Title

Associations of Amyloid Burden, White Matter Hyperintensities, and Hippocampal Volume With Cognitive Trajectories in the 90+ Study

Journal

Neurology, 103(3)

ISSN

0028-3878

Authors

Wang, Jingxuan
Ackley, Sarah
Woodworth, Davis C
et al.

Publication Date

2024-08-13

DOI

10.1212/wnl.0000000000209665

RESEARCH ARTICLE

Associations of Amyloid Burden, White Matter Hyperintensities, and Hippocampal Volume With Cognitive Trajectories in the 90+ Study

Jingxuan Wang, MPhil, Sarah Ackley, PhD, Davis C. Woodworth, PhD, Seyed Ahmad Sajjadi, Charles S. Decarli, MD, Evan F. Fletcher, PhD, M. Maria Glymour, ScD, Luohua Jiang, PhD, Claudia Kawas, MD, and Maria M. Corrada, ScM, ScD

Correspondence
Dr. Corrada
mcorrada@uci.edu

Neurology® 2024;103:e209665. doi:10.1212/WNL.0000000000209665

Abstract

Background and Objectives

Amyloid pathology, vascular disease pathology, and pathologies affecting the medial temporal lobe are associated with cognitive trajectories in older adults. However, only limited evidence exists on how these pathologies influence cognition in the oldest old. We evaluated whether amyloid burden, white matter hyperintensity (WMH) volume, and hippocampal volume (HV) are associated with cognitive level and decline in the oldest old.

Methods

This was a longitudinal, observational community-based cohort study. We included participants with ^{18}F-florbetapir PET and MRI data from the 90+ Study. Amyloid load was measured using the standardized uptake value ratio in the precuneus/posterior cingulate with eroded white matter mask as reference. WMH volume was log-transformed. All imaging measures were standardized using sample means and SDs. HV and log–WMH volume were normalized by total intracranial volume using the residual approach. Global cognitive performance was measured by the Mini-Mental State Examination (MMSE) and modified MMSE (3MS) tests, repeated every 6 months. We used linear mixed-effects models with random intercepts; random slopes; and interaction between time, time squared, and imaging variables to estimate the associations of imaging variables with cognitive level and cognitive decline. Models were adjusted for demographics, APOE genotype, and health behaviors.

Results

The sample included 192 participants. The mean age was 92.9 years, 125 (65.1%) were female, 71 (37.0%) achieved a degree beyond college, and the median follow-up time was 3.0 years. A higher amyloid load was associated with a lower cognitive level (β_{MMSE} = −0.82, 95% CI −1.17 to −0.46; β_{3MS} = −2.77, 95% CI −3.69 to −1.84). A 1-SD decrease in HV was associated with a 0.70-point decrease in the MMSE score (95% CI −1.14 to −0.27) and a 2.27-point decrease in the 3MS score (95% CI −3.40 to −1.14). Clear nonlinear cognitive trajectories were detected. A higher amyloid burden and smaller HV were associated with faster cognitive decline. WMH volume was not significantly associated with cognitive level or decline.

Discussion

Amyloid burden and hippocampal atrophy are associated with both cognitive level and cognitive decline in the oldest old. Our findings shed light on how different pathologies contributed to driving cognitive function in the oldest old.

From the Department of Epidemiology and Biostatistics (J.W.), University of California, San Francisco; Department of Epidemiology (J.W., S.A., M.M.G.), Boston University, MA; Department of Neurology (D.C.W., S.A.S., C.K., M.M.C.), University of California, Irvine; Imaging of Dementia and Aging Laboratory (C.S.D., E.F.F.), Department of Neurology, University of California, Davis; and Department of Epidemiology and Biostatistics (L.J., M.M.C.), and Department of Neurobiology and Behavior (C.K.), University of California, Irvine.

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.

Glossary

3MS = modified MMSE; **AD** = Alzheimer disease; **CIND** = cognitive impairment-no dementia; **EMIF-AD** = European Medical Information Framework for AD; **HV** = hippocampal volume; **LWCS** = Leisure World Cohort Study; **MMSE** = Mini-Mental State Examination; **SUVr** = standardized uptake value ratio; **TE** = echo time; **TI** = inversion time; **TIV** = total intracranial volume; **TR** = repetition time; **WMH** = white matter hyperintensity.

Introduction

As the general population ages, the number of the oldest old, individuals older than 90 years, is rapidly increasing.[1] The oldest old are particularly vulnerable to cognitive decline, dementia, and disability,[2-5] which can lead to functional impairments and decreased quality of life and become a significant concern for public health. Therefore, understanding the factors that contribute to cognitive decline in this population is important.

Extracellular β-amyloid is present in Alzheimer disease (AD), and its deposition is hypothesized to set off a cascade of pathologic changes. Previous studies have reported that amyloid burden is associated with poorer cognition, faster cognitive decline, and higher risk of dementia.[6-9] White matter hyperintensities (WMHs), which are thought to show areas of cerebral small vessel disease, are commonly seen in the oldest old.[10,11] The causes of WMH observed on MRI are heterogenous, and the clinical symptoms are for the most part only weakly correlated with volume of WMH.[11] For example, it was shown that volume of WMH is associated with worse cognitive function but the magnitude of association was weak.[10,12] Age-related hippocampal atrophy, which can be due to a variety of pathologic processes but is not specific to any single one, occurs with increasing age and is also related to cognitive decline.[13,14]

Extensive research has demonstrated amyloid and vascular pathologies, along with consequent neurodegeneration, to be associated with cognitive decline in younger populations.[15-17] While not exclusively focused on the oldest old, several previous studies have established clear relationships of amyloid pathology and MRI volumetric measures with cognition in older adults aged 75+ or 80+.[18-22] For example, a previous study found that both global AD pathology and hippocampal atrophy, derived from postmortem neuropathologic examination and MRI scans, were associated with accelerated cognitive decline among older adults with an average age of 80.4 years at baseline and of 90.4 years at death.[19] However, it has been suggested that the associations between brain neuropathologies and cognition become weaker with increasing age,[23] and it is not entirely clear how these associations will manifest in the oldest old aged beyond 90 years. In addition, evidence is limited on how different pathologies interact with each other in relation to cognitive trajectories in this population. Only 1 previous study (n = 122), a cross-sectional analysis of data from the Innovative Medicine Initiative European Medical Information Framework for AD (EMIF-AD) 90+ Study in the Netherlands, examined the association of amyloid aggregation, WMH volume, and hippocampal atrophy with cognition in the oldest old.[24] Furthermore, research on nonlinear cognitive trajectories in the oldest old and their relationships with these pathologies remains relatively unexplored.

In this article, we use longitudinal data from the 90+ Study in the United States, to evaluate whether amyloid burden, WMH volume, and hippocampal volume (HV) are associated with cognition at baseline or associated with the rate of cognitive decline. We also evaluated interactions between these different imaging variables and considered potential nonlinear cognitive trajectories because the rate of cognitive decline may increase with advancing age.[25]

Methods

Study Population

The 90+ Study is an ongoing longitudinal study of aging and dementia in individuals aged 90 years and older. Participants were originally recruited from survivors from the Leisure World Cohort Study (LWCS) in 2003.[26] Open recruitment for oldest-old participants beyond the LWCS who had no contraindications to brain imaging and resided within 100 miles of the study location was subsequently initiated through community outreach, earned media, direct mailings, and referrals.[27] In this study, we included participants who had ^{18}F-florbetapir PET and MRI imaging completed within 6 months of each other.

Standard Protocol Approvals, Registrations, and Patient Consents

The 90+ Study and its imaging substudy were approved by the Institutional Review Board of the University of California, Irvine. All participants provided written informed consent to participate in the studies.

MRI Acquisition and Processing

All participants were scanned using the same GE Discovery 750 W 3T scanner (General Electric Healthcare, Waukesha, WI). The protocol included a 3D T1-weighted inversion recovery fast-spoiled gradient recalled echo sequence based on the Alzheimer's Disease Neuroimaging Initiative 3 protocol, acquired with a 1-mm isotropic resolution, with an echo time (TE) of 4 milliseconds, a repetition time (TR) of 10 milliseconds, an inversion time (TI) of 400 milliseconds, and a flip angle of 11°. The protocol also included a 2D fluid-attenuated

inversion recovery sequence, acquired with 5-mm slices, a TE of 137 milliseconds, a TR of 11,000 milliseconds, and a TI of 2,250 milliseconds. Hippocampal volumes were estimated using an atlas-based diffeomorphic registration approach,[28] and WMH volumes were calculated using the Bayesian probabilistic approach.[29] WMH volume was log-transformed to normalize variance. All imaging measures were standardized by calculating the Z-scores using the sample means and SDs. HV and log–WMH volume were normalized by total intracranial volume (TIV) using the residual approach to correct for differences in cranium size.[30] That is, we first regressed log–WMH volume and HV against TIV and then used residuals from the first regression model as the TIV-corrected volumes.

Amyloid PET Acquisition and Processing

All participants were scanned using the same ECAT high-resolution research tomograph (CTI/Siemens, Knoxville, TN) PET scanner. Participants were administered 10 mCi (370 MBq) of ^{18}F-florbetapir and scanned using two 5-minute emission frames from 50 to 60 minutes after injection, followed by a 5-minute transmission scan that was used for attenuation correction. PET scans were reconstructed using 4 iterations of the 3D ordinary Poisson ordered subset expectation maximization algorithm with 5-mm smoothing. The 2 frames were realigned, averaged, and registered to a common amyloid PET atlas using diffeomorphic registration. Additional 6-mm 3D Gaussian smoothing was applied, and standardized uptake value ratios (SUVrs) were calculated using a region consisting of the posterior cingulate and precuneus, normalized to an eroded white matter mask.[31] The precuneus and posterior cingulate regions were selected for our SUVr calculation because (1) these are areas of early accumulation of amyloid; (2) global atrophy is considerable in this population and these regions are often affected at later stages of AD; and (3) our preliminary work had suggested that SUVrs calculated using this region had a high sensitivity and specificity for amyloid stage found at autopsy.[32] SUVr was also standardized using the sample mean and SD.

Clinical and Cognitive Assessment

Participants were followed longitudinally with assessments every 6 months on average. At each assessment, participants completed neurologic evaluation administered by a trained physician or nurse practitioner and a neuropsychological test battery.[33] Global cognitive performance was measured by the Mini-Mental State Examination (MMSE) and modified MMSE (3MS) tests.[34] Based on the global cognitive performance and functional assessment in the neurologic evaluation, examiners assessed the cognitive status of participants applying *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* criteria.[35] Participants without dementia were classified as normal or cognitively impaired, no dementia (CIND).

Assessment of Covariates

We controlled for covariates considered as potential confounders, which plausibly influence both imaging biomarkers and cognition. We conceptualized 3 sets of covariates. Our "base model" included age, sex (female or male), and race/ethnicity (White or other). Our "intermediate model" was further adjusted for the number of APOE-ε4 alleles (0, 1, or 2) and education (lower than college, some college or a college degree, and beyond a college degree). In fully adjusted models, we further controlled the history of depression, hypertension, diabetes, stroke, high cholesterol, and heart disease.

Statistical Analyses

The study baseline was defined as the time of the closest visit to the MRI scan. To assess the association of imaging variables with cognitive level and rate of cognitive decline, we fit linear mixed-effects models with random intercepts and slopes. Because the time intervals between consecutive visits varied and were not necessarily exactly 6 months, we used follow-up time since baseline in years as the time scale. All models were adjusted for practice effects using an indicator for the first visit. A linear, quadratic, or cubic term for time was selected based on the likelihood-ratio test. For both outcomes (MMSE and 3MS), the model including both quadratic time effect and quadratic interactions with imaging measures conferred a better fit based on the likelihood-ratio test. Therefore, a linear mixed model with time, quadratic time, amyloid, WMH volume, HV, interactions between both linear and quadratic time and imaging variables, and covariates with random intercepts and random slopes for both linear and quadratic time was used in the primary analysis. The estimates of imaging variables represent their effect on cognitive level. The estimates of interactions between time and imaging variables reflect their effect on longitudinal cognitive trajectories. We tested for the presence of longitudinal effects using likelihood-ratio tests. In addition, we performed an additional analysis to examine the interactions between imaging variables that are significantly associated with cognitive decline.

To better understand the relationship among the imaging variables, we calculated the Spearman correlation coefficient for each pair. In addition to the model with all imaging variables in the same model, we separately estimated the association for each imaging variable in our secondary analyses.

We conducted 4 sensitivity analyses. First, we considered different TIV normalization approaches for volumetric measures to investigate the robustness and potential impact of normalization for regional volumes.[36] In addition to the residual approach adopted in the primary analysis, we also considered the adjustment approach that adjusted for TIV as a covariate in the regression model examining associations between imaging measures and cognition. Second, we also assessed the influence of model specification by only including a term for linear time. Third, we excluded 12 participants who had dementia at baseline. Finally, we stratified the primary analysis in participants with high and low levels of amyloid burden, defined by the top and bottom 50th percentile.

All statistical analyses were performed using R version 4.2.1. Linear mixed models were fit using R package lme4.

Data Availability

Qualified researchers who meet the criteria for access to deidentified data from the 90+ Study can obtain access to all deidentified data used for this study.[37]

Results

Study Sample Characteristics

Demographic and imaging measures at baseline are presented in Table 1. Participants (n = 192) had an average age of 92.9 years, 125 (65.1%) were female, and 71 (37.0%) achieved a degree beyond a bachelor's degree. Participants completed a median of 5 visits (a total sample of 1,090 observations) over a median of 3.0 years of follow-up. Overall, 123 participants (64.1%) had normal cognition at baseline, 57 (29.7%) had CIND, and 12 (6.3%) had a diagnosis of dementia. 23 participants (11.0%) had at least 1 APOE ε4 allele while 15 participants (7.8%) did not provide genetic data. These participants were more likely to have CIND at baseline and had shorter follow-up time (eTable 1).

Associations of Amyloid Burden, WMH Volume, and HV With Cognitive Level

Neuroimaging and cognitive associations are presented in Table 2. Details on the model selection for a linear, quadratic, or cubic term for time variables are shown in eTable 2. A higher amyloid burden was associated with lower cognitive scores ($\beta_{MMSE} = -0.82$, 95% CI −1.17 to −0.46; $\beta_{3MS} = -2.77$, 95% CI −3.69 to −1.84). A 1-SD decrease in HV was associated with a 0.70-point decrease in the MMSE score (95% CI −1.14 to −0.27) and a 2.27-point decrease in the 3MS score (95% CI −3.40 to −1.14). WMH volume was not associated with cognitive level ($\beta_{MMSE} = -0.18$, 95% CI −0.52 to 0.16; $\beta_{3MS} = -0.40$, 95% CI −1.29 to 0.50).

Associations of Amyloid Burden, WMH Volume, and HV With Cognitive Decline

To better illustrate nonlinear effects of imaging measures, predicted cognitive trajectories for a 92.9-year-old (sample mean) woman with a college degree (most frequent categories) at varying degrees of amyloid load, WMH volume, and HV are shown in Figure 1. A clear nonlinear pattern in cognitive trajectories was detected by the model selection procedure. Longitudinally, a higher amyloid burden and smaller HV were associated with a faster decline in both MMSE and 3MS (Table 2, Figure 1). By contrast, WMH volume was not associated with the rate of cognitive decline. In the additional analysis of interaction effect between amyloid load and HV using the likelihood-ratio test, we did not find statistically significant 3-way interactions of amyloid, HV, and time variables ($\chi^2_{MMSE} = 6.19$, p-value = 0.10; $\chi^2_{3MS} = 3.24$, p-value = 0.36), suggesting that the effects of amyloid or HV on cognitive decline might be independent of each other.

Table 1 Demographic, Clinical, and Pathologic Characteristics of the Analytical Sample at Baseline

Characteristic	N (%)[a]
Age, y, mean (SD)	92.9 (2.6)
Sex	
Female	125 (65.1)
Male	67 (34.9)
Education	
Lower than college	41 (21.4)
College degree	80 (41.7)
Beyond a college degree	71 (37.0)
No. of APOE ε4 alleles	
0	154 (80.2)
1	20 (10.4)
2	3 (1.6)
Missing	15 (7.8)
Race/ethnicity	
White	178 (92.7)
Other	14 (7.3)
Cognitive status	
Normal	123 (64.1)
CIND	57 (29.7)
Dementia	12 (6.3)
Follow-up time, y, median (interquartile)	3.0 (1.2–4.2)
No. of cognitive visits, median (interquartile)	5 (3–8)
SUVr, mean (SD)	0.76 (0.07)
WMH,[b] mean (SD)	15.7 (14.8)
Log-WMH, mean (SD)	2.2 (1.4)
HV,[b] mean (SD)	5.6 (0.7)
TIV,[b] mean (SD)	1,170.8 (123.7)

Abbreviations: CIND = cognitive impairment, no dementia; HV = hippocampal volume; SUVr = standardized uptake value ratio; TIV = total intracranial volume; WMH = white matter hyperintensity.
[a] Percentages may not sum to 100 because of rounding.
[b] Unit is mm^3.

Secondary Analyses

Amyloid burden was positively associated with WMH volume, but the magnitude was small (Spearman $r = 0.18$, p-value = 0.01; Figure 2). WMH volume was negatively associated with HV (Spearman $r = -0.15$, p-value = 0.04). We did not find significant correlation between amyloid burden and HV (Spearman $r = 0.02$, p-value = 0.75). Associations of each imaging variable with cognitive level and

Table 2 Parameter Estimates of the Linear Mixed-Effects Model for the Effect of Time and Imaging Biomarkers on Cognitive Level and Cognitive Decline

	MMSE						3MS					
	Base model (n = 192)		Intermediate model (n = 177)		Full model (n = 174)		Base model (n = 191)		Intermediate model (n = 177)		Full model (n = 174)	
	Estimate (SE)	*p* Value	Estimate (SE)	*p* Value	Estimate (SE)	*p* Value	Estimate (SE)	*p* Value	Estimate (SE)	*p* Value	Estimate (SE)	*p* Value
Linear time	−0.26 (0.18)	0.14	−0.11 (0.17)	0.54	−0.10 (0.16)	0.53	−0.57 (0.49)	0.25	−0.22 (0.49)	0.66	−0.35 (0.48)	0.48
Quadratic time	−0.17 (0.05)	<0.01	−0.20 (0.05)	<0.01	−0.21 (0.04)	<0.01	−0.56 (0.16)	<0.01	−0.63 (0.16)	<0.01	−0.59 (0.15)	<0.01
Baseline age	−0.15 (0.07)	0.03	−0.16 (0.07)	0.02	−0.12 (0.07)	0.09	−0.23 (0.18)	0.21	−0.34 (0.17)	0.05	−0.24 (0.17)	0.17
Amyloid	−0.64 (0.18)	<0.01	−0.73 (0.18)	<0.01	−0.82 (0.18)	<0.01	−2.24 (0.48)	<0.01	−2.53 (0.47)	<0.01	−2.77 (0.47)	<0.01
WMH	−0.09 (0.18)	0.60	−0.10 (0.17)	0.55	−0.18 (0.17)	0.30	−0.27 (0.48)	0.58	−0.21 (0.45)	0.65	−0.40 (0.45)	0.38
HV	0.96 (0.18)	<0.01	0.81 (0.17)	<0.01	0.70 (0.18)	<0.01	3.00 (0.48)	<0.01	2.43 (0.46)	<0.01	2.27 (0.47)	<0.01
Amyloid × linear time	0.19 (0.16)	<0.01	0.15 (0.15)	<0.01	0.12 (0.14)	<0.01	0.59 (0.43)	<0.01	0.61 (0.43)	<0.01	0.59 (0.41)	<0.01
Amyloid × quadratic time	−0.15 (0.05)		−0.14 (0.05)		−0.14 (0.04)		−0.48 (0.15)		−0.47 (0.15)		−0.47 (0.15)	
WMH × linear time	−0.08 (0.14)	0.67	−0.09 (0.13)	0.63	−0.12 (0.12)	0.44	−0.28 (0.38)	0.59	−0.34 (0.37)	0.53	−0.42 (0.36)	0.49
WMH × quadratic time	0.00 (0.04)		0.00 (0.04)		0.02 (0.03)		0.01 (0.13)		0.04 (0.13)		0.08 (0.12)	
HV × linear time	0.15 (0.15)	0.02	0.07 (0.14)	0.02	0.05 (0.13)	0.01	1.06 (0.42)	<0.01	0.76 (0.42)	<0.01	0.69 (0.41)	<0.01
HV × quadratic time	0.06 (0.05)		0.08 (0.04)		0.09 (0.04)		0.05 (0.15)		0.11 (0.15)		0.17 (0.14)	

Abbreviations: 3MS = modified MMSE; HV = hippocampal volume; MMSE = Mini-Mental State Examination; SE = standard error; WMH = white matter hyperintensity.
The base model included time, time squared, amyloid, WMH volume, HV, and interactions between both linear and quadratic time and imaging biomarkers, baseline age, sex, and race/ethnicity. The intermediate model further controlled for APOE genotype and education. The full model further adjusted for hypertension, diabetes, stroke, depression, high cholesterol, and heart disease. *p* Values for interaction between each imaging variable and linear and quadratic time variables were obtained from the likelihood-ratio test.

cognitive decline in separate models were similar to those in the same model: Only amyloid burden and HV were significantly associated with cognitive level and cognitive decline (Table 3).

Sensitivity Analyses

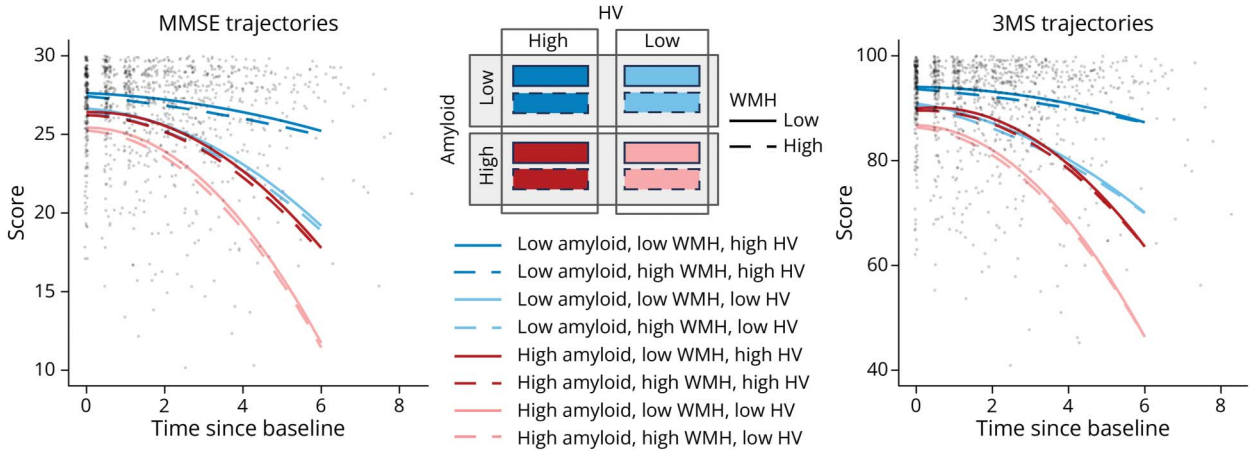
Alternative TIV normalization approaches did not substantially change the results (eTable 3). We found that results were comparable with a linear term for time only (eTable 4, eFigure 1). Only amyloid burden and HV were significantly associated with cognitive decline (β_{MMSE} = −0.68, 95% CI −1.03 to −0.33 and β_{3MS} = −2.22, 95% CI −3.20 to −1.44 for amyloid load; β_{MMSE} = 0.59, 95% CI 0.24–0.94 and β_{3MS} = 1.97, 95% CI 0.99–2.95 for HV; eTable 4). After we excluded participants with dementia at the baseline neurologic evaluation, the associations remained similar (eTable 5). Among participants with high levels of amyloid burden, amyloid burden was associated with lower MMSE and 3MS scores (β_{MMSE} = −1.39, 95% CI −2.23 to −0.55 and β_{3MS} = −4.62, 95% CI −7.01 to −2.23) and a faster decline in the 3MS score (eTable 6, eFigure 2). However, among participants with low levels of amyloid burden, these associations attenuated to null.

Discussion

In this study, we evaluated the association between 3 imaging measures and cognitive function at the time of imaging and cognitive trajectories in an oldest-old cohort. We found that amyloid burden and hippocampal atrophy were both associated with worse cognition and faster cognitive decline, although we did not detect statistically significant associations between volume of WMH and cognition. The association between amyloid and cognition was likely driven by high levels of amyloid burden.

Our results for amyloid burden and HV are consistent with previous studies describing the links of amyloid aggregation and hippocampal atrophy with cognition among the oldest old. Previous work found that amyloid abnormality, as defined by amyloid-β positivity, was associated with a decline in cognitive functioning, especially memory and processing speed.[38] This suggests that elevated levels of brain amyloid could negatively affect cognitive aging even in the oldest old. In a previous publication, also using data from the 90+ Study, the authors showed a negative association between hippocampal atrophy and rate of cognitive decline while assuming

Figure 1 Cognitive Trajectories for a 92.9-Year-Old (Mean Age) Woman With a College Degree Predicted at Varying Degrees of Amyloid Load, WMH Volume, and HV



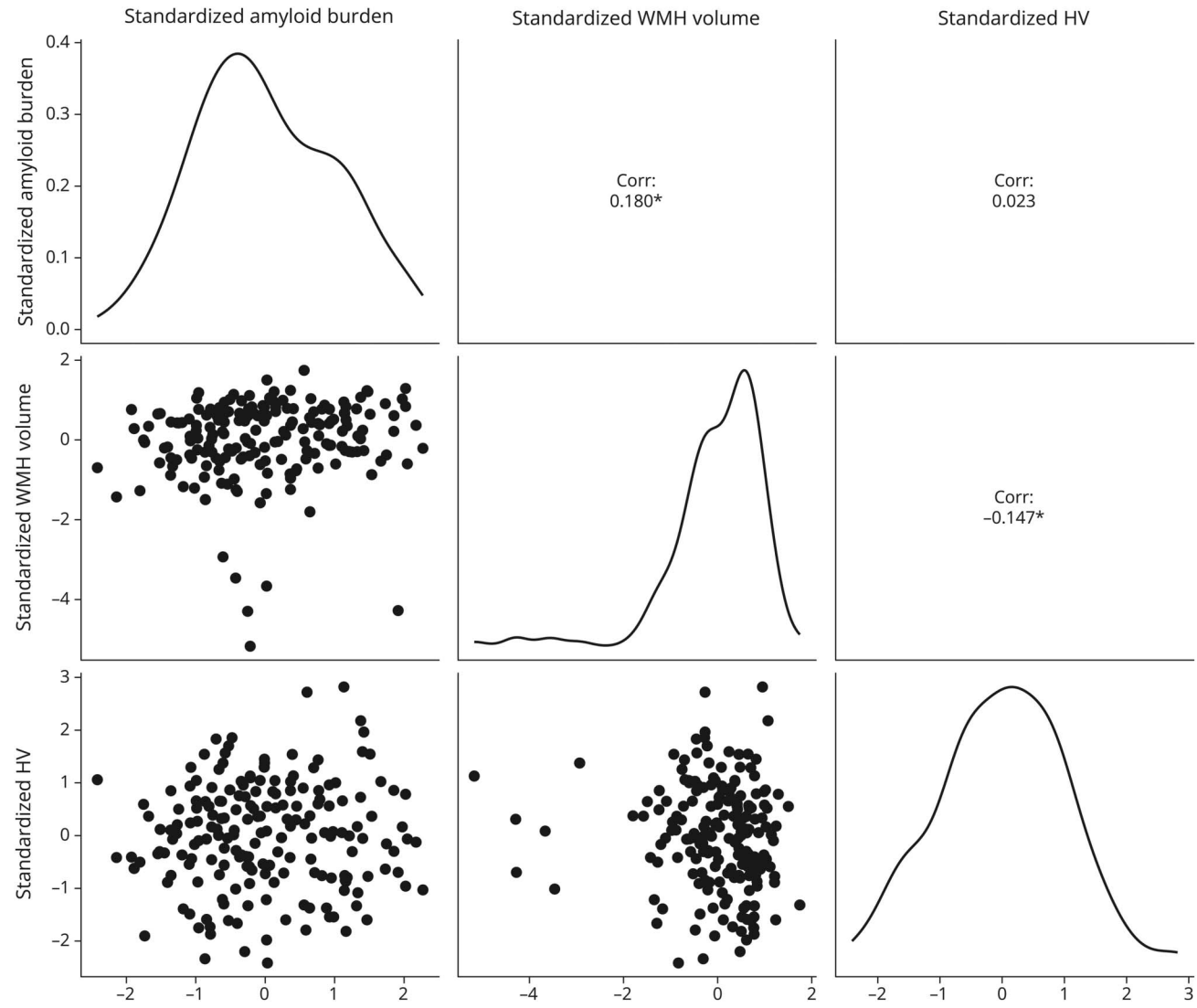
3MS = modified MMSE; HV = hippocampal volume; MMSE = Mini-Mental State Examination; WMH = white matter hyperintensity. Solid vs dashed lines differentiate low vs high WMH volume. Blue and red colors represent low and high amyloid burden. Dark and light shades denote high and low HV. All models included time, time squared, amyloid, WMH volume, HV, and interactions between both linear and quadratic time and imaging biomarkers, baseline age, sex, APOE genotype, race/ethnicity, education, hypertension, diabetes, stroke, depression, high cholesterol, and heart disease.

linear decline rates.[39] In addition, a previous study investigated the determinants of cognitive functioning in the EMIF-AD 90+ Study and found that both amyloid burden and hippocampal atrophy were linked to lower cognitive level.[24] Our results expand on these findings in a sample larger than the combined previous samples, with longer follow-up, and we also examined interactions between neuroimaging measures in relation to cognitive decline. Our findings indicate that amyloid pathology is linked to cognitive decline in this population and hippocampal atrophy is still associated with cognitive decline even when accounting for amyloid pathology. In addition, we found no evidence for an interactive effect between amyloid burden and hippocampal volume on cognition, suggesting that hippocampal volume may influence cognition independently of amyloid pathology. Together with the fact that amyloid burden and hippocampal volume were not correlated in our sample, this suggests hippocampal atrophy may be attributable to aging processes and other pathologies beyond amyloidosis.[40] Furthermore, we found that among those with low amyloid levels, there was no significant association between amyloid burden level and cognition. This likely indicates that the participants in this group were "amyloid negative" and likely also had lower levels of tau. Given that high amyloid burden is potentially associated with underlying tau burden,[41] this underscores the potential significance of tau pathology in the relationship between amyloid and cognition.

However, WMH volume did not have an association with either cognitive level or cognitive decline, which is inconsistent with some previous studies.[24,39] For example, a previous study found an association of WMH with cognitive decline in the oldest old, albeit with a less pronounced predictive effect compared with younger population.[39] This discrepancy may be attributed to a larger sample compared with the previous work[39] and potentially weaker associations between WMH volume and cognitive outcomes in the oldest-old population than in younger populations.[10] Thus, it is still unclear whether previous studies detected a causal relationship, systematic study biases, or chance. Furthermore, it has been shown that the significance of WMH varies based on the length of follow-up time. A recent meta-analysis focusing on cognitively normal populations found that only meta-analyzed estimates from studies with long (more than 5 years) follow-up demonstrated a significant association and the effect size was greater than in studies with short follow-up periods.[42] This suggests the importance of conducting studies with extended follow-up durations when investigating the impact of WMH on cognition. In addition, the limited variability of WMH volume within our analytical sample (Figure 2) might also explain the lack of an association between WMH volume and cognition because our assessment of WMH volume may not capture the full spectrum of cerebrovascular disease burden and pathology and their impacts on cognitive function. Finally, given that our sample consists of individuals aged 90 years and older, it is possible that these individuals have high cognitive reserve, which could potentially mask the association between WMH volume and cognition.

This study contributes to the growing body of literature on the neurobiological determinants of cognition in the oldest old. The longitudinal design and the inclusion of multiple imaging measures of the 90+ Study allowed us to study complex relationships between brain imaging measures and cognition in this vulnerable age group. Our findings may provide insights for future research on identifying potential

Figure 2 Correlation Among Amyloid Load, WMH Volume, and HV



HV = hippocampal volume; WMH = white matter hyperintensity.

targets for interventions aimed at enhancing cognitive function and reducing cognitive decline in the oldest old.

Our study has several limitations. First, although we have a relatively large cohort compared with previous studies, our sample size and follow-up time are modest. Future studies with larger sample sizes and longer follow-up are warranted to replicate our findings, especially for evaluating associations between WMH volume and cognition. Furthermore, we only focused on cross-sectional associations of imaging measures because we did not have longitudinal measures for amyloid burden, WMH volume, and HV. Future studies with longitudinal data on imaging measures will provide insights into the temporal ordering of the changes in brain structure and cognitive decline as well as the complex interplay between different factors in cognitive aging. In addition, we did not include CSF, plasma, or PET data on tau burden, which is an important factor in the association between amyloid and cognition. Future studies should consider tau pathology and investigate the interplay between 2 hallmark pathologies of AD in cognitive decline. Finally, our study predominantly involves individuals of White race/ethnicity with relatively high levels of education and likely high socioeconomic status. Consequently, the generalizability of our findings may be constrained. It is crucial for future research to include more diverse populations to enhance the external validity of our findings.

In this longitudinal study, we found significant nonlinear associations of amyloid burden and hippocampal atrophy with cognitive trajectories. Our findings shed light on how different pathologies contributed to driving cognitive function in the oldest old, providing a foundation for future research aimed at improving cognitive health in this population.

Table 3 Parameter Estimates of the Linear Mixed-Effects Model for the Effect of Time and Each Imaging Biomarker on Cognitive Level and Cognitive Decline, With Separate Models

	MMSE						3MS					
	Amyloid (n = 174)		WMH (n = 174)		HV (n = 174)		Amyloid (n = 174)		WMH (n = 174)		HV (n = 174)	
	Estimate (SE)	*p* Value	Estimate (SE)	*p* Value	Estimate (SE)	*p* Value	Estimate (SE)	*p* Value	Estimate (SE)	*p* Value	Estimate (SE)	*p* Value
Linear time	−0.16 (0.16)	0.34	−0.19 (0.17)	0.26	−0.20 (0.17)	0.25	−0.36 (0.47)	0.44	−0.38 (0.47)	0.41	−0.44 (0.49)	0.37
Quadratic time	−0.18 (0.04)	<0.01	−0.17 (0.04)	<0.01	−0.18 (0.05)	<0.01	−0.55 (0.15)	<0.01	−0.56 (0.15)	<0.01	−0.57 (0.16)	<0.01
Baseline age	−0.19 (0.07)	0.01	−0.19 (0.07)	0.01	−0.17 (0.07)	0.02	−0.40 (0.18)	0.03	−0.41 (0.19)	0.03	−0.33 (0.18)	0.07
Imaging variable	−0.79 (0.19)	<0.01	−0.32 (0.18)	0.08	0.69 (0.19)	<0.01	−2.73 (0.50)	<0.01	−0.93 (0.51)	0.07	2.24 (0.51)	<0.01
Imaging variable × linear time	0.09 (0.14)	<0.01	−0.13 (0.13)	0.67	0.13 (0.14)	0.02	0.59 (0.41)	<0.01	−0.49 (0.35)	0.24	0.85 (0.40)	<0.01
Imaging variable × quadratic time	−0.12 (0.04)		0.00 (0.04)		0.06 (0.04)		−0.44 (0.14)		0.04 (0.12)		0.11 (0.15)	

Abbreviations: 3MS = modified MMSE; HV = hippocampal volume; MMSE = Mini-Mental State Examination; SE = standard error; WMH = white matter hyperintensity.
All models included time, time squared, amyloid, WMH volume, HV, and interactions between both linear and quadratic time and imaging biomarkers, baseline age, sex, APOE genotype, race/ethnicity, education, hypertension, diabetes, stroke, depression, high cholesterol, and heart disease. *p* Values for interaction between each imaging variable and linear and quadratic time variables were obtained from the likelihood-ratio test.

Study Funding

This study received funding from NIH/NIA grants F99AG083306, K99AG073454, and R01AG021055.

Disclosure

The authors report no relevant disclosures. Go to Neurology.org/N for full disclosures.

Publication History

Received by *Neurology* February 16, 2024. Accepted in final form May 10, 2024. Submitted and externally peer reviewed. The handling editor was Associate Editor Linda Hershey, MD, PhD, FAAN.

Appendix Authors

Name	Location	Contribution
Jingxuan Wang, MPhil	Department of Epidemiology and Biostatistics, University of California, San Francisco; Department of Epidemiology, Boston University, MA	Drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data
Sarah Ackley, PhD	Department of Epidemiology, Boston University, MA	Drafting/revision of the manuscript for content, including medical writing for content
Davis C. Woodworth, PhD	Department of Neurology, University of California, Irvine	Drafting/revision of the manuscript for content, including medical writing for content
Seyed Ahmad Sajjadi	Department of Neurology, University of California, Irvine	Drafting/revision of the manuscript for content, including medical writing for content
Charles S. Decarli, MD	Imaging of Dementia and Aging Laboratory, Department of Neurology, University of California, Davis	Drafting/revision of the manuscript for content, including medical writing for content

Appendix *(continued)*

Name	Location	Contribution
Evan F. Fletcher, PhD	Imaging of Dementia and Aging Laboratory, Department of Neurology, University of California, Davis	Drafting/revision of the manuscript for content, including medical writing for content
M. Maria Glymour, ScD	Department of Epidemiology, Boston University	Drafting/revision of the manuscript for content, including medical writing for content
Luohua Jiang, PhD	Department of Epidemiology and Biostatistics, University of California, Irvine	Drafting/revision of the manuscript for content, including medical writing for content
Claudia Kawas, MD	Department of Neurology, and Department of Neurobiology and Behavior, University of California, Irvine	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Maria M. Corrada, ScM, ScD	Department of Neurology, and Department of Epidemiology and Biostatistics, University of California, Irvine	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data

References

1. Yang Z, Slavin MJ, Sachdev PS. Dementia in the oldest old. *Nat Rev Neurol*. 2013;9(7):382-393. doi:10.1038/nrneurol.2013.105
2. Corrada MM, Brookmeyer R, Paganini-Hill A, Berlau D, Kawas CH. Dementia incidence continues to increase with age in the oldest old: the 90+ study. *Ann Neurol*. 2010;67(1):114-121. doi:10.1002/ana.21915
3. Berlau DJ, Corrada MM, Peltz CB, Kawas CH. Disability in the oldest-old: incidence and risk factors in the 90+ study. *Am J Geriatr Psychiatry*. 2012;20(2):159-168. doi:10.1097/JGP.0b013e31820d9295
4. Lucca U, Tettamanti M, Logroscino G, et al. Prevalence of dementia in the oldest old: the Monzino 80-plus population based study. *Alzheimer Dement*. 2015;11(3):258-270.e3. doi:10.1016/j.jalz.2014.05.1750

5. Tanskanen M, Mäkelä M, Notkola IL, et al. Population-based analysis of pathological correlates of dementia in the oldest old. *Ann Clin Transl Neurol*. 2017;4(3):154-165. doi:10.1002/acn3.389
6. Vos SJ, Xiong C, Visser PJ, et al. Preclinical Alzheimer's disease and its outcome: a longitudinal cohort study. *Lancet Neurol*. 2013;12(10):957-965. doi:10.1016/S1474-4422(13)70194-7
7. Jansen WJ, Ossenkoppele R, Tijms BM, et al. Association of cerebral amyloid-β aggregation with cognitive functioning in persons without dementia. *JAMA Psychiatry*. 2018;75(1):84-95. doi:10.1001/jamapsychiatry.2017.3391
8. Donohue MC, Sperling RA, Petersen R, Sun CK, Weiner MW, Aisen PS; Alzheimer's Disease Neuroimaging Initiative. Association between elevated brain amyloid and subsequent cognitive decline among cognitively normal persons. *JAMA*. 2017;317(22):2305-2316. doi:10.1001/jama.2017.6669
9. Hedden T, Oh H, Younger AP, Patel TA. Meta-analysis of amyloid-cognition relations in cognitively normal older adults. *Neurology*. 2013;80(14):1341-1348. doi:10.1212/WNL.0b013e31828ab35d
10. Woodworth DC, Scambray KA, Corrada MM, Kawas CH, Sajjadi SA. Neuroimaging in the oldest-old: a review of the literature. *J Alzheimers Dis*. 2021;82(1):129-147. doi:10.3233/JAD-201578
11. Prins ND, Scheltens P. White matter hyperintensities, cognitive impairment and dementia: an update. *Nat Rev Neurol*. 2015;11(3):157-165. doi:10.1038/nrneurol.2015.10
12. Maillard P, Carmichael O, Fletcher E, Reed B, Mungas D, DeCarli C. Coevolution of white matter hyperintensities and cognition in the elderly. *Neurology*. 2012;79(5):442-448. doi:10.1212/WNL.0b013e3182617136
13. Jack CR, Petersen RC, Xu Y, et al. Rates of hippocampal atrophy correlate with change in clinical status in aging and AD. *Neurology*. 2000;55(4):484-489. doi:10.1212/wnl.55.4.484
14. Fraser MA, Shaw ME, Cherbuin N. A systematic review and meta-analysis of longitudinal hippocampal atrophy in healthy human ageing. *Neuroimage*. 2015;112:364-374. doi:10.1016/j.neuroimage.2015.03.035
15. Baker JE, Lim YY, Pietrzak RH, et al. Cognitive impairment and decline in cognitively normal older adults with high amyloid-β: a meta-analysis. *Alzheimers Dement (Amst)*. 2017;6:108-121. doi:10.1016/j.dadm.2016.09.002
16. Insel PS, Donohue MC, Sperling R, Hansson O, Mattsson-Carlgren N. The A4 study: β-amyloid and cognition in 4432 cognitively unimpaired adults. *Ann Clin Transl Neurol*. 2020;7(5):776-785. doi:10.1002/acn3.51048
17. van der Flier WM, Skoog I, Schneider JA, et al. Vascular cognitive impairment. *Nat Rev Dis Primers*. 2018;4:18003. doi:10.1038/nrdp.2018.3
18. Petersen RC, Wiste HJ, Weigand SD, et al. Association of elevated amyloid levels with cognition and biomarkers in cognitively normal people from the community. *JAMA Neurol*. 2016;73(1):85-92. doi:10.1001/jamaneurol.2015.3098
19. Dawe RJ, Yu L, Arfanakis K, Schneider JA, Bennett DA, Boyle PA. Late-life cognitive decline is associated with hippocampal volume, above and beyond its associations with traditional neuropathologic indices. *Alzheimer Dement*. 2020;16(1):209-218. doi:10.1002/alz.12009
20. Kantarci K, Lowe V, Przybelski SA, et al. APOE modifies the association between Aβ load and cognition in cognitively normal older adults. *Neurology*. 2012;78(4):232-240. doi:10.1212/WNL.0b013e31824365ab
21. Arvanitakis Z, Fleischman DA, Arfanakis K, Leurgans SE, Barnes LL, Bennett DA. Association of white matter hyperintensities and gray matter volume with cognition in older individuals without cognitive impairment. *Brain Struct Funct*. 2016;221(4):2135-2146. doi:10.1007/s00429-015-1034-7
22. Fletcher E, Gavett B, Harvey D, et al. Brain volume change and cognitive trajectories in aging. *Neuropsychology*. 2018;32(4):436-449. doi:10.1037/neu0000447
23. Savva GM, Wharton SB, Ince PG, Forster G, Matthews FE, Brayne C; Medical Research Council Cognitive Function and Ageing Study. Age, neuropathology, and dementia. *N Engl J Med*. 2009;360(22):2302-2309. doi:10.1056/NEJMoa0806142
24. Legdeur N, Badissi M, Yaqub M, et al. What determines cognitive functioning in the oldest-old? The EMIF-AD 90+ study. *J Gerontol B Psychol Sci Soc Sci*. 2021;76(8):1499-1511. doi:10.1093/geronb/gbaa152
25. Li G, Larson EB, Shofer JB, et al. Cognitive trajectory changes over 20 years before dementia diagnosis: a large cohort study. *J Am Geriatr Soc*. 2017;65(12):2627-2633. doi:10.1111/jgs.15077
26. Paganini-Hill A, Ross RK, Henderson BE. Prevalence of chronic disease and health practices in a retirement community. *J Chronic Dis*. 1986;39(9):699-707. doi:10.1016/0021-9681(86)90153-0
27. Melikyan ZA, Greenia DE, Corrada MM, Hester MM, Kawas CH, Grill JD. Recruiting the oldest-old for clinical research. *Alzheimer Dis Assoc Disord*. 2019;33(2):160-162. doi:10.1097/WAD.0000000000000260
28. Vercauteren T, Pennec X, Perchant A, Ayache N. Non-parametric diffeomorphic image registration with the demons algorithm. *Med Image Comput Comput Assist Interv*. 2007;10(pt 2):319-326. doi:10.1007/978-3-540-75759-7_39
29. Maillard P, Lu H, Arfanakis K, et al. Instrumental validation of free water, peak-width of skeletonized mean diffusivity, and white matter hyperintensities: MarkVCID neuroimaging kits. *Alzheimers Dement (Amst)*. 2022;14(1):e12261. doi:10.1002/dad2.12261
30. O'Brien L, Ziegler D, Deutsch C, et al. Adjustment for whole brain and cranial size in volumetric brain studies: a review of common adjustment factors and statistical methods. *Harv Rev Psychiatry*. 2006;14(3):141-151. doi:10.1080/10673220600784119
31. Landau SM, Fero A, Baker SL, et al. Measurement of longitudinal β-amyloid change with 18F-florbetapir PET and standardized uptake value ratios. *J Nucl Med*. 2015;56(4):567-574. doi:10.2967/jnumed.114.148981
32. Sajjadi SA, Fletcher E, Sheikh-Bahaei N, et al. P3-430: the relation between amyloid imaging and amyloid pathology in the oldest old: the 90+ study. *Alzheimers Dement*. 2019;15(7S_part_21):P1124-P1125. doi:10.1016/j.jalz.2019.06.3464
33. Whittle C, Corrada MM, Dick M, et al. Neuropsychological data in nondemented oldest old: the 90+ study. *J Clin Exp Neuropsychol*. 2007;29(3):290-299. doi:10.1080/13803390600678038
34. Tombaugh T, McDowell I, Kristjansson B, Hubley A. Mini-Mental State Examination (MMSE) and the Modified MMSE (3MS): a psychometric comparison and normative data. *Psychol Assess*. 1996;8(1):48-59. doi:10.1037//1040-3590.8.1.48
35. Guze SB. Diagnostic and Statistical Manual of Mental Disorders, 4th ed. (DSM-IV). *Am J Psychiatry*. 1995;152(8):1228. doi:10.1176/ajp.152.8.1228
36. Wang J, Hill-Jarrett T, Buto P, et al. Comparison of approaches to control for intracranial volume in research on the association of brain volumes with cognitive outcomes. *Hum Brain Mapp*. 2024;45(4):e26633. doi:10.1002/hbm.26633
37. The 90+ Study. *UC Irvine Institute for Memory Impairments and Neurological Disorders*. Accessed May 3, 2024. mind.uci.edu/research-studies/90plus-study/.
38. Pelkmans W, Legdeur N, Ten Kate M, et al. Amyloid-β, cortical thickness, and subsequent cognitive decline in cognitively normal oldest-old. *Ann Clin Transl Neurol*. 2021;8(2):348-358. doi:10.1002/acn3.51273
39. Legdeur N, Visser PJ, Woodworth DC, et al. White matter hyperintensities and hippocampal atrophy in relation to cognition: the 90+ study. *J Am Geriatr Soc*. 2019;67(9):1827-1834. doi:10.1111/jgs.15990
40. Woodworth DC, Sheikh-Bahaei N, Scambray KA, et al. Dementia is associated with medial temporal atrophy even after accounting for neuropathologies. *Brain Commun*. 2022;4(2):fcac052. doi:10.1093/braincomms/fcac052
41. Sperling RA, Mormino EC, Schultz AP, et al. The impact of amyloid-beta and tau on prospective cognitive decline in older individuals. *Ann Neurol*. 2019;85(2):181-193. doi:10.1002/ana.25395
42. Roseborough AD, Saad L, Goodman M, Cipriano LE, Hachinski VC, Whitehead SN. White matter hyperintensities and longitudinal cognitive decline in cognitively normal populations and across diagnostic categories: a meta-analysis, systematic review, and recommendations for future study harmonization. *Alzheimer Dement*. 2023;19(1):194-207. doi:10.1002/alz.12642