:10.3389/fphys.2020.601320
- Thomas T, Thomas G, McLendon C, Sutton T, Mullan M.  $\beta$ -Amyloid-mediated vasoactivity and vascular endothelial damage. *Nature*. 1996;380(6570):168-171. doi:10.1038/380168a0
- Greenberg SM, Bacskai BJ, Hernandez-Guillamon M, Pruzin J, Sperling R, van Veluw SJ. Cerebral amyloid angiopathy and Alzheimer disease — one peptide, two pathways. *Nat Rev Neurol*. 2020;16(1):30-42. doi:10.1038/s41582-019-0281-2
- Iadecola C. The neurovascular unit coming of age: a journey through neurovascular coupling in health and disease. *Neuron*. 2017;96(1):17-42. doi:10.1016/j.neuron.2017.07.030
- Charidimou A, Boulouis G, Frosch MP, et al. The Boston criteria version 2.0 for cerebral amyloid angiopathy: a multicentre, retrospective, MRI-neuropathology diagnostic accuracy study. *Lancet Neurol*. 2022;21(8):714-725. doi:10.1016/S1474-4422(22)00208-3
- Liu Y, Chan DK, Crawford JD, Sachdev PS, Braidy N. The contribution of cerebral vascular neuropathology to mild stage of Alzheimer's dementia using the NACC Database. *Curr Alzheimer Res*. 2020;17(13):1167-1176. doi:10.2174/1567205018666210212160902
- Huijts M, Duits A, van Oostenbrugge RJ, Kroon AA, de Leeuw PW, Staals J. Accumulation of MRI markers of cerebral small vessel disease is associated with decreased cognitive function. a study in first-ever lacunar stroke and hypertensive patients. *Front Aging Neurosci*. 2013;5:72. doi:10.3389/fnagi.2013.00072
- Harper L, Barkhof F, Scheltens P, Schott JM, Fox NC. An algorithmic approach to structural imaging in dementia. *J Neurol Neurosurg Psychiatry*. 2014;85(6):692-698. doi:10.1136/jnnp-2013-306285
- Farid K, Charidimou A, Baron JC. Amyloid positron emission tomography in sporadic cerebral amyloid angiopathy: a systematic critical update. *Neuroimage Clin*. 2017;15:247-263. doi:10.1016/j.nicl.2017.05.002
- Liu Y, Braidy N, Poljak A, Chan DKY, Sachdev P. Cerebral small vessel disease and the risk of Alzheimer's disease: a systematic review. *Ageing Res Rev*. 2018;47:41-48. doi:10.1016/j.arr.2018.06.002
- Planton M, Saint-Aubert L, Raposo N, et al. Florbetapir regional distribution in cerebral amyloid angiopathy and Alzheimer's disease: a PET study. *J Alzheimers Dis*. 2020;73(4):1607-1614. doi:10.3233/JAD-190625
- Tsai HH, Pasi M, Tsai LK, et al. Distribution of Lacunar infarcts in Asians with intracerebral hemorrhage: a magnetic resonance imaging and amyloid positron emission tomography study. *Stroke*. 2018;49(6):1515-1517. doi:10.1161/STROKEAHA.118.021539
- Tsai HH, Pasi M, Tsai LK, et al. Superficial cerebellar microbleeds and cerebral amyloid angiopathy: a magnetic resonance imaging/positron emission tomography study. *Stroke*. 2020;51(1):202-208. doi:10.1161/STROKEAHA.119.026235
- Twait EL, Min B, Beran M, Vonk JMJ, Geerlings MI. The cross-sectional association between amyloid burden and white matter hyperintensities in older adults without cognitive impairment: a systematic review and meta-analysis. *Ageing Research Reviews*. 2023;88:101952. doi:10.1016/j.arr.2023.101952
- Mueller SG, Weiner MW, Thal LJ, et al. The Alzheimer's disease neuroimaging initiative. *Neuroimaging Clin N Am*. 2005;15(4):869-877. doi:10.1016/j.nic.2005.09.008. xi-xii.

26. Weiner MW, Veitch DP, Aisen PS, et al. The Alzheimer's Disease Neuroimaging Initiative 3: continued innovation for clinical trial improvement. *Alzheimers Dement*. 2017;13(5):561-571. doi:10.1016/j.jalz.2016.10.006
27. Saykin AJ, Shen L, Foroud TM, et al. Alzheimer's disease neuroimaging initiative biomarkers as quantitative phenotypes: genetics core aims, progress, and plans. *Alzheimers Dement*. 2010;6(3):265-273. doi:10.1016/j.jalz.2010.03.013
28. Landau SM, Breault C, Joshi AD, et al. Amyloid- $\beta$  imaging with pittsburgh compound B and Florbetapir: comparing radiotracers and quantification methods. *Journal of Nuclear Medicine*. 2013;54(1):70-77. doi:10.2967/jnumed.112.109009
29. Landau SM, Thomas BA, Thurfjell L, et al. Amyloid PET imaging in Alzheimer's disease: a comparison of three radiotracers. *Eur J Nucl Med Mol Imaging*. 2014;41(7):1398-1407. doi:10.1007/s00259-014-2753-3
30. Roysse SK, Minhas DS, Lopresti BJ, et al. Validation of amyloid PET positivity thresholds in centiloids: a multisite PET study approach. *Alzheimers Res Ther*. 2021;13(1):99. doi:10.1186/s13195-021-00836-1
31. Okine DN, Knopman DS, Mosley TH, et al. Cerebral microbleed patterns and cortical amyloid- $\beta$ : the ARIC-PET Study. *Stroke*. 2023;54(10):2613-2620. doi:10.1161/STROKEAHA.123.042835
32. Austin PC, White IR, Lee DS, van Buuren S. Missing data in clinical research: a tutorial on multiple imputation. *Can J Cardiol*. 2021;37(9):1322-1331. doi:10.1016/j.cjca.2020.11.010
33. Revised Criteria for Diagnosis and Staging of Alzheimer's. AAIC. Accessed December 4, 2023. <https://aaic.alz.org/diagnostic-criteria.asp>
34. Yates PA, Desmond PM, Phal PM, et al. Incidence of cerebral microbleeds in preclinical Alzheimer disease. *Neurology*. 2014;82(14):1266-1273. doi:10.1212/WNL.0000000000000285
35. Hainsworth AH, Markus HS, Schneider JA. Cerebral small vessel disease, hypertension, and vascular contributions to cognitive impairment and dementia. *Hypertension*. 2024;81(1):75-86. doi:10.1161/HYPERTENSIONAHA.123.19943
36. Scheumann V, Schreiber F, Perosa V, et al. MRI phenotyping of underlying cerebral small vessel disease in mixed hemorrhage patients. *J Neurol Sci*. 2020;419:117173. doi:10.1016/j.jns.2020.117173
37. Charidimou A, Martinez-Ramirez S, Reijmer YD, et al. Total magnetic resonance imaging burden of small vessel disease in cerebral amyloid angiopathy: an imaging-pathologic study of concept validation. *JAMA Neurol*. 2016;73(8):994-1001. doi:10.1001/jamaneurol.2016.0832
38. Charidimou A, Boulouis G, Pasi M, et al. MRI-visible perivascular spaces in cerebral amyloid angiopathy and hypertensive arteriopathy. *Neurology*. 2017;88(12):1157-1164. doi:10.1212/WNL.0000000000003746
39. Alban SL, Lynch KM, Ringman JM, et al. The association between white matter hyperintensities and amyloid and tau deposition. *Neuroimage Clin*. 2023;38:103383. doi:10.1016/j.nicl.2023.103383
40. Garnier-Crussard A, Cotton F, Krolak-Salmon P, Chételat G. White matter hyperintensities in Alzheimer's disease: beyond vascular contribution. *Alzheimer's & Dementia*. 2023;19(8):3738-3748. doi:10.1002/alz.13057
41. Walsh P, Sudre CH, Fiford CM, et al. CSF amyloid is a consistent predictor of white matter hyperintensities across the disease course from aging to Alzheimer's disease. *Neurobiology of Aging*. 2020;91:5-14. doi:10.1016/j.neurobiolaging.2020.03.008
42. Luo J, Ma Y, Agboola FJ, et al. Longitudinal relationships of white matter hyperintensities and Alzheimer disease biomarkers across the adult life span. *Neurology*. 2023;101(2). doi:10.1212/WNL.0000000000207378
43. Provenzano FA, Muraskin J, Tosto G, et al. White matter hyperintensities and cerebral amyloidosis: necessary and sufficient for clinical expression of Alzheimer disease? *JAMA Neurol*. 2013;70(4):455-461. doi:10.1001/jamaneurol.2013.1321
44. Gorelick PB, Scuteri A, Black SE, et al. Vascular contributions to cognitive impairment and dementia: a statement for health-care professionals from the American Heart Association/American Stroke Association. *Stroke*. 2011;42(9):2672-2713. doi:10.1161/STR.0b013e3182299496
45. Yassi N, Hilal S, Xia Y, et al. Influence of comorbidity of cerebrovascular disease and amyloid- $\beta$  on Alzheimer's Disease. *J Alzheimers Dis*. 2020;73(3):897-907. doi:10.3233/JAD-191028
46. Howe MD, Atadja LA, Furr JW, et al. Fibronectin induces the perivascular deposition of cerebrospinal fluid-derived amyloid- $\beta$  in aging and after stroke. *Neurobiology of Aging*. 2018;72:1-13. doi:10.1016/J.NEUROBIOLAGING.2018.07.019
47. Howe MD, Furr JW, Munshi Y, et al. Transforming growth factor- $\beta$  promotes basement membrane fibrosis, alters perivascular cerebrospinal fluid distribution, and worsens neurological recovery in the aged brain after stroke. *GeroScience*. 2019;41(5):543-559. doi:10.1007/s11357-019-00118-7
48. Hansson O, Blennow K, Zetterberg H, Dage J. Blood biomarkers for Alzheimer's disease in clinical practice and trials. *Nat Aging*. 2023;3(5):506-519. doi:10.1038/s43587-023-00403-3
49. Hansson O, Edelmayer RM, Boxer AL, et al. The Alzheimer's Association appropriate use recommendations for blood biomarkers in Alzheimer's disease. *Alzheimers Dement*. 2022;18(12):2669-2686. doi:10.1002/alz.12756
50. Hansson O, Seibyl J, Stomrud E, et al. CSF biomarkers of Alzheimer's disease concord with amyloid- $\beta$  PET and predict clinical progression: a study of fully automated immunoassays in BioFINDER and ADNI cohorts. *Alzheimer's & Dementia*. 2018;14(11):1470-1481. doi:10.1016/j.jalz.2018.01.010
51. An SJ, Kim TJ, Epidemiology YoonBW. Risk factors, and clinical features of intracerebral hemorrhage: an update. *Journal of stroke*. 2017;19(1):3-10. doi:10.5853/jos.2016.00864
52. Feigin VL, Nichols E, Alam T, et al. Global, regional, and national burden of neurological disorders, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *The Lancet Neurology*. 2019;18(5):459-480. doi:10.1016/S1474-4422(18)30499-X
53. Zhang X, Wang Y, Jiao B, et al. Glymphatic system impairment in Alzheimer's disease: associations with perivascular space volume and cognitive function. *Eur Radiol*. 2024;34(2):1314-1323. doi:10.1007/s00330-023-10122-3
54. Jung NY, Je Y, Ham HG, et al. Comparison of enlarged perivascular spaces in early-onset and late-onset Alzheimer disease-related cognitive impairment: a single clinic-based study in South Korea. *Alzheimer Dis Assoc*. 2024;38(2):201-204. doi:10.1097/WAD.0000000000000614
55. Lauer A, van Veluw SJ, William CM, et al. Microbleeds on MRI are associated with microinfarcts on autopsy in cerebral amyloid angiopathy. *Neurology*. 2016;87(14):1488-1492. doi:10.1212/WNL.0000000000003184
56. li Y, Ishikawa H, Shindo A, et al. Association between cortical microinfarcts and total small vessel disease burden in cerebral amyloid angiopathy on 3-Tesla magnetic resonance imaging. *Eur J Neurol*. 2021;28(3):794-799. doi:10.1111/ene.14610
57. li Y, Ishikawa H, Nishigaki A, et al. Superficial small cerebellar infarcts in cerebral amyloid angiopathy on 3 T MRI: a preliminary study. *J Neurol Sci*. 2024;459:122975. doi:10.1016/j.jns.2024.122975
58. Huang SY, Zhang YR, Guo Y, et al. Glymphatic system dysfunction predicts amyloid deposition, neurodegeneration, and clinical progression in Alzheimer's disease. *Alzheimers Dement*. 2024;20(5):3251-3269. doi:10.1002/alz.13789

59. Salloway S, Chalkias S, Barkhof F, et al. Amyloid-related imaging abnormalities in 2 phase 3 studies evaluating aducanumab in patients with early Alzheimer disease. *JAMA Neurol.* 2022;79(1):13. doi:[10.1001/jamaneurol.2021.4161](https://doi.org/10.1001/jamaneurol.2021.4161)
60. Howe MD, Britton KJ, Joyce HE, et al. Initial experiences with amyloid-related imaging abnormalities in patients receiving aducanumab following accelerated approval. *J Prev Alz Dis.* 2023;10(4):765-770. doi:[10.14283/jpad.2023.96](https://doi.org/10.14283/jpad.2023.96)
61. Cummings J, Apostolova L, Rabinovici GD, et al. Lecanemab: appropriate use recommendations. *Journal of Prevention of Alzheimer's Disease.* 2023:1-16. doi:[10.14283/JPAD.2023.30/TABLES/11](https://doi.org/10.14283/JPAD.2023.30/TABLES/11). Published online March 27.

## 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:** Howe MD, Caruso MR, Manoochehri M, et al. Utility of cerebrovascular imaging biomarkers to detect cerebral amyloidosis. *Alzheimer's Dement.* 2024;1-12. <https://doi.org/10.1002/alz.14207>