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Original Research

Anxiety and Depressive Symptoms and Cortical Amyloid-β Burden in Cognitively Unimpaired Older Adults

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Abstract

BACKGROUND: There is evidence of relationships between behavioral symptoms and increased risk for Alzheimer's Disease and/or Alzheimer's Disease biomarkers. However, the nature of this relationship is currently unknown.

OBJECTIVES: To evaluate the relationship between anxiety and depressive symptoms and amyloid-β deposition in cognitively unimpaired older adults, and to assess mediating effects of either objective or subjective cognitive skills.

DESIGN: Cross-sectional analysis of screening data from participants enrolled in the Anti-Amyloid Treatment in Asymptomatic Alzheimer Disease (A4) Study (ClinicalTrials.gov Identifier: NCT02008357).

SETTING: Data analysis.

PARTICIPANTS: 4492 cognitively unimpaired adults, age 65-85, enrolled in the Anti-Amyloid Treatment in Asymptomatic Alzheimer Disease (A4) Study.

MEASUREMENTS: We used linear regression to estimate the associations between amyloid-β standard uptake value ratio (SUVR) and Geriatric Depression Scale (GDS) and State Trait Anxiety Inventory (STAI) scores while adjusting for potential confounding factors as well as for Cognitive Function Index (CFI) or Preclinical Alzheimer's Cognitive Composite (PACC) scores as possible mediational variables.

RESULTS: 4399 subjects with complete covariates were included (mean age: 71.3, 59% female), GDS ranged 0-13 (mean: 1.0), and STAI ranged 6-24 (mean: 9.9). Amyloid-β SUVR was modestly associated with STAI; mean STAI score was estimated to be 0.275 points higher (95% CI: 0.038, 0.526; p-value = 0.023) for each 0.5-point increase in cortical amyloid-β SUVR. Subjective cognitive decline (CFI) attenuated the relationship between SUVR and STAI, while objective cognitive function (PACC) did not. No statistically significant relationship between SUVR and GDS was observed (p = 0.326).

CONCLUSIONS: In cognitively unimpaired adults with low levels of depression and anxiety, cortical amyloid-β deposition is associated with anxiety but not depressive symptoms. Attenuation of this relationship by subjective cognitive difficulties suggests that anxiety may be partly due to such a perception resulting from cortical amyloid-β deposition.

Key words: Amyloid-β, depression, anxiety.

Introduction

Alzheimer's disease (AD) features a long preclinical stage in which the pathophysiological process progresses without overt decline in cognitive or functional skills. This preclinical phase is defined by increased amyloid-β burden, which can be detected by positron emission tomography (PET) imaging (1). While symptoms of episodic memory decline have been studied most in early AD, neuropsychiatric symptoms (NPS) such as apathy, depression, and anxiety may also represent the initial clinical presentation of the AD process (2, 3). The Mild Behavioral Impairment syndrome was developed to define the psychiatric and non-cognitive behavioral symptoms that may occur before the onset of memory and function impairment (2).

There is evidence of relationships between behavioral symptoms and increased risk for AD and/or AD biomarkers (4–11). The existing literature seems to support two main hypotheses: 1. early-life depression and anxiety are risk factors for later life neurodegeneration, AD (6, 8, 12) or late-life depression and 2. anxiety and depressive symptoms are an early clinical expression of neurodegeneration (4, 7, 11). It is still debated, however, whether depressive or anxiety symptoms are risk factors or a prodrome of dementia, if these processes are related at all. Singh-Manoux et. al., analyzed data from a 28-year longitudinal cohort study and found no evidence for late-life depression as a risk factor for dementia, concluding that associations between late-life depression and dementia are due to shared etiologies or risks (13). Other evidence suggests that depression may interact with amyloid-β or neurofibrillary tangle burden to promote more rapid cognitive decline in patients with AD (7, 9, 10). Currently, the relationship between anxiety and depressive symptoms and AD pathology is unclear. A better understanding of the relationship between underlying neuropathology and individual psychiatric symptoms could help define the sequence of events in the clinical expression of AD, with implications for improving preventive treatment strategies for AD or late-

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life psychiatric symptoms.

To better understand the relationship between anxiety and depressive symptoms and preclinical AD, marked by amyloid-β deposition, we utilized screening data from the Anti-Amyloid Treatment in Asymptomatic Alzheimer's Disease (A4) Study. The A4 study is a randomized placebo-controlled trial designed to test whether treatment with solanezumab, a monoclonal anti-amyloid antibody, can reduce cognitive decline in older adults with preclinical AD. We investigated the hypothesis that the extent of cortical amyloid-β deposition is positively correlated with severity of depressive and anxiety symptoms in these cognitively unimpaired older adults, prior to randomized treatment. We further investigated the hypothesis that, if present, the above associations are mediated by perceived and objective cognitive decline. Finally, because previous studies have shown that white matter hyperintensities and hippocampal volume on MR images may be associated with mood symptoms or the subsequent development of depressive symptoms (4, 6, 14) we also examined the effect of these measures on the observed relationships in A4 participants with elevated cortical amyloid-β.

Methods

A4 Study and Participants

The A4 study (ClinicalTrials.gov Identifier: NCT02008357) tested the ability of solanezumab treatment to slow the course of cognitive decline in cognitively unimpaired older adults with preclinical AD, as demonstrated by elevated cortical amyloid-β binding on PET imaging. The treatment phase is ongoing for this multisite, randomized, placebo-controlled, 240-week treatment study (15). The study design and measures have been described previously (15, 16). In brief, participants recruited to A4 were between age 65 and 85 inclusive and living independently. The study excluded those with dementia, unstable medical conditions, or substantial depression or anxiety posing possible risk with amyloid-β imaging disclosure, although there were no eligibility cutoff scores on symptom rating instruments (17).

Investigators utilized six screening visits to assess eligibility and collect participant background information. Assessments completed during the screening phase included demographic information, medical history, apolipoprotein ε4 genotype (APOE4), and clinical symptom measures described below. The primary A4 study treatment outcome was the Preclinical Alzheimer Cognitive Composite (PACC) (18), which represents the sum of normalized scores on four component tests: the Mini-Mental State Exam (MMSE), the Digit Symbol Substitution Test, the Logical Memory Delayed Recall Test (LMDR IIa), and the Free and Cued Selective Reminding Test (sum of free and total cued recall; FCSRT). To be eligible for amyloid-β imaging, participants had to have a Clinical Dementia Rating Scale global score of 0, a MMSE score of 25-30, and a LMDR IIa score of 6 to 18. To enroll participants with greater likelihood of elevated cortical amyloid-β and future cognitive decline, the study excluded those with LMDR IIa scores >1.5 SD above age-adjusted norms.

Next, participants underwent PET imaging with ^{18}F-florbetapir to measure cortical amyloid-β binding, as described previously (15, 19). Those with elevated amyloid-β, defined as a standard uptake value ratio SUVR > 1.15 or having SUVR 1.0-1.15 with confirmed expert visual read of elevated amyloid-β, proceeded with MRI and study randomization.

The current work focuses on a subset of 4492 participants in the A4 study who underwent screening ^{18}F-florbetapir PET imaging and had cortical SUVR values. We downloaded the analytic dataset from the LONI site on July 14, 2020. We removed 93 participants with missing covariate values for a final sample size of 4399 in our analyses. Most of the missingness was confined to race/ethnicity (N=61) and comorbidities (N=10).

Study Assessments

Clinical measures

Clinical measures included the PACC cognitive composite score and the Cognitive Function Index (CFI), a 15-item self-rated assessment of perceived decline in cognitive skills over the past year (20). Each CFI item is rated "yes," "no," or "maybe" (scored as 1, 0, and 0.5, respectively; possible total score: 0-15). Depressive symptoms were measured with the Geriatric Depression Scale (GDS) (21), a 15-item measure of mood symptoms experienced over the past week and self-rated as "yes" or "no" (scored as 1 or 0, respectively; possible total score: 0-15). Anxiety symptoms were measured using the state items from the State-Trait Anxiety Scale (STAI) (22), a self-assessment of six current anxiety symptoms, each rated "not at all," "somewhat," "moderately so," or "very much" (scored as 1, 2, 3, or 4, respectively; possible total score: 6-24). Participants completed all clinical assessments prior to amyloid-β PET imaging.

Neuroimaging

^{18}F-florbetapir PET was used to assess mean cortical amyloid-β SUVR in an AD composite that included six regions: frontal cortex, temporal cortex, precuneus, parietal cortex, anterior cingulate, and posterior cingulate (1). SUVR calculations were referenced to the mean activity in the cerebellum. To confirm study eligibility and to provide baseline volumetric data, participants who demonstrated elevated amyloid-β on ^{18}F-florbetapir PET imaging underwent MR imaging. This subset (1238 of the

4399 overall participants with ^{18}F-florbetapir SUVR PET values) was eligible for randomization to solanezumab or placebo.

Statistical Analysis

Descriptive statistics included all 4492 participants who underwent screening and ^{18}F-florbetapir imaging. We summarized continuous covariates by mean (standard deviation) and categorical covariates by count (percent). We stratified the descriptive statistics by low (< 1.15) and high (≥ 1.15) SUVR. Additionally, we examined violin plots of GDS and STAI scores split by SUVR strata of size 0.2. Finally, we fit the following models in the subset of participants (N=4399) with fully observed covariates.

We used linear regression to assess the relationship between amyloid-β deposition SUVR as a continuous variable predictor of interest and GDS and STAI scores as responses. In both models we adjusted for the a priori specified potential confounders of race, ethnicity, gender, age, employment, housing situation, marital status, education level, heavy alcohol use, any smoking use, medical morbidity score, hours of exercise per week, hours of sleep per night, and history of neurological disease. The medical morbidity score was defined as the sum of scores for individual medical illnesses, where we scored individual illnesses as 1, 2, or 3, representing mild, moderate, or severe morbidity, respectively. Heavy alcohol use was defined as drinking an average of 3 or more alcoholic beverages per day. All presented results utilize the robust variance estimator to account for potential deviations from the assumption of homoscedastic errors (23). We presented Wald-based confidence intervals and corresponding p-values for each association of interest.

In our secondary analysis we addressed substantial mood or anxiety symptoms by transforming the continuous responses to binary indicators to assess the difference in the odds of having high versus low test scores. Past literature suggests that a GDS score ≥ 5 is indicative of clinically meaningful depression so we a priori created an indicator for scores of 5 or above (21, 24). There is no standard cut point for the STAI, so we used the sample 75th percentile as the cut-point and created an indicator of a score greater than 12.

To assess if objective (PACC score) or subjective (CFI score) cognitive abilities mediated any association between amyloid-β deposition and depressive or anxiety symptoms, we repeated the previous models while additionally adjusting for these measures and evaluated any changes in the magnitude of the relationship between cortical amyloid-β SUVR and GDS or STAI score.

In exploratory analyses, we investigated if APOE4 status impacted the relationship between cortical amyloid-β SUVR, CFI, and depressive and anxiety symptoms. We fit all models used to assess the relationship with APOE4 with the subset of participants who had non-missing APOE4 values (N=4355). We compared the estimated association between SUVR and GDS and STAI when only adjusting for potential confounding variables, when additionally adjusting for CFI, when additionally adjusting for APOE4, and when adjusting for both CFI and APOE4.

We additionally assessed whether the extent of small-vessel cerebrovascular disease, represented as the total volume of WMH, or hippocampal volume, represented as the hippocampal occupancy score (HOC), mediated the relationship between cortical amyloid-β SUVR and GDS and STAI. The present study utilized MRI measures of hippocampal volume, reflected in the HOC (25), and volume of white matter hypointensities (WMH), as measured on T1- weighted images obtained only in the subset of participants with elevated cortical amyloid-β binding (N=1238), to assess their effects on relationships between ^{18}F-florbetapir SUVR and depression and anxiety symptoms, in an exploratory analysis. We averaged the left and right hemisphere volumes of WMH to obtain a global score. We compared the association between amyloid-β SUVR and GDS and STAI when only adjusting for confounders, also adjusting for WMH, HOC, or adjusting for both WMH and HOC.

As a sensitivity analysis, we repeated the primary analysis of relationships between GDS and STAI scores and amyloid-β SUVR, using amyloid-β SUVR values in two a priori specified cortical regions that are considered most likely related to depressive or anxiety symptoms: the anterior cingulate and the medial orbitofrontal cortex. Additionally, we repeated the linear regression model between SUVR and GDS but omitted the memory item from the total score of the GDS to assess if subjective cognitive decline was driving a relationship between amyloid-β deposition and depression. All analyses were performed using R version 4.0.3.

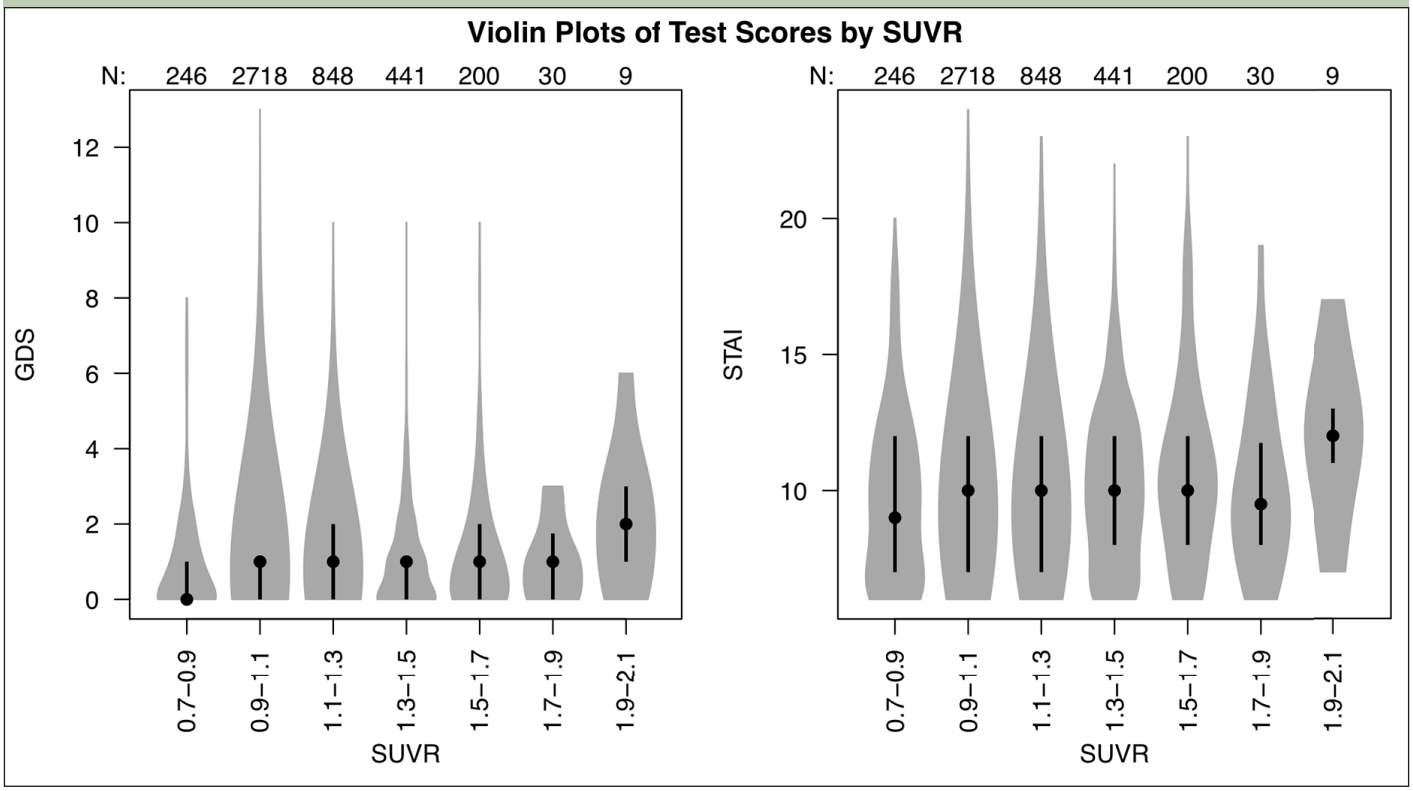
Results

Descriptive statistics stratified by SUVR are reported in Table 1. The mean age of participants was 71.3 years. 88% of participants were non-Hispanic (NH) white, 71% were college educated, and 59% were female. Mean GDS score was 1.03 (SD = 1.47; range: 0-13) and mean STAI score was 9.94 (SD = 3.11, range: 6-24). 147/4492 (3.3%) of participants had a GDS score of at least 5 and 842/4488 (18.8%) participants had an STAI score above 12. Mean cortical amyloid-β SUVR was 1.09; 27.4% of participants had elevated cortical amyloid-β, with SUVR ≥ 1.15. Participants with cortical amyloid-β SUVR ≥ 1.15 were observed to have higher CFI scores (mean of 2.41 versus 1.96) and lower PACC scores (-0.49 versus 0.19). They also were more likely to be older and NH white compared to participants with SUVR < 1.15. Mean GDS scores for those with amyloid-β SUVR ≥ 1.15 and with SUVR < 1.15 were 1.05 and 1.03, respectively; mean STAI scores were 10.06 and 9.90, respectively.

Table 1. Baseline demographics stratified by SUVR. Continuous covariates are summarized by mean (standard deviation; N missing) and categorical variables are summarized by N (%)

	SUVR < 1.15 N = 3261	SUVR ≥ 1.15 N = 1231	Total N = 4492
Race/ethnicity:			
Hispanic	89 (3%)	33 (3%)	122 (3%)
NH White	2835 (87%)	1112 (90%)	3947 (88%)
NH Asian	140 (4%)	29 (2%)	169 (4%)
NH Black	129 (4%)	28 (2%)	157 (3%)
Other	29 (1%)	7 (1%)	36 (1%)
Missing	39 (1%)	22 (2%)	61 (1%)
Gender:			
Female	1938 (59%)	730 (59%)	2668 (59%)
Male	1323 (41%)	501 (41%)	1824 (41%)
Education:			
College	2308 (71%)	886 (72%)	3194 (71%)
Some college	622 (19%)	223 (18%)	845 (19%)
High school	270 (8%)	97 (8%)	367 (8%)
Less than 12 years	57 (2%)	23 (2%)	80 (2%)
Missing	4 (0%)	2 (0%)	6 (0%)
Married:			
No	960 (29%)	362 (29%)	1322 (29%)
Yes	2301 (71%)	869 (71%)	3170 (71%)
Retired:			
No	760 (23%)	264 (21%)	1024 (23%)
Yes	2457 (75%)	948 (77%)	3405 (76%)
Not applicable	43 (1%)	19 (2%)	62 (1%)
Missing	1 (0%)	0 (0%)	1 (0%)
Housing situation:			
Independent	3196 (98%)	1209 (98%)	4405 (98%)
With family	44 (1%)	9 (1%)	53 (1%)
Other	20 (1%)	13 (1%)	33 (1%)
Missing	1 (0%)	0 (0%)	1 (0%)
Heavy alcohol use:			
No	3085 (95%)	1169 (95%)	4254 (95%)
Yes	175 (5%)	61 (5%)	236 (5%)
Missing	1 (0%)	1 (0%)	2 (0%)
Current smoker:			
No	3206 (98%)	1208 (98%)	4414 (98%)
Yes	52 (2%)	23 (2%)	75 (2%)
Missing	3 (0%)	0 (0%)	3 (0%)
Past neuro diagnosis:			
No	2310 (71%)	823 (67%)	3133 (70%)
Yes	942 (29%)	407 (33%)	1349 (30%)
Missing	9 (0%)	1 (0%)	10 (0%)
Continuous covariates			
Comorbidity score	7.06 (5.4; 9)	8.39 (6.2; 1)	7.42 (5.7; 10)
Age (years)	70.89 (4.5; 0)	72.36 (4.9; 0)	71.29 (4.7; 0)
Exercise/week (hr)	2.88 (3.8; 0)	2.93 (3.8; 1)	2.89 (3.8; 1)
Sleep/night (hr)	7.13 (1.1; 0)	7.04 (1.1; 0)	7.10 (1.1; 0)
Avg. WMH	0.46 (0.6; 3114)	0.82 (1.7; 116)	0.78 (1.6; 3230)
HOC	0.76 (0.1; 3114)	0.73 (0.1; 116)	0.73 (0.1; 3230)
CFI	1.96 (2.0; 1)	2.41 (2.2; 1)	2.08 (2.1; 2)
FTP	44.96 (10.8; 1)	44.13 (10.7; 0)	44.73 (10.8; 1)
PACC	0.19 (2.5; 3)	-0.49 (2.7; 0)	0.00 (2.5; 3)

Figure 1. Violin plots of Geriatric Depression Scale (GDS) scores and the state portion of State-Trait Anxiety Inventory (STAI) scores by Standard Uptake Value Ratio (SUVR) strata



The median is marked with a circle and the first and third quartiles are shown with a line inside each violin plot.

The estimated coefficients for the linear regression between SUVR and GDS are shown in Table 2. There was no statistically significant relationship between cortical amyloid-β SUVR and GDS score in either the unadjusted (p-value = 0.236) or the adjusted model (p-value = 0.326). The estimated regression coefficients for models assessing the association between SUVR and STAI are presented in Table 3. The mean STAI score was estimated to be 0.275 points higher (95% CI: 0.038, 0.512; p-value = 0.023) for each 0.5-unit difference in SUVR, when controlling for potential confounding factors. Violin plots of GDS and STAI scores by SUVR are presented in Figure 1, and estimated coefficients in three strata of SUVR levels are included in Tables 2 and 3. There were no substantial changes to the results in the sensitivity analysis that used amyloid-β SUVR values from the anterior cingulate and frontal cortex subregions as predictors of either GDS or STAI scores. The association between SUVR and the GDS score excluding the memory item was also not statistically significant.

The estimates from the logistic regression models of the association between SUVR and having a GDS ≥ 5 and between SUVR and an STAI > 12 were not statistically significant. The odds of having a GDS ≥ 5 were estimated to be 30% lower (95% CI: 0.43, 1.13; p-value = 0.143) for each 0.5-unit difference in SUVR when controlling for potential confounders. The odds of having STAI > 12 were estimated to be 11.4% higher (95% CI: 0.91, 1.36; p-value = 0.287) for each 0.5-unit difference in SUVR when adjusting for confounders. Acknowledging that there is little empiric support for specific GDS and STAI cut off scores, we repeated the logistic regression analyses using a lower threshold for the presence of symptoms, GDS ≥ 3 and STAI ≥ 8. In this post-hoc exploratory analysis, the odds of having a GDS ≥ 3 are estimated to be 14% higher (95% CI: 0.90, 1.45; p-value = 0.285) for each 0.5 unit difference in SUVR when controlling for potential confounders. The odds of having STAI ≥ 8 are estimated to be 32% higher (95% CI: 1.09, 1.59; p-value = 0.004) for each 0.5 unit difference in SUVR when adjusting for confounders.

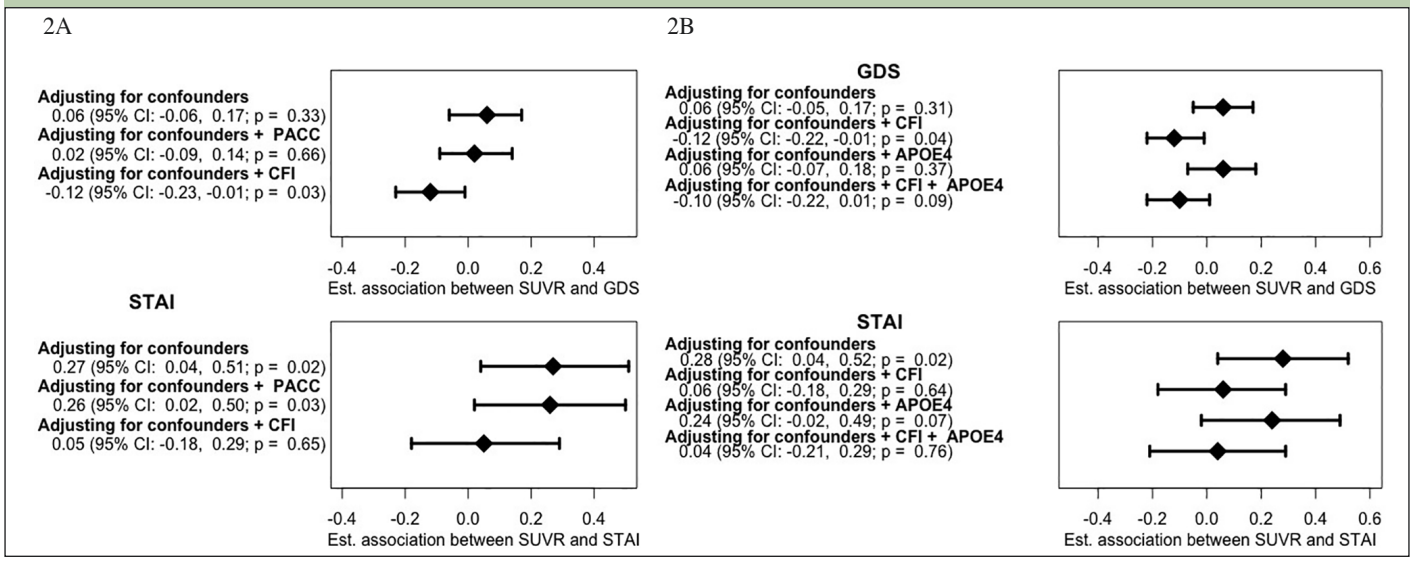
Additional adjustment for CFI, but not PACC, attenuated the relationship between SUVR and STAI (Figure 2A). The estimate of the SUVR effect on STAI decreased from 0.275 points higher when adjusting for potential confounders compared to 0.05 point higher when also adjusting for CFI. Although the association between SUVR and GDS was not statistically significant, there was a small negative association after adjusting for CFI. Adjusting for PACC did not substantially alter the coefficient estimate in either the GDS or STAI model.

To assess if APOE4 status changed relationships among SUVR, CFI, GDS and STAI, we compared models additionally adjusting for APOE4. When studying the 4355 participants who had APOE4 results, adding APOE4 into the models did not qualitatively alter the relationship

Table 2. Coefficient estimates for the linear regression between SUVR and GDS with adjustment variables

	N	Unadj. Est.	Unadjusted CI	Unadj. p-value	Adj. Est	Adjusted CI	Adj. p-value
SUVR (per 0.5 point)	4399	0.068	(-0.045, 0.182)	0.236	0.056	(-0.056, 0.169)	0.326
≤ 0.99	1608	0	-	-	0	-	-
0.99-1.09	1296	-0.013	(-0.122, 0.096)	0.813	0.003	(-0.104, 0.110)	0.959
> 1.09	1495	0	(-0.104, 0.103)	0.992	-0.013	(-0.115, 0.090)	0.805
Race/ethnicity:							
NH White	3921	0	-	-	0	-	-
Hispanic	122	0.358	(0.011, 0.704)	0.043	0.31	(-0.021, 0.642)	0.066
NH Asian	164	0.702	(0.417, 0.988)	<.001	0.69	(0.408, 0.971)	<.001
NH Black	156	0.064	(-0.190, 0.319)	0.619	0.005	(-0.239, 0.248)	0.97
Other	36	-0.07	(-0.468, 0.328)	0.73	-0.113	(-0.512, 0.287)	0.58
Gender:							
Female	2618	0	-	-	0	-	-
Male	1781	0.046	(-0.041, 0.134)	0.296	0.113	(0.023, 0.204)	0.014
Education:							
College	3140	0	-	-	0	-	-
Some college	823	0.008	(-0.098, 0.113)	0.887	-0.012	(-0.118, 0.093)	0.821
High school	360	0.446	(0.251, 0.640)	<.001	0.392	(0.203, 0.582)	<.001
Less than 12 yrs	76	0.094	(-0.281, 0.469)	0.623	0.136	(-0.226, 0.499)	0.461
Married:							
No	1289	0	-	-	0	-	-
Yes	3110	-0.179	(-0.279, -0.080)	<.001	-0.187	(-0.290, -0.085)	<.001
Retired:							
No	996	0	-	-	0	-	-
Yes	3342	-0.061	(-0.170, 0.048)	0.271	-0.073	(-0.184, 0.038)	0.2
Not applicable	61	0.261	(-0.136, 0.658)	0.198	0.16	(-0.228, 0.549)	0.419
Housing situation:							
Independent	4316	0	-	-	0	-	-
With family	51	0.352	(-0.101, 0.806)	0.128	0.223	(-0.222, 0.668)	0.326
Other	32	0.042	(-0.401, 0.486)	0.852	-0.135	(-0.572, 0.302)	0.544
Heavy alcohol use:							
No	4168	0	-	-	0	-	-
Yes	231	0.157	(-0.048, 0.362)	0.133	0.123	(-0.083, 0.329)	0.242
Current smoker:							
No	4325	0	-	-	0	-	-
Yes	74	0.662	(0.212, 1.112)	0.004	0.464	(0.035, 0.892)	0.034
Past neuro dx:							
No	3072	0	-	-	0	-	-
Yes	1327	0.294	(0.194, 0.394)	<.001	0.259	(0.157, 0.362)	<.001
Continuous covariates							
Comorbidity score	4399	0.024	(0.015, 0.033)	<.001	0.02	(0.011, 0.030)	<.001
Age (per 10 years)	4399	0.093	(0.002, 0.185)	0.046	0.024	(-0.070, 0.118)	0.618
Exercise (hr/week)	4399	-0.035	(-0.047, -0.022)	<.001	-0.031	(-0.043, -0.019)	<.001
Sleep (hr/night)	4399	-0.064	(-0.112, -0.016)	0.01	-0.043	(-0.091, 0.005)	0.082

Figure 2. 2A. Forest plots of the estimated association between the standardized uptake value ratio (SUVR) and the Geriatric Depression Scale (GDS) or the state portion of State-Trait Anxiety Inventory (STAI) when including different adjustment variables to assess possible mediation of cognition; 2B. Forest plots of the estimated associations between the standardized uptake value ratio (SUVR) and the Geriatric Depression Scale (GDS) or the state portion of State-Trait Anxiety Inventory (STAI) when adjusting for CFI, apolipoprotein ε4 (APOE4), neither, or both. All models are fit with the 4355 participants who had APOE4 status collected



between SUVR and GDS or STAI whether or not CFI was included (Figure 2B).

When comparing models fit on the subset of 1238 participants with elevated cortical amyloid-β, including HOC and/or WMH did not impact the relationship between SUVR and STAI or between SUVR and GDS. In the subset of elevated amyloid-β participants, the mean STAI score was estimated to be 0.47 points higher (95% CI: 0.01, 0.92; p-value = 0.04) for each 0.5-unit difference in SUVR, when controlling for potential confounding factors. A trend relationship was found between GDS and SUVR where the mean GDS score was estimated to be 0.21 points higher (95% CI: -0.01, 0.42; p = 0.06) for each 0.5-unit difference in SUVR, when controlling for potential confounding factor.

Discussion

We evaluated the relationships between the extent of cortical amyloid-β deposition and depressive and anxiety symptoms in cognitively unimpaired older adults with low levels of depression and anxiety. Increased amyloid-β burden was modestly associated with increased STAI scores. This finding is consistent with other studies that demonstrated a relationship between elevated amyloid-β levels and increased anxiety symptoms (4, 7, 11) and supports the MBI concept, with anxiety as a potential early correlate of cortical amyloid-β deposition. The range of possible STAI values is from 6 to 24 (sample mean: 9.9); an STAI score of 6 represents no anxiety symptoms. Although the magnitude of the regression coefficient linking amyloid-β to STAI score is small (0.275), it corresponds to 7% of the mean STAI score of the sample, when adjusted for the minimum possible STAI score. The magnitude of the relationship between STAI and SUVR is slightly larger (0.47) in the subset of participants with elevated amyloid-β. The extent of association overall in our study was similar to that seen by Krell-Roesch et al. in a recent study that included both cognitively unimpaired and MCI participants, using PIB PET amyloid imaging and Beck Anxiety Inventory total scores, although in that study the relationship in the cognitively unimpaired subsample was not significant (26). To provide additional context from our study, the association is similar in magnitude to the association between a one-hour decline of sleep per night and STAI score in this study (0.281), but less than the effect of sex (0.685). Having a history of smoking or a past neurological diagnosis also has an association of similar magnitude. The effect demonstrated here did not extend to those with clinically substantial STAI scores, given that no relationship was found in our logistic regression model with STAI > 12 defining clinically meaningful anxiety symptoms. Prior studies have also indicated that associations between amyloid-β and anxiety are modest, and also have noted low depression and anxiety levels in their community samples (11). When we reduced the STAI cutoff score to >8 for the presence of anxiety symptoms (indicating scores of "somewhat" or more on at least two STAI items, such as "I felt upset" or "I was worried"), higher amyloid SUVR was associated with an increased likelihood of anxiety symptoms. This supports our finding from the analysis with anxiety included as a continuous variable, indicates that mild anxiety symptoms are associated with higher cortical amyloid, and suggests that cognitively

Table 3. Coefficient estimates for the linear regression between SUVR and STAI with adjustment variables

	N	Unadj. Est.	Unadjusted CI	Unadj. p-value	Adj. Est	Adjusted CI	Adj. p-value
SUVR (per 0.5 point)	4399	0.347	(0.110, 0.584)	0.004	0.275	(0.038, 0.512)	0.023
≤ 0.99	1608	0	-	-	0	-	-
0.99-1.09	1296	0.179	(-0.048, 0.407)	0.123	0.171	(-0.054, 0.396)	0.137
> 1.09	1495	0.222	(0.003, 0.441)	0.046	0.149	(-0.067, 0.366)	0.176
Race/ethnicity:							
NH White	3921	0	-	-	0	-	-
Hispanic	122	-0.317	(-0.914, 0.280)	0.299	-0.410	(-0.976, 0.155)	0.155
NH Asian	164	0.646	(0.177, 1.115)	0.007	0.752	(0.265, 1.238)	0.002
NH Black	156	-0.446	(-0.987, 0.095)	0.106	-0.653	(-1.180, -0.126)	0.015
Other	36	-0.273	(-1.246, 0.700)	0.582	-0.348	(-1.233, 0.536)	0.440
Gender:							
Female	2618	0	-	-	0	-	-
Male	1781	-0.625	(-0.807, -0.443)	<.001	-0.685	(-0.879, -0.492)	<.001
Education:							
College	3140	0	-	-	0	-	-
Some college	823	-0.197	(-0.435, 0.041)	0.105	-0.312	(-0.547, -0.076)	0.010
High school	360	0.420	(0.060, 0.779)	0.022	0.253	(-0.103, 0.609)	0.163
Less than 12 yrs	76	-0.286	(-1.067, 0.494)	0.472	-0.430	(-1.189, 0.330)	0.268
Married:							
No	1289	0	-	-	0	-	-
Yes	3110	-0.111	(-0.316, 0.094)	0.287	0.092	(-0.119, 0.303)	0.393
Retired:							
No	996	0	-	-	0	-	-
Yes	3342	-0.424	(-0.639, -0.210)	<.001	-0.484	(-0.701, -0.266)	<.001
Not applicable	61	0.668	(-0.234, 1.570)	0.147	0.237	(-0.670, 1.144)	0.608
Housing situation:							
Independent	4316	0	-	-	0	-	-
With family	51	0.309	(-0.567, 1.185)	0.489	0.194	(-0.661, 1.050)	0.656
Other	32	0.980	(-0.347, 2.307)	0.148	0.829	(-0.532, 2.189)	0.233
Heavy alcohol use:							
No	4168	0	-	-	0	-	-
Yes	231	-0.084	(-0.501, 0.333)	0.693	0.044	(-0.368, 0.456)	0.835
Current smoker:							
No	4325	0	-	-	0	-	-
Yes	74	0.270	(-0.531, 1.072)	0.508	0.218	(-0.570, 1.007)	0.587
Past neuro dx:							
No	3072	0	-	-	0	-	-
Yes	1327	0.375	(0.176, 0.575)	<.001	0.283	(0.080, 0.486)	0.006
Continuous covariates							
Comorbidity score	4399	0.041	(0.025, 0.057)	<.001	0.034	(0.017, 0.050)	<.001
Age (per 10 years)	4399	-0.067	(-0.262, 0.127)	0.496	0.010	(-0.190, 0.210)	0.923
Exercise (hr/week)	4399	-0.039	(-0.063, -0.014)	0.002	-0.027	(-0.051, -0.003)	0.027
Sleep (hr/night)	4399	-0.276	(-0.366, -0.185)	<.001	-0.281	(-0.370, -0.191)	<.001

unimpaired older adults with mild anxiety symptoms may represent an enriched group in the screening process to identify those with preclinical AD.

Our analysis found that participants with higher cortical amyloid-β had higher CFI scores (Table 1) as seen previously (15, 27) and additionally demonstrated that CFI score attenuated the relationship between amyloid-β and anxiety symptoms, suggesting that anxiety symptoms might be partly due to concern for perceived cognitive decline or a direct consequence of cortical amyloid-β deposition. Alternatively, anxiety symptoms may contribute to the perception of cognitive decline. In contrast, objective cognitive performance, assessed by PACC score, did not impact the relationship between amyloid-β and STAI score. Notably, Pietrazk et. al. found that healthy older adults with elevated amyloid-β and elevated anxiety symptoms experienced greater cognitive decline over time compared to their counterparts without anxiety symptoms, suggesting that anxiety interacts with cortical amyloid-β, accelerating the decline in cognitive function (7). Our study did not assess change in cognitive functioning over time and cannot discern if anxiety symptoms are an expression of subjective cognitive complaints resulting from cortical amyloid-β, if amyloid-β deposition independently drives both anxiety symptoms and subjective cognitive impairment, or if anxiety symptoms are promoting amyloid-β deposition in AD.

Our results also suggest that the relationship between amyloid-β and anxiety symptoms are independent of APOE4 genotype. Presence of one or more APOE4 alleles is an important risk factor for the early development of AD and carrier status is associated with elevated amyloid-β deposition in the preclinical state and earlier age of onset of memory decline (15, 28, 29). The results of the present study indicate that the link between cortical amyloid-β deposition and anxiety symptoms is not mediated by APOE4 allele status.

In the subset of participants with elevated amyloid-β who subsequently underwent MRI imaging in the A4 screening process, neither hippocampal volume nor the extent of subcortical white matter hypointensities on T1-weighted images impacted the observed relationship between amyloid-β and anxiety symptoms. However, the extent of T1 white matter hypointensities in this sample, thought to represent small-vessel cerebrovascular disease, was generally mild. It is also possible that the low levels of anxiety and depression in this sample partially masked an effect of cerebrovascular disease or hippocampal atrophy on the relationship between cortical amyloid-β and anxiety symptoms. These findings, however, suggest that while microvascular disease or hippocampal atrophy may contribute to or be a consequence of depression or anxiety over the lifespan, they do not appear to be a significant driving factor linking the AD process to the expression of anxiety symptoms.

Our analysis did not find a significant relationship between cortical amyloid-β deposition and depressive symptoms. Interestingly, in this subset of participants with elevated amyloid-β, we did observe a trend relationship between GDS and SUVR, but it did not reach the threshold of significance and was small in clinical magnitude. This is consistent with existing literature demonstrating either non-significant (4, 7), or small (11, 30, 31) relationships between depression and AD biomarkers. The lack of an observed relationship between depressive symptoms and amyloid-β may be due to low GDS scores among this self-selecting study population of older adults with unique willingness to participate in clinical trial therapy. Additionally, the GDS scale was developed as a screening tool for clinical depression and may not be adequately sensitive to mild depressive symptoms. Furthermore, the study excluded participants with a history of major depressive disorder within the past two years, possibly further contributing to the low level of depression in the sample. Surprisingly, after adjusting for CFI there was a small negative association between amyloid-β deposition and depressive symptoms. We would not expect amyloid-β to be protective against depression for groups of participants with similar subjective memory decline. Such a finding warrants replication in future studies for confirmation and to further develop its basis.

While this analysis benefited from a large sample with carefully defined inclusion/exclusion criteria and detailed assessments, there are limitations. Our analysis is observational in nature and cross-sectional. Therefore, we cannot conclude a causal relationship between amyloid-β and anxiety symptoms nor how this relationship may change over AD progression. As additional findings from the A4 trial emerge, however, future analyses may be able to explore these questions. We have adjusted for variables identified a priori as potential confounders, but we could not account for unmeasured potential confounding factors such as income level, psychological characteristics, or history of cerebrovascular disease, major depressive disorder, or major psychiatric conditions in our analysis. Moreover, we were unable to assess relationships between cortical amyloid-β deposition and other important NPS such as apathy or irritability that may occur early in AD. In addition, the goal of this study was to address relationships between two current individual neuropsychiatric symptoms, depression and anxiety, and cortical amyloid-β deposition, rather than a broad range of more-enduring psychiatric symptoms such as those included in the MBI construct and the MBI-Checklist. Studies evaluating relationships between individual neuropsychiatric symptoms and AD biomarkers interrogate brain-behavior relationships differently from studies evaluating broader symptom clusters over time. The MBI-Checklist can address overall neuropsychiatric symptoms or five symptom classes using the domain subscores and can identify the overall MBI syndrome. However, measures of individual symptoms can help

define more specific relationships cross-sectionally or over time, and the MBI-Checklist cannot distinguish some individual symptoms such as anxiety and depression because they are scored in the same domain. Finally, the generalizability of our results is limited by inclusion of a relatively homogenous sample of participants with a unique willingness to participate in a treatment clinical trial and relatively low rates of depression compared to the larger population.

Despite these limitations, this study demonstrates in a large sample of cognitively healthy older adults that amyloid-β deposition is associated with increased anxiety symptoms, and that this relationship is attenuated by subjective cognitive difficulties. The study contributes to a growing understanding of NPS in early AD and the interacting pathophysiological pathways that may underlie their expression. Further studies investigating the progression of AD and NPS in this population will further elucidate the complex relationships among amyloid-β deposition, other specific pathologies, NPS, and cognitive decline in the AD process.

Author Contributions: Catriona Lewis, Olivia Bernstein, and David Sultzer conceived of the presented idea and designed the study. Olivia Bernstein and Daniel Gillen designed and executed the statistical analysis. All authors analyzed the data and contributed to the interpretation of the results. Catriona Lewis and Olivia Bernstein wrote the manuscript and designed the figures with significant input and feedback from Joshua Grill, Daniel Gillen, and David Sultzer.

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References

1. Johnson KA, Sperling RA, Gidicsin CM, et al. Florbetapir (F18-AV-45) PET to assess amyloid burden in Alzheimer's disease dementia, mild cognitive impairment, and normal aging. Alzheimers Dement. 2013;9(5S):S72-S83. doi:10.1016/j.jalz.2012.10.007
2. Ismail Z, Smith EE, Geda Y, et al. Neuropsychiatric symptoms as early manifestations of emergent dementia: Provisional diagnostic criteria for mild behavioral impairment. Alzheimers Dement. 2016;12(2):195-202. doi:10.1016/j.jalz.2015.05.017
3. Creese B, Brooker H, Ismail Z, et al. Mild behavioral impairment as a marker of cognitive decline in cognitively normal older adults. Am J Geriatr Psychiatry. 2019;27(8):823-834. doi:10.1016/j.jagp.2019.01.215
4. Banning LCP, Ramakers IHGB, Köhler S, et al. The association between biomarkers and neuropsychiatric symptoms across the Alzheimer's disease spectrum. Am J Geriatr Psychiatry. 2020;28(7):735-744. doi:10.1016/j.jagp.2020.01.012
5. Zhao Q-F, Tan L, Wang H-F, et al. The prevalence of neuropsychiatric symptoms in Alzheimer's disease: Systematic review and meta-analysis. J Affect Disord. 2016;190:264-271. doi:10.1016/j.jad.2015.09.069
6. Bennett S, Thomas AJ. Depression and dementia: cause, consequence or coincidence? Maturitas. 2014;79(2):184-190. doi:10.1016/j.maturitas.2014.05.009
7. Pietrzak RH, Lim YY, Neumeister A, et al. Amyloid-β, anxiety, and cognitive decline in preclinical Alzheimer Disease: A multicenter, prospective cohort study. JAMA Psychiatry. 2015;72(3):284. doi:10.1001/jamapsychiatry.2014.2476
8. Kim HK, Nunes PV, Oliveira KC, Young LT, Lafer B. Neuropathological relationship between major depression and dementia: a hypothetical model and review. Prog Neuropsychopharmacol Biol Psychiatry. 2016;67:51-57. doi:10.1016/j.pnpbp.2016.01.008
9. Babulal GM, Chen S, Williams MM, et al. Depression and Alzheimer's disease biomarkers predict driving decline. J Alzheimers Dis. 2018;66(3):1213-1221. doi:10.3233/JAD-180564
10. Ehrenberg AJ, Suemoto CK, França Resende E de P, et al. Neuropathologic correlates of psychiatric symptoms in Alzheimer's disease. J Alzheimers Dis. 2018;66(1):115-126. doi:10.3233/JAD-180688
11. Krell-Roesch J, Lowe VJ, Neureiter J, et al. Depressive and anxiety symptoms and cortical amyloid deposition among cognitively normal elderly persons: The Mayo Clinic Study of Aging. Int Psychogeriatr. 2018;30(2):245-251. doi:10.1017/S1041610217002368
12. Ownby RL, Crocco E, Acevedo A, John V, Loewenstein D. Depression and risk for Alzheimer disease: Systematic review, meta-analysis, and metaregression analysis. Arch Gen Psychiatry. 2006;63(5):530. doi:10.1001/archpsyc.63.5.530
13. Singh-Manoux A, Dugravot A, Fournier A, et al. Trajectories of depressive symptoms before diagnosis of dementia. JAMA Psychiatry. 2017;74(7):712-718. doi:10.1001/jamapsychiatry.2017.0660
14. Teodorczuk A, O'Brien JT, Firbank MJ, et al. White matter changes and late-life depressive symptoms: Longitudinal study. Br J Psychiatry. 2007;191(3):212-217. doi:10.1192/bjp.bp.107.036756
15. Sperling RA, Donohue MC, Raman R, et al. Association of factors with elevated amyloid burden in clinically normal older individuals. JAMA Neurol. 2020;77(6):735. doi:10.1001/jamaneurol.2020.0387
16. Sperling RA, Rentz DM, Johnson KA, et al. The A4 study: Stopping AD before symptoms begin? Sci Transl Med. 2014;6(228):228fs13. doi:10.1126/scitranslmed.3007941
17. Grill JD, Raman R, Ernstrom K, et al. Short-term psychological outcomes of disclosing amyloid imaging results to research participants who do not have cognitive impairment. JAMA Neurol. 2020;77(12):1504. doi:10.1001/jamaneurol.2020.2734
18. Mormino EC, Papp KV, Rentz DM, et al. Early and late change on the preclinical Alzheimer's cognitive composite in clinically normal older individuals with elevated amyloid β. Alzheimers Dement J Alzheimers Assoc. 2017;13(9):1004-1012. doi:10.1016/j.jalz.2017.01.018
19. Pontecorvo MJ, Arora AK, Devine M, et al. Quantitation of PET signal as an adjunct to visual interpretation of florbetapir imaging. Eur J Nucl Med Mol Imaging. 2017;44(5):825-837. doi:10.1007/s00259-016-3601-4
20. Amariglio RE, Donohue MC, Marshall GA, et al. Tracking early decline in cognitive function in older individuals at risk for Alzheimer disease dementia: The Alzheimer's disease cooperative study cognitive function instrument. JAMA Neurol. 2015;72(4):446. doi:10.1001/jamaneurol.2014.3375
21. Yesavage JA, Sheikh JI. Geriatric depression scale (GDS): recent evidence and development of a shorter version. Clin Gerontol. 1986;5(1-2):165-173. doi:10.1300/J018v05n01_09
22. Marteau TM, Bekker H. The development of a six-item short-form of the state scale of the Spielberger State—Trait Anxiety Inventory (STAI). Br J Clin Psychol. 1992;31(3):301-306. doi:https://doi.org/10.1111/j.2044-8260.1992.tb00997.x
23. White H. A heteroskedasticity-consistent covariance matrix estimator and a direct test for heteroskedasticity. Econometrica. 1980;48(4):817-838. doi:10.2307/1912934

24. Lyness JM. Screening for depression in elderly primary care patients: A comparison of the Center for Epidemiologic Studies-Depression Scale and the Geriatric Depression Scale. Arch Intern Med. 1997;157(4):449-454. doi:10.1001/archinte.157.4.449
25. Heister D, Brewer JB, Magda S, Blennow K, McEvoy LK. Predicting MCI outcome with clinically available MRI and CSF biomarkers. Neurology. 2011;77(17):1619-1628. doi:10.1212/WNL.0b013e3182343314
26. Krell-Roesch J, Syrjanen JA, Rakusa M, et al. Association of cortical and subcortical β-amyloid with standardized measures of depressive and anxiety symptoms in adults without dementia. J Neuropsychiatry Clin Neurosci. 2021;33(1):64-71. doi:10.1176/appi.neuropsych.20050103
27. Amariglio RE, Sikkes SAM, Marshall GA, et al. Item-level investigation of participant and study partner report on the cognitive function index from the A4 Study screening data. J Prev Alzheimers Dis. Published online 2021:1-6. doi:10.14283/jpad.2021.8
28. Corder EH, Saunders AM, Strittmatter WJ, et al. Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. Science. 1993;261(5123):921-923. doi:10.1126/science.8346443
29. Lim YY, Kalinowski P, Pietrzak RH, et al. Association of β-amyloid and apolipoprotein E ε4 with memory decline in preclinical Alzheimer disease. JAMA Neurol. 2018;75(4):488. doi:10.1001/jamaneurol.2017.4325
30. Harrington KD, Gould E, Lim YY, et al. Amyloid burden and incident depressive symptoms in cognitively normal older adults: Amyloid burden and depressive symptoms. Int J Geriatr Psychiatry. 2017;32(4):455-463. doi:10.1002/gps.4489
31. Krell-Roesch J, Syrjanen JA, Mielke MM, et al. Association between neuropsychiatric symptoms and functional change in older non-demented adults: Mayo Clinic Study of Aging. J Alzheimers Dis JAD. 2020;78(3):911-917. doi:10.3233/JAD-200764

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