Received: 11 June 2020 | Revised: 15 July 2020 | Accepted: 24 July 2020 | Published online: 22 September 2020

DOI: 10.1002/dad2.12091

Alzheimer's & Dementia
Diagnosis, Assessment & Disease Monitoring

RESEARCH ARTICLE

The temporal relationships between white matter hyperintensities, neurodegeneration, amyloid beta, and cognition

Mahsa Dadar[1] | **Richard Camicioli**[2] | **Simon Duchesne**[1,3] | **D. Louis Collins**[4,5,6] | **for the Alzheimer's Disease Neuroimaging Initiative**[1,*]

[1] CERVO Brain Research Center, Centre intégré universitaire santé et services sociaux de la Capitale Nationale, Québec, Quebec, Canada

[2] Department of Medicine, Division of Neurology, University of Alberta, Edmonton, Alberta, Canada

[3] Department of Radiology and Nuclear Medicine, Faculty of Medicine, Université Laval, Québec City, Quebec, Canada

[4] McConnell Brain Imaging Centre, Montreal Neurological Institute, McGill University, Montreal, Quebec, Canada

[5] Department of Neurology and Neurosurgery, Faculty of Medicine, McGill University, Montreal, Quebec, Canada

[6] Department of Biomedical Engineering, Faculty of Medicine, McGill University, Montreal, Quebec, Canada

Correspondence
Mahsa Dadar, Cervo Brain Research Centre, 2601 Chemin de la Canardière, Québec, G1J 2G3, Canada.
E-mail: mahsa.dadar.1@ulaval.ca, mahsa.dadar@mail.mcgill.ca

[*] Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (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 analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wp-ontent/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf

Funding information
Alzheimer's Disease Neuroimaging Initiative; National Institutes of Health, Grant/Award Number: U01 AG024904

Abstract

Introduction: Cognitive decline in Alzheimer's disease is associated with amyloid beta (Aβ) accumulation, neurodegeneration, and cerebral small vessel disease, but the temporal relationships among these factors is not well established.

Methods: Data included white matter hyperintensity (WMH) load, gray matter (GM) atrophy and Alzheimer's Disease Assessment Scale-Cognitive-Plus (ADAS13) scores for 720 participants and cerebrospinal fluid amyloid (Aβ1–42) for 461 participants from the Alzheimer's Disease Neuroimaging Initiative. Linear regressions were used to assess the relationships among baseline WMH, GM, and Aβ1–42 to changes in WMH, GM, Aβ1–42, and cognition at 1-year follow-up.

Results: Baseline WMHs and Aβ1–42 predicted WMH increase and GM atrophy. Baseline WMHs and Aβ1–42 predicted worsening cognition. Only baseline Aβ1–42 predicted change in Aβ1–42.

Discussion: Baseline WMHs lead to greater future GM atrophy and cognitive decline, suggesting that WM damage precedes neurodegeneration and cognitive decline. Baseline Aβ1–42 predicted WMH increase, suggesting a potential role of amyloid in WM damage.

KEYWORDS
Alzheimer's disease, mild cognitive impairment, neurodegenerative disease, small-vessel disease, white matter hyperintensities

1 | INTRODUCTION

White matter hyperintensities (WMHs) on T2-weighted (T2w) and fluid-attenuated inversion recovery (FLAIR) magnetic resonance images (MRIs) are indicative of the presence of cerebrovascular pathology.[1] Pathologically, WMHs have been associated with gliosis, demyelination, axonal loss, and arteriosclerosis due to hypoxia, hypoperfusion, blood–brain barrier leakage, inflammation, degeneration, and amyloid angiopathy.[2] Clinically, WMHs have been associated with increased risks of cognitive decline in otherwise normal aging (NA), individuals with mild cognitive impairment (MCI), and patients with probable Alzheimer's disease (AD).[3–8]

Accumulating evidence indicates that cerebrovascular pathology is very common in AD patients and has an important role in AD pathology, lowering the threshold for a clinical diagnosis of dementia due to AD.[9] What is less clear is whether cerebrovascular pathology occurs before, after, or at the same time as the progression of AD, and whether it has a synergistic interaction with AD pathology and neurodegeneration.[9]

A number of recent studies have suggested that cerebrovascular pathology might be the starting point of a chain of events leading to AD neurodegeneration and cognitive decline.[10,11] Hypo-perfusion and ischemic changes associated with aging and vascular risk factors can result in blood supply and metabolism disturbances. Such disturbances can cause neuronal energy failure, leading to neuronal injury and acceleration in over-production and reduction in clearance of amyloid beta (Aβ), resulting in progressive cognitive deficits and neurodegeneration characteristic of AD.[12,13]

On the other hand, Aβ deposition could also increase WMH burden by accelerating processes that are not necessarily vascular in nature, including neuroinflammation, reactive oxygen species production, and oxidative stress.[14–16] In this scenario, an initial rise in Aβ would damage the white matter (WM), which in turn would further elevate Aβ levels, leading to more WM damage in a cyclical process. This initial rise in Aβ would be noticeable in cerebrospinal fluid (CSF) assays.[17]

Another contributing link belongs to risk factors that are associated with WMHs and cognitive decline including hypertension, high systolic and diastolic blood pressure, hypercholesterolemia, diabetes, obesity, high glucose levels, and smoking.[2,9] These risk factors are particularly important because they are amenable to prevention and treatment[9] and their reduction might impede WMH progression and cognitive deterioration.[18–24]

Regarding neuro-degeneration, a well-established marker of disease progression in AD is atrophy of cortical and subcortical gray matter (GM) structures. This atrophy is associated with cognitive deficits and decline in aging, MCI, and AD populations.[25–29] Whole brain measures of atrophy are strongly associated with cognitive decline and increased risk of dementia in aging, MCI, and AD.[30–32]

Although it is known that both WMHs and GM atrophy contribute to cognitive deficits on the spectrum from aging to probable AD, it remains unclear whether they have an independent, synergistic, or sequential impact on cognition. In this study, we take advantage of the longitudinal data from the Alzheimer's Disease Neuroimaging Initiative (ADNI) to investigate the temporal relationships among WMHs, GM atrophy, cognitive decline, and Aβ. Specifically, we aimed to investigate: (1) whether WMHs precede neurodegeneration and cognitive decline; and (2) whether WMHs impact Aβ progression or vice versa.

RESEARCH IN CONTEXT

1. Systematic Review: Previous studies have reported associations between amyloid beta (Aβ) accumulation, neurodegeneration, cerebral small vessel disease, and cognitive decline in Alzheimer's disease patients, but the temporal relationships among these factors as well as their interplay is not well established.
2. Interpretation: In this study, we assess the relationships among change in Aβ, neurodegeneration, white matter hyperintensity burden, and cognitive decline and their baseline variables simultaneously. We found an association between baseline white matter hyperintensities (WMHs) and greater future gray matter atrophy and cognitive decline, suggesting that WM damage precedes neurodegeneration and cognitive decline. Baseline Aβ was also associated with WMH increase, suggesting a potential role of amyloid in WM damage.
3. Future Directions: Future studies including longitudinal measurements of Aβ, neurodegeneration, cerebrovascular disease, and cognition in larger and more representative cohorts with longer follow-up intervals are needed to further establish these temporal relationships.

2 | METHODS

2.1 | Participants

We selected participants from the ADNI-1, ADNI-2, and ADNI-GO database (adni.loni.usc.edu) that had cognitive evaluations and associated T1w, T2w/PDw, and FLAIR MRIs at 1-year intervals (Figure 1). The ADNI was launched in 2003 as a public-private partnership, led by Principal Investigator Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial MRI, positron emission tomography, other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of MCI and early AD. The study was approved by the institutional review board of all participating sites and written informed consent was obtained from all participants before inclusion in the study.

2.2 | MRI acquisition and preprocessing

Table S1 in supporting information summarizes MR imaging parameters for the data used in this study.

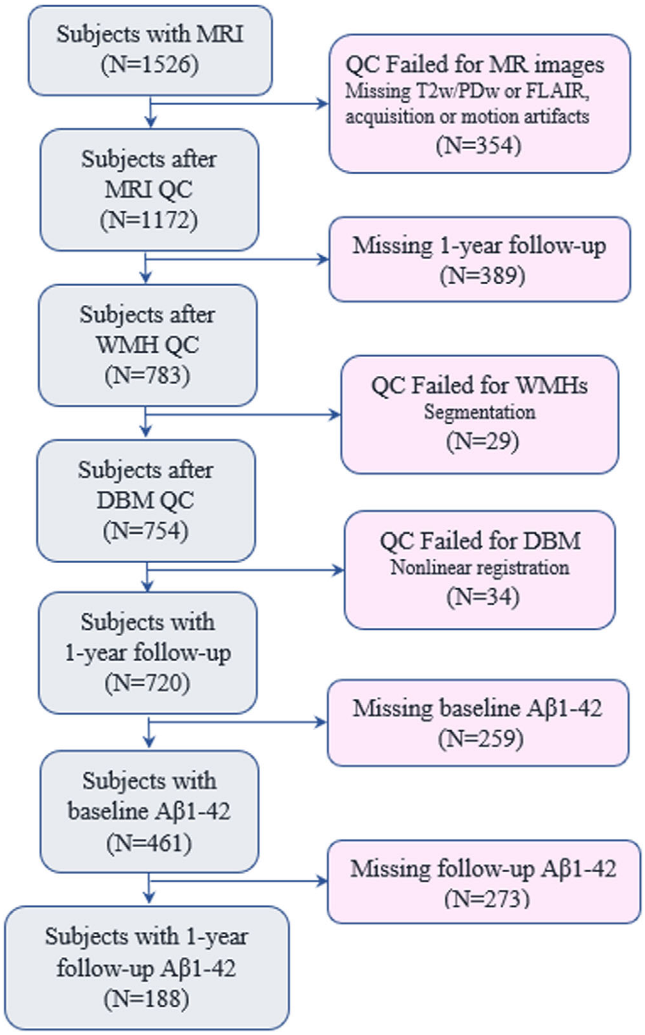

FIGURE 1 Study flowchart. Aβ, amyloid beta; DBM, deformation-based morphometry; FLAIR, fluid-attenuated inversion recovery; MRI, magnetic resonance imaging; QC, quality control; WMH, white matter hyperintensity

T1w, T2w/PDw, and FLAIR scans were pre-processed as follows: (1) image denoising,[33] (2) intensity inhomogeneity correction, and (3) intensity scaling to a 0–100 range. For each subject, the T2w, PDw, or FLAIR scans were then co-registered to the structural T1w scan of the same time point using a six-parameter rigid registration and a mutual information objective function.[34] The T1w scans were also linearly[34] and nonlinearly[35] registered to the MNI-ICBM152 unbiased average template.[36]

2.3 | WMH measurements

Using a previously validated WMH segmentation method and a library of manual segmentations based on 100 subjects from ADNI (independent of the 720 subjects studied here), WMHs were automatically segmented at both baseline and 1-year follow-up time points.[7,37,38] The technique uses a set of location and intensity features in combination with a random forests classifier to detect WMHs using either T1w+FLAIR or T1w+T2w/PDw images. WMH load was used as a proxy for cerebrovascular pathology and was defined as the volume of all voxels identified as WMH in the standard space (in mm^3) and are thus normalized for head size. WMH volumes were log-transformed to achieve normal distribution.

2.4 | GM measurements

Deformation-based morphometry (DBM) is used to identify macroscopic anatomical changes within the population by spatially normalizing the T1w MRIs so that they all conform to the same stereotaxic space. Cross-sectional non-linear registration to the MNI-ICBM152 template resulted in a deformation field sampled on a 1 mm^3 grid for each subject/time point. DBM maps were calculated by taking the Jacobian determinant of the inverse deformation field.[39] Jacobian determinant reflects voxel volumes relative to the MNI-ICBM152 template; ie, a value of 1 indicates similar volume to the same voxel in the template, and values lower/higher than 1 indicate volumes smaller/larger than the template. The difference in the Jacobian determinant at two time points can be used to estimate change in volume. A decrease in the Jacobian determinant values of a specific region between two time points can be interpreted as a reduced cerebral structure volume, ie, atrophy. Using a GM mask obtained based on CerebrA atlas of the GM regions for the MNI-ICBM152 template,[40] mean DBM values in the GM were calculated as whole brain measures of GM volume and used as proxies of neurodegeneration.

2.5 | Cognitive evaluations

All subjects received a comprehensive battery of clinical assessments and cognitive testing based on a standardized protocol (adni.loni.usc.edu).[41] At each visit, participants underwent a series of assessments including the Alzheimer's Disease Assessment Scale-13 (ADAS13),[42] which was used as a proxy of cognitive function.

2.6 | Aβ levels

CSF Aβ1–42 measures provided by the ADNI biomarker core (University of Pennsylvania) using microbead-based multiplex immunoassay were used to assess Aβ burden. Out of the 720 subjects, 461 and 188 had Aβ1–42 measures at baseline and follow-up visits, respectively.

2.7 | Quality control

Preprocessed and registered images were visually assessed for quality control (presence of imaging artifacts, failure in either linear or nonlinear registrations). WMH segmentations were also visually assessed for missing hyperintensities or oversegmentation. Either failures resulted in the participant being removed from the analyses. All MRI processing, segmentation, and quality control (QC) steps were blinded to clinical outcomes. Figure 1 summarizes the QC information for the subjects that were excluded. The final sample included 720 subjects with WMH, GM volume, and ADAS13 measures available at 1-year intervals.

2.8 | Statistical analyses

Paired *t*-tests were used to compare baseline versus follow-up WMH, GM atrophy, ADAS13, and Aβ1–42 values. Unpaired *t*-tests were used to assess differences across NA, MCI, and AD groups in demographics and clinical variables. Linear regression models were used to assess the relationships between WMH load and vascular risk factors, controlling for age, sex, diagnostic cohort, and WMH segmentation modality. The following linear regression models were first used to assess the relationship between baseline WMH and GM measurements, and change in WMH, GM, and cognitive function in the 720 subjects that had these measurements available:

$$\begin{aligned}\Delta\ \text{Measure} = {} & 1 + \text{WMH}_{\text{Baseline}} + \text{GM}_{\text{Baseline}} + \text{ADAS13}_{\text{Baseline}} \\ & + \text{Age} + \text{Sex} + \text{Education} + \text{Vascular risk factors} \\ & + \text{APOE4} + \text{Modality} \qquad (1)\end{aligned}$$

Where *ΔMeasure* indicates change in measures of interest (ie, WMH load, GM volume, and ADAS13) between baseline and one-year follow-up visits (ie, $\text{Measure}_{\text{Follow-up}}$-$\text{Measure}_{\text{Baseline}}$). *Vascular risk factors* include hypertension, systolic and diastolic blood pressure, body mass index (BMI), glucose, cholesterol, and triglyceride levels. Apolipoprotein E (*APOE*)*4* is a categorical variable contrasting subjects with one or two APOE ε4 alleles against those with zero. *Modality* is a categorical variable indicating whether WMHs were segmented using T1w+FLAIR or T1w+T2w/PDw scans to account for any potential differences in the segmentations.

A second model was used to also assess relationships with Aβ levels in the subsample that had Aβ1–42 measurements available:

$$\begin{aligned}\Delta\ \text{Measure} = {} & 1 + \text{A}\beta_{\text{Baseline}} + \text{WMH}_{\text{Baseline}} + \text{GM}_{\text{Baseline}} \\ & + \text{ADAS13}_{\text{Baseline}} + \text{Age} + \text{Sex} + \text{Education} \\ & + \text{Vascular risk factors} + \text{APOE4} + \text{Modality} \qquad (2)\end{aligned}$$

Here, *ΔMeasure* indicates change in measures of interest (ie, WMH load, GM volume, ADAS13, and Aβ1–42). All continuous values were z-scored within the population prior to the regression analyses.

3 | RESULTS

3.1 | Participants

A total of 1526 participants were available from the ADNI. After preprocessing, and WMH and DBM extraction, 444 participants were removed due to failed quality control (Figure 1). The majority of these cases were missing or had significant artifacts in T2w/PD or FLAIR images. In the end, we included 720 individuals that had all MRI and clinical variables of interest available at 1-year intervals (time between the two visits = 1±0.1 year).

Table 1 summarizes the descriptive characteristics separately for NA, MCI, and AD participants. AD patients had significantly higher WMH load and GM atrophy levels than NA in both baseline and follow-up visits ($P < .0003$). MCI and AD groups had significantly lower CSF Aβ levels, compared to controls ($P < .00001$), and AD patients had significantly lower Aβ levels ($P < .00001$) than the MCI group. Baseline ADAS13 scores were significantly different across all groups ($P < .00001$). Controlling for age, sex, years of education, vascular risk factors, and modality of segmentation, all baseline variables were significantly associated with each other ($P < .01$, Figure S1 in supporting information).

MCI and AD groups had a significantly greater proportion of subjects with APOE4 alleles ($P < .001$), compared to NA. There were no significant associations between baseline WMHs or GM volume and APOE4 status. However, individuals with one or two APOE4 alleles had significantly higher ADAS13 scores and lower Aβ1–42 levels ($P < .00001$).

3.2 | Vascular risk factors

Controlling for age, sex, diagnostic cohort, and segmentation modality, hypertension (T stat = 5.78, $P < .00001$), higher systolic (T stat = 2.48, $P = .01$) and diastolic blood pressure (T stat = 3.09, $P = .002$), higher glucose levels (T stat = 3.45, $P = .0006$), and higher BMI (T stat = 2.61, $P = .009$) were associated with higher WMH loads at baseline. There were no differences among NA, MCI, and AD groups in proportion of hypertensives, systolic blood pressure, diastolic blood pressure, BMI, glucose, cholesterol or triglyceride levels (Table 1). There was no significant association between baseline GM volume, Aβ1–42, or ADAS13 and vascular risk factors.

3.3 | Longitudinal comparisons

There was a significant increase in WMH load (1.23cm^3, 11.63% of the average baseline load) and ADAS13 scores (0.92, 5.53% of the average baseline score) indicating worsening cognitive performance, and a significant decrease in GM volume (0.0082, 0.86% of the average baseline value) indicating GM atrophy at the 1-year follow-up visit compared to baseline (paired *t*-tests, $P < .000001$). There was no significant difference in Aβ1–42 levels between the baseline and follow-up visits ($P = .57$) for the 188 participants with available CSF results at 1-year follow-up (0.97 pg/mL decrease, 0.58% of the average baseline value).

3.4 | Relationships between baseline measurements and longitudinal change (model 1)

Baseline WMH load predicted change in WMH load over follow-up (T stat = 6.54, $P < .00001$). Regarding all other variables, there was

TABLE 1 Descriptive statistics for the participants enrolled in this study. Data are number (N) or mean ± standard deviation. *P*-values indicate group comparison results, determined by unpaired *t*-tests for continuous variables and $\chi 2$ tests for categorical variables

Cohort	NA	MCI	AD	MCI vs. NA	AD vs. NA	MCI vs. AD
Number of subjects (N)	207	396	117	–	–	–
N_{Female}	92	144	50	0.07	0.85	0.25
Baseline age (years)	75.69 ± 5.73	73.50 ± 7.36	74.49 ± 7.80	**0.002**	0.09	0.23
Education (years)	16.03 ± 2.81	16.11 ± 2.83	15.32 ± 2.82	0.72	**0.03**	**0.008**
BMI (Kg/m^2)	26.78 ± 4.57	26.84 ± 4.63	25.94 ± 4.07	0.88	0.10	0.06
APOE4 (0/1/2)	142/59/6	192/156/48	37/56/24	**0.001**	**<0.0001**	**0.002**
Diastolic blood pressure (mmHg)	75.02 ± 10.46	75.38 ± 9.34	75.08 ± 8.86	0.67	0.96	0.75
Systolic blood pressure (mmHg)	134.96 ± 17.2	135.57 ± 17.1	135.51 ± 17.9	0.68	0.78	0.97
Hypertension (N)	101	189	61	0.87	0.64	0.46
Cholesterol (mg/dL)	193.38 ± 39.8	195.95 ± 40.3	192.18 ± 40.6	0.54	0.80	0.44
Triglyceride (mg/dL)	139.30 ± 89.3	147.17 ± 84.7	139.69 ± 75.3	0.30	0.97	0.41
Glucose (mg/dL)	99.22 ± 17.94	100.64 ± 23.3	98.12 ± 18.98	0.49	0.62	0.34
Baseline ADAS-cog13	4.36 ± 9.55	16.82 ± 6.61	29.08 ± 6.49	**<0.00001**	**<0.00001**	**<0.00001**
Follow-up ADAS-cog13	8.87 ± 4.60	17.69 ± 8.31	32.86 ± 9.34	**<0.00001**	**<0.00001**	**<0.00001**
Baseline Aβ1-42 (pg/mL)	198.64 ± 54.8	170.60 ± 51.9	139.31 ± 42.2	**<0.00001**	**<0.00001**	**<0.00001**
Follow-up Aβ1-42 (pg/mL)	202.02 ± 58.1	160.29 ± 50.1	132.13 ± 31.02	**<0.00001**	**<0.00001**	**0.001**
Baseline WMH load (cm^3)	9.92 ± 13.09	10.15 ± 12.88	15.86 ± 20.83	0.67	**0.0003**	**<0.00001**
Follow-up WMH load (cm^3)	10.79 ± 13.44	11.39 ± 13.90	18.05 ± 22.22	0.51	**<0.0001**	**<0.00001**
Baseline GM Jacobian	0.962 ± 0.04	0.958 ± 0.05	0.944 ± 0.04	0.24	**<0.0001**	**0.005**
Follow-up GM Jacobian	0.957 ± 0.04	0.949 ± 0.05	0.932 ± 0.04	**0.03**	**<0.00001**	**0.0001**

Abbreviations: Aβ, amyloid beta; AD, Alzheimer's disease; ADAS, Alzheimer's Disease Assessment Scale; CC, cubic centimeter; GM, gray matter; NA, normal aging; MCI, mild cognitive impairment; WMH, white matter hyperintensity.

no significant association between change in WMH load and age, sex, years of education, APOE4 alleles, vascular risk factors, modality of segmentation, baseline GM, or baseline ADAS13. There was no significant difference across cohorts in the slopes. Figure 2 (first row) shows the relationships among baseline GM atrophy, baseline WMH load, and baseline ADAS13 and change in WMH load. Based on the model predictions, each additional 1 cm^3 of WMHs at baseline leads to 0.70cm^3 additional increase in WMH load during the following year, equivalent to 6.43% of the average baseline WMH load.

A decrease in GM volume between baseline and follow-up (ie, GM atrophy) was predicted by higher baseline WMH load (T stat = 3.54, P = .0004) and baseline ADAS13 (T stat = -4.24, $P < .0001$), but not by age, sex, years of education, presence of APOE4 alleles, vascular risk factor, segmentation modality, or baseline GM volume. There was no significant difference across cohorts in the regression slopes. Figure 2 (second row) shows the relationship between baseline GM volume, baseline WMH load, and baseline ADAS13 and change in GM volume. Based on the model predictions, each additional 1 cm^3 of WMHs at baseline leads to 0.0014cm^3 additional decrease in GM during the following year, equivalent to 0.15% of the average baseline GM volume.

An increase in ADAS13 scores (ie, worsening cognitive performance) was predicted by both baseline WMH load (T stat = 2.04, P = .03) and baseline ADAS13 score (T stat = 3.79, P = .0001), but not by age, sex, years of education, presence of APOE4 alleles, vascular risk factors, segmentation modality, or baseline GM volume. Figure 2 (third row) shows the relationships among baseline GM volume, baseline WMH load, and baseline ADAS13 and change in ADAS13 scores. Based on the model predictions, each additional 1 cm^3 of WMHs at baseline leads to 0.45 additional increase in ADAS13 score during the following year, equivalent to 2.7% of the average baseline score. Similarly, a 1-point higher baseline ADAS13 score leads to an additional 0.15 increase in ADAS13 score during the following year, equivalent to 0.87% of the average baseline score.

3.5 | Relationships with Aβ (model 2)

In the subsample of 461 participants that had Aβ1–42 data available at baseline, baseline Aβ1–42 levels were associated with change in WMH volume at the 1-year follow-up (T stat = −2.13, P = .03) and change in ADAS13 scores (T stat = −2.69, P = .007), but not to GM atrophy (Table 2). Figure 3 (first row) shows the relationship between baseline Aβ1–42 levels and change in GM, WMHs, and ADAS13, respectively. In the subsample of 188 participants that had Aβ1–42 data available at baseline and follow-up visits, change in Aβ1–42 levels was only

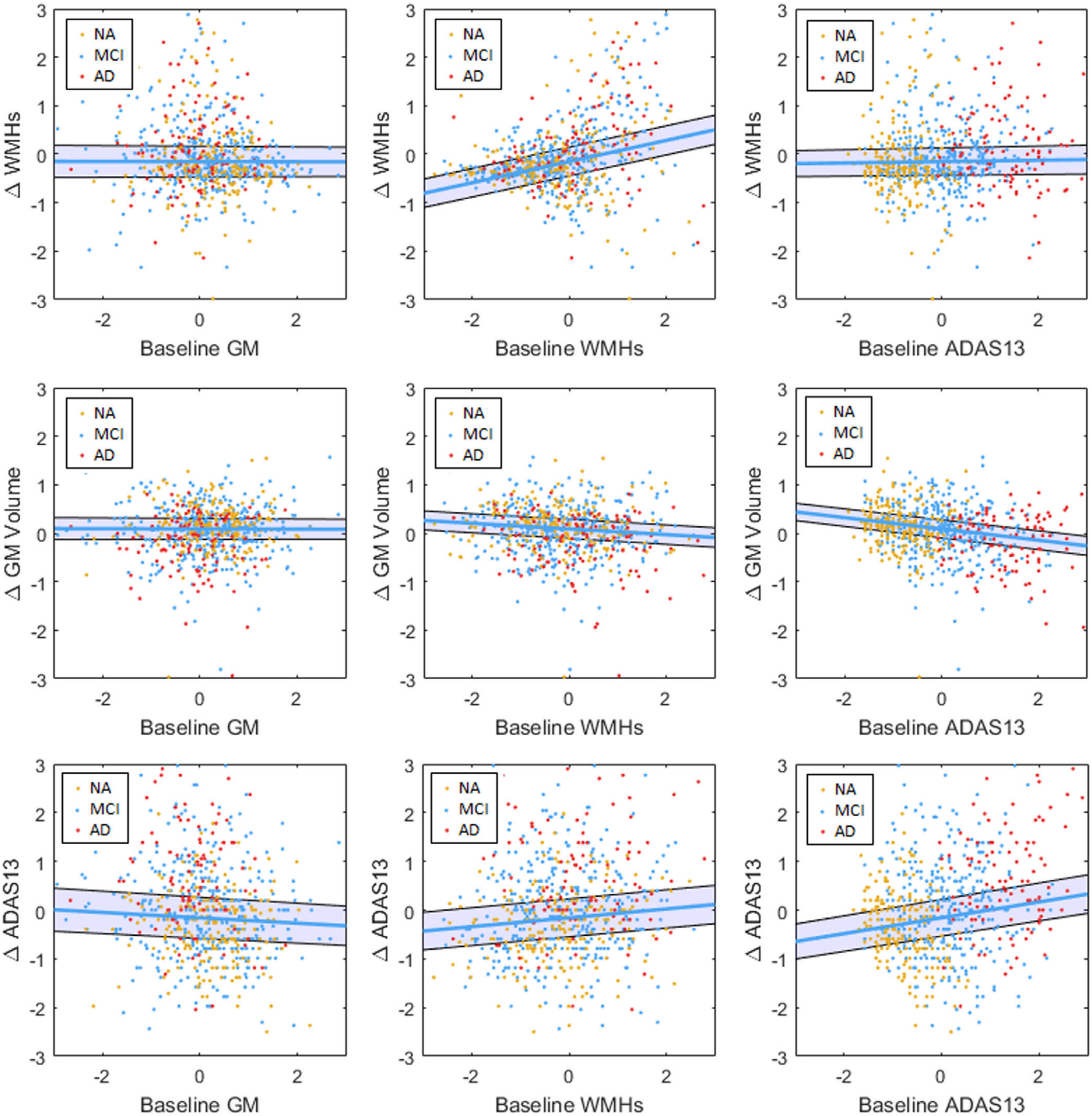

FIGURE 2 Baseline measurements and longitudinal changes in WMHs (first row), GM (second row), and ADAS13 (third row). All variables are z-scored. $\Delta WMH = WMH_{Follow\text{-}up} - WMH_{Baseline}$. $\Delta GM = GM_{Follow\text{-}up} - GM_{Baseline}$. $\Delta ADAS13 = ADAS13_{Follow\text{-}up} - ADAS13_{Baseline}$. AD, Alzheimer's disease; ADAS, Alzheimer's Disease Assessment Scale-13; CSF, cerebrospinal fluid; GM, gray matter; NA, normal aging; MCI, mild cognitive impairment; WMH, white matter hyperintensity

associated with baseline Aβ1–42 (T stat = −3.35, *P* = .0009), and not to WMH load or GM volume. There was no significant association with age, sex, years of education, presence of APOE4 alleles, vascular risk factors, or segmentation modality. Figure 3 (second row) shows the relationship between change in Aβ1–42 levels and baseline Aβ1–42, GM, WMHs, and baseline ADAS13, respectively.

3.5.1 | Final model

Table 2 summarizes the estimated parameters for each model (Eq. 2). Figure 4 summarizes the associations among APOE4, vascular risk factors, and baseline and longitudinal measurements. The arrows indicate significant associations based on the analyses in the previous sections.

TABLE 2 Mixed-effects model parameter estimates

	Δ WMH		Δ GM		Δ ADAS13		Δ Aβ	
Measure	*T* stat	*P* value	*T* stat	*P* value	*T* stat	*P* value	*T* stat	*P* value
$WMH_{Baseline}$	**4.41**	**<.0001**	**−2.62**	**.009**	**2.37**	**.01**	0.16	.87
$GM_{Baseline}$	−0.66	.51	−0.66	.51	−0.43	.66	−0.46	.64
$ADAS13_{Baseline}$	−0.55	.58	**−2.69**	**.007**	**2.73**	**.006**	−1.80	.07
$A\beta_{Baseline}$	**−2.13**	**.03**	0.33	.74	**−2.68**	**.007**	**−3.35**	**.0009**
Age	0.44	.66	1.28	.20	−2.01	.05	0.30	.76
Sex - Female	−0.35	.72	−1.29	.19	0.97	.33	−1.58	.11
Education	0.60	.55	−1.32	.19	−0.22	.82	−1.74	.08
APOE4 - 1 allele	−0.30	.76	0.49	.62	1.20	.23	0.09	.93
APOE4 - 2 alleles	0.74	.45	−0.16	.87	0.89	.37	−0.61	.54
Hypertension	−0.82	.41	−0.54	.59	−2.01	.05	−1.09	.27
Systolic BP	−0.10	.92	0.14	.88	1.91	.06	−2.03	.05
Diastolic BP	−1.09	.28	−0.62	.53	−1.34	.18	0.84	.40
BMI	−0.20	.84	0.72	.47	−0.20	.84	0.99	.32
Glucose	−0.14	.88	1.30	.19	0.69	.49	0.91	.37
Cholesterol	1.17	.24	0.05	.97	1.10	.16	−1.00	.32
Triglyceride	−0.004	.99	0.35	.72	0.13	.90	−0.54	.58
Modality	0.15	.87	0.05	.95	−1.42	.15	0.008	.99

Significant results are shown in bold font.
Abbreviations: ADAS, Alzheimer's Disease Assessment Scale-13; APOE, apolipoprotein E; BMI, body mass index; BP, blood pressure; GM, gray matter; WMH, white matter hyperintensity.

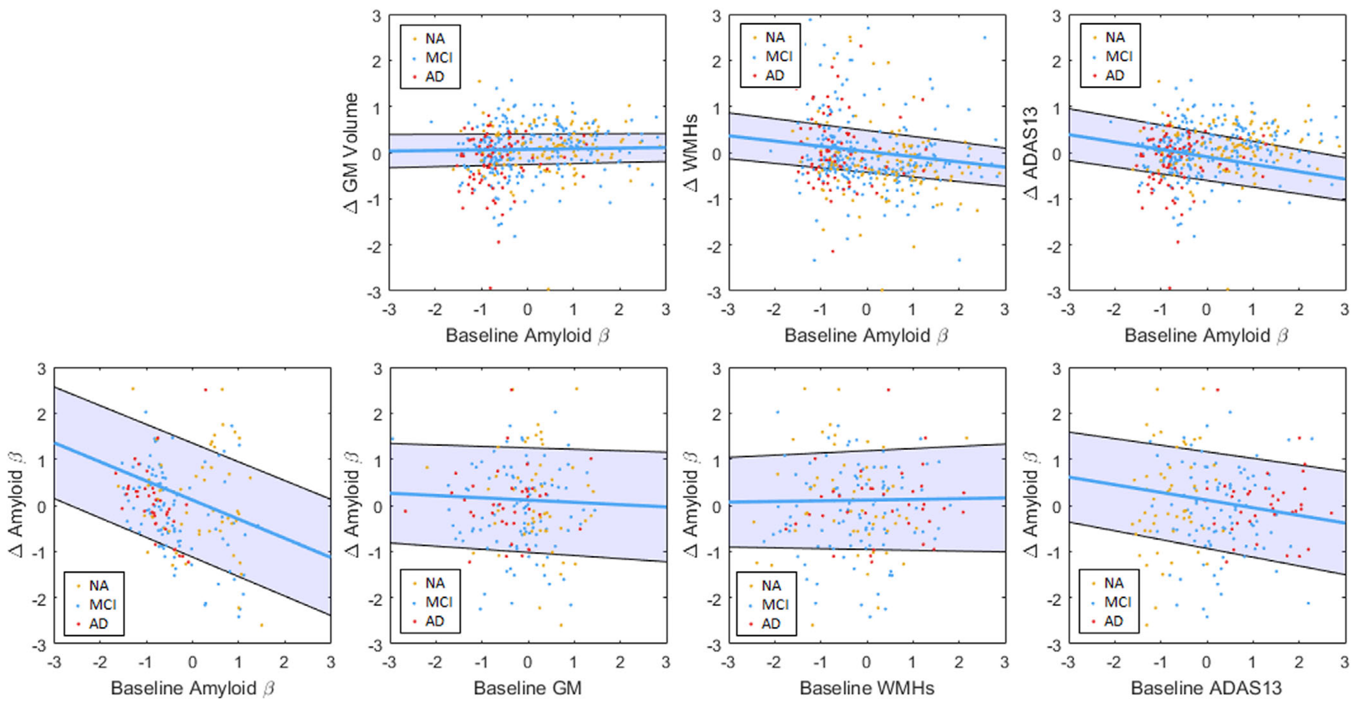

FIGURE 3 The relationship between CSF Aβ levels and longitudinal measurements (first row) and change in CSF Aβ levels and baseline measurements (second row). All variables are z-scored. ΔAmyloid β = Amyloid $\beta_{Follow\text{-}up}$ - Amyloid $\beta_{Baseline}$. $\Delta WMH = WMH_{Follow\text{-}up} - WMH_{Baseline}$. $\Delta GM = GM_{Follow\text{-}up} - GM_{Baseline}$. $\Delta ADAS13 = ADAS13_{Follow\text{-}up} - ADAS13_{Baseline}$. Aβ, amyloid beta; AD, Alzheimer's disease; ADAS, Alzheimer's Disease Assessment Scale-13; CSF, cerebrospinal fluid; GM, gray matter; NA, normal aging; MCI, mild cognitive impairment; WMH, white matter hyperintensity

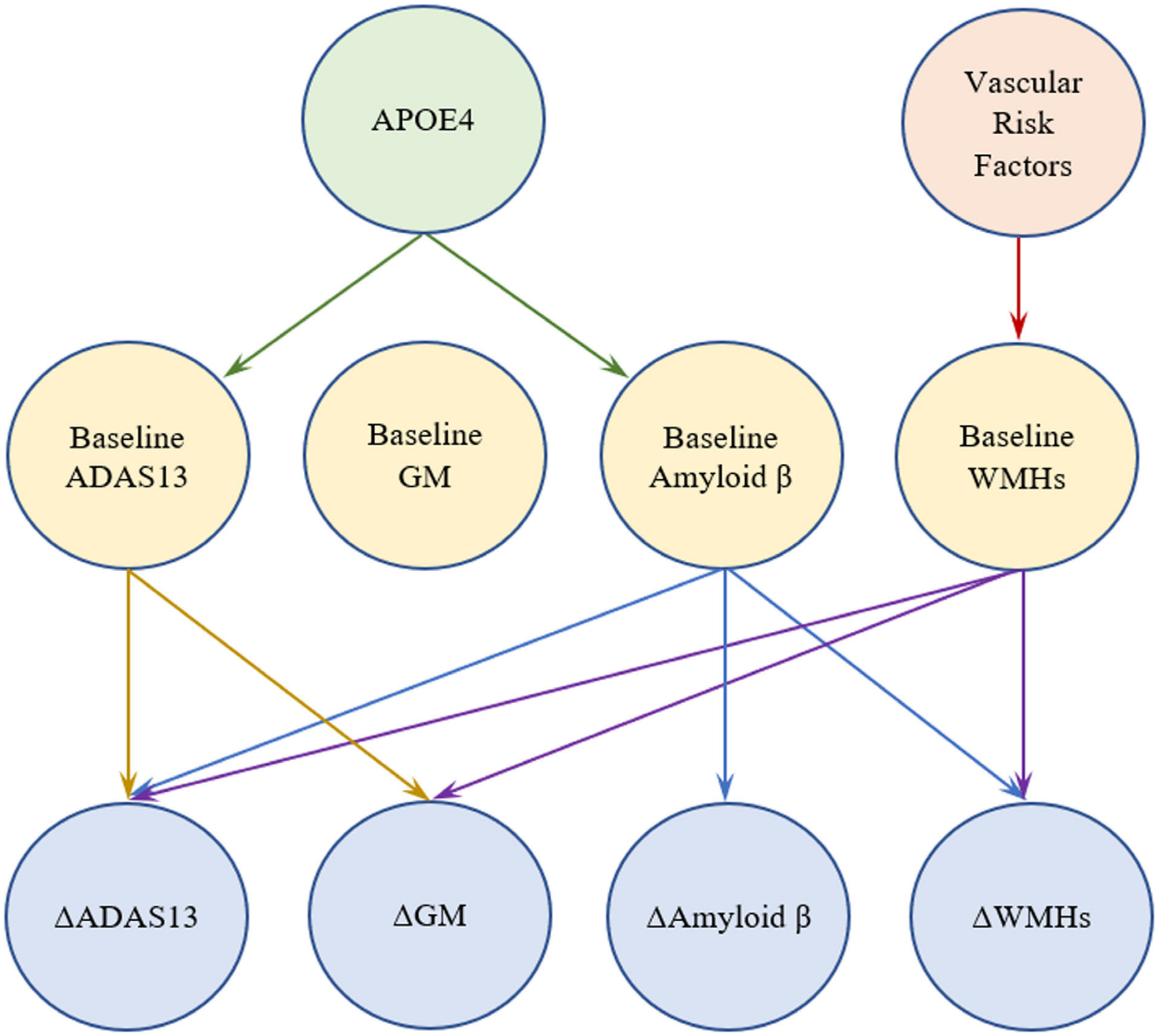

FIGURE 4 The model summarizing the relationships among APOE4, vascular risk factors, and baseline and longitudinal measurements. ΔAmyloid β = Amyloid $\beta_{\text{Follow-up}}$ - Amyloid β_{Baseline}. ΔWMH = $\text{WMH}_{\text{Follow-up}}$-$\text{WMH}_{\text{Baseline}}$. ΔGM = $\text{GM}_{\text{Follow-up}}$-$\text{GM}_{\text{Baseline}}$. ΔADAS13 = $\text{ADAS13}_{\text{Follow-up}}$-$\text{ADAS13}_{\text{Baseline}}$. ADAS, Alzheimer's Disease Assessment Scale-13; APOE, apolipoprotein E; GM, gray matter; WMH; white matter hyperintensity

4 | DISCUSSION

In this study, we investigated the temporal relationships among WMHs, GM volume, Aβ, and cognitive performance in a cohort of cognitively healthy aging, MCI, and probable AD individuals. Our results showed a contribution of baseline WMH burden and Aβ to increase in WMHs, GM atrophy, and cognitive decline (Figure 4 and Table 2).

4.1 | Findings

There was a significant association between baseline WMH load and decrease in GM volume (ie, atrophy), while change in WMH load was not associated with baseline GM volume (Figure 4 and Table 2). These results indicate that WMHs might precede GM atrophy. Taken together with the fact that WMH progression can be slowed down and possibly even prevented through anti-hypertensive mediations and lifestyle changes,[43] this is an important finding, raising the possibility for intervention before irreversible neurological damage occurs. This is also in line with the studies showing that reduction of vascular disease risk and WMHs decreases the risk of cognitive deterioration.[18–24]

Change in ADAS13 scores (indicating worsening cognitive performance) was significantly associated with baseline WMH load, ADAS13, and Aβ levels, but not with baseline GM atrophy (Figure 4 and Table 2). Baseline GM atrophy was, however, associated with change in cognitive performance if included in the model without baseline ADAS13 score, indicating that although GM atrophy relates to cognitive performance, baseline cognition explains more of the variability in the ADAS13 scores than GM atrophy. These findings are also in line with previous studies reporting an impact of WMH burden[3–8] on cognitive performance/decline.[31,32] However, those studies had not assessed the impact of WMHs and GM atrophy simultaneously. Bilello et al. reported a contribution of both WMHs and GM atrophy in preselected regions of interest to cognitive decline measured by the Consortium to Establish a Registry for AD (CERAD) scores in a similar but smaller ($N = 158$) sample; however, they did not assess WMH and GM atrophy measures in the same model.[44] Similarly, in a cohort of 65 non-demented elderly individuals, van der Flier et al. reported an association between both WMH burden and whole brain atrophy and decline in the Cambridge Cognitive Examination (CAMCOG) scores.[30] In this study, using a much larger sample (N = 720) and controlling for vascular risk factors and baseline Aβ levels (in a subset of 461 individuals), we were able to show a contribution of WM pathology to worsening cognitive performance.

Finally, controlling for vascular risk factors, we observed an association trend between lower baseline CSF Aβ1–42 levels and increase in WMH loads, lending support to the hypothesis that Aβ deposition in the brain could increase WMH burden by accelerating processes that are not necessarily vascular in nature, such as neuroinflammation and oxidative stress.[14–16,45] On the other hand, baseline WMH loads were not associated with change in Aβ1–42 levels. However, because the sample including follow-up Aβ1–42 values was significantly smaller (188 versus 461), this finding should be interpreted with caution. In addition, the participants that had Aβ1–42 testing might have different characteristics than those that did not. In fact, a marginally higher proportion of the AD subjects than NA ($P = .07$) and MCI ($P = .06$) had Aβ1–42 values available, leading to significantly lower GM volumes in this subsample ($P = .0003$). There was no significant difference in WMHs or ADAS13 scores.

4.2 | Strengths and limitations

The image processing, registration, and segmentation methods used were all developed and extensively validated in multi-center/scanner datasets, and have since been used in many such studies.[8,34,38,46–50]

We used a relatively short follow-up term (1 year) to assess change in MRI and clinical measures. Although this might prevent us from detecting more extensive levels of change, it allowed us to capture the more subtle changes that occur in a shorter duration. Although a longer follow-up would likely allow us to observe greater associations among the variables, it might also obfuscate the temporal relationships due to the prolonged co-existence of the pathologies. In addition, we were able to include a larger number of subjects with all the MRI and clinical measurements available for the follow-up period.

WMHs were segmented using T1w+FLAIR and T1w+T2w/PDw scans in ADNI1 and ADNI2/GO data, respectively. To ensure that differences in FLAIR versus T2w/PDw characteristics did not affect the results, we performed an experiment segmenting WMHs in 70 cases that had T2w/PDw and FLAIR scans, using either T1w+FLAIR or T1w+T2w/PDw scans, respectively. The obtained volumes had a very high correlation ($r = 0.97$, $P < .00001$), and were not significantly different ($P = .65$, paired t-test). In addition, we included segmentation modality as a covariate to account for any remaining differences.

The ADNI database is a cohort of relatively well-educated individuals with good access to medical care. While this relative homogeneity allows for investigation of MRI and clinical changes without excess confounds, it might not be representative of other populations with lower socioeconomic status for whom access to health services are more limited and a higher degree of vascular risk factors are generally present. Further investigations in more representative cohorts are necessary to observe the full spectrum of associations.

5 | CONCLUSION

Understanding the temporal relationships among WMHs, GM atrophy, Aβ, and cognitive decline might elucidate some of the underlying mechanisms of cognitive decline in the aging population. Our results suggest that a higher WMH load at baseline might lead to greater future GM atrophy and decline in cognitive performance, indicating that earlier WM damage might precede neurodegeneration and cognitive decline. Furthermore, we observed an impact of baseline Aβ levels on increase in WMH loads, independent of vascular risk factors, indicating that (a portion of) the WMHs observed in AD patients might result from Aβ deposition and AD-related pathologies.

ACKNOWLEDGMENTS

We would like to acknowledge funding from the Famille Louise & André Charron. Data collection and sharing for this project was funded by the Alzheimer's Disease Neuroimaging Initiative (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). 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.

CONFLICTS OF INTEREST

Mahsa Dadar is supported by a scholarship from the Canadian Consortium on Neurodegeneration in Aging in which Simon Duchesne and Richard Camicioli are co-investigators as well as an Alzheimer Society Research Program (ASRP) postdoctoral award. The Consortium is supported by a grant from the Canadian Institutes of Health Research with funding from several partners including the Alzheimer Society of Canada, Sanofi, and Women's Brain Health Initiative. This work was also supported by grants from the Canadian Institutes of Health Research (MOP-111169). The authors have no conflicts of interest to report.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

How to cite this article: Dadar M, Camicioli R, Duchesne S, Collins DL, for the Alzheimer's Disease Neuroimaging Initiative. The temporal relationships between white matter hyperintensities, neurodegeneration, amyloid beta, and cognition. *Alzheimer's Dement*. 2020;12:e12091. https://doi.org/10.1002/dad2.12091