

Full title: White matter hyperintensities may be an early marker for age-related cognitive decline in the ADNI cohort

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Abstract

Background: Previous research suggests that white matter hyperintensities, amyloid, and tau contribute to age-related cognitive decline. It remains unknown as to how these factors relate to one another and how they jointly contribute to cognitive decline in normal aging. This project examines the association between these pathologies and their relationship to cognitive decline.

Methods: Cognitively normal older adult data from the Alzheimer's Disease Neuroimaging Initiative were examined. Participants were included if they had no subjective cognitive decline, had baseline white matter hyperintensity, CSF A β 42/40, CSF pTau181, and cognitive scores. Of the 102 participants included, only 79 had follow-up cognitive scores. Linear regressions examined the influence of white matter hyperintensities, amyloid, and tau on baseline and follow-up cognitive scores. Linear regressions also examined the association of amyloid and tau on white matter hyperintensities and between tau and amyloid.

Results: Increased white matter hyperintensity load was associated with lower baseline memory ($\beta = -0.20$, $p = .046$), follow-up executive functioning ($\beta = -0.32$, $p < .001$), and follow-up ADAS-13 ($\beta = 2.69$, $p < .001$) scores. White matter hyperintensities were not related to pTau or A β 42/40. Lower A β 42/40 was associated with increased pTau ($p = .025$). pTau was not associated with decline in any cognitive score. Lower A β 42/40 was associated with lower baseline ($p = .015$) but not follow-up executive function.

Discussion: White matter hyperintensities may be one of the earliest pathologies observed in healthy older adults that contribute to cognitive decline. The inclusion of white matter hyperintensities as an additional marker for early cognitive decline may improve our current understanding of age-related changes.

Introduction

Alzheimer's disease (AD) is characterized by several neuropathological brain changes such as senile plaques (β -amyloid, A β) and neurofibrillary tangles (Tau) deposition^{1,2}. These accumulations have been associated with the hallmarked progressive cognitive decline observed in people with AD. Both CSF A β and tau pathologies³⁻⁵ and position emission tomography (PET) A β and tau⁶⁻⁸ have been associated with cognitive decline in healthy older adults. Tau pathology markers have been observed to be better predictors of cognitive decline than amyloid^{6,9}.

Another pathological change, cerebral small vessel disease, results in structural damage to the white matter of the brain that is often observed as white matter hyperintensities (WMH) in T2w or FLAIR MRI in both non-clinical healthy aging populations and individuals with cognitive decline¹⁰. An association between high WMH load and decreased cognitive functioning in healthy older adults is often reported. A meta-analysis observed that WMH impacts all cognitive domains in healthy older adults, with the strongest association seen between WMH and attention and executive functioning¹¹. WMH load increases a healthy older adults' risk for future development of mild cognitive impairment (MCI)¹² and dementia¹³. WMH also continues to contribute to cognitive decline observed in AD¹⁴ because many cases of AD have a mixed etiology with cerebral small vessel disease¹⁵. WMH has been observed to precede neurodegeneration and cognitive decline in MCI, AD, and Parkinson's disease^{16,17}, suggesting that WMH may be involved with the etiology of cognitive decline in normal aging and cognitive impairment due to MCI and Alzheimer's disease (AD).

While many studies have examined the effects of CSF tau and amyloid on cognitive functioning³⁻⁵ and the relationship between WMH and amyloid^{16,18,19} there is limited research

examining the interaction between WMH, amyloid, and tau. One study found that increases in WMH were associated with increases in amyloid-PET in cognitively healthy older adults, but no relationship between tau-PET and WMH²⁰. However, this study did examine the relationship between these pathologies and cognitive decline. In contrast, another study observed no association between WMH burden and amyloid-PET²¹. This study also observed that increased WMH was associated with lower executive functioning whereas amyloid measured with PET had no effect on cognitive function²¹.

One difficulty when studying these AD-related pathologies is that they occur years prior to the onset of clinical symptoms^{1,22}, emphasizing the need to evaluate these changes in the healthy aging population. The goal of this study was thus to examine the relationship between WMH, amyloid, and tau and their association with cognitive functioning in healthy older adults. The first aim was to explore how these pathologies are related to one another and whether they impact each other's progression. Furthermore, we sought to examine how these AD-related pathologies are associated with current cognitive function and cognitive decline in healthy older adults.

Methods

Alzheimer's Disease Neuroimaging Initiative

Data used in the preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). 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 magnetic resonance imaging (MRI), positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of MCI and early AD. Participants were

between 55 and 90 years old at the time of recruitment. The study received ethical approval from the review boards of all participating institutions. Written informed consent was obtained from participants or their study partner.

Participants

The purpose of this paper was to examine healthy cognitive aging. Including people with subjective cognitive decline (SCD) may bias the associations between the pathologies being observed. Therefore people with SCD were excluded to avoid possible confounds of normal controls that may already be on the AD trajectory²³.

ADNI-1 and ADNI-GO did not measure subjective cognitive decline; therefore, we applied the following study inclusion and exclusion criteria to the 406 cognitively normal controls with no SCD from the ADNI-2 and ADNI-3 cohorts with MRI scans. Full participant inclusion/exclusion criteria can be downloaded from www.adni-info.org. Briefly, Participants were between 55 and 90 years old at the time of recruitment and had no evidence of cognitive decline on either the Mini Mental Status Examination or Clinical Dementia Rating. Cognitively normal older adults were excluded if they had scored >16 on the Cognitive Change Index, signifying SCD. Inclusion criteria included having a PD+T2w or FLAIR MRI scan from which WMH load could be estimated and having both tau and amyloid measures. Inclusion criteria also included baseline executive functioning, memory, and ADAS-13 scores. These criteria resulted in 102 participants for our study at baseline. At follow-up, 79 of these participants had cognitive scores. Figure 1 summarizes the methodology used to select participants. This project is a cohort study design that followed healthy older adults over a period of time.

We used executive functioning (ADNI-EF²⁴) and memory (ADNI-MEM²⁵) composite scores that have been previously developed and validated in ADNI. Alzheimer's Disease

Assessment Scale- Cog13 (ADAS-13²⁶) scores were also included for all participants. The ADAS-13 measures severity of cognitive decline, for a total of 85 points, with higher scores indicating greater severity. These scores were downloaded from the ADNI public website.

To obtain cerebrospinal fluid (CSF) samples, lumbar punctions were performed as described in the ADNI procedures manual. CSF A β 42/40 ratio and phosphorylated p-Tau181 (pTau) were measured using the multiplex xMAP Luminex platform (Luminex Corp, Austin, TX, USA) with the INNO-BIA AlzBio3 kit (Innogenetics)^{27,28}.

Structural MRI acquisition and processing

All participants were imaged using a 3T scanner with T1-weighted imaging parameters (see <http://adni.loni.usc.edu/methods/mri-tool/mri-analysis/> for the detailed MRI acquisition protocol). Baseline scans were downloaded from ADNI.

T1w scans for each participant were pre-processed through our standard pipeline including noise reduction²⁹, intensity inhomogeneity correction³⁰, and intensity normalization into range [0-100]. The pre-processed images were then both linearly (9 parameters: 3 translation, 3 rotation, and 3 scaling)³¹ and nonlinearly (1 mm³ grid)³² registered to the MNI-ICBM152-2009c average template³³. The quality of the linear and nonlinear registrations was visually verified by an experienced rater.

WMH measurements

WMH measurements were obtained through a previously validated WMH segmentation technique and a library of manual segmentations based on 50 ADNI participants (independent of the 102 studied here). WMHs were automatically segmented at baseline using the T1w contrasts, along with a set of location and intensity features obtained from a library of manually segmented scans in combination with a random forest classifier to detect the WMHs in new images^{34,35}.

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.

Data availability statement

The data used for this analysis are available on request from the ADNI database (ida.loni.usc.edu).

Statistical Analysis

Analyses were performed using MATLAB R2019b. Participant demographic information is presented in Table 1. Linear regression models were conducted to examine whether WMH, amyloid, and tau would influence cognitive scores. *CognitiveScore_bl* represents executive function (or memory composite) score at baseline. For baseline measurements, 102 participants were included for both the executive functioning and memory composite models. Both CSF Aβ42/40 and pTau levels were downloaded from ADNI.

$$CognitiveScore_bl \sim WMH + Amyloid + Tau + Age + Sex + Education \quad (1).$$

For follow-up measurements, 79 participants had follow-up scores over periods 0-1 year (n=23), 1-2 years (n=44), and 2-3 years (n=12) that were included for both the executive functioning and memory composite models. Baseline cognitive scores were also included in the follow-up model to ensure that the follow-up results account for more variance than what can be explained by the baseline scores.

$$CognitiveScore_followup \sim CognitiveScore_bl + WMH + Amyloid + Tau + Age + Sex + Education \quad (2).$$

A linear regression was completed to examine whether amyloid and tau influence white matter hyperintensities. All 102 participants were included in this analysis:

$$WMH \sim Amyloid + Tau + Age + Sex + Education \quad (3).$$

A linear regression was also completed to examine whether tau and amyloid are associated. All 102 participants were included in this analysis:

$$Amyloid \sim Tau + Age + Sex + Education \quad (4).$$

A descriptive analysis was completed to examine the number of participants who had elevated pTau and A β 42/40 levels. A threshold of A β 42/40 of <0.075 was employed based on previously research as the optimal cut-off for amyloid positivity³⁶. The pTau threshold was based on previous research that determined the optimal threshold, in the ADNI dataset, for distinguishing between A β negative and A β positive cognitively normal older adults is 26.64 pg/ml³⁷.

Results

Cognitive Score Analysis

Figures 2 and 3 display executive functioning composite, memory composite, and ADAS-13 scores with A β 42/40, pTau, and WMH at baseline and follow-up. Table 2 summarizes the regression model results. At baseline, increased scores in executive functioning were associated with higher CSF A β 42/40 ($t = 2.48, p = .015$) and higher education ($t = 2.26, p = .026$), and lower scores on executive functioning were associated with increased age ($t = -2.42, p = .017$). At follow-up, increased executive functioning scores were associated with increased education ($t = 3.62, p < .001$) and increased baseline executive functioning ($t = 7.61, p < .001$). At follow-up, lower executive functioning scores were associated with increased WMHs ($t = -2.90, p = .004$).

At baseline, increased memory was associated with higher education ($t = 2.38, p = .019$) and lower memory scores were associated with increased WMHs ($t = -2.02, p = .046$) and male sex

($t = -3.49, p < .001$). At follow-up, increased memory was only associated with higher education ($t = 2.02, p = .047$) and higher baseline memory ($t = 11.13, p < .001$).

At baseline, increases in ADAS-13 scores were only positively associated with male sex, ($t = 2.25, p = .027$). At follow-up, lower ADAS-13 scores were associated with age ($t = -3.61, p < .001$) whereas higher ADAS-13 scores were associated with increased WMHs ($t = 4.10, p < .001$) and higher baseline ADAS score ($t = 9.12, p < .001$).

WMH, Tau, and Amyloid Analysis

At baseline, WMH were not associated with either pTau ($t = -1.19, p = 0.24$) or amyloid burden ($t < 1, p = 0.48$), however significant increased WMHs were associated with increased age ($t = 4.62, p < .001$). Decreases in amyloid was observed to be associated with increases in tau ($t = -2.28, p = .025$).

Tau and amyloid accumulation

At baseline, 48/102 participants had amyloid levels below the threshold of 0.075 and only 22/102 participants had elevated pTau levels above 26.64 pg/ml. Figure 5 presents individual values, means, and confidence intervals for the A β 42/40 and pTau levels.

Discussion

The current study investigated the effects of WMH, amyloid, and tau on current and future cognitive decline in cognitively normal older adults. We observed that CSF pTau was not associated with current or future decline for either memory or executive function in this cohort. CSF A β burden measured with the 42/40 ratio was associated with only decreased baseline executive functioning. Increased WMH loads were associated with reduced performance on

follow-up executive function and baseline memory. Increased WMH loads were also associated with reduced ADAS-13 follow-up scores. WMH loads were not related to either tau or amyloid, whereas decreases in A β 42/40 was associated with increases in pTau. These results suggest WMH may contribute to the initial stages of cognitive decline in healthy older adults.

In this sample of cognitively unimpaired participants with no subjective cognitive decline, WMH loads appeared to have the largest association with future cognitive decline in cognitively normal older adults. Vascular deterioration, as measured by WMHs, may be one of the first pathologies observed in the healthy older adult population that affects cognitive functioning. Pathologies that occur later in the aging process (i.e., tau and amyloid accumulation) may require less deposition to result in deterioration in cognitive functioning in those with high WMH loads. Reducing WMH may thus reduce the risk of future cognitive decline and the impact of other pathologies. The observation that future cognitive decline is impacted in healthy aging by WMH supports previous findings suggesting that WMHs increase the risk of MCI and dementia¹⁵ by lowering the threshold for cognitive decline due to AD. Risk factors that contribute to WMHs (e.g., hypertension and cardiovascular disease) are also associated with cognitive decline in healthy older adults^{21,38} and a higher conversion rate from MCI to AD³⁹. Taken together, these findings provide support for the need for aggressive treatments of vascular factors to help reduce future cognitive decline. For example, previous research has observed that people who undergo antihypertensive treatment exhibit less cognitive decline⁴⁰ and a reduced risk of dementia⁴¹ than those with untreated high blood pressure.

In MCI and AD, both PET and CSF tau and amyloid deposition is reported to be a strong predictor of cognitive decline⁴²⁻⁴⁴. It is well-known that this accumulation of pathological amyloid and tau begins years before deficits in cognitive functioning can be detected⁴⁵, and thus

may occur during healthy aging. The relationship between tau and amyloid in healthy older adults is, however, less prominent. Associations between CSF tau and amyloid³⁻⁵ with reduced cognitive performance in healthy older adults have been observed. In our study, we observed that a decrease in CSF A β 42/40 was associated with increases in pTau. Lower A β 42/40 is indicative of more brain amyloid, thus lower CSF A β 42/40 is associated with increased burden measured by pTau. Neither CSF pTau nor amyloid was associated with cognitive decline in healthy older adults with no subjective cognitive decline. The sample of participants in this study comprises healthy older adults who exhibit low overall pTau burdens⁴⁶ making it difficult to detect associations between tau and cognition at this stage. Amyloid deposition may occur on average 13.3 years earlier than tau accumulation⁴⁷. Thus, it is not surprising that more participants had elevated amyloid burden in the absence of elevated tau. Both elevated amyloid and tau deposition may be necessary for measurable memory decline in the preclinical phases of AD⁷. Therefore, despite the “somewhat” elevated amyloid burden, the lack of elevated tau may have inhibited our ability to observe measurable associations with tau and amyloid in our healthy older adult sample.

The low amyloid and tau values also make it difficult to determine whether these individuals will remain healthy older adults or will progress to MCI/AD or another dementia. In the current study, we only have 2-3yrs of follow-up data so we cannot examine differences in people who develop more advanced accumulation. Future research should examine longer follow-ups to determine whether cognitively normal healthy older adults with WMHs have a faster rate of decline once elevated amyloid and tau contribute to cognitive decline. In this study, we did not observe a relationship between WMH load and either tau or amyloid. Graff-Radford et al. reported no associations between tau-PET and WMH burden, however, they reported that

amyloid-PET load correlated with WMH (2019). One explanation for the current study not observing the correlation between WMH and amyloid is related to the low levels of amyloid burden in our healthy controls. The lack of association between WMH and amyloid is consistent with other research²¹. Future research should further explore these inconsistent results in the healthy aging population.

The limitations of the current study include the inability to examine the influence of *APOE* status, limited follow-up, limited sample size, and high participant education. Only 28 participants had *APOE* $\epsilon 4$ positivity (24 with one $\epsilon 4$ allele and 4 with two $\epsilon 4$ alleles). Since *APOE* $\epsilon 4$ positivity increases the risk of future AD²³, future research would benefit from replicating this study in a sample comparing more participants with *APOE* $\epsilon 4$ positivity. Our follow-up times were limited to 3 years because we included participants from ADNI-3. Longer follow-ups may demonstrate stronger associations between tau and amyloid pathologies and cognitive decline. The relatively limited sample in this study did not allow for the testing of the interaction between amyloid, tau, and WMH on cognition with enough statistical power. The high education of this sample may limit the generalizability of these results to other populations.

The image processing methods employed in this study have been developed and extensively validated for use in multi-center and multi-scanner studies. These processing methods have previously observed WMH effects in PD^{16,48}, healthy aging, and AD¹⁶. Therefore, the lack of association between WMH with amyloid, tau, and some cognitive scores is not the result of poor sensitivity of the image processing methods employed.

Conclusion

The current study sought to examine the relationship between WMHs, amyloid, and tau measured with CSF and their effects on cognitive functioning in healthy older adults. Our findings suggest that in healthy older adults, WMHs may be one of the first pathologies to

contribute to age-related cognitive decline. It is possible that WMH burden may precede tau and amyloid deposition, however, without being able to determine who converts to AD, this hypothesis needs to be further examined. Despite not being able to determine which participants will eventually develop dementia in this study, our findings that WMHs contribute to cognitive decline aligns with previous work suggesting that vascular biomarkers may improve our current understanding of preclinical AD if incorporated into the AD research framework⁴⁹.

Table 1: Descriptive statistics for the participants included in this study. Data are number (N) or mean \pm standard deviation.

	Healthy Older Adults
Participants (N _{total})	102
Female (N)	61 (60%)
Age at baseline	72.05 (\pm 6.54)
Education	17.09 (\pm 2.19)
ADNI-EF at baseline	1.13 (\pm 0.82)
ADNI-EF at Follow-up	1.08 (\pm 0.86)
ADNI-MEM at baseline	1.06 (\pm 0.55)
ADNI-MEM at follow-up	1.25 (\pm 0.61)
ADAS-13 at baseline	11.05 (\pm 4.66)
ADAS-13 at follow-up	10.36 (\pm 4.42)
CSF A β 42/40 at baseline	0.07 (\pm 0.03)
CSF p-Tau181 at baseline	21.61 (\pm 9.36)
WMH Load at baseline	8.71 (\pm 0.55)

Notes: ADNI-EF and ADNI-MEM are z-scored values; ADAS-13 is a raw score; WMHs are log transformed. Abbreviations: ADAS-13, Alzheimer's Disease Assessment Scale-13; WMH. White matter hyperintensities.

Figure 1: Flowchart summarizing the participant inclusion and exclusion criteria based on WMH, amyloid, tau, and cognitive score measurements.

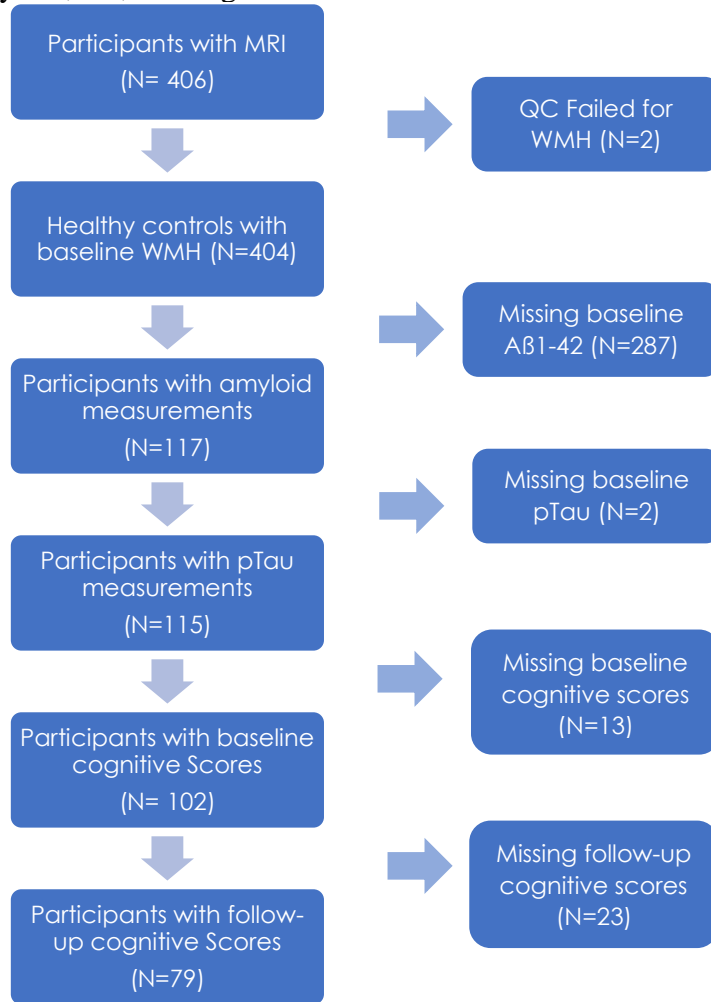
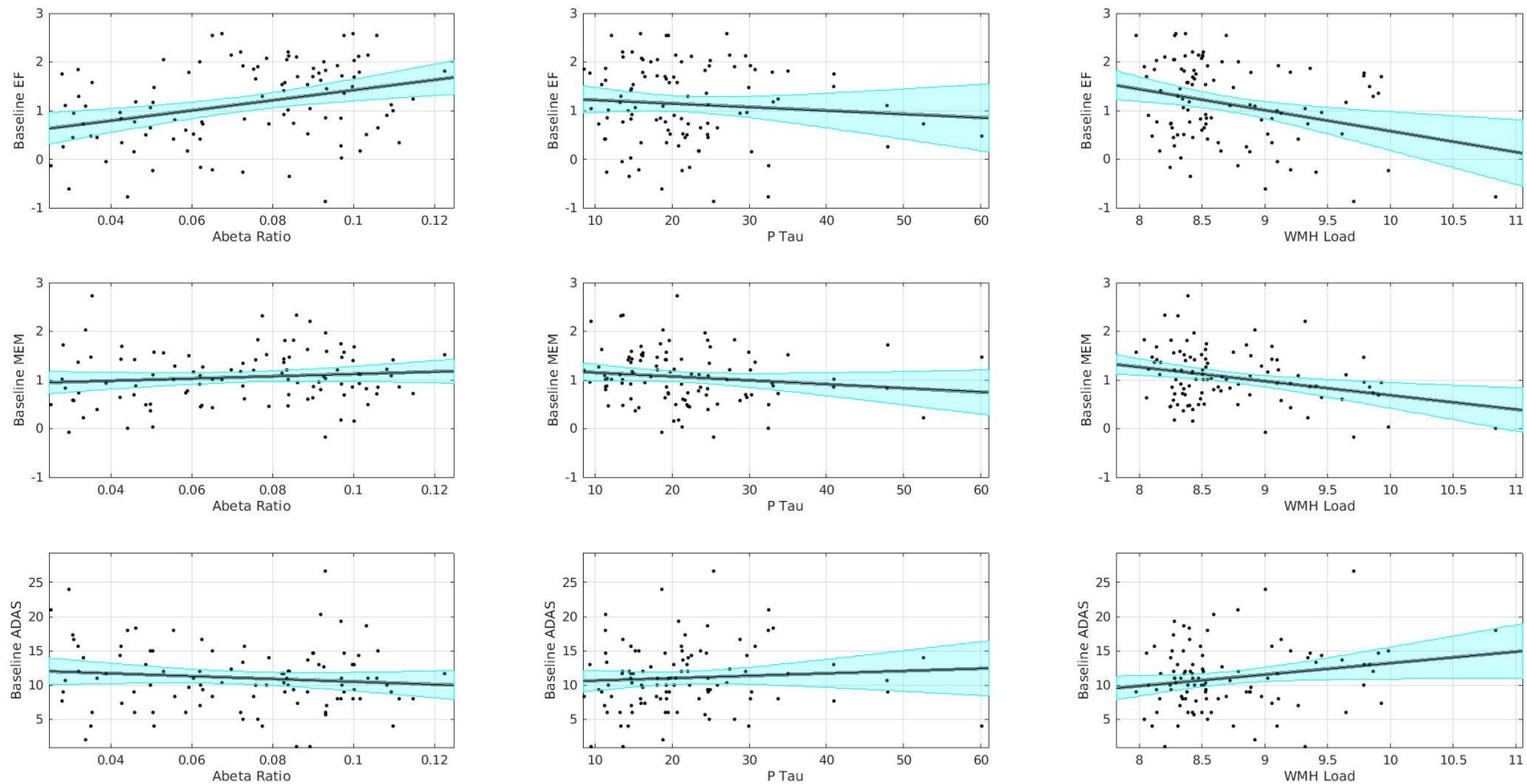


Table 2: Regression model outputs.

Model	ADNI-EF Baseline	ADNI-EF Follow-up	ADNI-MEM Baseline	ADNI-MEM Follow-up	ADAS-13 Baseline	ADAS-13 Follow-up	WMH	Amyloid
Age	$\beta = -0.03$, $t = -2.42$, $p = .017$	$\beta = -0.009$, $t = -0.85$, $p = .40$	$\beta = -0.01$, $t = -1.54$, $p = .13$	$\beta = 0.009$, $t = 1.37$, $p = .17$	$\beta = 0.07$, $t = 0.77$, $p = .44$	$\beta = -0.22$, $t = -3.61$, $p < .001$	$\beta = 0.04$, $t = 4.62$, $p < .001$	$\beta = -0.01$, $t = -1.89$, $p = .062$
Sex	$\beta = -0.01$, $t = -0.03$, $p = .97$	$\beta = -0.13$, $t = -1.06$, $p = .29$	$\beta = -0.35$, $t = -3.49$, $p < .001$	$\beta = -0.12$, $t = -1.43$, $p = .16$	$\beta = 2.15$, $t = 2.25$, $p = .027$	$\beta = -0.19$, $t = -0.27$, $p = .79$	$\beta = -0.039$, $t = -0.38$, $p = .71$	$\beta = 0.004$, $t = 0.78$, $p = .44$
Education	$\beta = 0.76$, $t = 2.27$, $p = .026$	$\beta = 0.10$, $t = 3.63$, $p < .001$	$\beta = 0.05$, $t = 2.38$, $p = .019$	$\beta = 0.035$, $t = 2.02$, $p = .047$	$\beta = -0.23$, $t = -1.07$, $p = .28$	$\beta = -0.004$, $t = -0.03$, $p = .98$	$\beta = 0.01$, $t = 0.52$, $p = .61$	$\beta = 0.001$, $t = 1.13$, $p = .26$
WMH	$\beta = -0.22$, $t = -1.48$, $p = .14$	$\beta = -0.32$, $t = -2.90$, $p = .005$	$\beta = -0.20$, $t = -2.02$, $p = .046$	$\beta = -0.13$, $t = -1.72$, $p = .090$	$\beta = 1.10$, $t = 1.19$, $p = .23$	$\beta = 2.69$, $t = 4.10$, $p < .001$	----	----
Amyloid	$\beta = 7.57$, $t = 2.48$, $p = .015$	$\beta = 2.74$, $t = 1.11$ $p = .29$	$\beta = 0.07$, $t = 0.36$, $p = .97$	$\beta = 2.56$, $t = 1.72$, $p = .089$	$\beta = -10.86$, $t = -0.56$, $p = .57$	$\beta = -5.48$, $t = -0.41$, $p = .68$	$\beta = -1.50$, $t = -0.72$, $p = .48$	----
pTau	$\beta = 0.01$, $t = 0.86$, $p = .39$	$\beta = -0.001$, $t = -0.13$, $p = .89$	$\beta = 0.003$, $t = -0.62$, $p = .54$	$\beta = 0.001$, $t = 0.11$, $p = .91$	$\beta = 0.003$, $t = 0.05$, $p = .96$	$\beta = 0.003$, $t = 0.07$, $p = .94$	$\beta = -0.007$, $t = -1.19$, $p = .24$	$\beta = -0.001$, $t = -2.28$, $p = .025$
Cognitive score at baseline	----	$\beta = 0.63$, $t = 7.61$, $p < .001$	----	$\beta = 0.86$, $t = 11.13$, $p < .001$	----	$\beta = 0.71$, $t = 9.12$, $p < .001$	----	----

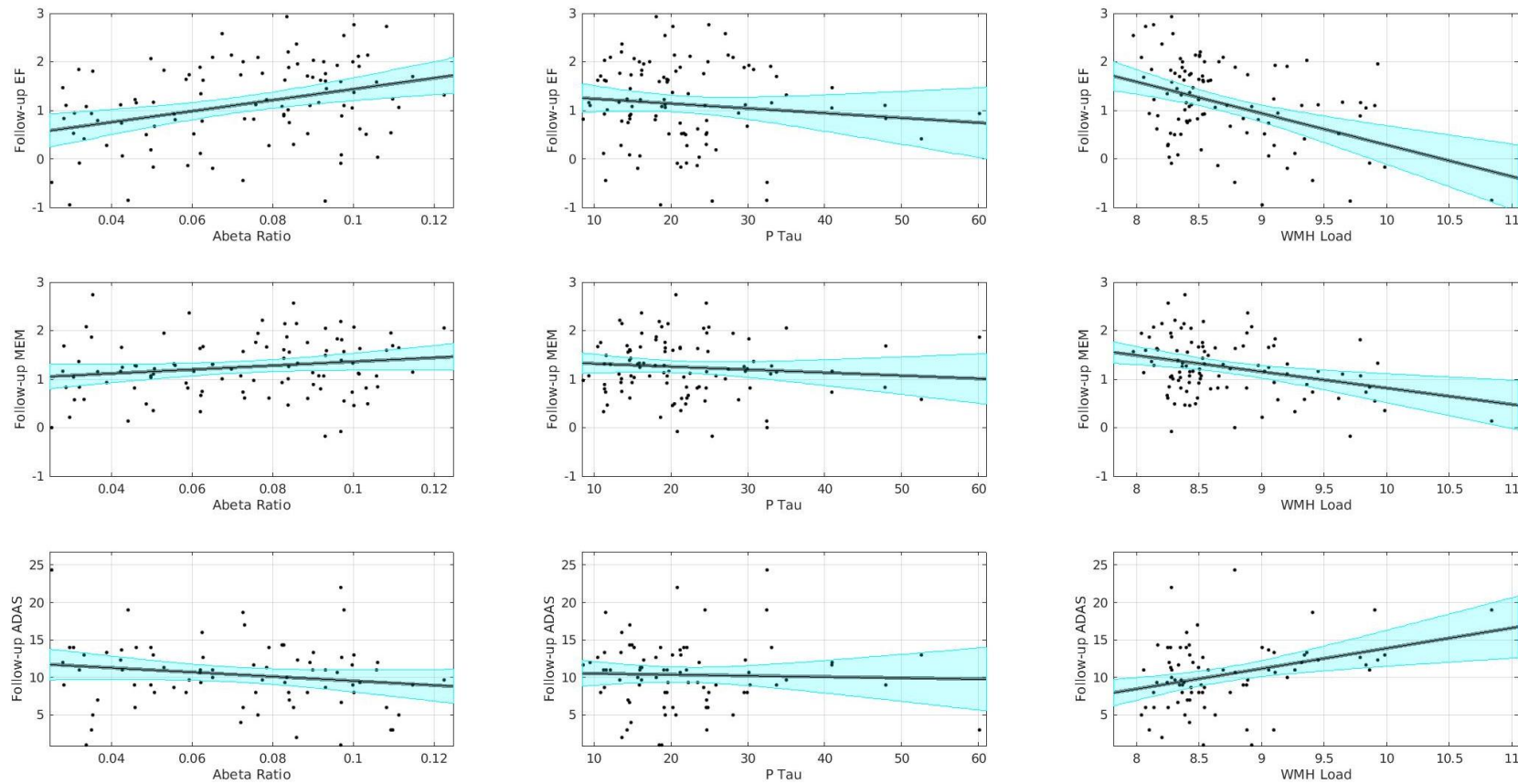
Notes: Significant results are shown in bold. Abbreviations: ADAS-13, Alzheimer's Disease Assessment Scale-13; WMH, White matter hyperintensity.

Figure 2: Baseline cognitive scores and their relationship with amyloid, pTau and WMH load.



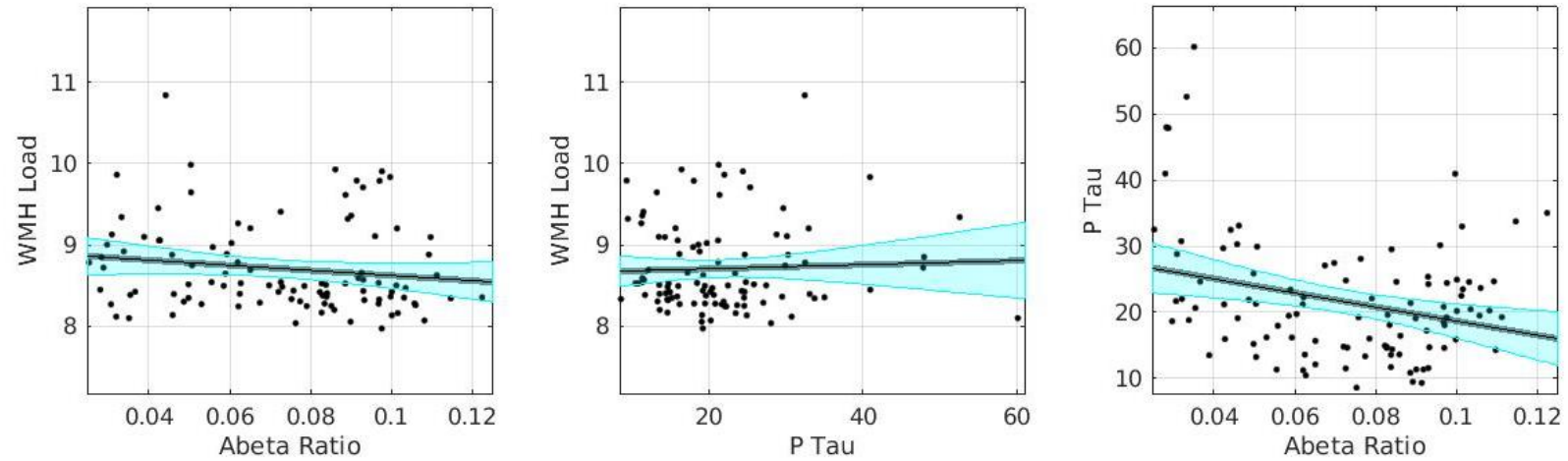
Figures show executive functioning (first row), memory (second row) and ADAS-13 (third row) scores and their association with Abeta Ratio (first column), P Tau (Second column), and WMH Load (third column). Abbreviations: EF, executive functioning; MEM, memory; ADAS, Alzheimer's Disease Assessment Scale, WMH, white matter hyperintensity.

Figure 3: Follow-up cognitive scores and their relationship with amyloid, pTau and WMH load.



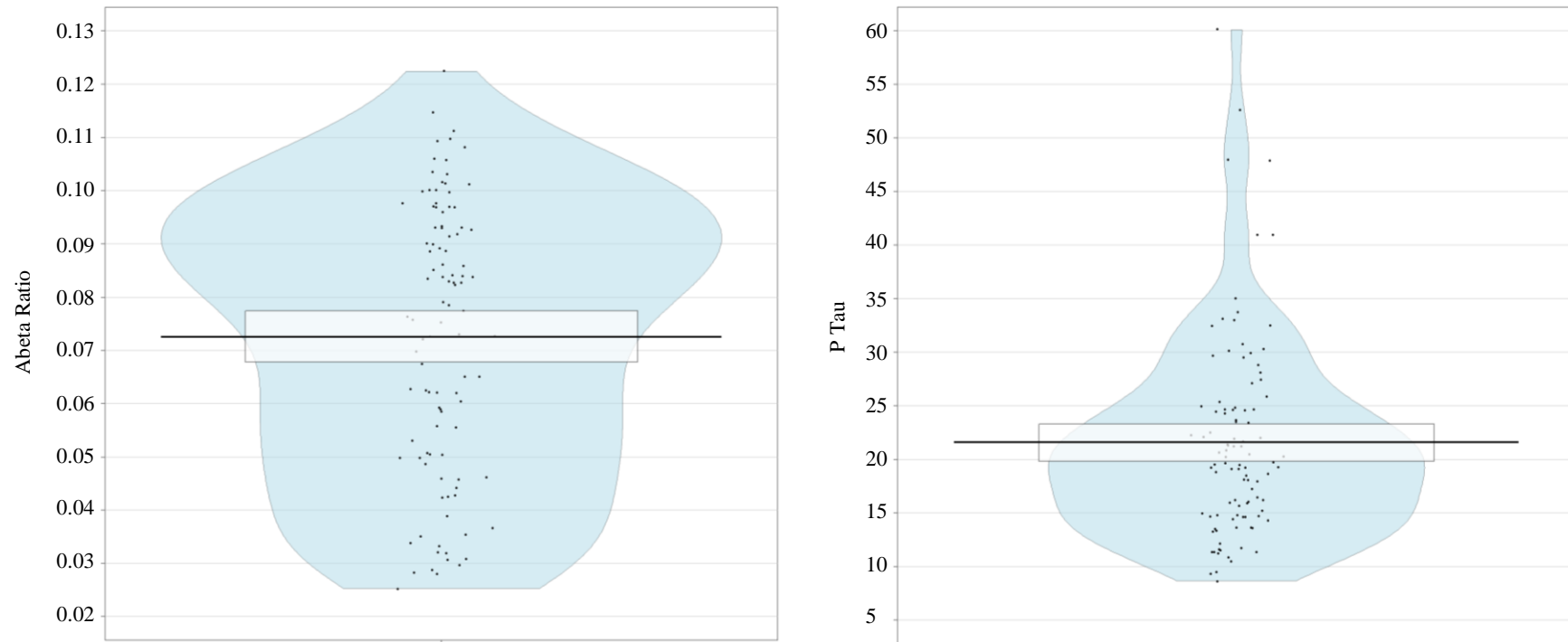
Figures show executive functioning (first row), memory (second row) and ADAS-13 (third row) scores and their association with Abeta Ratio (first column), pTau (Second column), and WMH Load (third column). Abbreviations: EF, executive functioning; MEM, memory; ADAS, Alzheimer's Disease Assessment Scale, WMH, white matter hyperintensity.

Figure 4: Baseline measurements of white matter hyperintensity load, amyloid, and pTau.



From left to right, WMH association with Abeta Ratio, WMH association with pTau, and pTau association with Abeta Ratio. Abbreviations: WMH, white matter hyperintensity.

Figure 5: Piratplots of participant Abeta ratio and pTau values.



Figures present the mean values (thick, solid horizontal line), 95% confidence intervals (light horizontal box), smooth frequency distribution (shaded area), and individual data points (jittered).

1. Sperling RA, Aisen PS, Beckett LA, et al. Toward defining the preclinical stages of Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's Dement.* 2011;7(3):280-292. doi:10.1016/j.jalz.2011.03.003
2. Perrin R, Fagan AM, Holtzman DM. Multi-modal techniques for diagnosis and prognosis of Alzheimer's disease. *Nature.* 2009;461(7266):916-922. doi:10.1038/nature08538
3. Donohue MC, Sperling RA, Petersen R, Sun CK, Weiner M, Aisen PS. 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
4. Stomrud E, Hansson O, Zetterberg H, Blennow K, Minthon L, Londos E. Correlation of longitudinal cerebrospinal fluid biomarkers with cognitive decline in healthy older adults. *Arch Neurol.* 2010;67(2):217-223. doi:10.1001/archneurol.2009.316
5. Verberk IMW, Hendriksen HMA, van Harten AC, et al. Plasma amyloid is associated with the rate of cognitive decline in cognitively normal elderly: the SCIENCE project. *Neurobiol Aging.* 2020;89:99-107. doi:10.1016/j.neurobiolaging.2020.01.007
6. Aschenbrenner AJ, Gordon BA, Benzinger TLS, Morris JC, Hassenstab JJ. Influence of tau PET, amyloid PET, and hippocampal volume on cognition in Alzheimer disease. *Neurology.* 2018;91(9):e859-e866. doi:10.1212/WNL.0000000000006075
7. 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
8. Schöll M, Lockhart SN, Schonhaut DR, et al. PET Imaging of Tau Deposition in the Aging Human Brain. *Neuron.* 2016;89(5):971-982. doi:10.1016/j.neuron.2016.01.028
9. Malpas CB, Sharmin S, Kalincik T. The histopathological staging of tau, but not amyloid, corresponds to antemortem cognitive status, dementia stage, functional abilities and neuropsychiatric symptoms. *Int J Neurosci.* 2021;131(8):800-809. <https://doi.org/10.1080/00207454.2020.1758087>
10. Rhodius-Meester HFM, Benedictus MR, Wattjes MP, et al. MRI visual ratings of brain atrophy and white matter hyperintensities across the spectrum of cognitive decline are differently affected by age and diagnosis. *Front Aging Neurosci.* 2017;9:1-12. doi:10.3389/fnagi.2017.00117
11. Kloppenborg RP, Geerlings MI. Presence and progression of white matter hyperintensities and cognition: a meta-analysis." *Neurology.* 2014;82(23): 2127-2138. doi:10.1212/WNL.0000000000000505
12. Boyle PA, Yu L, Fleischman DA, et al. White matter hyperintensities, incident mild

- cognitive impairment, and cognitive decline in old age. *Ann Clin Transl Neurol*. 2016;3(10):791-800. doi:10.1002/acn3.343
13. Prins ND, Van Dijk EJ, Den Heijer T, et al. Cerebral white matter lesions and the risk of dementia. *Arch Neurol*. 2004;61(10):1531-1534. doi:10.1001/archneur.61.10.1531
 14. Kaskikallio A, Karrasch M, Koikkalainen J, et al. White Matter Hyperintensities and Cognitive Impairment in Healthy and Pathological Aging: A Quantified Brain MRI Study. *Dement Geriatr Cogn Disord*. 2020;48(5-6):297-307. doi:10.1159/000506124
 15. 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
 16. Dadar M, Camicioli R, Duchesne S, Collins DL. The temporal relationships between white matter hyperintensities, neurodegeneration, amyloid beta, and cognition. *Alzheimer's Dement Diagnosis, Assess Dis Monit*. 2020;1:e12091. doi:10.1002/dad2.12091
 17. Dadar M, Zeighami Y, Yau Y, et al. White matter hyperintensities are linked to future cognitive decline in de novo Parkinson's disease patients. *NeuroImage Clin*. 2018;20:892-900. doi:10.1016/j.nicl.2018.09.025
 18. Hedden T, Mormino EC, Amariglio RE, et al. Cognitive profile of amyloid burden and white matter hyperintensities in cognitively normal older adults. *J Neurosci*. 2012;32(46):16233-16242. doi:10.1523/JNEUROSCI.2462-12.2012
 19. Vemuri P, Lesnick TG, Przybelski SA, et al. Vascular and amyloid pathologies are independent predictors of cognitive decline in normal elderly. *Brain*. 2015;138(3):761-771. doi:10.1093/brain/awu393
 20. Graff-Radford J, Arenaza-Urquijo EM, Knopman DS, et al. White matter hyperintensities: Relationship to amyloid and tau burden. *Brain*. 2019;142(8):2483-2491. doi:10.1093/brain/awz162
 21. Marchant NL, Reed BR, DeCarli CS, et al. Cerebrovascular disease, beta-amyloid, and cognition in aging. *Neurobiol Aging*. 2012;33(5):1006.e25-1006.e36. doi:10.1016/j.neurobiolaging.2011.10.001
 22. Craig-schapiro R, Fagan AM, Holtzman DM. Biomarkers of Alzheimer's disease. *Neurobiol Dis*. 2009;35(2):128-140. doi:10.1016/j.nbd.2008.10.003
 23. Rabin LA, Smart CM, Amariglio RE. Subjective Cognitive Decline in Preclinical Alzheimer's Disease. *Annu Rev Clin Psychol*. 2017;13:369-396. doi:10.1146/annurev-clinpsy-032816-045136

24. Gibbons LE, Carle AC, Mackin RS, et al. ADNI : A composite score for executive functioning, validated in Alzheimer's Disease Neuroimaging Initiative (ADNI) participants with baseline mild cognitive impairment. *Brain Imaging Behav.* 2012;6(4):517-527. doi:10.1007/s11682-012-9176-1
25. Crane PK, Carle A, Gibbons LE, et al. Development and assessment of a composite score for memory in the Alzheimer's Disease Neuroimaging Initiative (ADNI). *Brain Imaging Behav.* 2012;6(4):502-516. doi:10.1007/s11682-012-9186-z
26. Mohs RC, Knopman DS, Petersen RC, et al. Development of cognitive instruments for use in clinical trials of antidementia drugs: Additions to the Alzheimer's Disease Assessment Scale that broaden its scope. *Alzheimer Dis Assoc Disord.* 1997;11(Suppl2):S13-S21. <https://psycnet.apa.org/doi/10.1097/00002093-199700112-00003>.
27. Olsson A, Vanderstichele H, Andreasen N, et al. Simultaneous measurement of β -amyloid(1-42), total Tau, and phosphorylated Tau (Thr181) in cerebrospinal fluid by the xMAP technology. *Clin Chem.* 2005;51(2):336-345. doi:10.1373/clinchem.2004.039347
28. Shaw LM, Vanderstichele H, Knapik-Czajka M, et al. Cerebrospinal fluid biomarker signature in Alzheimer's disease neuroimaging initiative subjects. *Ann Neurol.* 2009;65(4):403-413. doi:10.1002/ana.21610
29. Coupe P, Yger P, Prima S, Hellier P, Kervrann C, Barillot C. An optimized blockwise nonlocal means denoising filter for 3-D magnetic resonance images. *IEEE Trans Med Imaging.* 2008;27(4):425-441. doi:10.1109/TMI.2007.906087
30. Sled JG, Zijdenbos AP, Evans AC. A nonparametric method for automatic correction of intensity nonuniformity in MRI data. *IEEE Trans Med Imaging.* 1998;17(1):87-97. doi:10.1109/42.668698
31. Dadar M, Fonov VS, Collins DL. A comparison of publicly available linear MRI stereotaxic registration techniques. *Neuroimage.* 2018;174:191-200. doi:10.1016/j.neuroimage.2018.03.025
32. 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(1):26-41. doi:10.1016/j.media.2007.06.004
33. Manera AL, Dadar M, Fonov V, Collins DL. CerebrA , registration and manual label correction of Mindboggle-101 atlas for MNI-ICBM152 template. *Sci Data.* 2020:1-9. doi:10.1038/s41597-020-0557-9
34. Dadar M, Misquitta K, Anor CJ, et al. NeuroImage Performance comparison of 10 different classification techniques in segmenting white matter hyperintensities in aging.

Neuroimage. 2017;157:233-249. doi:10.1016/j.neuroimage.2017.06.009

35. Dadar M, Pascoal TA, Manitsirikul S, et al. Validation of a Regression Technique for Segmentation of White Matter Hyperintensities in Alzheimer's Disease. *IEEE Trans Med Imaging*. 2017;36(8):1758-1768.
36. Schindler SE, Gray JD, Gordon BA, et al. Cerebrospinal fluid biomarkers measured by Elecsys assays compared to amyloid imaging. *Alzheimer's Dement*. 2018;14(11):1460-1469. doi:10.1016/j.jalz.2018.01.013
37. Meyer PF, Pichet Binette A, Gonneaud J, Breitner JCS, Villeneuve S. Characterization of Alzheimer Disease Biomarker Discrepancies Using Cerebrospinal Fluid Phosphorylated Tau and AV1451 Positron Emission Tomography. *JAMA Neurol*. 2020;77(4):508-516. doi:10.1001/jamaneurol.2019.4749
38. Walker KA, Power MC, Gottesman RF. Defining the Relationship Between Hypertension, Cognitive Decline, and Dementia: a Review. *Curr Hypertens Rep*. 2017;19(3). doi:10.1007/s11906-017-0724-3
39. Ettore E, Cerra E, Marigliano B, et al. Role of cardiovascular risk factors (CRF) in the patients with mild cognitive impairment (MCI). *Arch Gerontol Geriatr*. 2012;54(2):330-332. doi:http://dx.doi.org/10.1016/j.archger.2011.04.025
40. Streit S, Poortvliet RKE, Den Elzen WPJ, Blom JW, Gussekloo J. Systolic blood pressure and cognitive decline in older adults with hypertension. *Ann Fam Med*. 2019;17(2):100-107. doi:10.1370/afm.2367
41. Ding J, Davis-Plourde KL, Sedaghat S, et al. Antihypertensive medications and risk for incident dementia and Alzheimer's disease: a meta-analysis of individual participant data from prospective cohort studies. *Lancet Neurol*. 2020;19(1):61-70. doi:10.1016/S1474-4422(19)30393-X
42. Bejanin A, Schonhaut DR, La Joie R, et al. Tau pathology and neurodegeneration contribute to cognitive impairment in Alzheimer's disease. *Brain*. 2017;140(12):3286-3300. doi:https://dx.doi.org/10.1093/brain/awx243
43. Lim YY, Maruff P, Pietrzak RH, et al. Effect of amyloid on memory and non-memory decline from preclinical to clinical Alzheimer's disease. *Brain*. 2014;137(1):221-231. doi:10.1093/brain/awt286
44. Rolstad S, Berg AI, Bjerke M, et al. Amyloid- β 42 is associated with cognitive impairment in healthy elderly and subjective cognitive impairment. *J Alzheimer's Dis*. 2011;26(1):135-142. 10.3233/JAD-2011-110038

45. Leal, S. L., Lockhart, S. N., Maass, A., Bell, R. K., & Jagust, W. J. Subthreshold amyloid predicts tau deposition in aging. *J Neurosci.* 2018;38(19), 4482-4489. doi:10.1523/JNEUROSCI.0485-18.2018
46. Jack CR, Wiste HJ, Weigand SD, et al. Defining imaging biomarker cut points for brain aging and Alzheimer's disease. *Alzheimer's Dement.* 2017;13(3):205-216. doi:10.1016/j.jalz.2016.08.005
47. Therneau TM, Knopman DS, Lowe VJ, et al. Relationships between β -amyloid and tau in an elderly population: An accelerated failure time model. *Neuroimage.* 2021;242:118440. doi:10.1016/j.neuroimage.2021.118440
48. Dadar M, Miyasaki J, Duchesne S, Camicioli R. White matter hyperintensities mediate the impact of amyloid β on future freezing of gait in Parkinson's disease. *Park Relat Disord.* 2021;85:95-101. doi:10.1016/j.parkreldis.2021.02.031
49. Sweeney MD, Montagne A, Sagare AP, et al. Vascular dysfunction—The disregarded partner of Alzheimer's disease. *Alzheimer's Dement.* 2019;15(1):158-167. doi:10.1016/j.jalz.2018.07.22

Figure Titles and Legends:

Figure 1: Flowchart summarizing the participant inclusion and exclusion criteria based on WMH, amyloid, tau, and cognitive score measurements.

Figure 2: Baseline cognitive scores and their relationship with amyloid, pTau and WMH load.

Figures show executive functioning (first row), memory (second row) and ADAS-13 (third row) scores and their association with Abeta Ratio (first column), P Tau (Second column), and WMH Load (third column). Abbreviations: EF, executive functioning; MEM, memory; ADAS, Alzheimer's Disease Assessment Scale, WMH, white matter hyperintensity.

Figure 3: Follow-up cognitive scores and their relationship with amyloid, pTau and WMH load.

Figures show executive functioning (first row), memory (second row) and ADAS-13 (third row) scores and their association with Abeta Ratio (first column), pTau (Second column), and WMH Load (third column). Abbreviations: EF, executive functioning; MEM, memory; ADAS, Alzheimer's Disease Assessment Scale, WMH, white matter hyperintensity.

Figure 4: Baseline measurements of white matter hyperintensity load, amyloid, and pTau.

From left to right, WMH association with Abeta Ratio, WMH association with pTau, and pTau association with Abeta Ratio. Abbreviations: WMH, white matter hyperintensity.

Figure 5: Piratplots of participant Abeta ratio and pTau values.

Figures present the mean values (thick, solid horizontal line), 95% confidence intervals (light horizontal box), smooth frequency distribution (shaded area), and individual data points (jittered).