Title

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Journal

Alzheimer's & Dementia, 20(12)

ISSN

1552-5260

Authors

Maillard, Pauline

Fletcher, Evan

Carmichael, Owen

et al.

Publication Date

2024-12-01

DOI

10.1002/alz.14358

Peer reviewed

Received: 10 May 2024 | Revised: 11 September 2024 | Accepted: 2 October 2024

DOI: 10.1002/alz.14358

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

REVIEW ARTICLE

Cerebrovascular markers of WMH and infarcts in ADNI: A historical perspective and future directions

Pauline Maillard[1] | **Evan Fletcher**[1] | **Owen Carmichael**[2] | **Christopher Schwarz**[3] | **Stephan Seiler**[1,4] | **Charles DeCarli**[1] | **for the Alzheimer's Disease Neuroimaging Initiative**

[1]Department of Neurology, University of California at Davis, Sacramento, California, USA

[2]Biomedical Imaging, Pennington Biomedical Research Center, Louisiana State University, Baton Rouge, Louisiana, USA

[3]Department of Radiology, Mayo Clinic, Rochester, Minnesota, USA

[4]Department of Neurology, Medical University of Graz, Graz, Austria

Correspondence
Charles DeCarli, Department of Neurology, University of California at Davis, 1651 Alhambra Blvd, Suite 200A, Sacramento, CA 95816, USA.
Email: cdecarli@ucdavis.edu

Funding information
National Institute on Aging, Grant/Award Numbers: U01 AG024904, P30 AG072972

Abstract

White matter hyperintensities (WMH) and infarcts found on magnetic resonance imaging (MR infarcts) are common biomarkers of cerebrovascular disease. In this review, we summarize the methods, publications, and conclusions stemming from the Alzheimer's Disease Neuroimaging Initiative (ADNI) related to these measures. We combine analysis of WMH and MR infarct data from across the three main ADNI cohorts with a review of existing literature discussing new methodologies and scientific findings derived from these data. Although ADNI inclusion criteria were designed to minimize vascular risk factors and disease, data across all the ADNI cohorts found consistent trends of increasing WMH volumes associated with advancing age, female sex, and cognitive impairment. ADNI, initially proposed as a study to investigate biomarkers of AD pathology, has also helped elucidate the impact of asymptomatic cerebrovascular brain injury on cognition within a cohort relatively free of vascular disease. Future ADNI work will emphasize additional vascular biomarkers.

KEYWORDS
Alzheimer's disease, Alzheimer's Disease Neuroimaging Initiative, cerebrovascular disease, magnetic resonance infarcts, white matter hyperintensities

Highlights

- White matter hyperintensities (WMHs) are common to advancing age and likely reflect brain vascular injury among older individuals.
- WMH and to a lesser extent, magnetic resonance (MR) infarcts, affect risk for transition to cognitive impairment.
- WMHs and MR infarcts are present, even among Alzheimer's Disease Neuroimaging Initiative (ADNI) participants highly selected to have Alzheimer's disease (AD) as the primary pathology.
- WMH burden in ADNI is greater among individuals with cognitive impairment and has been associated with AD neurodegenerative markers and cerebral amyloidosis.

- The negative additive effects of cerebrovascular disease appear present, even in select populations, and future biomarker work needs to further explore this relationship.

1 | INTRODUCTION

Consistent evidence indicates that cognitive impairment and transition to dementia with advancing age is a multifactorial process.[1,2] Multiple pathologies are often present in the brains of individuals with late-life dementia, and non–Alzheimer's disease (AD) pathologies account for a substantial proportion of cognitive decline, even when AD pathology is present.[3–11] For example, between 80% to 100% of mild cognitive impairment (MCI) and AD cases have mixed pathologies at *post mortem* examination including vascular brain injury and non-amyloid, non-tau protein aggregates.[4,12,13] Evidence also indicates that mixed pathologies leading to dementia are more common when assessed by community-based studies,[14] or among diverse populations.[15,16]

Vascular brain injury is one of the most frequent non-AD pathologies contributing to cognitive decline.[17] White matter hyperintensities (WMHs) identified as increased signal intensities on T2-weighted imaging[18] and asymptomatic infarcts found on magnetic resonance imaging (s; MR infarcts) are two of the most commonly recognized biomarkers of cerebrovascular disease,[18,19] sharing many of the same vascular risk factors associated with clinical stroke.[20,21] WMH, and to a similar extent, asymptomatic MR infarcts,[22] influence brain and cognitive health, even during middle life.[23,24] In later life, the progression of WMHs is associated with declines in both memory and executive function.[25] Extensive WMHs or the presence of MR infarcts also predict incident MCI, stroke, and dementia.[26] While WMHs also accompany AD, studies examining individuals with normal cognition or MCI find that WMHs and infarction have a negative impact on cognition independent of, or in addition to, concurrent amyloid and tau measures.[27,28]

Since the inception of the Alzheimer's Disease Neuroimaging Initiative (ADNI) MRI protocol, the Imaging of Dementia and Aging (IDeA) laboratory at University of California (UC) Davis has been tasked with evaluating WMH burden and the presence, location, and type (ischemic vs. hemorrhagic) of MR infarctions. As ADNI use of current MR technologies evolved over the three grant cycles, so did MR sequences designed to evaluate WMH and MR infarction. This evolution particularly affected the quantification of the WMH burden. In this article, we review the three phases of ADNI (1, GO/2, 3) relating to differences in imaging sequences and analytical methodology related to measures of WMH and MR infarcts. We also summarize results across all three phases of ADNI emphasizing similarities and differences in findings by sequence type and analytical method as well as highlighting the impact of these findings on clinical diagnosis, summarizing publications related to these methods, and discussing future investigations that derive from current findings.

2 | METHODS

2.1 | Subjects of this review

Participant selection has been described for each of the phases of ADNI.[29–34] While ADNI investigators strived to retain participants throughout the course of ADNI, the constituencies of the various cohorts have changed with each new cycle of funding. For ADNI 1, the subject selection was limited to participants identified as cognitively normal (CN), with MCI, or demented. ADNI GO expanded the recruitment criterion to include individuals identified as having early MCI.[32] This recruitment criterion was continued during ADNI 2. Recruitment selection was further enhanced in ADNI 3 to include individuals with subjective cognitive decline (SCD).[34] To facilitate participant comparison of results across the three cohorts for this review, clinical diagnoses were grouped into CN (with and without SCD), MCI (both early and late MCI), or dementia. Exclusion criteria focused mostly on limiting individuals with non-AD pathologies, particularly cerebrovascular diseases such as stroke or high vascular risk.[30]

2.2 | MRI sequences

As previously discussed, MRI sequences evolved over the various funding periods and are summarized on the ADNI website https://adni.loni.usc.edu/methods/mri-tool/mri-analysis/ and in Jack et al.[35] Specifically, in ADNI 1, vascular markers were determined from the combined sequences of T1-weighted, proton density (PD), and T2-weighted sequences. The PD and T2-weighted images were acquired as part of a double echo sequence with in-plane resolution of 0.94 mm with 3 mm thick interleaved slice thickness. ADNI 2 modified this protocol to substitute a 2D fluid-attenuated inversion recovery (FLAIR) sequence instead of the double-echo, with an in-plane resolution of 0.86 mm with 5 mm thick interleaved slice thickness. The FLAIR sequence was further modified for ADNI 3 with the substitution of a 3D acquisition with an in-plane resolution of 1 mm and slice thickness of 1.2 mm.

2.3 | Analytic methodology

2.3.1 | ADNI 1 WMH segmentation methodology

ADNI 1 WMH segmentation methodology focused on WMH detection using the combined sequences of T1, T2, and PD weighted images as input.[36] WMHs are hyperintense on PD and T2 and hypointense on T1,

but none of these images alone provides sufficient contrast between normal white matter (WM) and WMHs. This approach, therefore, combined image intensity information with prior anatomical knowledge about WMH location in the brain as a function of overall burden.[37] Specifically, prior probabilities of WMH occurring at a given pixel were developed from FLAIR-based, ground-truth segmentation masks from an independent cohort ($n = 114$ older adults with T1-weighted, FLAIR, and double echo T2/PD, from the UC Davis Alzheimer's Disease Center). Prior probabilities were combined with contextual priors (i.e., the conditional probability of a WMH occurring at a given pixel, given that WMHs are present at neighboring pixels, based on a Markov random field [MRF]). It was presumed that, for most older individuals, the spatial and contextual priors are highly structured and capture a characteristic spatial distribution of WMH occurrence and progression; specifically, WMHs in AD and healthy aging tend to begin in periventricular zones and spread upward and outward.[37,38] Implementation of the method involved the use of the prior model learned from the FLAIR-based ground-truth WMH detections in the training phase combined with intensity information at run-time within an MRF framework to detect WMHs in novel sets of coregistered (PD, T1, T2) MRIs. Accuracy of the trained method using a six-connected MRF achieved an intraclass correlation coefficient (ICC) of 0.916 using leave-one-out cross-validation.[36]

RESEARCH IN CONTEXT

1. **Systematic review**: All publications acknowledging the Alzheimer's Disease Neuroimaging Initiative were selected from a PubMed search to identify studies that used white matter hyperintensity (WMH) or magnetic resonance (MR) infarct data as a primary source of examination.
2. **Interpretation**: WMH volumes were shown to differ by age, sex, and clinical diagnosis. WMHs also were associated with cognitive performance, atrophy in brain regions thought unique to the Alzheimer's disease (AD) process, and amyloid burden.
3. **Future directions**: The additional impact of cerebrovascular injury on the pathophysiology of cognitive impairment among individuals suspected to have AD should be determined and treated to improve dementia outcomes.

2.3.2 | ADNI GO, 2, 3 segmentation methodology

This WMH algorithm uses a Bayesian approach to the segmentation of high-resolution 3D T1 and FLAIR sequences. The FLAIR image is affine transformed to the 3DT1 image using the FLIRT method from the FSL toolbox, with error estimation based on correlation ratio. Inhomogeneity correction of the 3D T1 is performed using interleaved bias estimation and B-spline deformation with a template.[39] This multiple iteration method updates a B-spline intensity deformation between an unbiased template image and the subject image with an estimation of a bias field based on the current template-to-image alignment. The bias field is modeled using a spatially smooth thin-plate spline interpolation based on ratios of local image patch intensity means between the deformed template and subject images. FLAIR inhomogeneity corrections after co-registration of the FLAIR to the 3D T1 image are based on a previously published local histogram normalization method.[40] Before WMH calculation, each 3D T1 image is non-linearly aligned to a common template atlas, and each of the accompanying images is transformed onto the same atlas using the same transformation parameters. Estimation of WMHs is then performed using a modified Bayesian probability structure based on a previously published method of histogram fitting.[41] Prior probability maps for WMH were created from > 700 individuals with semi-automatic detection of WMH followed by manual editing. Likelihood estimates of the native image are calculated through histogram fitting of brain pixel intensities and thresholding above 3.5 standard deviations (SDs) as previously described.[41] All segmentation is initially performed in standard template space resulting in probability likelihood values of WMH at each voxel in the WM. Final segmentation is based on a modified Bayesian approach that combines image likelihood estimates, spatial priors, and tissue class constraints. The segmented WMH masks are then back transformed into native space for lesion volume calculation. Excellent precision results of the method have been published.[42] In this study, brain MRI using a harmonized image acquisition protocol was collected on 20 individuals using four different MRI machines to test for the impact of machine differences on the method. An additional group of individuals had repeated MRIs within 14 days on the same machine to assess the retest reliability of the method. Finally, seven sites analyzed the data to evaluate inter-rater reliability. Average inter-rater, inter-scanner, and test–retest reliabilities had intraclass coefficients > 0.95, which is considered excellent.[42] The software and instructions for this method are available at https://github.com/davisidealab/UCD_WMH_Segmentation

2.3.3 | Subsequent methodological approaches

The availability of WMH volume data in ADNI has promoted the publication of additional methodologies[43–49] using various approaches including Bayesian methods[46] and methods based solely on T1 images.[45] One study that compared 10 different methods found fairly high compatibility,[43] although another study suggested that methodological differences, particularly for methods that do not emphasize lesion specificity, could impact associations with cognitive function and clinical diagnosis.[49]

2.3.4 | MRI infarction detection and characterization

The presence of an MRI infarction was determined from the size, location, and imaging characteristics of the lesion. For ADNI 1, the

image analysis system allowed for superimposition of the T1, PD, and T2-weighted images at three times magnified views to assist in the interpretation of lesion characteristics. For all other cohorts, the image analysis system allowed for superimposition of T1, FLAIR, and T2 or gradient echo images if available. Signal void, best seen on the T2-weighted (including T2*-weighted gradient echo or susceptibility-weighted imaging) images were interpreted to indicate a vessel. Only lesions ≥ 3 mm qualified for consideration as cerebral infarcts. Other necessary imaging characteristics included (1) cerebrospinal fluid (CSF) density on T1-weighted imaging and (2) if the stroke was in the basal ganglia area, distinct separation from the circle of Willis vessels. Kappa values for agreement among the three raters (neuroradiologist, stroke neurologist, and specialist in vascular imaging) are generally good and range from 0.73 to 0.90.[50]

In summary, extensive ADNI data on WMH burden and the presence and extent of MR infarction are available to the public to pursue relevant research questions. Additionally, the presence of WMH measures in ADNI has spurred others to develop and test additional segmentation methods. Results find that most published methods give similar results although subtle differences in the relationship between a given method and outcomes may be seen. We conclude that the WMH data derived from all ADNI cohorts can be considered robust. We do, however, caution that users of these data carefully consider the impact of differences in cohort constituency and MR sequences and analytical methods (e.g., across the different phases of ADNI), and across acquisition sites and scanners (both within and across phases of ADNI), when evaluating associations between WMH primarily, and MR infarction secondarily, with other variables of interest. Statistical methods that account for machine type, image sequences, and analytical methods should be used to compare results across the various ADNI cohorts. Results, even using this approach, however, should be considered cautiously.

3 | RESULTS

3.1 | Summary data across ADNI grant cycles: similarities and differences

3.1.1 | Clinical cohorts

Table 1 summarizes cohort differences in select demographics. Significant differences were found for all measures, reflecting differences in cohort constituency (i.e., participant selection stratification), MRI sequences, and WMH quantification. Although the exclusion criteria of all subjects remained the same throughout the studies,[30] inclusion criteria varied considerably. For example, ADNI 1 focused on recruitment of a traditional cohort of persons determined to be CN or have MCI or dementia. These individuals were more likely to be male, have less education, lower Mini-Mental State Examination (MMSE), and have greater functional impairment based on the Clinical Dementia Rating Sum of Boxes.[51] Differences between ADNI 2 and ADNI 3 are less pronounced and tend to have less impairment due mostly to more individuals with normal cognition, particularly for participants of the ADNI 3 cohort.

3.1.2 | WMH

Table 1 also shows that unadjusted raw and natural log (nl) transformed volumes both differ significantly across each of the cohorts with the ADNI 1 cohort having the smallest and the ADNI 2 cohort having the largest mean volumes of WMH and nlWMH. These differences likely reflect differences in image sequences. This difference is obvious for double-spin echo sequences, but data also show that 3D FLAIR acquisition results in lower WMH volumes.[52] Further analyses performed adjusting for age, sex, and clinical diagnosis at the time of MRI are graphically displayed in Figure 1. Because most participants had serial scans, the data are reported from the initial scan. The top row shows the distribution for both the raw and nl-transformed data. It is apparent that the distribution of raw WMH volumes is highly skewed, and that natural log transformation normalizes the distribution substantially, thereby allowing for better statistical inference, particularly when used as a residual of intracranial volume. The second row summarizes nlWMH as a residual of intracranial volume in relation to age and sex differences, adjusting for clinical diagnosis at the time of MRI. All groups show a consistent increase in residual nlWMH with age. The main effects of age ($p < 0.0001$), sex ($p < 0.0001$), and ADNI cohort ($p < 0.0001$) were all highly significant with increasing age, female sex, and the ADNI 2 cohort associated with larger WMH volumes. The third row summarizes group differences in residualized nlWMH by clinical diagnosis at the time of MRI adjusting for age, sex, and educational achievement. Again, all groups show similar relationships with significant trends of increasing nlWMH for CN, MCI, and dementia participants ($p < 0.0001$). Post hoc analyses using Tukey honestly significant differences, however, find that mean nlWMH volumes differ significantly among all levels of diagnosis for the ADNI 3 cohort. For the ADNI 1 cohort, however, dementia mean nlWMH volumes differ significantly from CN and MCI, but MCI and CN do not differ. For the ADNI 2 cohort, CN differed from MCI and dementia, which did not differ from one another.

Summarizing these results, we find that, although absolute differences in volume are found among the three cohorts, we find relatively consistent associations between WMH measures and age, sex, and clinical diagnosis.

3.1.3 | MR infarction

MR infarcts were determined by clinical assessment and therefore did not have the same methodological issues as WMH measurement. Consequently, this section summarizes the assessment of MR infarction across ADNI 1, 2/GO, and 3. Because most participants had serial scans, the data are reported for the presence and number of MR infarcts on the final participant scan for which MR infarct data are available. Asymptomatic MR infarcts were found for a total of 348

TABLE 1 ADNI cohort descriptives.

	ADNI 1	ADNI 2/GO	ADNI 3	*p* for trend
Imaging sequences*	Double spin echo	3DT1, FLAIR	3DT1, FLAIR	
Mean age (SD)	76.3 (6.7)[a]	73.4 (7.3)[b]	74.9 (7.8)[c]	<0.0001
%Sex (female)	41	46	51	<0.0001
Education	15.7 (3)[a]	16.3 (2.6)[b]	16.4 (2.5)[b]	<0.0001
% Diagnosis (CN/MCI/D)	29/42/29	32/54/12	52/36/12	<0.0001
% *APOE* ε4 (−/−,ε3/ε4,ε4/ε4)	51/38/11	56/35/9	62/31/7	<0.0001
CDR SB (SD)	2.3 (2.5)[a]	1.4 (1.9)[b]	1.3 (2.2)[b]	<0.0001
MMSE (SD)	26 (4.0)[a]	27.5 (2.9)[b]	27.7 (3.3)[b]	<0.0001
MoCA (SD)	—	23.6 (4.2)	24.0 (4.5)	<0.0001
Mean WMH in cc (SD)	1.0 (3.0)[a]	7.2 (9.7)[b]	5.8 (10.4)[c]	<0.0001
Mean log WMH (SD)	−1.2 (1.6)[a]	1.3 (1.2)[b]	0.78 (1.5)[c]	<0.0001

Abbreviation: ADNI, Alzheimer's Disease Neuroimaging Initiative; *APOE*, apolipoprotein E; CDR SB, Clinical Dementia Rating Sum of Boxes; CN, cognitively normal; D, dementia; FLAIR, fluid-attenuated inversion recovery; MCI, mild cognitively impaired; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; SD, standard deviation; WMH, white matter hyperintensities.
*The analytical methods used also varied between ADNI 1 and ADNI 2/GO and 3. See text for details.
[a,b,c]indicate significant differences by Tukey HSD post-hoc analysis.

(16%) of ADNI participants who were 79 ± 7 years of age on average. MR infarct prevalence as well as the number of infarcts are summarized in Figure 2. The prevalence and mean number of MR infarcts detected increased significantly with age ($p < 0.0001$). Neither the prevalence nor mean number of MR infarcts differed by sex. A total of 264 individuals had an incident MR infarction detected during the time of observation. Participants with normal cognition at baseline had greater prevalent ($p = 0.001$), incidence ($p = 0.003$), and total number of MR infarctions ($p = 0.0002$) compared to dementia participants, whereas participants diagnosed with MCI at baseline had greater incidence ($p = 0.03$), and total number of MR infarctions ($p = 0.01$) compared to dementia participants. Prevalent, incident, or total MR infarcts were not associated with specific cognitive measures.

3.2 | Summary of published works using WMH data

3.2.1 | Association with neurodegeneration

Subcortical vascular disease (SVD) defined as extensive WMH and/or presence of MRI infarcts[18] is a major driver of vascular cognitive impairment (VCI),[17] which can contribute to dementia associated with other neurodegenerative diseases. Understanding how SVD and amyloid pathology each contribute to neurodegenerative processes may provide insight into potentially shared pathways of disease. Using various MRI markers of neurodegeneration, several studies have explored the contribution of WMH on neurodegenerative processes in the ADNI cohort.

3.3 | Entorhinal cortex volume

Atrophy in temporal lobe regions, particularly the entorhinal cortex, is the most proximal marker of neurodegeneration in AD.[53] In 199 amnestic MCI ADNI participants, Guzman et al.[54] examined whether CSF amyloid beta ($A\beta_{1\text{-}42}$, tau, and regional WMH are associated with entorhinal cortex and hippocampus atrophy. For each lobar region, higher regional WMH volume was found to be associated with smaller entorhinal cortex volume (ECV). When also including CSF AD biomarkers ($A\beta_{1\text{-}42}$ and tau levels) in the models, only temporal WMH volume remained associated with ECV. Interestingly, none of the CSF biomarker variables were associated with ECV. Findings remained unchanged when including only MCI patients who progressed to AD during the subsequent ADNI follow-up visits. Regional WMH volumes were not associated with hippocampal volume either when considered alone or together with the CSF biomarkers. These findings highlight the potential role of regional SVD in the pathogenesis of AD through entorhinal cortex atrophy. In another study of 169 amnestic MCI participants from ADNI 1, authors assessed whether regional WMH volume predicts neurodegeneration and change in clinical status independently or synergistically with respect to markers of tau pathology.[55] Results indicated that baseline regional WMH volumes modified the effect of CSF-derived total tau (t-tau) on entorhinal cortex atrophy rates as participants with lower baseline t-tau and higher frontal and parietal WMH volumes had disproportionately greater entorhinal cortex atrophy rates compared to those with low baseline t-tau and lower regional WMH volumes. This study suggests that while increased tau burden is clearly a primary source of neurodegeneration, in the presence of low tau levels, regional WMH burden may contribute to accelerated neurodegeneration.

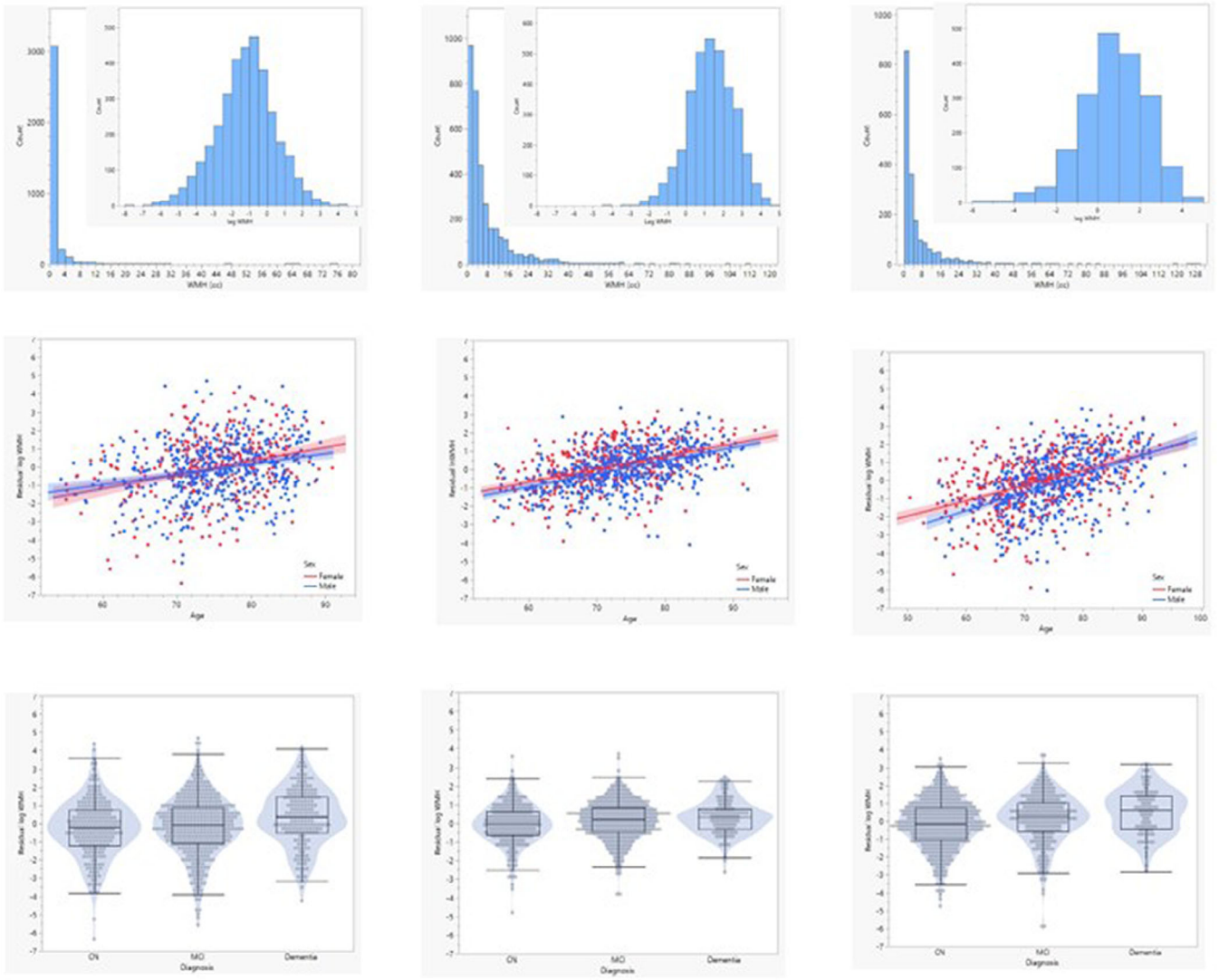

FIGURE 1 Graphic summary of WMH volumes and relation to age, sex, and clinical diagnosis across the three main ADNI cohorts. The first row summarizes the distribution of raw and natural log normalized WMH volumes for each cohort. Note, as reviewed in Table 1, mean volumes were lowest in ADNI 1 and highest in ADNI 2. This likely reflects differences in image sequence acquisition, analytical method, and constituency of the cohort as described in the text. The second row summarizes the relationship between age and residualized nlWMH volume stratified by sex. Consistent relationships are seen across cohorts. The bottom row summarizes the relationship between residualized nlWMH volume and clinical diagnosis adjusted for age, sex, and education. Similar relationships are also seen across cohorts. ADNI, Alzheimer's Disease Neuroimaging Initiative; nl, natural log; WMH, white matter hyperintensity.

3.3.1 | Brain and hippocampal atrophy

Through the analysis of longitudinal data collected as part of the ADNI 2 study ($N = 351$), hypothetical mechanisms underlying WMH regression were explored by examining cognitive and structural brain changes (i.e., brain atrophy) that occur in the setting of WMH volume regression.[56] Selected participants were categorized into three groups based on WMH change over time, including those that demonstrated regression ($n = 96$; 25.5%), stability ($n = 72$; 19.1%), and progression ($n = 209$; 55.4%). Those with WMH regression had a reduction in cognitive decline and decreased brain atrophy compared to those with WMH progression, with no differences in either atrophy or memory performance between the regression and stable groups, suggesting that the WMH dynamic is associated with changes in atrophy and cognition. In another longitudinal study of 697 cognitively diverse (CN, MCI, and AD) ADNI participants, including 353 with CSF $A\beta_{42}$ and tau, the authors investigated relationships among WMH volume, CSF AD markers, and brain and hippocampal volume loss.[57] WMH volume was associated with disproportionately greater hippocampal atrophy in controls and MCI subjects relative to whole-brain atrophy. Further, the associations in control subjects remained statistically significant when adjusting for CSF $A\beta_{42}$ and tau. Higher baseline WMH volume was also associated with accelerated atrophy rate of the whole brain and hippocampus and of the hippocampus in those with MCI.

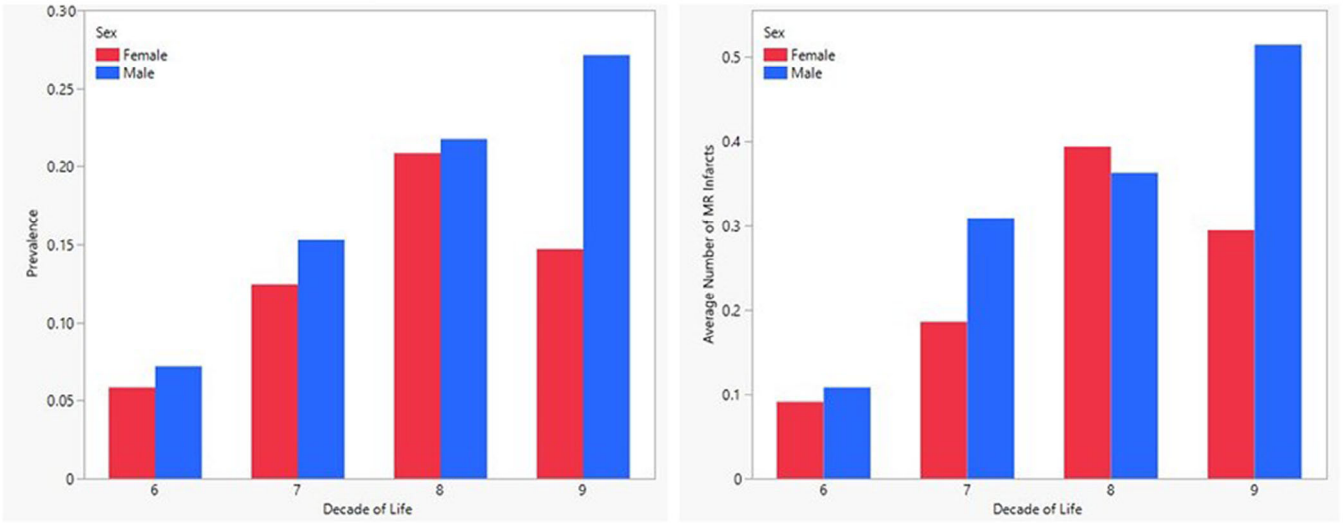

FIGURE 2 Age-related prevalence and mean number of MR infarcts stratified by sex in the ADNI cohorts. ADNI, Alzheimer's Disease Neuroimaging Initiative; MR, magnetic resonance.

These results suggest that vascular damage alongside AD pathology is associated with disproportionately greater hippocampal atrophy in non-demented older adults.

3.3.2 | Cortical thickness

In a longitudinal study of 604 ADNI participants including CN, MCI, and AD, authors investigated the longitudinal relationship between biomarkers of amyloid (Florbetapir [AV45] positron emission tomography [PET] standardized uptake volume ratio [SUVR]), cardiovascular disease (CVD; WMH volume), and neurodegeneration (cortical thickness), and the extent to which amyloid or CVD drive neurodegeneration over time.[58] Results indicated that amyloid burden and WMH volume additively contribute to the overall mean cortical thickness and that WMH volume only contributes to the rate of cortical thinning in AD-associated regions (medial/inferior temporal, temporal pole, angular gyrus, superior/inferior frontal, superior parietal, supramarginal gyrus, precuneus), even in the absence of amyloid pathophysiology. These findings support that WMHs are not simply a reflection of Wallerian damage but rather a promotion of neurodegeneration, including regions commonly believed to represent AD pathology.

3.3.3 | Boundary shift integral

The brain boundary shift integral (BSI) gives an estimate of tissue loss over time directly from each scan pair. In a longitudinal study of 674 cognitively diverse participants, including individuals with CSF $A\beta_{1\text{-}42}$ ($n = 351$) and tau ($n = 346$), relationships among WMH, AD CSF markers, and brain volume loss, as measured by BSI, were assessed.[59] Both increased WMH volume and decreased CSF $A\beta$ level were independently associated with an increase in BSI change (atrophy rate) in control subjects. In those subjects, WMH explained nearly as much variance in volume loss as CSF $A\beta$, with both explaining much more than tau. By contrast, in subjects with MCI or AD, in whom the atrophy rates were higher, WMH volume was not found to be associated with BSI change. The finding that WMHs and $A\beta$ levels are independently associated with longitudinal brain volume loss in individuals lacking clinically significant cognitive decline contributes to a growing body of literature suggesting that AD, vascular pathology, and mixed pathology are significant causes of neuronal loss accompanying aging, even when this brain injury or neuronal loss has no clinically apparent cognitive manifestation.

3.4 | Associations with growth factors

Brain-derived neurotrophic factor (BDNF) and platelet-derived growth factor (PDGF) are biomarkers with anti-apoptotic activity that play an important role in regulating synaptic activity, neurotransmission, neuronal repair, and plasticity in the central nervous system.[60,61] BDNF is associated with neuronal survival adaptation in the entorhinal cortex[62] and has been linked to long-term memory formation.[63] PDGF modulates endothelial and smooth muscle cell proliferation and is involved in maintaining the integrity of the blood–brain barrier.[64] In ADNI participants without dementia, Brenner et al. investigated whether WMH is a moderator of the effect of BDNF on hippocampal volume and cognition in 454 individuals including 49 with type 2 diabetes (T2DM) and 405 without diabetes.[65] BDNF level was found to play a role in the associations between WMH and both hippocampal volume and cognition in participants without T2DM. More specifically, among individuals without diabetes and with low BDNF, WMH increase was associated with bilateral hippocampal volume decrease and processing speed decline, supporting the protective role that BDNF plays on cognitive decline in this population. In another study involving 64 ADNI participants

without dementia,[66] increased circulating levels of PDGF-BB were found to be selectively related to small vessel damage, as reflected by WMH volume, in apolipoprotein E (*APOE*) ε4 carriers, suggesting activation of PDGFs, and the role of pericytes and blood–brain barrier dysfunction, in the context of cerebrovascular injury, specifically in individuals at genetic risk of AD.

3.5 | Association with cerebral metabolism of glucose

In 204 amnestic MCI ADNI participants who had [^{18}F]-Fluorodeoxyglucose (FDG) PET scans available, authors examined cerebrovascular disease and AD markers (CSF Aβ) in relation to brain glucose metabolism using composite measures of temporoparietal and frontal FDG PET.[67] Authors evidenced that increased WMH volume is associated with decreased frontal metabolism, while greater CSF Aβ is associated with increased temporoparietal metabolism, supporting the hypothesis that WMH, as a measure of vascular pathology and vascular burden, is associated with frontal lobe dysfunction rather than dysfunction in those brain regions more closely linked to AD neurodegeneration. This dissociative pattern adds to evidence that these respective pathologic conditions, when they co-occur, are operating simultaneously through metabolic alterations in different brain regions that potentially represent independent pathways to AD progression in MCI.

3.6 | Associations with AD biomarkers

There has been an increased interest in the potential contributions of SVD to the clinical presentation and pathogenesis of AD. It is, however, unclear whether SVD represents an independent pathological factor that confers additive risk for clinical severity and course, whether it is a result of AD pathology, and/or whether it plays a primary role in promoting AD-related changes. We described below associations between WMH and AD pathology biomarkers, including amyloid and tau, from cross-sectional and longitudinal studies conducted using ADNI data.

3.7 | Cerebral amyloid

In a study involving 148 subjects from ADNI 2 and ADNI GO, authors performed the first comprehensive comparative evaluation of a variety of biomarkers, including neurodegenerative, genetic, functional, and cognitive biomarkers, as well as WMH volume, to predict the presence of preclinical AD pathology determined using Florbetapir PET in a CN population.[68] They found that WMHs are more highly correlated with cerebral Aβ positivity status than any of the standard AD imaging biomarkers (mean FDG PET SUVR of AD meta-region of interest [ROI], hippocampal volume, mean cortical thickness of AD meta-ROI) or cognitive tests, suggesting that in the earliest stages of AD, vascular disease, as reflected by WMH, may play a significant role in the development of cerebral amyloidosis or be an early downstream effect of this molecular pathology. In the longitudinal study conducted by Lao and Brickman on cortical thickness (see above),[58] authors also looked at the interplay between amyloid deposition, as reflected by Florbetapir PET SUVR, and CVD, as reflected by WMH volume, biomarkers. They did not find evidence of a direct association between amyloid and WMH volume. Baseline WMH volume, however, was associated with amyloid accumulation rate, but baseline amyloid was not associated with WMH volume rate, suggesting that WMHs are not simply a consequence of amyloidosis and that WMH may drive faster amyloid accumulation.

3.7.1 | CSF and plasma tau

In the study of Tosto et al. described above,[55] authors also investigated a subset of participants who had longitudinal CSF t-tau data (N = 67, mean follow-up time: 36 months). They found that individuals with higher baseline parietal WMH volume had accelerated CSF t-tau increases compared to those with low parietal WMH. Conversely, t-tau at baseline did not predict WMH change over time. This study suggests that the pathology underlying WMH may vary by region but also that tau pathology may partially result from ischemic damage, as reflected by WMH. Alternatively, WMH may be the result of Wallerian degeneration in these regions as suggested by the Dominantly Inherited Alzheimer's Network (DIAN)[69] as well as neuropathological studies.[70,71] In a study of 391 ADNI participants, including CN, MCI, and AD individuals, authors investigated the relationship between plasma tau concentration and WMH volume across diagnostic groups.[72]They showed a direct relationship between increased WMH volume and plasma t-tau levels, particularly among individuals diagnosed clinically with AD, suggesting the effect of small vessel CVD on risk and expression of AD is due partially to its promotion of tau pathology. The interaction between WMH and tau, independent of amyloid pathology, was associated with an increased likelihood of clinical AD and MCI. These findings support that cerebrovascular abnormalities may be one initiator of a tau pathway for AD pathogenesis that is independent of Aβ pathology as previously suggested.[73]

3.8 | Associations with cognition and clinical diagnosis

Extensive literature describes the negative effects of WMH on cognitive function.[74] Several studies have been conducted in ADNI that contribute to understanding the various mechanisms linking WMH to cognitive decline.

3.8.1 | Cross-sectional studies

In a study of 608 older adults free of dementia from ADNI 1, the authors sought to clarify the associations of lobar WMH volumes

with episodic memory and executive function.[75] For each lobar region, higher regional WMH volume was associated with poorer episodic memory and speed/executive function. When the sample was restricted to CN participants only, findings were attenuated, and only associations between temporal and occipital WMH volumes and episodic memory remained significant. The pattern of findings suggests that WMH may affect multiple cognitive functions regardless of location, although only occipital and temporal WMH were associated with cognition when including individuals with normal cognition only. In another study including 559 non-demented ADNI participants, the association between regional WMH and objectively defined subtle cognitive decline (Obj-SCD) status was assessed.[76] Global and regional WMH volumes were found to vary across cognitive groups: compared to the CN group, the Obj-SCD group had higher temporal, occipital, and frontal WMH whereas the MCI group had larger WMH increases affecting all regions, which is in line with the greater severity of cognitive impairment in the MCI group. These findings add to growing evidence of associations between Obj-SCD and imaging biomarkers, particularly WMH,[77] providing support for the utility of these criteria to capture subtle cognitive changes that are biologically based.

3.8.2 | Longitudinal studies

In a longitudinal study including data from 804 ADNI 1 subjects[78] with CN, MCI, and AD, authors assessed the significance of WMH as a predictor of cognitive change and the strength of association between longitudinally measured WMH and longitudinally measured cognition using three time points over the course of 1 year. WMH volume at baseline was significantly associated with greater subsequent declines in global cognition over 1 year, as measured by MMSE and Alzheimer's Disease Assessment Scale Cognitive subscale (ADAS-Cog) scores (each SD increase in WMH at a given time point was associated with an additional 0.1 SD lower MMSE and 0.036 SD higher ADAS-Cog score at that time point), independently of relationships between key MRI markers of AD-associated neurodegeneration (brain and hippocampus volume) and cognition. Their findings suggest that, even in a sample that was intentionally designed to mimic a clinical trial, with frequent evaluations, short-term follow-up, and a relatively mild profile of cardiovascular risk, WM disease may be an important predictor of subsequent short-term global cognitive change. In another longitudinal study including amnestic MCI ($n = 230$), non-amnestic MCI ($n = 85$), and CN ($n = 303$) ADNI participants,[79] associations between regionally distributed WMH and MCI clinical subtypes were explored. The amnestic MCI group showed elevated temporal and occipital WMH volume relative to the CN group whereas the non-amnestic MCI group showed elevated WMH volume across frontal, parietal, temporal, and occipital regions, suggesting more widespread WMH accumulation. In addition, the non-amnestic MCI participants showed greater occipital WMH relative to the amnestic MCI affirming the contributions of WMH to cognitive impairment among individuals thought to have AD as the primary pathology.

3.8.3 | Interaction with *APOE*

As part of a replication study,[80] 198 participants from ADNI 1 were used to examine the role of *APOE* ε4 on the association between WMH and cognitive domains in patients with AD and patients with dementia with Lewy bodies (DLB). The study found that, in carriers of the *APOE* ε4 allele, WMH burden is inversely associated with cognitive performance, including executive function, memory, and language, whereas no such effect was seen in non-carriers. This relationship was found to be consistent across the AD/DLB spectrum. The authors conclude that information about the *APOE* ε4 status of patients may be useful to understand the relative contributions of different pathologies to an individual's unique dementia syndrome and to guide therapy as well.

3.8.4 | Interaction with neurodegeneration

In a study including 374 ADNI participants diagnosed with MCI,[81] the authors found that greater WMH volume, *APOE* ε4 status, and smaller ECV at baseline were associated with increased risk of aggressive decline (decrease in MMSE score of 3 points over 6 months or 6 points over 1 year between consecutive visits). WMH volume modified the effect of ECV on aggressive decline risk indicating that individuals with high ECV and low WMH were at a particularly low likelihood of decline. This study suggests that WMH and ECV predict rapid cognitive decline among individuals with MCI both additively and multiplicatively.

3.8.5 | effects of WMH

Recently, an international consortium, titled Meta VCI, was established to perform studies of lesion mapping, initially focusing on infarctions.[82] More recent work, however, has focused on the spatial distributions of WMH[83] that include data from 994 ADNI participants. In the initial study, the authors combined data across 11 different cohorts to create composite images of WMH frequency in the Montreal Neurological Institute 152 space and showed highly significant relationships between domain-specific cognitive performance and tract-specific WMH locations with a more pronounced effect among non-demented individuals[84] (Figure 3; with permission). Additionally, by summing the amount of tract-specific WMH into a strategic WMH score, the authors also find significant associations with all cognitive measures even after adjusting for concurrent brain atrophy (Table 2; with permission). In their most recent work including 3132 participants, the Meta VCI consortium further examined the impact of vascular risk and amyloid status.[85] A vascular risk compound score (VRCS) was derived from the sum of the risk factors, including current smoking, hypertension, hypercholesterolemia, diabetes mellitus, obesity, and history of a vascular event other than stroke.[84] Correcting for total WMH volume, higher VRCS was associated with higher WMH volumes in the middle cerebellar peduncle, anterior and superior corona radiata, and external capsule, and a lower WMH volume in the posterior thalamic

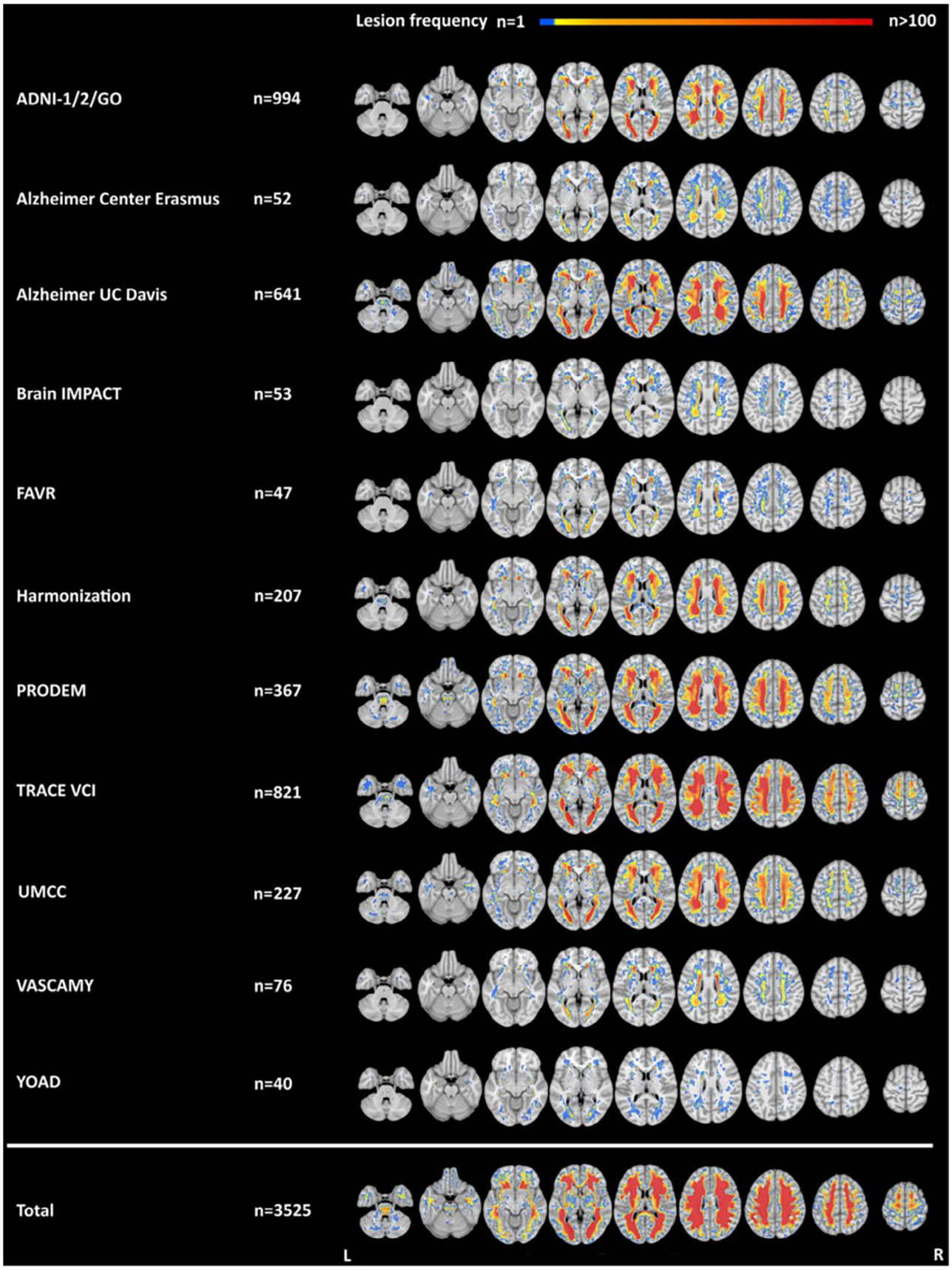

FIGURE 3 WMH prevalence map of individual cohorts and merged cohort. This figure shows how often each location in the brainwas affected by WMH in individual cohorts and the collective dataset. Blue voxels are WMH in less than five subjects. Bottom row: merging of datasets (yellow: n = 5; red: n ≥ 100). L = left, R = Right (by convention for lesion symptommapping analysis).

TABLE 2 Associations between strategic WMH score and various cognitive domains.

Independent variables	Attention & executive functioning			Information processing speed			Language			Verbal memory		
	Coefficient	SE	*p* value	Coefficient	SE	*p* value	Coefficient	SE	*p* value	Coefficient	SE	*p* value
Age	0.121	0.022	<0.001*	0.193	0.042	<0.001*	−0.006	0.047	0.921	0.068	0.028	0.015*
Sex	0.041	0.035	0.238	−0.006	0.067	0.943	−0.061	0.072	0.402	−0.013	0.044	0.775
Education	0.624	0.041	<0.001*	0.530	0.091	<0.001*	1.229	0.084	<0.001*	0.376	0.052	<0.001*
Brain volume	0.349	0.023	<0.001*	0.568	0.043	<0.001*	0.327	0.047	<0.001*	0.420	0.030	<0.001*
Strategic WMH score	−0.146	0.021	<0.001*	−0.090	0.040	0.023*	−0.124	0.042	0.003*	−0.128	0.026	<0.001*

Abbreviations: SE, standard error; WMH, white matter hyperintensity.
*statistically significant by *p*-value < 0.05.

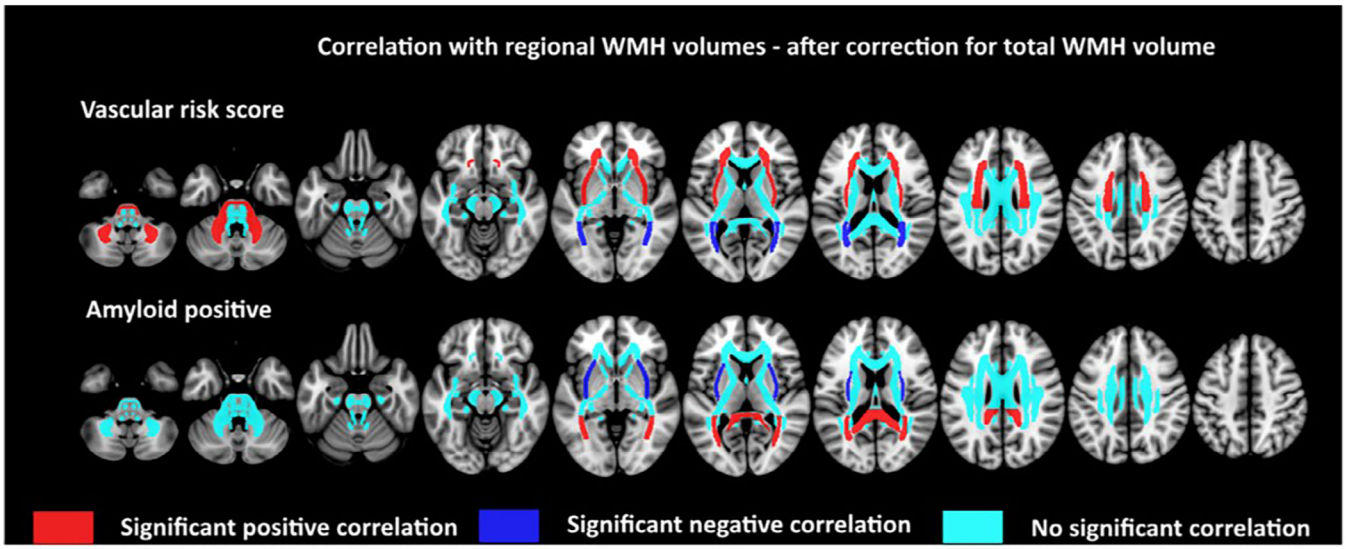

FIGURE 4 Distribution of WMHs in specific WM tracts of the Meta VCI consortium significantly associated with vascular risk or amyloidosis. VCI, vascular cognitive impairment; WM, white matter; WMH, white matter hyperintensity.

radiation and tapetum (Figure 4; with permission). In a separate model that included a subgroup of 1258 with amyloid measures, from either PET or CSF, a significant association was found between Aβ42-positive status and WMH volumes in the splenium of the corpus callosum and the posterior thalamic radiation. These studies indicate that WMH commonly affects specific cerebral WM tracts that influence specific cognitive domains. The specific tracts affected by WMH also appear to differ by etiology as previously proposed by much earlier work,[38,86] as well as results from the DIAN[69] and neuropathological studies.[70,71,87]

4 | DISCUSSION

As ADNI approaches its 20th year, the foresight of the ADNI team to include MRI measures of asymptomatic cerebrovascular disease to assess a common pathology that contributes to cognitive decline in later life has become apparent, even within this select cohort free of symptomatic cerebrovascular disease. Over the same time span, the dementia field has also come to see the importance of mixed pathologies as they relate to cognitive aging and transition to impairment.[88–93] This review summarizes similarities and differences in changing methodology to detect WMH as well as analytic strategies to evaluate their impact and interaction with AD pathology. Multiple MRI sequences and methodologies were used to measure WMH with generally consistent results. Data from all the ADNI cohorts find that, although absolute measures of WMH volume differ by both image sequence and analytic method, consistent trends with increasing volumes associated with advancing age, female sex, and cognitive impairment, comparing CN to MCI to dementia, are clearly present, confirming the biological relevance of WM tissue injury to impaired cognitive ability.

Additionally, despite careful selection to exclude individuals with symptomatic cerebrovascular disease, infarcts were detected on MRI at a frequency similar to community-based studies,[50] in which the presence of MR infarcts was shown to increase the risk for dementia, stroke, and death.[26] We note, however, that participants with

dementia had the lowest prevalence of MR infarcts. We hypothesize that the cause for this finding reflected increased attention to excluding vascular risk factors and disease among individuals with dementia leading to results divergent from the true prevalence of infarcts among persons with dementia in the community.[14]

These findings indicate that, even after careful selection for cerebrovascular health, asymptomatic vascular brain injury contributes to cognitive impairment among older individuals. Importantly, these findings should not be considered representative of the general US aging population as the prevalence of vascular risk factors and vascular disease are more common.[94] This is particularly true among diverse populations, which make up only a small fraction of the current ADNI cohorts, but are a growing part of our aging population.[95]

Affiliated publications arising from the use of these ADNI data have further elucidated the role of WMH on cognition, neurodegenerative measures, and even some AD biomarkers. For example, findings from one study suggest that, even in a sample that was intentionally designed to mimic a clinical trial, with frequent evaluations, short-term follow-up, and a relatively mild profile of cardiovascular risk, WMH is an important predictor of subsequent short-term global cognitive change.[78] Advancing analytical techniques have also enabled combined studies from large cohorts including ADNI that give further evidence for the impact of WMH on cognition, including memory and language performance,[82,84] two domains commonly associated with AD pathology. Other ADNI studies showed that WMHs lead to atrophy of brain regions identified as essential features of AD neurodegeneration, such as the entorhinal cortex,[54] hippocampus,[57] cortical thinning in AD-related brain regions,[58] and longitudinal differences in brain boundary shift interval,[58] a method commonly used to assess treatment response in AD clinical trials.

Associations between WMHs and AD biomarkers were also explored. One study, using Florbetapir PET in a CN population[68] found that WMHs are more highly correlated with cerebral Aβ positivity status than any of the standard AD imaging biomarkers. Further analysis also showed that, while baseline WMH volume was associated with the rate of amyloid accumulation, baseline amyloid was not associated with WMH volume rate, suggesting that WMHs are not simply a consequence of amyloidosis and that WMHs may drive faster amyloid accumulation. The relationship between WMHs and amyloidosis, however, has been an area of differing results. Early studies suggested a lack of correlation[96,97] with more recent studies identifying clear overlap with cerebral amyloid angiopathy (CAA) due to the AD process, particularly in persons with autosomal dominant inherited disease in whom CVD risk is low.[69,98] Among persons with later-life cognitive impairment, the relationship is likely to be complex with the possibility of independent but combined influences being most likely.[99,100,101] Not only do these pathologies appear to have additive influence, but they also appear to affect different WM tracts[85] and therefore potentially different cognitive systems.

These results reflect the complex etiologies of WMHs, which can be the consequence of concurrent CAA [102] as well as axonal degeneration due to parietal tauopathy in AD[70,71] in addition to the commonly ascribed vascular etiology.[18] While the etiology of WMHs can differ by the location where posterior WMHs, particularly in the splenium of the corpus collosum, are associated with cerebral amyloid burden and WMHs in more anterior tracts are associated with vascular risk factors,[85] the presence of WMHs is not sufficient to determine underlying disease pathophysiology, particularly among individuals with dementia for whom multiple and co-occurring pathologies are common.[12] Lack of disease specificity of WMHs, however, should not diminish the importance of WM injury on cognition as reviewed.

This review, however, is not without limitations. Additional features of vascular brain injury not reviewed include the presence of cerebral microbleeds (CMBs) identified on gradient echo MRI as punctate areas of signal loss presumed to represent hemosiderin deposition.[103] The etiology of CMBs is complex. CMBs are associated with arteriosclerotic vasculopathy, particularly in lenticular striate vessels;[104] are commonly seen in patients presenting with ischemic stroke or intracranial hemorrhage;[105] and are associated with incident dementia.[106] CMBs are also the defining imaging feature of CAA.[102,107] In CAA, CMBs are associated with deposition of the Aβ_{40} fragment in blood vessels and are most frequent among carriers of the *APOE* ε4 genotype.[108] CAA is also associated with the extent and progression of WMHs, correlates with plasma measures of Aβ_{40} concentration in serum,[102] and can cause cognitive impairment independent of AD pathology[109] emphasizing likely vascular contributions to the disease. CMBs, however, are also common in persons with AD, particularly at the junction of the gray matter and WM within the occipital and parietal cortices. The presence of CMBs among cognitively impaired individuals, therefore, likely reflects multiple, and synergistic, processes of vascular injury and neurodegeneration.[110]

Enlarged perivascular spaces (ePVS) have also been studied as potential markers of cerebrovascular disease. ePVS are seen as linear or rounded areas that are hypointense on T1 or hyperintense on T2 images.[18] The etiology of ePVS is similarly complex as they are postulated to reflect pathologic processes from both direct vascular effects due to increased vascular resistance and impaired vasomotor reactivity as well as amyloid deposition due to AD or CAA.[111] ePVS are more common among individuals with hypertension[112] and may even decrease in size with aggressive anti-hypertensive treatment.[113] They are also present among patients with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy[114] and are a risk factor for incident lacunar infarction.[115] ePVS are similarly associated with MCI[116] and dementia[117] thought due to AD processes. Despite the varying etiologies of ePVS, it is hypothesized that waste product clearance, including amyloid proteins, through perivascular spaces (either by the glymphatic system or the intramural periarterial drainage pathway) may be diminished, accelerating brain injury due to these vascular alterations.[111]

These limitations reflect that the ADNI study was designed for the "Identification of those neuroimaging measures, cognitive measures, and biomarkers, which provide the maximum power for the diagnosis of MCI and AD and for the assessment of treatment effects in trials involving healthy elderly, MCI, and AD"[118] and therefore did not focus on cerebrovascular markers such as recently done for the Mark VCID consortium.[119,120] Additionally, the study cohorts emphasized exclu-

sion of individuals with non-AD pathologies such as cerebrovascular disease.[30] ADNI leadership, however, also recognized that, despite limiting enrollment to individuals without stroke or extensive vascular risk, the ADNI protocol still required assessment of subclinical vascular disease[29,121] as a potential contributor to cognitive impairment even in cohorts highly selected for the presence of AD pathology.

Beginning with Geschwind,[122,123] advances in cognitive neuroscience have emphasized the presence of multiple cognitive systems, connected through specific WM tracts, that subserve specific brain functions and are often differentially engaged during the demands of various cognitive tasks.[124] Seeley et al. identified unique, disease-specific vulnerability to these systems,[125] including AD, which is considered the paradigmatic disconnection syndrome.[126] While Seeley et al. emphasized neuronal proteinopathies as the driving force for impairment to these connected systems, the possible impact of co-occurring cerebrovascular disease affecting axonal integrity was not discussed. Yet, WM makes up 50% of brain structure consisting of major WM tracts necessary for cerebral integration.[127] It is also evident from diseases such as multiple sclerosis that isolated WM injury is sufficient to cause cognitive impairment. Structural connectivity methods that examine the number and integrity of axonal pathways (for example, using diffuse tensor imaging quantification) are furthering our understanding of how various brain networks are involved in cognitive function.[128] New methods to directly image myelin from MRI are also being developed.[129,130] Progress in understanding the impact of cerebrovascular risk factors and disease on cognitive decline and transition to dementia, therefore, will be made through the development and use of both synaptic and axonal imaging measures. We hope the application of data from past and future ADNI cohorts (which will include a greater proportion of individuals from more diverse backgrounds, more individuals with cerebrovascular risk factors, and expanded imaging sequences to more fully evaluate cerebrovascular brain injury) will further the goal of ADNI to improve the clinical trial design of AD therapeutics as well as expand our understanding of the multiple pathologies leading to dementing disorders, possibly illuminating new biological pathways for therapeutic discovery while simultaneously being more representative of our aging population at risk for late-life dementia.

ACKNOWLEDGMENTS

Data used in the preparation of this article were obtained from the ADNI database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in the analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wpcontent/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf. This study was supported by the National Institute on Aging (U01 AG024904 and P30 AG072972).

CONFLICT OF INTEREST STATEMENT

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

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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: Maillard P, Fletcher E, Carmichael O, et al. Cerebrovascular markers of WMH and infarcts in ADNI: A historical perspective and future directions. *Alzheimer's Dement*. 2024;20:8953–8968.
https://doi.org/10.1002/alz.14358