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

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Abstract

Background: Research suggests that cerebral small vessel disease (CSVD), amyloid, and pTau contribute to age-related cognitive decline. It remains unknown how these factors relate to one another, nor how they jointly contribute to cognitive decline in normal aging. This project examines the association between these pathologies and their relationship to cognitive decline in cognitively normal older adults without subjective cognitive decline.

Methods: A total of 230 subjects with CSF Aß42, CSF pTau181, white matter hyperintensities (WMHs) used as a proxy of CSVD and cognitive scores from the Alzheimer's Disease Neuroimaging Initiative were included. Associations between each pathology and cognitive score were investigated using regression models. Furthermore, relationships between the three pathologies were also examined using regression models.

Results: At baseline, there was an inverse association between WMH load and Aß42 (t=-4.20, p<.001). There was no association between WMH load and pTau (t=0.32, p=0.75), nor with Aß42 and pTau (t=0.51, p=.61). Correcting for age, sex and education, baseline WMH load was associated with baseline ADAS-13 scores (t=2.59, p=.01) and lower follow-up executive functioning (t= -2.84, p=.005). Baseline Aß42 was associated with executive function at baseline (t=3.58, p<.004) but not at follow-up (t=1.05, p=0.30), nor with ADAS-13 at baseline (t=-0.24, p0.81) or follow-up (t=0.09, p=0.93). Finally, baseline pTau was not associated with any cognitive measure at baseline or follow-up.

Conclusion: Both baseline Aß42 and WMH load are associated with some baseline cognition scores, but only baseline WMH load is associated with follow-up executive functioning, indicating that it may be one of the earliest pathologies that contributes to future cognitive decline, in cognitively healthy older adults. Given that healthy older adults with WMH pathology exhibit declines in cognitive functioning, they may be less resilient to future pathology increasing their risk for cognitive impairment due to dementia than those without WMHs.

Introduction

Alzheimer's disease (AD) is characterized by several neuropathological brain changes such as senile plaques (ß-amyloid, Aß) and neurofibrillary tangles (Tau) deposition (Perrin et al., 2009; Sperling et al., 2011). These accumulations have been associated with the hallmarked progressive cognitive decline observed in people with AD. Both CSF Aß and tau pathologies (Donohue et al., 2017; Stomrud et al., 2010; Verberk et al., 2020) and position emission tomography (PET) Aß and tau (Aschenbrenner et al., 2018; Schöll et al., 2016; Sperling et al., 2019) 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 (Aschenbrenner et al., 2018; Malpas et al., 2021).

Another pathological change, cerebral small vessel disease (CSVD), 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 decline (Rhodius-Meester et al., 2017). An association between high WMH load and decreased cognitive functioning in healthy older adults is often reported. A meta-analysis observed that CSVD impacts all cognitive domains in healthy older adults, with the strongest association seen between WMH and attention and executive functioning (Kloppenborg and Geerlings, 2014). WMH load increases a healthy older adults' risk for future development of mild cognitive impairment (MCI)(Boyle et al., 2016) and dementia (Prins et al., 2004). CSVD also continues to contribute to cognitive decline observed in AD (Kaskikallio et al., 2020) because many cases of AD have a mixed etiology (Prins and Scheltens, 2015). CSVD (as measured by WMH) has been observed to precede neurodegeneration and cognitive decline in MCI, AD, and Parkinson's disease (Dadar et al., 2020a, 2018b), suggesting that CSVD 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 functioning (Donohue et al., 2017; Stomrud et al., 2010; Verberk et al., 2020) and the relationship between WMH and amyloid (Dadar et al., 2020a; Hedden et al., 2012; Vemuri et al., 2015) there is limited research examining the interaction between WMH, amyloid, and tau and their joint effects on cognitive decline in healthy older adults. One study, observed no association between WMH burden and amyloid-PET but also found that increased WMH was associated with lower executive functioning whereas amyloid measured with PET had no effect on cognitive function (Marchant et al., 2012). Another study observed the association between WMHs and tau- and amyloid-PET but did not compare these pathologies to cognitive decline (Graff-Radford et al., 2019). They observed that increases in WMH were associated with increases in amyloid-PET in cognitively healthy older adults, but no relationship between tau-PET and WMH was observed (Graff-Radford et al., 2019).

One difficulty when studying these AD-related pathologies is that they occur years prior to the onset of clinical symptoms (Craig-Schapiro et al., 2009; Sperling et al., 2011), emphasizing the need to evaluate these changes in the healthy aging population. The goal of this study was thus to expand on current research by examining the relationship between cognitive changes and all three pathologies (CSVD, amyloid, and tau) in healthy older adults. The novelty of this paper was to focus on cognitively heathy older adults by excluding people with subjective cognitive decline (SCD) to avoid possible confounds caused by cognitively heathy older adults that may already be on the AD trajectory (Rabin et al., 2017). Current findings in cognitively normal elderly showing associations between the pathologies may be biased because of the

inclusion of people with SCD. Another aim was to explore whether these pathologies are present in healthy older adults who are unlikely to be in the preclinical AD phase of AD. We wanted to examine how these AD-related pathologies at baseline are associated with current cognitive function and cognitive decline in healthy older adults. Furthermore, we also examined how these pathologies are related to one another.

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

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 healthy adults were considered if they were labelled as 'Normal control' and if they scored <16 on the Cognitive Change Index, signifying no indication of SCD. The following inclusion criteria were applied to the 406 healthy controls: having an MRI scan from which WMH load could be estimated and having both pTau and amyloid measures. Inclusion criteria also included baseline executive functioning, memory, and ADAS-13 scores. These criteria resulted in 230 participants for our study at baseline. At follow-up, 199 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.

<Insert Color Figure 1 about here>

We used executive functioning (ADNI-EF; Gibbons et al., 2012) and memory (ADNI-MEM; Crane et al., 2012)) composite scores that have been previously developed and validated in ADNI. Alzheimer's Disease Assessment Scale- Cog13 (ADAS-13;Mohs et al., 1997) 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 Aß42 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) (Olsson et al., 2005; Shaw et al., 2009). The Elecsys Aß42 assay has not been established for measuring concentrations above 1700 pg/ml. Any values above this concentration were, therefore, truncated at 1700 pg/ml (Sutphen et al., 2018).

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 reduction (Coupe et al., 2008), intensity inhomogeneity correction (Sled et al., 1998), and intensity normalization into range [0-100]. The pre-processed images were then both linearly (9 parameters: 3 translation, 3 rotation, and 3 scaling) (Dadar et al., 2018a) and nonlinearly (1 mm^3 grid) (Avants et al., 2008) registered to the MNI-ICBM152-2009c average template (Fonov et al., 2011). The quality of the linear and nonlinear registrations was visually verified by an experienced rater (co-author MD).

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(Dadar et al., 2017a, 2017b). WMH load often reflects cerebrovascular disease, thus WMH load was used as a proxy for cerebrovascular pathology and was defined as the volume of all voxels identified as WMH in the standard space (in mm^3) and are thus normalized for head size. WMH volumes were log-transformed to achieve normal distribution. This WMH technique has been developed and extensively tested specifically for assessment of WMHs in multi-center studies including

validation in the ADNI cohort. For example, these techniques have been used in examining WMHs in HIV infection studies(Sanford et al., 2019) and multi-center studies including, The Parkinson's Markers Initiative (Dadar et al., 2020b) and UK Brain bank (Dadar et al., 2020c) to assess WMHs in Parkinson's, and the National Alzheimer's Coordinating Center (Anor et al., 2021) and ADNI (Dadar et al., 2019) to assess WMHs in MCI and AD.

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 pTau would influence cognitive scores. Correction of multiple comparisons was completed using false discovery rate (FDR), p-values are reported as raw values with significance determined by FDR correction. *CognitiveScore_bl* represents executive function (or memory composite) score at baseline. For baseline measurements, 230 participants were included for both the executive functioning and memory composite models. Both CSF Aß42 and CSF pTau levels were downloaded from ADNI.

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

For follow-up measurements, 199 participants had follow-up scores over periods, 1-2 years (n=45), and 2-3 years (n=154) 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.

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

A linear regression was completed to examine whether amyloid and pTau influence white matter hyperintensities. All 230 participants were included in this analysis:

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

A linear regression was also completed to examine whether pTau and amyloid are associated. All 230 participants were included in this analysis:

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

Additional t-tests were completed to compare the baseline characteristics of the 31 participants who did not have follow-up data to that of the 199 participants that had follow-up data to observe if there was evidence of selective attrition. The participants' age, sex, education, CSF Aß42, CSF p-Tau181, ADNI-EF, ADNI-MEM, ADAS-13, and WMH load were compared between the two groups. At baseline, those that did not have follow-up scores had significantly increased ADAS-13 scores ($p<.001$, uncorrected); that is those who did not have follow-ups had lower performance at baseline in general cognitive functioning. No other group differences were significant (See Table 1).

<Insert Table 1 about here>

Results

Cognitive Score Analysis

Figures 2 and 3 display executive functioning composite, memory composite, and ADAS-13 scores with Aß42, pTau, and WMH at baseline and follow-up. Table 2 summarizes the regression model results. At baseline, increased executive functioning scores were associated with higher CSF Aß42 (t= 3.58, p<.001) and higher education (t= 2.95, p=.003), and inversely associated with age (t= -5.63, p<.001). At follow-up, lower executive functioning scores were associated with increased WMHs (t= -2.84, p=.005), male sex (t= -2.22, p=.027), and increased age (t=-1.99, p=.049), however, age and sex were no longer significant after FDR correction. At follow-up, increased executive functioning scores were associated with increased education (t= 4.39, p<.001) and increased baseline executive functioning (t= 12.38, p<.001).

At baseline, increased memory was associated with higher education (t= 2.81, p=.005). Lower memory scores were associated with increased age (t= -4.26, p<.001) and male sex (t= -3.56, p<.001). At follow-up, increased memory was associated higher baseline memory (t= 14.28, p<.001). At follow-up increased memory was also associated with increased education (t=1.97, p=.05) and lower memory scores were associated with male sex (t= -2.21, p=.028) and marginally associated with increased WMHs (t=1.76, p=.081). However, the association between education, sex, and WMH with follow-up did not remain significant after FDR correction.

At baseline, higher ADAS-13 scores (i.e., worse performance) were associated with increased WMHs (t= 2.59, p=.01), age (t= 2.04, p=.042), and male sex (t= 2.39, p=.018); age and sex did were no longer significant after FDR correction. At follow-up, higher ADAS-13 scores were associated with higher baseline ADAS-13 scores (t= 11.66, p<.001) and marginally associated with increased WMHs (t= 1.76, p=.08).

<Insert Color Figure 2&3 and Table 2 about here>

WMH, Tau, and Amyloid Analysis

Figure 4 displays the baseline associations between WMHs, CSF Aß42, and pTau. At baseline, WMHs were associated with increased CSF Aß42 (t= -4.20, p<.001) and age (t= 5.03, p<.001) but not pTau (t=0.32, p=0.75). CSF Aß42 was not observed to be associated with pTau (t= 0.51, p=.61), age (t= -1.29, p=.020) or male sex (t=0.89, p=0.37).

<Insert Color Figure 4 about here>

Discussion

The current study investigated the effects of WMH, CSF Aß42, and CSF pTau 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 Aß42 burden was associated with only decreased baseline executive functioning. Increased WMH loads were associated with reduced performance on baseline global cognition (as measured by ADAS-13) and follow-up executive functioning. WMH loads were also related to baseline CSF Aß42 but not pTau. CSF Aß42 was not associated with CSF pTau. These results suggest WMH may contribute to the initial stages of cognitive decline in healthy older adults. While additional data and analysis are necessary, healthy older adults with WMH pathology may be less resilient to future pathology and at greater risk of cognitive impairment due to dementia than those without WMHs.

In this sample of cognitively unimpaired participants with no subjective cognitive decline, WMH loads appeared to have the largest association with cognitive changes in cognitively normal older adults. CSVD, 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 dementia (Prins and Scheltens, 2015) by lowering the threshold for cognitive decline due to Alzheimer's dementia. Risk factors that contribute to WMHs (e.g., hypertension and cardiovascular disease) are also associated with cognitive decline in healthy older adults (Marchant et al., 2012; Walker et al., 2017) and a higher conversion rate from MCI to AD (Ettorre et al., 2012). Taken together, these findings provide support an aggressive treatment strategy of vascular factors to help reduce future cognitive decline. For example, previous research has observed that people who undergo antihypertensive treatment exhibit less cognitive decline (Streit et al., 2019) and a reduced risk of dementia (Ding et al., 2020) than those with untreated high blood pressure. However, a recent meta-analysis suggests there is limited evidence to support the use of aggressive antihypertensive treatment to reduce cognitive decline (Dallaire-Théroux et al., 2021).

In MCI and AD, both PET and CSF tau and amyloid deposition is reported to be a strong predictor of cognitive decline (Bejanin et al., 2017; Lim et al., 2014; Rolstad et al., 2011). It is well-known that this accumulation of pathological amyloid and tau begins years before deficits in cognitive functioning can be detected (Leal et al., 2018), and thus may occur during healthy aging. The relationship between tau and amyloid in healthy older adults is, however, less prominent. Nevertheless, some associations between CSF tau and amyloid (Donohue et al., 2017; Stomrud et al., 2010; Verberk et al., 2020) with reduced cognitive performance in healthy older adults have been observed. CSF pTau was not associated with cognitive decline in our sample of

healthy older adults without subjective cognitive decline. The sample of participants in this study comprises healthy older adults who exhibit low overall pTau burdens making it difficult to detect associations between tau and cognition at this stage (Jack et al., 2017). Amyloid deposition may occur on average 13.3 years earlier than tau accumulation (Therneau et al., 2021). Thus, it is not surprising that Aß42 was associated with baseline executive functioning in the absence of associations between pTau and cognition. The fastest rates of cognitive decline are observed in those who have both elevated amyloid and tau deposition (Sperling et al., 2019). Therefore, the low pTau levels in our sample may have influenced why we did not observe an association between pTau and cognition at baseline or follow-up or between Aß42 and cognition at follow-up in our healthy older adult sample.

The participants who did not have follow-up data had higher ADAS-13 scores (i.e., more cognitive impairment) at baseline than those who had follow-up data. This finding suggests that those participants may be closer to the dementia/AD trajectory. In the current study, we only have 2 to 3 years of follow-up data so we cannot examine differences in people who develop more advanced accumulation or convert to dementia/AD. Future research should examine longer follow-ups to determine whether cognitively normal healthy older adults with WMHs have a faster rate of cognitive decline, if they are more likely to convert to dementia/AD, and if elevated amyloid and tau contribute to this decline. In this study, while we did observe a relationship between WMH and amyloid at baseline we did not observe a relationship between WMH and tau. This finding is similar to a previous study that reported no associations between tau-PET and WMH burden, but reported that amyloid-PET load correlated with WMH (Graff-Radford et al., 2019).

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 (Dadar et al., 2021, 2020a), healthy aging and AD (Dadar et al., 2020a). 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.

The limitations of the current study include the relatively short follow-up period, limited sample size, and high participant education. 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. Some research has shown that WMHs may also be associated with other pathologies than cerebrovascular disease (McAleese et al., 2021). However, the methodologies needed to differentiate these pathologies are unavailable in this dataset, limiting our ability to identify the cause of the WMHs. Future research is needed to examine the underlying pathologies associated with WMHs.

Conclusion

The current study sought to examine the relationship between CSVD as measured by WMH load, with amyloid, and tau measured with CSF, and their effects on cognitive functioning in healthy older adults without subjective cognitive decline. Our findings suggest that in healthy older adults who are not likely to be in the preclinical AD stage, as reflected by low tau levels, WMHs may be one of the first pathologies to contribute to age-related cognitive decline. It is

possible that WMH burden may preceded tau and amyloid deposition, however, without being able to determine who converts to AD, this hypothesis needs to be further examined. Despite being unable 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 AD pathophysiology and dementia (Sweeney et al., 2019).

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

	Full Sample Healthy Older Adults	Follow-up Sample	Baseline only Sample
Participants (N_{total})	230	199	31
Female (N)	129 (56%)	108 (54%)	21 (67%)
Age at baseline (years)	73.08 ± 6.49	73.26 ± 6.42	71.98 ± 6.94
Education (years)	16.68 ± 2.45	16.65 ± 2.53	16.87 ± 1.91
ADNI-EF at baseline	1.00 ± 0.85	0.99 ± 0.85	1.08 ± 0.90
ADNI-EF at follow-up	----	0.96 ± 0.89	----
ADNI-MEM at baseline	1.06 ± 0.58	1.09 ± 0.60	0.88 ± 0.47
ADNI-MEM at follow-up	----	1.22 ± 0.62[1]	----
ADAS-13 at baseline	10.09 ± 4.72	9.65 ± 4.57	12.93 ± 4.80[2]
ADAS-13 at follow-up	----	9.09 ± 4.76	----
CSF Aß42 at baseline (pg/mL)	1228 ± 445	1235 ± 448	1187 ± 430
CSF pTau181 at baseline (pg/mL)	21.55 ± 9.06	21.52 ± 9.12	21.73 ± 8.81
WMH Load at baseline	8.67 ± 0.54	8.68 ± 0.56	8.61 ± 0.42

Notes: ADNI-EF and ADNI-MEM are composite scores that 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. [1]Follow-up participants had higher memory composites (ADNI-MEM, $p<.001$) and lower ADAS-13 ($p=.045$) scores at follow-up than baseline. [2]The sample with only baseline measures had marginally significantly higher ADAS-13 scores than the sample with follow-up measures ($p<.001$, uncorrected).

Figure 1: Flowchart summarizing the participant inclusion and exclusion criteria based on WMH, Aß42, pTau, and cognitive score measurements.

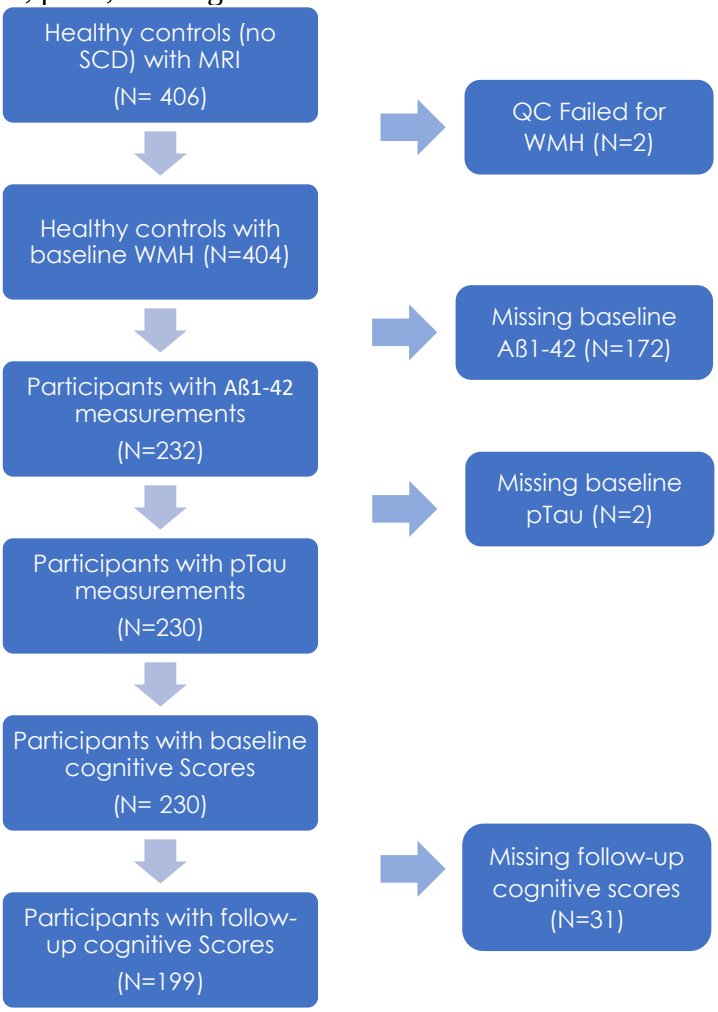
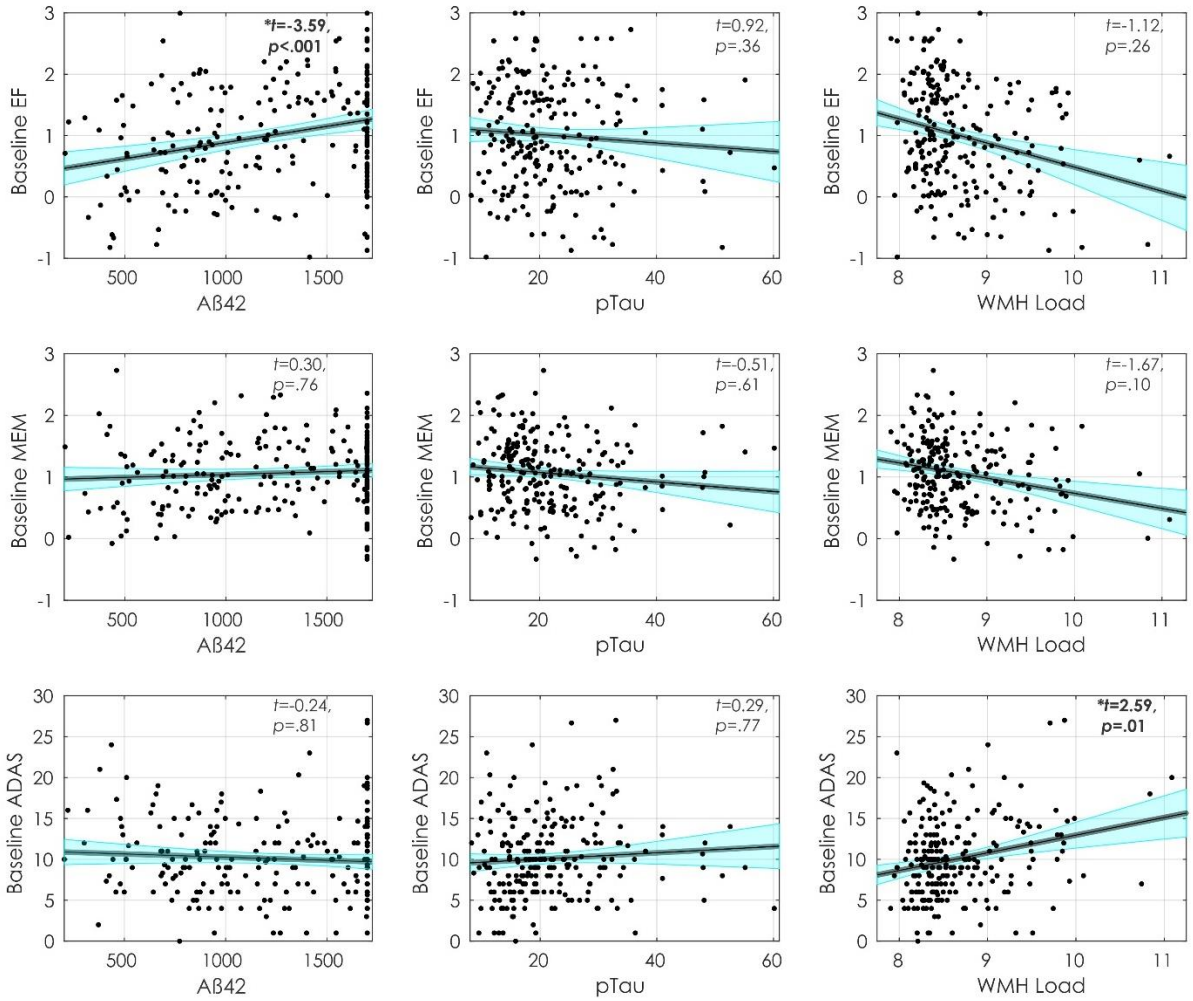


Table 2: Regression model outputs.

Model	ADNI-EF Baseline	ADNI-EF Follow-up	ADNI-MEM Baseline	ADNI-MEM Follow-up	ADAS-13 Baseline	ADAS-13 Follow-up	WMH load	Aß42
Age	**ß= -0.05, *t*= -5.63, *p*<.001***	**ß= -0.01, *t*= -1.99, *p*=.049**	**ß= -0.03, *t*= -4.26, *p*<.001***	ß= -0.001, *t*= -0.19, *p*=.85	**ß=0.11, *t*=2.04, *p*=.042**	ß= -0.001, *t*= -0.01, *p*=0.99	**ß=0.03, *t*=5.03, *p*<.001***	ß= -6.25, *t*= -1.29, *p*=.20
Sex	ß=0.05, *t*=0.53, *p*=.60	**ß= -0.18, *t*= -2.22, *p*= .027**	**ß= -0.26, *t*= -3.56 *p*<.001***	**ß= -0.13, *t*= -2.21, *p*=.028**	**ß=1.50, *t*=2.39, *p*=.018**	ß= -0.17, *t*= -0.32, *p*=.75	ß= -0.02, *t*= -0.23, *p*=.82	ß=54.17, *t*=0.89, *p*=.37
Education	**ß=0.06, *t*=2.95, *p*=.003***	**ß=0.07, *t*=4.39, *p*<.001***	**ß=0.04, *t*=2.81, *p*=.005***	**ß= 0.02, *t*= 1.97, *p*=.050**	ß= -0.12, *t*= -0.99, *p*=.32	ß=0.03, *t*=0.29, *p*=.77	----	----
WMH load	ß= -0.11, *t*= -1.12, *p*=.26	**ß= -0.22, *t*= -2.84, *p*=.005***	ß= -0.12, *t*= -1.67, *p*=.096	ß= -0.10, *t*= -1.76, *p*=.081	**ß=1.59, *t*=2.59, *p*=.01***	ß=0.89, *t*=1.76, *p*=.080	----	----
Aß42	**ß=0.001, *t*=3.58, *p*<.001***	ß=0.001, *t*=1.05, *p*= .30	ß=0.001, *t*=0.30, *p*=.76	ß= 0.001, *t*= 1.18 *p*=.24	ß= -0.001, *t*= -0.24, *p*=.81	ß=-0.001, *t*=0.09, *p*=.93	**ß= -0.001, *t*= -4.20, *p*<.001***	----
pTau	ß=0.005, *t*=0.92, *p*=.35	ß= -0.003, *t*= -0.84, *p*=.40	ß= -0.002, *t*= -0.51, *p*=.61	ß= -0.003, *t*= -0.94, *p*=.35	ß=0.01, *t*=0.29, *p*=.76	ß=0.02, *t*=0.72, *p*=.47	ß=0.001, *t*=0.32, *p*=.75	ß=1.76, *t*=0.51, *p*=.61
Cognitive score at baseline	----	**ß= 0.65, *t*= 12.38, *p*<.001***	----	**ß=0.75, *t*=14.28, *p*<.001***	----	**ß=0.68 *t*=11.66, *p*<.001***	----	----

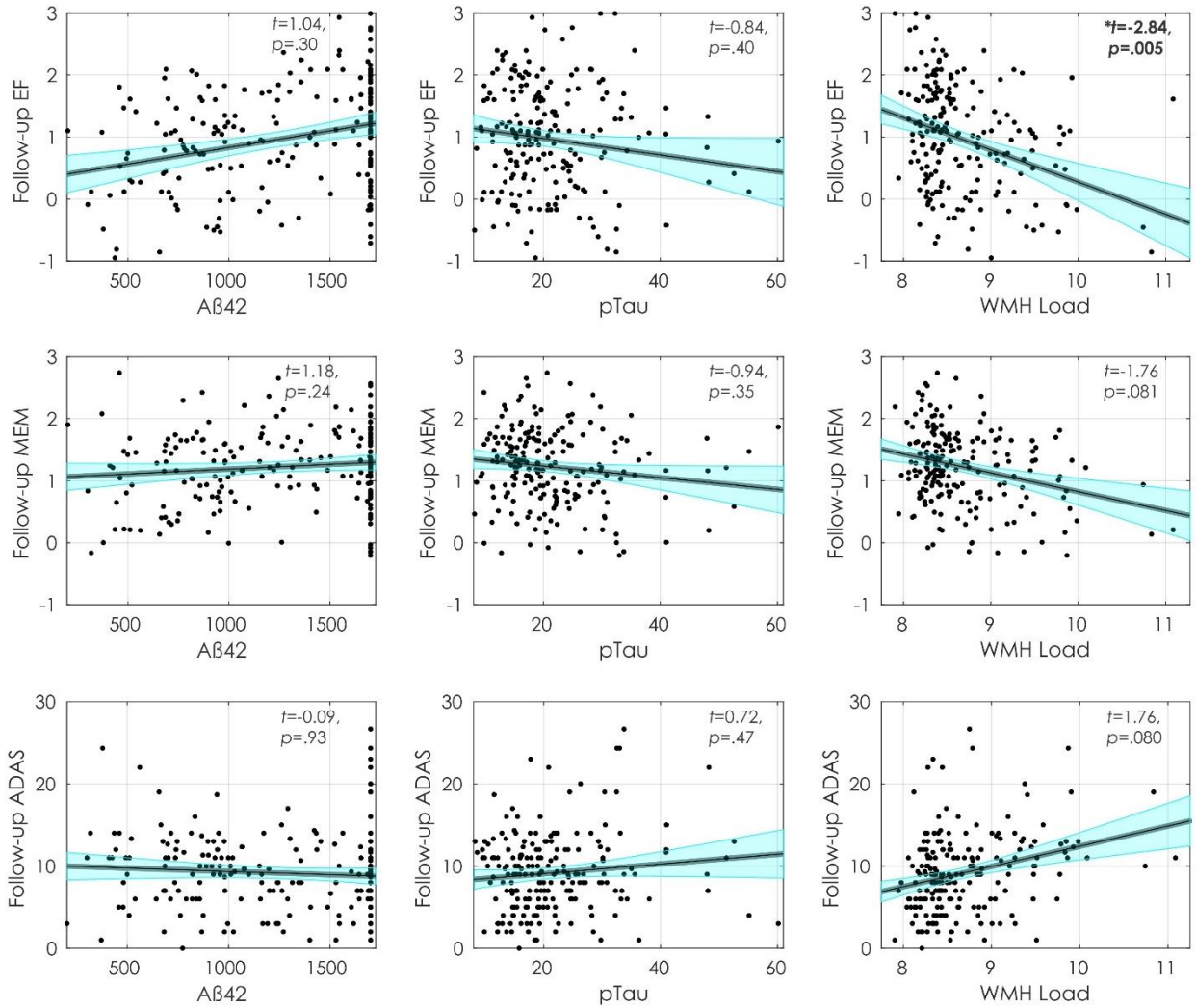
Notes: Significant results are shown in bold. *= results that were significant after false discovery rate correction for multiple comparisons. Abbreviations: ADAS-13, Alzheimer's Disease Assessment Scale-13; WMH, White matter hyperintensity.

Figure 2: Baseline cognitive scores and their relationship with Aß42, pTau and WMH load.



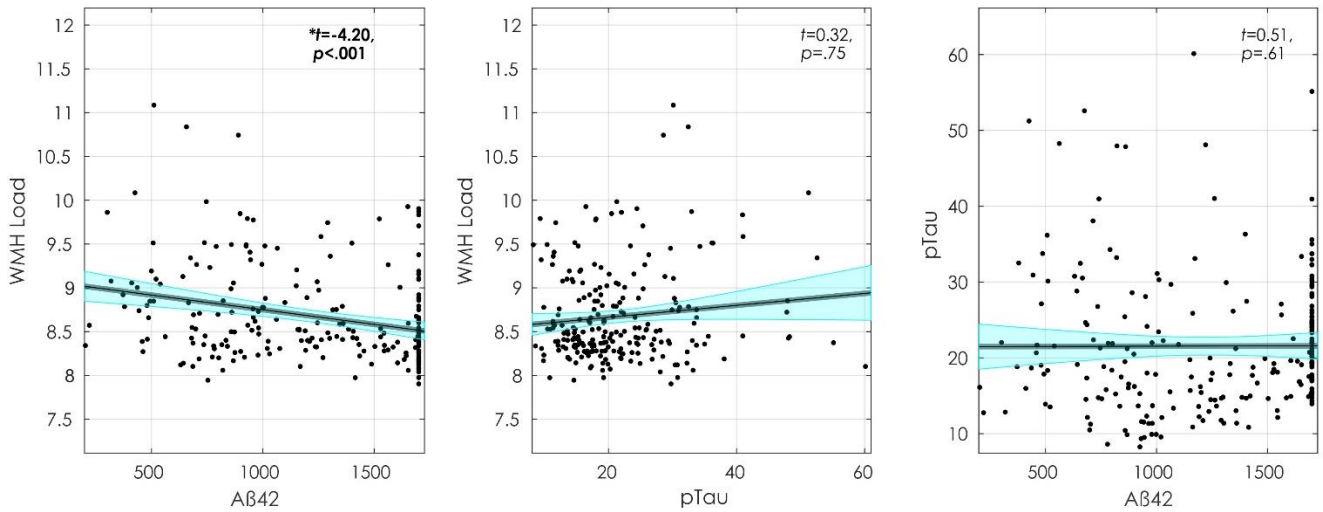
Figures show baseline executive functioning (first row), memory (second row) and ADAS-13 (third row) scores and their association with Aß42 (first column), pTau (Second column), and WMH Load (third column). Abbreviations: EF, executive functioning; MEM, memory; ADAS, Alzheimer's Disease Assessment Scale; WMH, white matter hyperintensity.

Figure 3: Follow-up cognitive scores and their relationship with Aß42, pTau and WMH load.



Figures show follow-up executive functioning (first row), memory (second row) and ADAS-13 (third row) scores and their association with Aß42 (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 WMH load, Aß42, and pTau.



Figures show, from left to right, WMH association with Aß42, WMH association with pTau, and pTau association with Aß42. Abbreviations: WMH, white matter hyperintensity.

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