The Temporal Relationships between White Matter Hyperintensities, Neurodegeneration, Amyloid β , and Cognition

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http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf

ABSTRACT

INTRODUCTION: Cognitive decline in Alzheimer's disease is associated with amyloid- β accumulation, neurodegeneration and cerebral small vessel disease, but the temporal relationships between these factors is not well established.

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

RESULTS: Baseline WMHs and A β 1-42 predicted WMH increase and GM atrophy. Baseline WMHs, GM, and A β 1-42 predicted worsening cognition. Only baseline A β 1-42 predicted change in A β 1-42.

DISCUSSION: Baseline WMHs lead to greater future GM atrophy and cognitive decline, suggesting that WM damage precedes neurodegeneration and cognitive decline. Baseline A β 1-42 predicted WMH increase, suggesting a potential role of amyloid in WM damage.

Keywords: White matter hyperintensities, small-vessel disease, neurodegenerative disease, Alzheimer's disease, mild cognitive impairment

Research in Context

1. **Systematic Review:** Both amyloid β and neurodegeneration are primary pathologies in Alzheimer's disease. White matter hyperintensities (indicative of presence of cerebrovascular disease) might also be part of the pathological changes in Alzheimer's. However, the temporal relationship between white matter hyperintensities, amyloid β , neurodegeneration, and cognitive decline is still unclear.

2. **Interpretation:** Our results establish a potential temporal order between white matter hyperintensities, amyloid β , neurodegeneration, and cognitive decline, showing that white matter hyperintensities precede neurodegeneration and cognitive decline. The results provide some evidence that amyloid β deposition, in turn, precedes accumulation of white matter hyperintensities.

3. **Future Directions:** The current findings reinforce the need for future longitudinal investigations of the mechanisms through which white matter hyperintensities impact the aging population in general and Alzheimer's disease patients, in particular.

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, 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 (A β), resulting in progressive cognitive deficits and neurodegeneration characteristic of AD [12,13].

On the other hand, A β 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 A β would damage the white matter (WM), which in turn would further elevate A β levels, leading to more WM damage in a cyclical process. This initial rise in A β would be noticeable in cerebro-spinal 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, hypercholesterolaemia, diabetes, obesity, high glucose levels, and smoking [2,9]. These risk factors are particularly important since they are

[†] Abbreviations: A β : Amyloid beta; AD: Alzheimer’s disease; ADAS13: Alzheimer’s Disease Assessment Scale-13; CSF: Cerebrospinal fluid; DBM: Deformation-based morphometry; FLAIR: Fluid attenuated inversion recovery; GM: Grey matter; MCI: Mild cognitive impairment; MRI: Magnetic resonance imaging; NA: normal aging; T2w: T2-weighted; WM: White matter; WMH: White matter hyperintensities

amenable to prevention and treatment [9] and their reduction might impede WMH progression and cognitive deterioration [18–24].

Regarding neurodegeneration, a well-established marker of disease progression in AD is atrophy of cortical and subcortical grey 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 relationship between WMHs, GM atrophy, cognitive decline, and A β . Specifically, we aimed to investigate: 1) whether WMHs precede neurodegeneration and cognitive decline; and 2) whether WMHs impact A β progression or vice versa.

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 one-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 1 summarizes MR imaging parameters for the data used in this study.

Table 1 – Scanner information and MRI acquisition parameters for ADNI1, and ADNI2/GO datasets.

	Sequence	T1w	T2w/PDw	FLAIR
ADNI1 N=421 N _{NA} =124 N _{MCI} =213 N _{AD} =84	Slice thickness	1.2 mm	3 mm	
	No. of slices	160	56	
	Field of view	192×192 cm ²	256×256 cm ²	
	Scan Matrix	192×192 cm ²	256×256 cm ²	
	Repetition time (TR)	3000 ms	3000/3000 ms	
	Echo time (TE)	3.55 ms	95.2/10.5 ms	
ADNI2/GO N=299 N _{NA} =83 N _{MCI} =183 N _{AD} =33	Slice thickness	1.2 mm		5 mm
	No. of slices	196		42
	Field of view	256×256 cm ²		256×256 cm ²
	Scan Matrix	256×256 cm ²		256×256 cm ²
	Repetition time (TR)	7.2 ms		11000 ms
	Echo time (TE)	3.0 ms		150 ms

T1w, T2w/PDw, and FLAIR scans were pre-processed as follows: (a) image denoising [33]; (b) intensity inhomogeneity correction; and (c) 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 timepoint using a 6-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 one-year follow-up timepoints [37,38,7]. 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 mm³) 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 1mm³ grid for each subject/timepoint. 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; i.e. a value of 1 indicates similar volume to the same voxel in the template, and values lower/higher than one indicate volumes smaller/larger than the template. The difference in the Jacobian determinant at two timepoints can be used to estimate change in volume. A decrease in the

Jacobian determinant values of a specific region between two timepoints can be interpreted as a reduced cerebral structure volume, i.e. 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. A β Levels

CSF Amyloid β 1-42 measures provided by the ADNI biomarker core (University of Pennsylvania) using microbead-based multiplex immunoassay were used to assess A β burden. Out of the 720 subjects, 461 and 188 had A β 1-42 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 over-segmentation. Either failures resulted in the participant being removed from the analyses. All MRI processing, segmentation and quality control 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 one-year intervals.

Figure 1. Study flowchart.

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, 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:

$$\Delta Measure = 1 + WMH_{Baseline} + GM_{Baseline} + Age + Sex + Education + Vascular\ risk\ factors + APOE4 + Modality \quad (eq. 1)$$

Where $\Delta Measure$ indicates change in measures of interest (i.e. WMH load, GM volume, and ADAS13) between baseline and one-year follow-up visits (i.e. $Measure_{Follow-up} - Measure_{Baseline}$). *Vascular risk factors* include hypertension, systolic and diastolic blood pressure, BMI, glucose, cholesterol, and triglyceride levels. *APOE4* is a categorical variable contrasting subjects with one or two APOE4 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 A β levels in the subsample that had A β 1-42 measurements available:

$$\Delta Measure = I + A\beta_{Baseline} + WMH_{Baseline} + GM_{Baseline} + Age + Sex + Education + Vascular\ risk\ factors + APOE4 + Modality \quad (eq. 2)$$

Here, $\Delta Measure$ indicates change in measures of interest (i.e. WMH load, GM volume, ADAS13 and A β 1-42). All continuous values were z-scored within the population prior to the regression analyses. The threshold for significance was $P < 0.01$, after correction for multiple comparisons using Bonferroni method.

3. RESULTS

3.1. Participants

A total of 1526 participants were available from the ADNI. After preprocessing, 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 one-year intervals (time between the two visits = 1 ± 0.1 year).

Table 2 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 ($P < 0.0003$). MCI and AD groups had significantly lower CSF A β levels, compared to controls ($P < 0.00001$), and AD patients had significantly lower A β levels ($P < 0.00001$) than the MCI group. MCI and AD groups had a significantly greater proportion of subjects with APOE4 alleles ($P < 0.001$), compared to NA. There were no significant association between baseline WMHs or GM volume and APOE4 status. However, individuals with one or two APOE4 alleles had significantly higher ADAS13 scores and lower A β 1-42 levels ($P < 0.00001$).

Table 2. Descriptive statistics for the participants enrolled in this study. Data are number (N) or mean $\pm$ standard deviation. *p*-values indicate group comparison results, determined by unpaired *t*-tests for continuous variables and χ^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 $\pm$ 5.73	73.50 $\pm$ 7.36	74.49 $\pm$ 7.80	0.002	0.09	0.23
Education (years)	16.03 $\pm$ 2.81	16.11 $\pm$ 2.83	15.32 $\pm$ 2.82	0.72	0.03	0.008
BMI (Kg/m ²)	26.78 $\pm$ 4.57	26.84 $\pm$ 4.63	25.94 $\pm$ 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 $\pm$ 10.46	75.38 $\pm$ 9.34	75.08 $\pm$ 8.86	0.67	0.96	0.75
Systolic Blood Pressure (mmHg)	134.96 $\pm$ 17.2	135.57 $\pm$ 17.1	135.51 $\pm$ 17.9	0.68	0.78	0.97
Hypertension (N)	101	189	61	0.87	0.64	0.46
Cholesterol (mg/dL)	193.38 $\pm$ 39.8	195.95 $\pm$ 40.3	192.18 $\pm$ 40.6	0.54	0.80	0.44
Triglyceride (mg/dL)	139.30 $\pm$ 89.3	147.17 $\pm$ 84.7	139.69 $\pm$ 75.3	0.30	0.97	0.41
Glucose (mg/dL)	99.22 $\pm$ 17.94	100.64 $\pm$ 23.3	98.12 $\pm$ 18.98	0.49	0.62	0.34
Baseline ADAS-cog13	4.36 $\pm$ 9.55	16.82 $\pm$ 6.61	29.08 $\pm$ 6.49	<0.00001	<0.00001	<0.00001
Follow-up ADAS-cog13	8.87 $\pm$ 4.60	17.69 $\pm$ 8.31	32.86 $\pm$ 9.34	<0.00001	<0.00001	<0.00001
Baseline Amyloid β 1-42 (pg/mL)	198.64 $\pm$ 54.8	170.60 $\pm$ 51.9	139.31 $\pm$ 42.2	<0.00001	<0.00001	<0.00001
Follow-up Amyloid β 1-42 (pg/mL)	202.02 $\pm$ 58.1	160.29 $\pm$ 50.1	132.13 $\pm$ 31.02	<0.00001	<0.00001	0.001
Baseline WMH load (cm ³)	9.92 $\pm$ 13.09	10.15 $\pm$ 12.88	15.86 $\pm$ 20.83	0.67	0.0003	<0.00001
Follow-up WMH load (cm ³)	10.79 $\pm$ 13.44	11.39 $\pm$ 13.90	18.05 $\pm$ 22.22	0.51	<0.0001	<0.00001
Baseline GM Jacobian	0.962 $\pm$ 0.04	0.958 $\pm$ 0.05	0.944 $\pm$ 0.04	0.24	<0.0001	0.005
Follow-up GM Jacobian	0.957 $\pm$ 0.04	0.949 $\pm$ 0.05	0.932 $\pm$ 0.04	0.03	<0.00001	0.0001

NA= Normal Aging. MCI= Mild Cognitive Impairment. AD= Alzheimer's Dementia. ADAS= Alzheimer's Disease Assessment Scale. WMH= White Matter Hyperintensity. CC= Cubic Centimetre. GM= Grey Matter.

3.2. Vascular risk factors

Controlling for age, sex, and segmentation modality, hypertension (Tstat=5.78, $P < 0.00001$), higher systolic (Tstat=2.50, $P = 0.01$) and diastolic blood pressure (Tstat=3.00, $P = 0.002$), higher glucose levels (Tstat=3.29, $P = 0.001$), and higher BMI (Tstat=2.29, $P = 0.02$) were associated with higher WMH loads at baseline. There were no differences between NA, MCI and AD groups in proportion of hypertensives, systolic blood pressure, diastolic blood pressure, BMI, glucose, cholesterol or triglyceride levels (Table 2). There was no significant association between baseline GM volume, A β 1-42, or ADAS13 and vascular risk factors.

3.3. Longitudinal comparisons

There was a significant increase in WMH load (1.23 cm³, 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 one-year follow-up visit compared to baseline (paired *t*-tests, $P < 0.000001$). There was no significant difference in A β 1-42 levels between the baseline and follow-up visits ($P = 0.57$) for the 188 participants with available CSF results (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 ($T_{\text{stat}} = 6.96, P < 0.00001$). There was no significant association between change in WMH load and age ($T_{\text{stat}} = 0.52, P = 0.60$), sex ($T_{\text{stat}} = 0.78, P = 0.43$), baseline GM volume ($T_{\text{stat}} = -0.42, P = 0.67$), or years of education ($T_{\text{stat}} = -0.24, P = 0.80$). There was no significant association with presence of APOE4 alleles or vascular risk factors. There was no significant difference across cohorts in the slopes. Figure 2 (first row) shows the relationship between age, baseline GM atrophy, and baseline WMH load and change in WMH load. Based on the model predictions, each additional 1 cm³ of WMHs at baseline leads to 0.71 cm³ additional increase in WMH load during the following year, equivalent to 6.45% of the average baseline WMH load.

Higher baseline WMH load ($T_{\text{stat}} = -3.48, P = 0.0005$) and presence of two APOE4 alleles ($T_{\text{stat}} = -2.37, P = 0.01$) predicted a decrease in GM volume during the follow-up period (i.e. atrophy). There was no significant association between age ($T_{\text{stat}} = 1.52, P = 0.13$), sex ($T_{\text{stat}} = -1.05, P = 0.29$), presence of one APOE4 allele ($T_{\text{stat}} = -1.24, P = 0.21$), baseline GM volume ($T_{\text{stat}} = 0.38, P = 0.70$), or years of education ($T_{\text{stat}} = -0.33, P = 0.74$) and change in GM volume. There was no significant association with vascular risk factors. There was no significant difference across cohorts in the regression slopes. Figure 2 (second row) shows the relationship between age, baseline GM volume, and baseline WMH load and change in GM volume. Based on the model predictions, each additional 1 cm³ of WMHs at baseline leads to 0.0014 cm³ additional decrease in GM during the following year, equivalent to 0.15% of the average baseline GM volume.

Both baseline WMH load and baseline GM volume predicted increases in ADAS13 scores ($T_{\text{stat}} = 2.63, P = 0.008$, GM $T_{\text{stat}} = -2.42, P = 0.01$), indicating worsening cognitive performance for individuals with higher WMH burden and lower GM volume at baseline. Presence of one ($T_{\text{stat}} = 2.73, P = 0.01$) or two ($T_{\text{stat}} = 2.56, P = 0.01$) APOE4 alleles also associated with additional worsening of cognitive performance. There was no significant association between change in ADAS13 and age ($T_{\text{stat}} = -1.45, P = 0.14$), sex ($T_{\text{stat}} = 0.17, P = 0.76$), or years of education ($T_{\text{stat}} = -1.72, P = 0.09$). There was no significant association with vascular risk factors. Figure 2 (third row) shows the relationship between age, baseline GM atrophy, and baseline WMH load and change in ADAS13 scores. Based on the model predictions, each additional 1 cm³ 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% lower baseline GM volume leads to an additional 0.12 increase in ADAS13 score during the following year, equivalent to 0.7% of the average baseline score; while the presence of one or two APOE4 alleles leads to an additional 1.16 and 1.70 increase in ADAS13 score during the following year, equivalent to 6.97% and 10.22% of the average baseline score, respectively.

Figure 2. Baseline measurements and longitudinal changes in WMHs (first row), GM (second row), and ADAS13 (third row). All variables are z-scored. Δ WMH=WMH_{Follow-up}-WMH_{Baseline}. Δ GM=GM_{Follow-up}-GM_{Baseline}. Δ ADAS13=ADAS13_{Follow-up}-ADAS13_{Baseline}. GM=Grey Matter. WMH= White Matter Hyperintensity. NA= Normal Aging. MCI= Mild Cognitive Impairment. AD= Alzheimer's Dementia. ADAS= Alzheimer's Disease Assessment Scale-13. CSF= Cerebrospinal Fluid.

3.5. Relationships with A β (model 2)

In the subsample of 461 participants that had A β 1-42 data available at baseline, baseline A β 1-42 levels were associated with change in WMH volume (Tstat = -2.07, P = 0.03), change in GM volume (Tstat = 1.96, P = 0.05), and change in ADAS13 scores (Tstat = -3.84, P = 0.0001). However, the relationships with WMH loads and GM volume did not survive correction for multiple comparisons. Figure 3 (first row)

shows the relationship between baseline A β 1-42 levels and change in GM, WMHs, and ADAS13, respectively. In the subsample of 188 participants that had A β 1-42 data available at baseline and follow-up visits, change in A β 1-42 levels was only associated with baseline A β 1-42 (Tstat = -2.96, P = 0.003), and not WMH load (Tstat = -0.07, P = 0.94) or GM volume (Tstat = 0.11, P = 0.91). There was no significant association with vascular risk factors or APOE4. Figure 3 (second row) shows the relationship between change in A β 1-42 levels and baseline A β 1-42, GM, and WMHs, respectively.

Figure 3. The relationship between CSF amyloid β levels and longitudinal measurements and change in CSF amyloid β levels and with baseline measurements. All values z-scored. Δ Amyloid β = Amyloid β Follow-up - Amyloid β Baseline. Δ WMH = WMH Follow-up - WMH Baseline. Δ GM = GM Follow-up - GM Baseline. Δ ADAS13 = ADAS13 Follow-up - ADAS13 Baseline. GM = Grey Matter. WMH = White Matter Hyperintensity. NA = Normal Aging. MCI = Mild Cognitive Impairment. AD = Alzheimer's Dementia. ADAS = Alzheimer's Disease Assessment Scale-13. CSF = Cerebrospinal Fluid.

3.6. Summary Model

Figure 4 summarizes the associations between APOE4, vascular risk factors, and baseline and longitudinal measurements. The arrows indicate significant associations based on the analyses in the previous sections.

Figure 4. The model summarizing the relationships between APOE4, vascular risk factors, and baseline and longitudinal measurements. All values z-scored. Δ Amyloid β = Amyloid β Follow-up - Amyloid β Baseline. Δ WMH = WMH Follow-up - WMH Baseline. Δ GM = GM Follow-up - GM Baseline. Δ ADAS13 = ADAS13 Follow-up - ADAS13 Baseline. GM = Grey Matter. WMH = White Matter Hyperintensity. ADAS = Alzheimer's Disease Assessment Scale-13.

4. DISCUSSION

In this study, we investigated the temporal relationships between WMHs, GM volume, A β , 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 A β to increase in WMHs, GM atrophy and cognitive decline (Figure 4).

4.1. Findings

There was a significant association between baseline WMH load and decrease in GM volume (i.e. atrophy), while change in WMH load was not associated with baseline GM volume (Figure 4). 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, GM volume, A β levels, and presence of one or two APOE alleles (Figure 4). These findings are also in line with previous studies reporting an impact of WMH burden [3–6,8,7] and GM atrophy on cognitive performance/decline [31,32]. However, those studies had not assessed the impact of

WMHs and GM atrophy simultaneously. Billelo 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 A β levels (in a subset of 461 individuals), we were able to show a contribution of both GM and WM pathology to worsening cognitive performance.

Finally, controlling for vascular risk factors, we observed an association trend between lower baseline CSF A β 1-42 levels and increase in WMH loads, lending support to the hypothesis that A β 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 A β 1-42 levels. However, since the sample including follow-up A β 1-42 values was significantly smaller (188 versus 461), this finding should be interpreted with caution. In addition, the participants that had A β 1-42 testing might have different characteristics than those that did not. In fact, a marginally higher proportion of the AD subjects than NA ($P = 0.07$) and MCI ($P = 0.06$) had A β 1-42 values available, leading to significantly lower GM volumes in this subsample ($P = 0.0003$). 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 [46,8,34,47,38,48–50].

We used a relatively short follow-up term (one-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 between 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 ($r=0.97$, $P < 0.00001$), and were not significantly different ($P = 0.65$, 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 where 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 between WMHs, GM atrophy, A β , 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 A β 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 A β deposition and AD related pathologies.

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8. REFERENCES

- [1] Raman MR, Kantarci K, Murray ME, Jack CR, Vemuri P. Imaging markers of cerebrovascular pathologies: Pathophysiology, clinical presentation, and risk factors. *Alzheimers Dement Diagn Assess Dis Monit* 2016;5:5–14. <https://doi.org/10.1016/j.dadm.2016.12.006>.
- [2] Abraham HMA, Wolfson L, Moscufo N, Guttmann CR, Kaplan RF, White WB. Cardiovascular risk factors and small vessel disease of the brain: blood pressure, white matter lesions, and functional decline in older persons. *J Cereb Blood Flow Metab* 2016;36:132–142.
- [3] Yoshita M, Fletcher E, DeCarli C. Current concepts of analysis of cerebral white matter hyperintensities on magnetic resonance imaging. *Top Magn Reson Imaging TMRI* 2005;16:399.
- [4] Kim S, Choi SH, Lee YM, Kim MJ, Kim YD, Kim JY, et al. Periventricular white matter hyperintensities and the risk of dementia: a CREDOS study. *Int Psychogeriatr* 2015;27:2069–77. <https://doi.org/10.1017/S1041610215001076>.
- [5] Li J-Q, Tan L, Wang H-F, Tan M-S, Tan L, Xu W, et al. Risk factors for predicting progression from mild cognitive impairment to Alzheimer's disease: a systematic review and meta-analysis of cohort studies. *J Neurol Neurosurg Psychiatry* 2016;87:476–84. <https://doi.org/10.1136/jnnp-2014-310095>.
- [6] Bangen KJ, Preis SR, Delano-Wood L, Wolf PA, Libon DJ, Bondi MW, et al. Baseline White Matter Hyperintensities and Hippocampal Volume are Associated With Conversion From Normal Cognition to Mild Cognitive Impairment in the Framingham Offspring Study. *Alzheimer Dis Assoc Disord* 2018;32:50–6. <https://doi.org/10.1097/WAD.0000000000000215>.
- [7] Dadar M, Maranzano J, Ducharme S, Carmichael OT, Decarli C, Collins DL, et al. Validation of T1w-based segmentations of white matter hyperintensity volumes in large-scale datasets of aging. *Hum Brain Mapp* 2018;39:1093–1107.

- [8] Dadar M, Maranzano J, Ducharme S, Collins DL. White matter in different regions evolves differently during progression to dementia. *Neurobiol Aging* 2019;76:71–9. <https://doi.org/10.1016/j.neurobiolaging.2018.12.004>.
- [9] van der Flier WM, Skoog I, Schneider JA, Pantoni L, Mok V, Chen CLH, et al. Vascular cognitive impairment. *Nat Rev Dis Primer* 2018;4:18003. <https://doi.org/10.1038/nrdp.2018.3>.
- [10] Iturria-Medina Y, Sotero RC, Toussaint PJ, Mateos-Pérez JM, Evans AC. Early role of vascular dysregulation on late-onset Alzheimer’s disease based on multifactorial data-driven analysis. *Nat Commun* 2016;7:11934. <https://doi.org/10.1038/ncomms11934>.
- [11] Thal DR. The Precapillary Segment of the Blood-Brain Barrier and Its Relation to Perivascular Drainage in Alzheimer’s Disease and Small Vessel Disease. *ScientificWorldJournal* 2009;9:etsw.2009.72. <https://doi.org/10.1100/tsw.2009.72>.
- [12] De la Torre JC. Critically attained threshold of cerebral hypoperfusion: the CATCH hypothesis of Alzheimer’s pathogenesis. *Neurobiol Aging* 2000;21:331–342.
- [13] Honjo K, Black SE, Verhoeff NP. Alzheimer’s disease, cerebrovascular disease, and the β -amyloid cascade. *Can J Neurol Sci* 2012;39:712–728.
- [14] Scott JA, Braskie MN, Tosun D, Thompson PM, Weiner M, DeCarli C, et al. Cerebral Amyloid and Hypertension are Independently Associated with White Matter Lesions in Elderly. *Front Aging Neurosci* 2014;7:221–221.
- [15] Snyder HM, Corriveau RA, Craft S, Faber JE, Greenberg SM, Knopman D, et al. Vascular contributions to cognitive impairment and dementia including Alzheimer’s disease. *Alzheimers Dement* 2015;11:710–717.
- [16] Yamada M. Predicting cerebral amyloid angiopathy-related intracerebral hemorrhages and other cerebrovascular disorders in Alzheimer’s disease. *Front Neurol* 2012;3:64.
- [17] Lleó A, Cavedo E, Parnetti L, Vanderstichele H, Herukka SK, Andreasen N, et al. Cerebrospinal fluid biomarkers in trials for Alzheimer and Parkinson diseases. *Nat Rev Neurol* 2015;11:41–55. <https://doi.org/10.1038/nrneurol.2014.232>.
- [18] Ngandu T, Lehtisalo J, Solomon A, Levälähti E, Ahtiluoto S, Antikainen R, et al. A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): a randomised controlled trial. *The Lancet* 2015;385:2255–63. [https://doi.org/10.1016/S0140-6736\(15\)60461-5](https://doi.org/10.1016/S0140-6736(15)60461-5).
- [19] Lam LC, Chan WC, Leung T, Fung AW, Leung EM. Would older adults with mild cognitive impairment adhere to and benefit from a structured lifestyle activity intervention to enhance cognition?: a cluster randomized controlled trial. *PloS One* 2015;10.

- [20] Norton S, Matthews FE, Barnes DE, Yaffe K, Brayne C. Potential for primary prevention of Alzheimer's disease: an analysis of population-based data. *Lancet Neurol* 2014;13:788–94. [https://doi.org/10.1016/S1474-4422\(14\)70136-X](https://doi.org/10.1016/S1474-4422(14)70136-X).
- [21] Debette S, Markus HS. The clinical importance of white matter hyperintensities on brain magnetic resonance imaging: systematic review and meta-analysis. *Bmj* 2010;341:c3666.
- [22] de Leeuw F-E, de Groot JC, Oudkerk M, Witteman JCM, Hofman A, Van Gijn J, et al. Hypertension and cerebral white matter lesions in a prospective cohort study. *Brain* 2002;125:765–772.
- [23] Dufouil C, de Kersaint-Gilly A, Besancon V, Levy C, Auffray E, Brunnereau L, et al. Longitudinal study of blood pressure and white matter hyperintensities The EVA MRI Cohort. *Neurology* 2001;56:921–926.
- [24] Lee KS, Lee Y, Back JH, Son SJ, Choi SH, Chung Y-K, et al. Effects of a multidomain lifestyle modification on cognitive function in older adults: an eighteen-month community-based cluster randomized controlled trial. *Psychother Psychosom* 2014;83:270–278.
- [25] Yi H-A, Möller C, Dieleman N, Bouwman FH, Barkhof F, Scheltens P, et al. Relation between subcortical grey matter atrophy and conversion from mild cognitive impairment to Alzheimer's disease. *J Neurol Neurosurg Psychiatry* 2016;87:425–32. <https://doi.org/10.1136/jnnp-2014-309105>.
- [26] McDonald CR, Gharapetian L, McEvoy LK, Fennema-Notestine C, Hagler DJ, Holland D, et al. Relationship between regional atrophy rates and cognitive decline in mild cognitive impairment. *Neurobiol Aging* 2012;33:242–53. <https://doi.org/10.1016/j.neurobiolaging.2010.03.015>.
- [27] Dickerson BC, Wolk DA. MRI cortical thickness biomarker predicts AD-like CSF and cognitive decline in normal adults. *Neurology* 2012;78:84–90.
- [28] Fox NC, Scahill RI, Crum WR, Rossor MN. Correlation between rates of brain atrophy and cognitive decline in AD. *Neurology* 1999;52:1687–1687.
- [29] Mouton PR, Martin LJ, Calhoun ME, Dal Forno G, Price DL. Cognitive decline strongly correlates with cortical atrophy in Alzheimer's dementia. *Neurobiol Aging* 1998;19:371–7. [https://doi.org/10.1016/S0197-4580\(98\)00080-3](https://doi.org/10.1016/S0197-4580(98)00080-3).
- [30] Flier WM van der, Vlies AE van der, Weverling-Rijnsburger AWE, Boer NL de, Admiraal-Behloul F, Bollen ELEM, et al. MRI measures and progression of cognitive decline in nondemented elderly attending a memory clinic. *Int J Geriatr Psychiatry* 2005;20:1060–6. <https://doi.org/10.1002/gps.1392>.
- [31] Fotenos AF, Snyder AZ, Girton LE, Morris JC, Buckner RL. Normative estimates of cross-sectional and longitudinal brain volume decline in aging and AD. *Neurology* 2005;64:1032–1039.

- [32] Sluimer JD, van der Flier WM, Karas GB, Fox NC, Scheltens P, Barkhof F, et al. Whole-Brain Atrophy Rate and Cognitive Decline: Longitudinal MR Study of Memory Clinic Patients. *Radiology* 2008;248:590–8. <https://doi.org/10.1148/radiol.2482070938>.
- [33] Manjón JV, Coupé P, Martí-Bonmatí L, Collins DL, Robles M. Adaptive non-local means denoising of MR images with spatially varying noise levels. *J Magn Reson Imaging* 2010;31:192–203.
- [34] Dadar M, Fonov VS, Collins DL, Initiative ADN. A comparison of publicly available linear MRI stereotaxic registration techniques. *NeuroImage* 2018;174:191–200.
- [35] Avants BB, Epstein CL, Grossman M, Gee JC. Symmetric diffeomorphic image registration with cross-correlation: evaluating automated labeling of elderly and neurodegenerative brain. *Med Image Anal* 2008;12:26–41. <https://doi.org/10.1016/j.media.2007.06.004>.
- [36] Fonov V, Coupé P, Eskildsen SF, Collins LD. Atrophy specific MRI brain template for Alzheimer’s disease and Mild Cognitive Impairment. *Alzheimers Assoc. Int. Conf.*, vol. 7, France: 2011, p. S58.
- [37] Dadar M, Pascoal T, Manitsirikul S, Misquitta K, Tartaglia C, Brietner J, et al. Validation of a Regression Technique for Segmentation of White Matter Hyperintensities in Alzheimer’s Disease. *IEEE Trans Med Imaging* 2017.
- [38] Dadar M, Maranzano J, Misquitta K, Anor CJ, Fonov VS, Tartaglia MC, et al. Performance comparison of 10 different classification techniques in segmenting white matter hyperintensities in aging. *NeuroImage* 2017;157:233–49. <https://doi.org/10.1016/j.neuroimage.2017.06.009>.
- [39] Ashburner J, Friston KJ. Voxel-based morphometry—the methods. *Neuroimage* 2000;11:805–821.
- [40] Manera AL, Dadar M, Fonov V, Collins DL. Cerebra: Accurate registration and manual label correction of Mindboggle-101 atlas for MNI-ICBM152 template. *BioRxiv* 2019.
- [41] Petersen RC, Aisen PS, Beckett LA, Donohue MC, Gamst AC, Harvey DJ, et al. Alzheimer’s disease Neuroimaging Initiative (ADNI) clinical characterization. *Neurology* 2010;74:201–209.
- [42] Mohs RC, Cohen L. Alzheimer’s Disease Assessment Scale (ADAS). *Psychopharmacol Bull* 1987;24:627–628.
- [43] Dufouil C, Chalmers J, Coskun O, Besançon V, Bousser M-G, Guillon P, et al. Effects of Blood Pressure Lowering on Cerebral White Matter Hyperintensities in Patients With Stroke. *Circulation* 2005;112:1644–50. <https://doi.org/10.1161/CIRCULATIONAHA.104.501163>.
- [44] Bilello M, Doshi J, Nabavizadeh SA, Toledo JB, Erus G, Xie SX, et al. Correlating Cognitive Decline with White Matter Lesion and Brain Atrophy Magnetic Resonance Imaging Measurements in Alzheimer’s Disease. *J Alzheimers Dis* 2015;48:987–94. <https://doi.org/10.3233/JAD-150400>.

- [45] Walsh P, Sudre CH, Fiford CM, Ryan NS, Lashley T, Frost C, et al. CSF amyloid is a consistent predictor of white matter hyperintensities across the disease course from ageing to Alzheimer's Disease. *Neurobiol Aging* 2020.
- [46] Anor CJ, Dadar M, Collins DL, Tartaglia MC. The Longitudinal Assessment of Neuropsychiatric Symptoms in Mild Cognitive Impairment and Alzheimer's disease and their Association with White Matter Hyperintensities in the National Alzheimer's Coordinating Center's Uniform Data Set. *Biol Psychiatry Cogn Neurosci Neuroimaging* 2020.
- [47] Dadar M, Zeighami Y, Yau Y, Fereshtehnejad S-M, Maranzano J, Postuma RB, et al. White matter hyperintensities are linked to future cognitive decline in de novo Parkinson's disease patients. *NeuroImage Clin* 2018;20:892–900.
- [48] Manera AL, Dadar M, Collins DL, Ducharme S, Initiative FLDN. Deformation based morphometry study of longitudinal MRI changes in behavioral variant frontotemporal dementia. *NeuroImage Clin* 2019;102079.
- [49] Sanford R, Strain J, Dadar M, Maranzano J, Bonnet A, Mayo NE, et al. HIV infection and cerebral small vessel disease are independently associated with brain atrophy and cognitive impairment. *Aids* 2019;33:1197–1205.
- [50] Zeighami Y, Ulla M, Iturria-Medina Y, Dadar M, Zhang Y, Larcher KM-H, et al. Network structure of brain atrophy in de novo Parkinson's disease. *ELife* 2015;4:e08440. <https://doi.org/10.7554/eLife.08440>.