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ARTICLE

White matter hyperintensities and CSF Alzheimer disease biomarkers in preclinical Alzheimer disease

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Abstract

Objective

Recent studies suggest that white matter hyperintensities (WMH) on MRI, which primarily reflect small vessel cerebrovascular disease, may play a role in the evolution of Alzheimer disease (AD). In a longitudinal study, we investigated whether WMH promote the progression of AD pathology, or alter the association between AD pathology and risk of progression from normal cognition to mild cognitive impairment (MCI).

Methods

Two sets of analyses were conducted. The relationship between whole brain WMH load, based on fluid-attenuated inversion recovery MRI, obtained in initially cognitively normal participants (n = 274) and time to onset of symptoms of MCI (n = 60) was examined using Cox regression models. In a subset of the participants with both MRI and CSF data (n = 204), the interaction of WMH load and CSF AD biomarkers was also evaluated.

Results

Baseline WMH load interacted with CSF total tau (t-tau) with respect to symptom onset, but not with CSF β-amyloid 1–42 or phosphorylated tau (p-tau) 181. WMH volume was associated with time to symptom onset of MCI among individuals with low t-tau (hazard ratio [HR] 1.35, confidence interval [CI] 1.06–1.73, $p = 0.013$), but not those with high t-tau (HR 0.86, CI 0.56–1.32, $p = 0.47$). The rate of change in the CSF biomarkers over time was not associated with the rate of change in WMH volumes.

Conclusion

These results suggest that WMH primarily affect the risk of progression when CSF measures of neurodegeneration or neuronal injury (as reflected by t-tau) are low. However, CSF biomarkers of amyloid and p-tau and WMH appear to have largely independent and nonsynergistic effects on the risk of progression to MCI.

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Go to Neurology.org/N for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

BIOCARD Research Team coinvestigators are listed in the appendix at the end of the article.

Glossary

$A\beta_{1-42}$ = β-amyloid 1–42; **AD** = Alzheimer disease; **CDR** = Clinical Dementia Rating; **CI** = confidence interval; **FLAIR** = fluid-attenuated inversion recovery; **GPB** = Geriatric Psychiatry Branch; **HR** = hazard ratio; **JHU** = Johns Hopkins University; **MCI** = mild cognitive impairment; **NIA** = National Institute on Aging; **p-tau** = phosphorylated tau; **t-tau** = total tau; **WMH** = white matter hyperintensities.

Alzheimer disease (AD) and cerebrovascular disease frequently co-occur among older adults.[1] It remains unclear, however, whether these 2 pathologies independently affect the risk of cognitive impairment, or whether they have synergistic effects on cognitive decline.[2]

White matter hyperintensities (WMH), as measured on MRI, are primarily markers of small-vessel cerebrovascular disease.[1] A recent systematic review on the association between brain amyloid, as measured by PET, and WMH concluded that amyloid and WMH have independent but additive effects on dementia risk.[3] This conclusion, however, was based primarily on cross-sectional work, due to a dearth of longitudinal investigations. Thus, it remains unclear if WMH accelerate amyloid pathology or exacerbate the effect of amyloid pathology on the risk of developing cognitive impairment. Even less is known about the combined effects of WMH and neurodegeneration on clinical progression to mild cognitive impairment (MCI) or dementia, particularly as reflected by measures derived from CSF. Cross-sectional studies using CSF measures of β-amyloid 1–42 ($A\beta_{1-42}$), total tau (t-tau), and phosphorylated tau (p-tau) reported that lower levels of amyloid were associated with higher WMH burden among individuals with normal cognition,[4–6] MCI,[4] and AD dementia,[7–9] while associations between WMH and t-tau or p-tau were not significant among older, cognitively normal individuals[5] and patients with AD dementia.[9] However, associations between WMH and CSF amyloid and tau and longitudinal changes in cognition or the risk of progression to MCI have not been examined among individuals with normal cognition at baseline.

The aim of the current study was to investigate whether WMH and CSF biomarkers of AD pathology, measured among cognitively normal individuals, independently or interactively affect the risk of progression to MCI due to AD. The overall goal was to provide a more complete picture of the dynamics of WMH and AD pathology during the preclinical phase of AD.

Methods

Study design

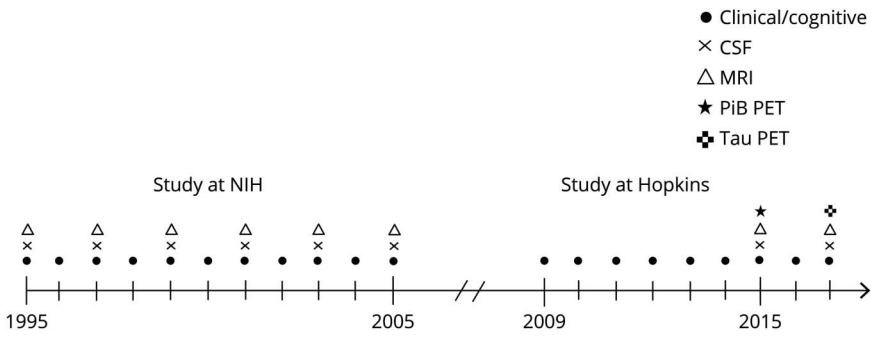
This report is based on data from the BIOCARD study. As described previously,[10] the study was initiated at the NIH in 1995 to identify measures that could predict the subsequent development of mild to moderate symptoms of AD among cognitively normal individuals. Participants were administered a comprehensive neuropsychological battery annually. MRI scans, CSF, and blood specimens were obtained approximately every 2 years. About 3-quarters of participants had a first-degree relative with AD dementia, by design. In 2005, the study was discontinued for administrative reasons. The study was reinitiated at Johns Hopkins University (JHU) in 2009, and participants have since completed annual clinical and cognitive evaluations and donated blood specimens. Beginning in 2015, the biannual collection of CSF and MRI biomarkers was reinitiated; PET amyloid and tau imaging were started in 2015 and 2017, respectively. A timeline of the study is shown in figure 1. The CSF and MRI data analyzed for the purposes of this study were collected at the NIH and do not include follow-up data from 2015 onward because data harmonization is not yet complete. The JHU Institutional Review Board approved this study.

Selection of participants

Recruitment was conduced the Geriatric Psychiatry Branch (GPB) of the intramural program of the National Institute of Mental Health via advertisements in newspapers, informal lectures, or by word of mouth. Enrollment occurred over time, beginning in 1995 and ending in 2005 (total n = 354 with normal cognition at baseline). All participants provided written informed consent. During the 3-day baseline visit, participants received standard laboratory tests (e.g., complete blood count, vitamin B_{12}, thyroid function), Clinical Dementia Rating (CDR) scale, a comprehensive neuropsychological battery (for details, see reference 10), a physical and neurologic examination, ECG, MRI, and a lumbar puncture to obtain CSF. The GPB staff excluded participants who were judged to be cognitively impaired, as determined by the cognitive testing or by evidence of clinical symptoms based on reports by collateral sources. Participants were also excluded if they had substantial medical problems, including severe cardiovascular disease (e.g., atrial fibrillation), chronic psychiatric disorders (e.g., schizophrenia, alcohol or drug abuse), or chronic neurologic disorders (e.g., epilepsy, multiple sclerosis). A total 349 participants met entry criteria and were followed over time.

Fluid-attenuated inversion recovery (FLAIR) images were obtained from 317 participants at the NIH. Of these, 43 participants were excluded from the current analyses for the following reasons: (1) poor scan quality (n = 3); (2) participants had not yet re-enrolled in the study at JHU or had not given permission to use their previously acquired data (n = 28); and (3) participants' estimated age at onset of clinical

Figure 1 Timeline shows the design of the BIOCARD study



Symbols indicate the types of data collected for the BIOCARD study each year (from 1995 to 2017). PiB = Pittsburgh compound B.

symptoms (the primary outcome measure in this study) was determined to be at or prior to their baseline MRI scan (n = 12). Thus, the analyses examining baseline WMH values in relationship to time to symptom onset are based on 274 participants (mean time from baseline visit to baseline FLAIR scan = 0.9 years) (SD 1.5).

CSF specimens were obtained from 307 participants. Of the 274 participants with useable MRI data, a total of 204 participants had CSF collection within 12 months of their baseline MRI scans. The analyses examining the interrelationship of WMH MRI data and CSF measures and clinical progression are based on these 204 participants (mean gap time between MRI and CSF measures = 4.5 days, SD 17.2).

MRI assessments and analysis

MRI scans were acquired on a GE (Chicago, IL) 1.5T scanner while the study was at the NIH (i.e., 1995–2005). The scanning protocol included an axial FLAIR sequence (repetition time 9,002, echo time 157.5, field of view 256 × 256, thickness/gap 5.0/0.0 mm, flip angle 90, 28 slices).

An automated method was used to quantify a measure of global WMH volume from each scan[11] (for additional details, see alz.washington.edu/WEB/adni_proto.pdf). First, the skull was removed using an automatic atlas-based method,[12] followed by a quality control check. The images were then nonlinearly registered by a cubic B-spline deformation to a minimal deformation template synthetic brain image,[13] adapted for ages 60 years and older. Second, a template-based iterative method was used for correcting field inhomogeneity bias.[14] The bias field was modeled using a spatially smooth thin-plate spline interpolation based on ratios of local image patch intensity means between the deformed template and participant images. Third, to segment gray, white, and CSF tissues, we used an expectation-maximization algorithm, which generates segmentations that are most consistent with the input intensities from the native-space T1 images along with a model of image smoothness using an iterative process.[15] Fourth, WMH measures were calculated based on a combination of FLAIR and 3D T1 images using a modified Bayesian probability structure utilizing histogram fitting[11] (for further details, see alz.washington.edu/WEB/adni_proto.pdf). Initially, all segmentation was performed in standard space, which produced probability likelihood values of WMH at each voxel in the white matter. We then thresholded these probabilities using a cutoff of 3.5 SDs above the mean to create a binary WMH mask. Further segmentation involved a modified Bayesian approach, in which image likelihood estimates are combined with spatial priors and with constraints on tissue class. For the calculation of tissue volumes, the segmented WMH masks were back-transformed to native space.

CSF assessments

CSF was collected between 1995 and 2005 while the study was at the NIH. Investigators at JHU subsequently analyzed all samples at a single point in time using the xMAP-based AlzBio3 kit (Innogenetics, Ghent, Belgium) run on the Bioplex 200 system. This kit contains monoclonal antibodies specific for $A\beta_{1-42}$ (4D7A3), t-tau (AT120), and p-tau_{181} (AT270), each chemically bonded to unique sets of color-coded beads, and analyte-specific detector antibodies (HT7 and 3D6). All participants had their samples analyzed on the same plate and run in triplicate. Performance characteristics of the assay have been published previously[16,17] and the coefficients of variation, dynamic range, and plate-to-plate variability of our assays are well within published norms.[18,19]

Clinical and cognitive assessment of participants

Clinical and cognitive assessments were completed annually at both the NIH and JHU (for details, see reference 10). The present study utilizes consensus diagnoses completed by the staff of the JHU BIOCARD Clinical Core. The diagnostic procedure was comparable to that employed in the National Institute on Aging (NIA) Alzheimer's Disease Centers program. First, 3 types of information are used to determine whether a participant is cognitively impaired (syndromic diagnosis): (1) clinical data regarding the participant's medical, neurologic, and psychiatric status; (2) evidence of decline on

longitudinal cognitive testing (and comparison to published norms); and (3) reports of changes in cognition by the individual and by collateral sources.

Second, for participants who were judged to be cognitively impaired, the likely etiology of the syndrome was determined based on the neurologic, psychiatric, and medical data from each visit, and, where necessary, additional medical records obtained from the participant (including vascular risks). Multiple etiologies could be endorsed (e.g., AD and vascular disease). Our consensus diagnoses adhered to the recommendations by working group reports of the NIA–Alzheimer's Association for the diagnosis of MCI[20] and dementia due to AD.[21] The diagnosis of impaired not MCI was given when the CDR interview and the cognitive test scores provided contrasting information (i.e., there were no changes in cognitive testing, but the participant or collateral source had concerns about cognitive changes in daily life, or vice versa). The diagnoses and their likely etiologies were made blind to the biomarker measures.

Once an individual receives a diagnosis of MCI, information from the CDR interview, conducted with both the participant and the collateral source, is used to estimate the age at which the clinical symptoms began. This age is reconfirmed on subsequent visits so that that each participant with a diagnosis of MCI or dementia has a single age at symptom onset. For participants who had become cognitively impaired while the study was at the NIH, the same diagnostic process was applied retrospectively.

APOE genotyping and coding

APOE genotypes were determined by restriction endonuclease digestion of PCR amplified genomic DNA (Athena Diagnostics, Worcester, MA). *APOE* ε4 carrier status was coded dichotomously, with ε4 noncarriers coded as 0 and carriers coded as 1. Analyses that included *APOE* ε4 carrier status excluded 6 individuals with the ε2/ε4 genotype because these alleles have contrasting effects on dementia risk.[22,23]

Statistical methods

For all analyses, baseline age was defined as the age at the first MRI scan. Because WMH volume was not normally distributed, analyses using WMH volume as the dependent variable used the log-transformed WMH volume, though similar results were obtained using the untransformed variable.

Group differences in descriptive statistics were compared with 2-tailed Wilcoxon rank sum tests for continuous variables or χ^2 tests for dichotomous variables, with a significance level of $p < 0.05$, uncorrected for multiple comparisons. Associations between baseline WMH volume and baseline CSF measures were tested using partial correlations (covarying baseline age and sex).

General linear mixed regression models (specified with a random intercept and slope) were used to test if baseline WMH volume (or rate of change in WMH volume) was associated with the rate of change in the CSF biomarkers over time. Separate models were run using each of the 3 CSF variables as the outcome (including the baseline and all available follow-up values). All participants with both baseline CSF and MRI data were included in these analyses (n = 204). The predictors included baseline age, sex, baseline WMH volume (or slope of WMH volume), time, and the interaction (i.e., cross-product) of each predictor with time. Education was not covaried because it was not correlated with levels or rates of change in WMH or CSF measures. In these models, the WMH volume × time interaction (or slope of WMH volume × time interaction) tests if the rate of change in the CSF biomarker differs over time as a function of baseline WMH volume (or slope of WMH volume). Because the direction of the relationship between WMH volumes and AD biomarker levels remains unclear, we also examined the reverse association, using baseline CSF biomarkers (or slope of CSF biomarkers) as predictors and the rate of change in log-WMH volume over time as the dependent variable.

Cox regression models (i.e., proportional hazard models) were used to determine if baseline WMH volume was associated with time to clinical symptom onset (with age, sex, and education as covariates). The models compared 2 groups: (1) participants who were cognitively normal at baseline and their last visit and (2) participants who were normal at baseline but were diagnosed with MCI or dementia at their last follow-up. The outcome variable was the estimated time to clinical symptom onset for participants with a diagnosis of MCI or dementia. Models were adjusted for left truncation because of the requirement of individuals to be symptom-free at study entry. The last date of diagnosis was used as the censoring time. Participants with a diagnosis of impaired not MCI (n = 36) were included with the cognitively normal participants, but results were comparable when they were excluded. All continuous variables were standardized (i.e., *z* scored) before model fitting.

To examine whether the relationship between baseline WMH volume and time to clinical symptom onset differs as a function of the level of CSF AD biomarkers, the interaction terms among the 3 CSF biomarkers and WMH volume were tested in separate models. To determine whether the observed associations were independent of *APOE* ε4 genotype, Cox models were rerun including *APOE* ε4 genotype as an additional predictor.

Hazard ratios (HRs; i.e., the relative hazard) and 95% confidence intervals (CIs) were calculated for the variables in the Cox models. The HR indicates the change in relative risk of progression per 1 *z* score unit change in the predictor. Because we standardized all continuous variables, the HRs for these predictors can be directly compared. The main models were rerun with the WMH volume predictor variable dichotomized based on quartiles (high = highest quartile and low = lowest 3 quartiles) and the CSF variables dichotomized

based on tertiles (high = highest tertile and low = lowest 2 tertiles). All analyses were run in R, version 3.5.0.

Data availability

Anonymized study data pertaining to this report are available upon request from any qualified investigator for purposes of replicating the results.

Results

Table 1 shows the baseline characteristics for the entire BIOCARD cohort as well as for participants included in the present analyses. Table 2 shows baseline characteristics of participants stratified by clinical outcome (i.e., remained cognitively normal vs progressed to MCI or dementia). There were no group differences in the mean follow-up time, sex, ethnicity, education, baseline MMSE score, or *APOE* ε4 carrier status. However, individuals who progressed were older and had greater WMH volumes, lower CSF $A\beta_{1-42}$ levels, and higher CSF t-tau and p-tau levels at baseline compared to those who remained cognitively normal (table 2). Participants who progressed were also more likely to have hypercholesterolemia and showed a greater tendency for hypertension at baseline ($p = 0.055$, table 2), though overall rates of vascular risk were relatively low.

Relationship between WMH volumes and CSF biomarkers of AD

Table 3 shows the number of participants with multiple CSF or MRI measures and the number of assessments over time for these individuals. Because the study was stopped in 2005 and biomarker collection occurred every other year, participants enrolled between 2003 and 2005 generally only had a single MRI scan (41%) or CSF measure (35%). However, approximately 40% of participants had 3 or more assessments.

Higher baseline WMH volumes were correlated with lower baseline CSF $A\beta_{1-42}$ (covarying age and sex, $r[200] = -0.20$, $p = 0.003$; see supplemental material at doi.org/10.5061/dryad.cv35gc3), but this correlation was not significant after removal of an outlier ($p = 0.089$) or when using a robust correlation approach that excludes data points lower than 2.5% or higher than 97.5% of the distributions ($p = 0.24$). Baseline WMH volumes were not correlated with t-tau or p-tau levels, whether the outlier was included or not (all $p > 0.4$). Baseline WMH volume was also not associated with the rate of change in any of the CSF measures over time (all $p > 0.7$). The level of baseline

Table 1 Participant characteristics at baseline

Variable	Cohort as a whole (n = 349)	Participants in analyses	
		With baseline MRI FLAIR scan (n = 274)	With baseline MRI FLAIR scan and CSF (n = 204)
Age, y, mean (SD)	57.3 (10.4)	57.8 (10.5)	57.6 (10.5)
Age, y, range	20.0–85.8	20.4–85.7	22.1–85.7
Follow-up time, y, mean (SD)	12.4 (5.4)	11.4 (4.6)	12.8 (3.2)
Female, n (%)	201 (57.6)	168 (60.7)	122 (59.8)
White, n (%)	339 (97.1)	270 (97.5)	198 (97.1)
APOE ε4 carrier, n (%)	117 (33.6)	82 (29.6)	61 (29.9)
MMSE score, mean (SD)	29.5 (0.9)	29.6 (0.8)	29.6 (0.9)
Education, y, mean (SD)	17.0 (2.4)	17.1 (2.4)	17.1 (2.3)
Education, y, range	12–20	12–20	12–20
Hypertension, n (%)	34 (13.6)[a]	21 (12.0)[b]	15 (11.2)[c]
Hypercholesterolemia, n (%)	39 (15.6)[a]	33 (18.9)[b]	25 (18.7)[c]
Diabetes, n (%)	5 (2.0)[a]	4 (2.3)[b]	2 (1.5)[c]
Current smoker, n (%)	17 (6.8)[a]	12 (6.9)[b]	8 (6.0)[c]
Body mass index ≥30, n (%)	46 (18.7)[a]	34 (19.4)[b]	22 (16.4)[c]

Abbreviations: FLAIR = fluid-attenuated inversion recovery; MMSE = Mini-Mental State Examination.
[a] Total n with available data for all vascular risk variables at baseline = 251.
[b] Total n with available data for all vascular risk variables at baseline FLAIR scan = 175.
[c] Total n with available data for all vascular risk variables at baseline FLAIR scan = 134.

Table 2 Baseline characteristics of participants in analyses stratified by outcomes

Variable	With baseline MRI FLAIR scan		With baseline MRI FLAIR scan and CSF	
	Remained normal (n = 214)	Progressed to MCI or AD dementia (n = 60)	Remained normal (n = 162)	Progressed to MCI or AD dementia (n = 42)
Age, y, mean (SD)	56.2 (9.9)	63.8 (10.6)†	55.9 (10.0)	64.0 (9.7)†
Clinical follow-up time, y, mean (SD)	12.8 (3.9)	13.0 (3.0)	12.8 (3.3)	12.7 (2.8)
Female, n (%)	134 (62.0)	32 (52.5)	98 (60.5)	24 (57.1)
White, n (%)	213 (98.6)	57 (93.4)	160 (98.8)	38 (90.5)
APOE ε4 carrier, n (%)	62 (28.7)	20 (32.8)	46 (28.4)	15 (35.7)
MMSE score, mean (SD)	29.7 (0.8)	29.6 (0.9)	29.6 (0.8)	29.6 (1.0)
Education, y, mean (SD)	17.2 (2.3)	16.7 (2.5)	17.2 (2.3)	17.0 (2.3)
Total WMH volume, cm^3, mean (SD)	2.8 (5.4)	5.2 (7.6)†	2.2 (3.0)	5.8 (8.7)†
CSF $A\beta_{1–42}$, pg/mL, mean (SD)	—	—	412.2 (88.4)	358.8 (105.4)†
CSF p-tau_{181}, pg/mL, mean (SD)	—	—	34.9 (12.3)	43.5 (20.8)*
CSF t-tau, pg/mL, mean (SD)	—	—	65.8 (27.2)	83.7 (36.9)†
Hypertension, n (%)	13 (9.3)[a]	8 (22.9)[a]	10 (9.3)[b]	5 (19.2)[b]
Hypercholesterolemia, n (%)	20 (14.3)[a]	13 (37.1)†,[a]	16 (14.8)[b]	9 (34.6)*,[b]
Diabetes, n (%)	4 (2.9)[a]	0 (0)[a]	2 (1.9)[b]	0 (0)[b]
Current smoker, n (%)	10 (7.1)[a]	2 (5.7)[a]	6 (5.6)[b]	2 (7.7)[b]
Body mass index ≥30, n (%)	27 (19.3)[a]	7 (20.0)[a]	19 (17.6)[b]	3 (11.5)[b]

Abbreviations: AD = Alzheimer disease; FLAIR = fluid-attenuated inversion recovery; MCI = mild cognitive impairment; MMSE = Mini-Mental State Examination; WMH = white matter hyperintensities.
For WMH volume and the CSF measures, group differences remained significant when adjusting for age and sex; group differences in vascular risk were no longer significant after adjustment for age and sex (all $p > 0.1$). *$p < 0.05$; †$p \leq 0.01$ assessing group difference between those who remained normal and those who progressed.
[a] Total n with available data for all vascular risk variables at baseline FLAIR scan = 175.
[b] Total n with available data for all vascular risk variables at baseline FLAIR scan = 134.

CSF biomarkers was not associated with the rate of change in log-WMH volumes over time, all $p > 0.11$. The rates of change in the CSF measures (i.e., slopes) were also not associated with the rate of change in WMH volume (all $p \geq 0.10$).

Relationship between WMH volumes and CSF AD biomarkers and time to onset of clinical symptoms of MCI

Across all participants, WMH volumes ranged from 0.03 to 51.98 cm^3 (median 1.81 cm^3). Among the 274 individuals with baseline FLAIR scans, 60 subsequently developed symptoms of MCI (n = 37) or dementia (n = 23), with 90% having AD as a primary or secondary etiology contributing to their diagnosis. The mean time from baseline scan to symptom onset was 6.4 years (SD 3.4). The first set of Cox regression models showed that baseline WMH volume was not significantly associated with time to clinical symptom onset (HR 1.19, CI 0.92–1.54, $p = 0.19$). The results remained the same when *APOE* ε4 status was included as an additional predictor and when WMH volume was dichotomized (all $p > 0.5$). There was no interaction between *APOE* ε4 status and WMH volume with respect to the risk of progression ($p > 0.3$). Among the 60 participants who progressed to MCI/dementia, 24 were judged to have vascular disease contributing as a primary or secondary etiology to their diagnosis of MCI (n = 13) or dementia (n = 11), based on their clinical records, not their biomarker values. When the outcome in the Cox models was restricted to this subset of participants, baseline WMH volume was again not associated with time to symptom onset ($p > 0.2$).

Next, we examined whether the baseline CSF biomarkers modified the association between WMH volumes and the risk of progression. Among the 204 participants with both CSF and WMH volume data available at baseline, 42 became symptomatic after an average of 6.0 years (SD 3.4). There were no interactions between baseline WMH volume and CSF $A\beta_{1–42}$ (HR 0.97, CI 0.78–1.19, $p = 0.75$) or p-tau (HR 0.92, CI 0.75–1.12, $p = 0.37$) with respect to the time to symptom onset. However, lower $A\beta_{1–42}$ and higher p-tau were each associated with an increased risk of progression to

Table 3 Duration and frequency of biomarker collection

Variable	Participants with baseline MRI FLAIR and CSF (n = 204)
CSF measures	
Number of CSF measures over time	2.3 (1.3)
Time (in years) between baseline MRI scan and first CSF	0.005 (0.05)
Time (in years) between baseline MRI scan and last CSF	2.1 (1.9)
Participants with 2+ CSF measures	132
Number of CSF measures over time for participants with 2+ CSF measures	3.0 (1.0)
Time (in years) between baseline MRI scan and last CSF for participants with 2+ CSF measures	3.2 (1.4)
Participants with 3+ CSF measures	87
Number of CSF measures over time for participants with 3+ CSF measures	3.6 (0.9)
Time (in years) between baseline MRI scan and last CSF for participants with 3+ CSF measures	3.9 (1.0)
MRI measures	
Number of MRI scans over time	2.1 (1.1)
Time (in years) between baseline CSF and first MRI scan	−0.005 (0.05)
Time (in years) between baseline CSF and last MRI scan	2.0 (2.0)
Participants with 2+ MRI scan measures	120
Number of MRI scans over time for participants with 2+ MRI scans	2.8 (0.8)
Time (in years) between baseline CSF and last MRI scan for participants with 2+ MRI scans	3.4 (1.3)
Participants with 3+ MRI scan measures	77
Number of MRI scans over time for participants with 3+ MRI scans	3.2 (0.6)
Time (in years) between baseline CSF and last MRI scan for participants with 3+ MRI scans	4.1 (0.8)

Abbreviation: FLAIR = fluid-attenuated inversion recovery.
Values are mean (SD) or n.

symptom onset. The same results were obtained when covarying t-tau, p-tau, or both in the model assessing the association between WMH and $A\beta_{1-42}$, or when covarying $A\beta_{1-42}$ in the model assessing WMH volume and p-tau in relationship to symptom onset (table 4). Results remained the same when treating WMH volume as a dichotomous variable (table 4) or when covarying *APOE* ε4 status.

There was a significant main effect of t-tau (HR 1.41, CI 1.11–1.79, $p = 0.004$) and an interaction between WMH volume and t-tau with respect to the time to symptom onset of MCI (HR 0.81, CI 0.66–1.00, $p = 0.05$, figure 2). Follow-up Cox models stratified by high vs low t-tau level showed a significant association between baseline WMH volume and time to symptom onset among individuals with low t-tau (HR 1.35, CI 1.06–1.73, $p = 0.013$), but not among those with high t-tau (HR 0.86, CI 0.56–1.32, $p = 0.474$). This interaction remained significant when $A\beta_{1-42}$ was covaried (table 4) and when the CSF predictors or WMH volume were dichotomized (all $p <$ 0.05, table 2), suggesting that the interaction between WMH volume and t-tau was independent of $A\beta_{1-42}$ levels.

In a follow-up analysis, we investigated the issue of timing more directly by including an indicator term for time (<6 years) as part of the coefficient for WMH volume. This allowed us to examine whether the interaction between t-tau and WMH with respect to symptom onset was significant for progression within 6 years from baseline (i.e., the mean time from baseline to symptom onset) and for progression after 6 years from baseline (for additional details about the method, see reference 24). The interaction between t-tau and WMH was significant for progression within 6 years of baseline (HR 0.65, CI 0.54–0.78, $p = 0.02$), but not for progression after 6 years ($p = 0.98$).

Discussion

The current study examined the interrelationship of WMH volumes and CSF AD biomarkers in a cohort of individuals

Table 4 Hazard ratios (HRs) for baseline WMH volume and CSF biomarkers in relation to onset of clinical symptoms

	Continuous WMH values		Dichotomous WMH values	
Variable	**HR (95% CI)**	***p* Value**	**HR (95% CI)**	***p* Value**
$A\beta_{1–42}$	0.70 (0.51–0.97)	0.031	0.56 (0.37–0.86)	0.007
WMH volume	0.83 (0.58–1.18)	NS	1.13 (0.52–2.48)	NS
WMH × $A\beta_{1–42}$	1.04 (0.84–1.29)	NS	1.53 (0.83–2.82)	NS
p-tau	1.47 (1.14–1.90)	0.003	1.77 (1.25–2.50)	0.001
WMH volume	1.18 (0.93–1.50)	NS	1.11 (0.54–2.30)	NS
WMH × p-tau	0.88 (0.72–1.07)	NS	0.63 (0.39–1.02)	NS
t-tau	1.38 (1.08–1.76)	0.008	1.91 (1.33–2.75)	<0.001
WMH volume	1.21 (0.98–1.49)	NS	1.26 (0.62–2.58)	NS
WMH × t-tau	0.80 (0.65–0.99)	0.048	0.47 (0.28–0.80)	0.004

Abbreviations: $A\beta_{1–42}$ = β-amyloid 1–42; CI = confidence interval; NS = not significant at $p = 0.05$; p-tau = phosphorylated tau; t-tau = total tau; WMH = white matter hyperintensities.
All models adjusted for baseline age, sex, and education (n = 204 for all models). The model with $A\beta_{1–42}$ was also adjusted for t-tau, while the models with p-tau and t-tau were also adjusted for $A\beta_{1–42}$ to be able to assess the interaction between WMH volume and each CSF biomarker on the time to symptom onset of MCI independent of the level of other AD biomarkers.

who were cognitively normal at baseline. WMH were associated with the time to onset of symptoms of MCI primarily among participants with low levels of CSF t-tau, but not for those with high levels of t-tau. There were no interactions, in relation to symptom onset, between WMH volumes and CSF $A\beta_{1–42}$ or CSF p-tau_{181}.

These findings suggest that small vessel cerebrovascular disease, as reflected in WMH volumes, increases the risk of progression to MCI when levels of neurodegeneration/neuronal injury are low (as reflected by t-tau levels). Importantly, WMH burden was associated with risk of progression to MCI proximal to symptom onset (i.e., within 6 years and provided that t-tau levels are low), but not more distally to symptom onset (i.e., more than 6 years from baseline). These findings are consistent with evidence demonstrating that vascular risks, such as hypertension, increase the likelihood of subsequent cognitive decline when present in midlife, but not at older ages when levels of neurodegeneration/injury are likely to be higher.

CSF measures thought to directly reflect AD pathology (i.e., CSF $A\beta_{1–42}$ and p-tau) had a consistent and predictable effect on risk of cognitive impairment (even when present in middle age), independent of WMH, whereas WMH alone or in the presence of $A\beta_{1–42}$ and p-tau were not associated with progression. This finding is inconsistent with a synergistic relationship between WMH and these AD biomarkers. We did not, however, have enough power to directly analyze a synergistic relationship between WMH and $A\beta_{1–42}$ and p-tau, by evaluating participants with low tau only.

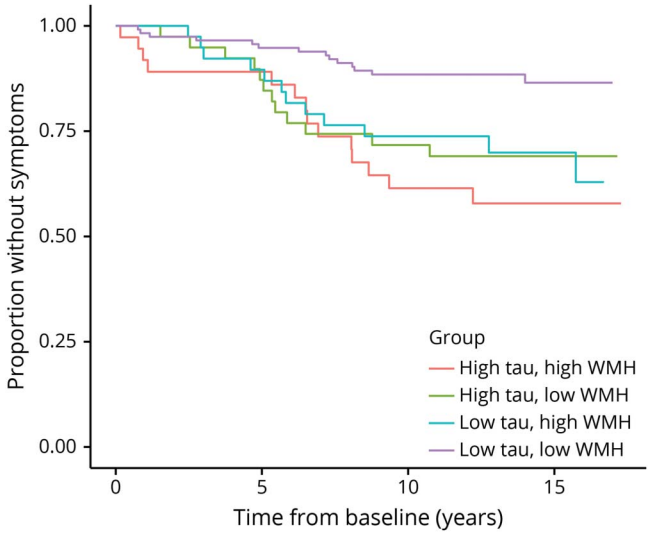
The finding that WMH burden does not add to the risk of progression when tau burden is high also argues against synergistic effects of WMH and t-tau on risk of progression. A possible reason for this finding is that levels of t-tau broadly reflect neurodegeneration or neuronal injury from AD and non-AD sources that may overshadow the more specific effects of WMH on risk of cognitive impairment.

Taken together, our findings support the idea that cerebral small vessel disease and AD pathology have largely independent effects on the risk of progression to MCI. Future studies with longer biomarker follow-up are needed to examine the relative timing of changes in WMH burden and AD biomarkers and how these changes relate to clinical symptom onset.

Although CSF p-tau and t-tau tend to be highly correlated ($r = 0.69$ in this study), the present findings highlight the differential roles of CSF t-tau and p-tau during the evolution of AD. This difference is emphasized in the recent AD biomarker framework,[25] which argued that p-tau is more closely related to the pathophysiology of AD, with p-tau levels correlating with neurofibrillary tangle pathology in patients with AD.[26] Elevations in t-tau, by comparison, are more reflective of general levels of neurodegeneration/injury and also seen in other diseases.[27] Our findings are also consistent with neuropathologic studies suggesting that when both AD pathology and cerebrovascular disease are present, AD pathology has the greatest effect on cognitive decline.[28,29]

The present study found no cross-sectional relationship between baseline WMH volumes and t-tau levels, or with the rate of change in CSF t-tau over time. While a number of previous studies among individuals with normal cognition at baseline have reported associations between WMH and subsequent neurodegeneration, as measured by atrophy on

Figure 2 Kaplan-Meier plot shows the proportion of participants who remain symptom-free as a function of baseline level of CSF total tau (t-tau) and white matter hyperintensity (WMH) load



The survival plot shows the interaction between baseline CSF t-tau and WMH load with respect to the time to symptom onset. The x-axis shows time since baseline and the y-axis represents the proportion of participants remaining without symptoms. There was no significant difference in survival time between participants with high t-tau and high WMH load (red line) compared with those with high t-tau and low WMH load (green line). However, among participants with low CSF t-tau, those with high WMH load (blue line) were more likely to become symptomatic than those with low WMH load (purple line); see Results for details. Note that the survival curves are not adjusted for age, sex, or education.

MRI,[30,31] or by FDG PET,[32] other studies have failed to find such associations,[33,34] consistent with our results. There are several potential reasons for this discrepancy, including differences in WMH burden, variations in follow-up time, or differences in brain regions examined in prior studies. In addition, given that CSF t-tau reflects neuronal injury not only due WMH, but also due to other causes, the specific relationship between WMH-related neurodegeneration and t-tau may be difficult to detect.

A number of recent studies have suggested that WMH may play a more central role in AD than thought previously.[35–37] For example, several cross-sectional studies have reported that lower (i.e., more abnormal) levels of $A\beta_{1-42}$ are associated with higher WMH burden.[4–9,38] In the present study, we did not find any cross-sectional associations between baseline WMH volumes and CSF levels of $A\beta_{1-42}$, p-tau, or t-tau after the removal of an outlier. We also did not observe any associations between baseline CSF biomarker levels and the rate of change in WMH over time, or between baseline WMH volumes and the rate of change in CSF biomarkers, consistent with prior findings.[5,32] However, since both the CSF and the WMH measures in this study represent whole-brain measures of pathology, these relationships may differ for regionally specific measures of WMH or AD biomarkers. Consistent with this hypothesis, several prior studies have found regionally specific associations between WMH and markers of AD pathology.[35–37] It is also possible that the correlation between CSF $A\beta_{1-42}$ and WMH observed in other studies is mediated by cerebral amyloid angiopathy,[35,36] which is also elevated among *APOE* ε4 carriers,[39] or by blood–brain barrier dysfunction.[7]

Although a number of prior studies have reported associations between baseline WMH volumes among cognitively normal participants and risk of progression to MCI when levels of neurodegeneration/injury were not considered,[40–43] findings have been somewhat mixed. For example, some studies have reported null results,[44,45] while others reported significant associations between WMH and risk of MCI only in subgroups,[46] or found different results when treating WMH as a continuous or dichotomous variable, suggesting a weak association.[47] Likewise, studies examining rates of WMH accumulation and risk of MCI have produced conflicting findings.[42,47] The current study suggests that some of these inconsistencies may be related to differences in levels of neurodegeneration/injury across studies. In line with this interpretation, a recent review and meta-analysis concluded that among patients with MCI (who tend to have higher levels of neurodegeneration than cognitively normal individuals), WMH burden is not associated with risk of progression to AD dementia.[48]

This study has limitations. First, our results may not generalize to the broader population because participants were primarily white and highly educated and had a strong family history of AD. Second, although the clinical and cognitive follow-up of participants was very long, the biomarker follow-up was more limited. Furthermore, since studies involving CSF cannot examine regional differences in distribution, studies involving PET amyloid and tau imaging will be needed to address the question of regionally specific associations. It will also be important to examine if similar findings are obtained using other CSF or neuroimaging markers of neurodegeneration/injury, and to replicate these results in other cohorts.

This study also has strengths. Previous studies have examined the individual associations between CSF AD biomarkers and onset of clinical symptoms,[17,49] as well as WMH and progression of cognitive decline.[40–43,47] This is the first time, to our knowledge, that the interactions between these sets of biomarkers in relation to symptom onset of MCI have been examined. Our results support the hypothesis that at least during preclinical AD, WMH burden alters the risk of progression from normal cognition to MCI primarily at low levels of neurodegeneration/injury and that AD CSF biomarkers ($A\beta_{1-42}$ and p-tau) alter the risk of progression independent of WMH levels. This suggests that WMH and CSF AD pathologies operate largely via independent and nonsynergistic mechanisms. It will be important to examine, in this and other cohorts, whether vascular risk factors that promote cerebrovascular disease (such as hypertension) have a similar relationship with AD biomarkers as observed in the present study.

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Disclosure

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Appendix 1 Authors

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Corinne Pettigrew, PhD	Johns Hopkins University, Baltimore	Author	Study concept or design, supervised the analysis of the data, interpretation of the data, drafted and revised the manuscript for content
Yuxin Zhu, PhD	Johns Hopkins University, Baltimore	Author	Performed the statistical analyses, interpretation of the data, revised the manuscript for content
Mei-Cheng Wang, PhD	Johns Hopkins University, Baltimore	Author	Supervised the analysis of the data, interpretation of the data, revised the manuscript for content
Abhay Moghekar, MBBS	Johns Hopkins University, Baltimore	Author	Supervised the analysis of CSF, interpretation of the data, revised the manuscript for content
Rebecca Gottesman, MD, PhD	Johns Hopkins University, Baltimore	Author	Interpretation of the data, revised the manuscript for content
Baljeet Singh	University of California, Davis	Author	Performed the analysis of the MRI data, interpretation of the data
Oliver Martinez, BS	University of California, Davis	Author	Performed the analysis of the MRI data, interpretation of the data
Evan Fletcher, PhD	University of California, Davis	Author	Performed the analysis of the MRI data, interpretation of the data, revised the manuscript for content
Charles DeCarli, MD	University of California, Davis	Author	Supervised the analysis of the MRI data, interpretation of the data, revised the manuscript for content
Marilyn Albert, PhD	Johns Hopkins University, Baltimore	Author	Study concept or design, interpretation of the data, drafted and revised the manuscript for content, study supervision and coordination

Appendix 2 Coinvestigators

The BIOCARD Study consists of 7 Cores with the following members: (1) the Administrative Core (Marilyn Albert, Rostislav Brichko); (2) the Clinical Core (Marilyn Albert, Anja Soldan, Corinne Pettigrew, Rebecca Gottesman, Ned Sacktor, Scott Turner, Leonie Farrington, Maura Grega, Gay Rudow, Daniel D'Agostino, Scott Rudow); (3) the Imaging Core (Michael Miller, Susumu Mori, Tilak Ratnanather, Timothy Brown, Hayan Chi, Anthony Kolasny, Kenichi Oishi, Laurent Younes); (4) the Biospecimen Core (Abhay Moghekar, Jacqueline Darrow, Richard O'Brien); (5) the Informatics Core (Roberta Scherer, David Shade, Ann Ervin, Jennifer Jones, Hamadou Coulibaly, April Patterson); (6) the Biostatistics Core (Mei-Cheng Wang, Daisy Zhu, Jiangxia Wang); and (7) the Neuropathology Core (Juan Troncoso, Olga Pletnikova, Gay Rudow, Karen Fisher).

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