*Journal of the International Neuropsychological Society* (2023), 1–15
doi:10.1017/S135561772300070X

## Research Article

# Alzheimer disease biomarkers are associated with decline in subjective memory, attention, and spatial navigation ability in clinically normal adults

Taylor F. Levine[1], Steven J. Dessenberger[1], Samantha L. Allison[2], Denise Head[1,3,4] and the Alzheimer's Disease Neuroimaging Initiative*

[1]Department of Psychological and Brain Sciences, Washington University, St. Louis, MO, USA, [2]Neurosciences Institute at Intermountain Medical Center, Murray, UT, USA, [3]Charles F. and Joanna Knight Alzheimer Disease Research Center, Washington University, St. Louis, MO, USA and [4]Department of Radiology, Washington University School of Medicine, St. Louis, MO, USA

### Abstract

**Objective:** Subtle changes in memory, attention, and spatial navigation abilities have been associated with preclinical Alzheimer disease (AD). The current study examined whether baseline AD biomarkers are associated with self- and informant-reported decline in memory, attention, and spatial navigation. **Method:** Clinically normal (Clinical Dementia Rating Scale (CDR®) = 0) adults aged 56–93 ($N = 320$) and their informants completed the memory, divided attention, and visuospatial abilities (which assesses spatial navigation) subsections of the Everyday Cognition Scale (ECog) annually for an average of 4 years. Biomarker data was collected within (±) 2 years of baseline (i.e., cerebrospinal fluid (CSF) p-tau$_{181}$/A$\beta_{42}$ ratio and hippocampal volume). Clinical progression was defined as CDR > 0 at time of final available ECog. **Results:** Self- and informant-reported memory, attention, and spatial navigation significantly declined over time ($ps < .001$). Baseline AD biomarkers were significantly associated with self- and informant-reported decline in cognitive ability ($ps < .030$), with the exception of p-tau$_{181}$/A$\beta_{42}$ ratio and self-reported attention ($p = .364$). Clinical progression did not significantly moderate the relationship between AD biomarkers and decline in self- or informant-reported cognitive ability ($ps > .062$). Post-hoc analyses indicated that biomarker burden was also associated with self- and informant-reported decline in total ECog ($ps < .002$), and again clinical progression did not significantly moderate these relationships ($ps > .299$). **Conclusions:** AD biomarkers at baseline may indicate risk of decline in self- and informant-reported change in memory, attention, and spatial navigation ability. As such, subjectively reported decline in these domains may have clinical utility in tracking the subtle cognitive changes associated with the earliest stages of AD.

**Keywords:** Preclinical Alzheimer disease; memory; attention; spatial navigation; Everyday Cognition Scale; biomarkers

(Received 20 November 2022; final revision 27 September 2023; accepted 2 October 2023)

## Introduction

Preclinical Alzheimer disease (AD) refers to the point at which an individual is clinically normal but exhibits AD-related neuropathological changes: amyloidosis, tauopathy, and/or neurodegeneration of medial temporal structures, including the hippocampus (Gordon et al., 2016; Jack et al., 2018; Storandt et al., 2009). These neurologic changes can begin a decade or more before the onset of symptomatic AD (Jack et al., 2018). As such, there has been an emphasis on identifying the earliest signs of cognitive change and on tracking cognitive change as the disease progresses (Öhman et al., 2021; Weintraub et al., 2018).

Although people with preclinical AD perform within expected limits (e.g., within 1.5 standard deviations of the age-corrected means) on neuropsychological and experimental cognitive tasks, there are subtle, yet observable, cognitive changes associated with this stage (Sperling et al., 2011). Specifically, subtle changes in tasks of memory, attentional control, and spatial navigation are associated with concurrent preclinical status and with risk of clinical progression (Allison et al., 2016; Balota et al., 2010; Hedden et al., 2013; Hutchison et al., 2010; Langbaum et al., 2014; Levine et al., 2020). Additionally, AD biomarkers at baseline have been associated with decline in performance on tasks of memory and

**Corresponding author:** Taylor F. Levine; Email: trhendershott@wustl.edu

*Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf

**Cite this article:** Levine T.F., Dessenberger S.J., Allison S.L., & Head D. the Alzheimer's Disease Neuroimaging Initiative. Alzheimer disease biomarkers are associated with decline in subjective memory, attention, and spatial navigation ability in clinically normal adults. *Journal of the International Neuropsychological Society*, 1–15, https://doi.org/10.1017/S135561772300070X

attention in clinically normal adults (Aschenbrenner et al., 2015; Baker et al., 2017; Millar et al., 2017), whereas, to our knowledge, the relationship between AD biomarkers and longitudinal change in spatial navigation has yet to be explored (Daugherty & Raz, 2017; Korthauer et al., 2016).

Application of objective tasks to track subtle cognitive change is not presently feasible for widespread clinical use because they are time-consuming and have demonstrated pronounced practice effects (Goldberg et al., 2015). While neuropsychological and experimental cognitive tasks remain the gold standard for detecting current cognitive deficits and tracking cognitive change, there is support for the use of brief cognitive assessments, such as global cognitive screens, computerized neuropsychological assessment, phone screens, or questionnaires, as cost-effective and time-efficient methods to identify and track individuals who may benefit from comprehensive neuropsychological assessment (Öhman et al., 2021; Harrington et al., 2022; Roebuck-Spencer et al., 2017; Tong et al., 2017). Questionnaires assessing memory, attention, or spatial navigation difficulties may represent a potential screening tool for AD pathology without the limitations of objective cognitive tasks. Specifically, questionnaires are potentially less time-consuming (5–10 minutes), can require fewer materials to administer than neuropsychological and experimental tasks, can be administered remotely (e.g., online or over the phone) without the need for a trained technician, can be completed by both the patient and someone who knows them well (e.g., an informant), and some have been shown to lack practice effects (Allison et al., 2019). Self-reported memory and spatial navigation ability have been associated with CSF amyloid burden cross-sectionally (Allison et al., 2018; Allison et al., 2019; Cantero et al., 2016).

Although there is a limited body of literature examining the relationship between CSF AD biomarkers and longitudinal subjective change in cognition in clinically normal older adults, a recent review (14 studies) and meta-analysis (8 studies) suggests that subjective cognitive decline in conjunction with presence of AD biomarker burden (i.e., amyloid or the combination of amyloid and tau) is associated with greater risk of clinical progression and/or dementia compared to subjective cognitive decline without AD biomarkers (Rostamzadeh et al., 2022; Scarth et al., 2021). For example, individuals presenting with subjective cognitive decline who were positive for AD biomarkers showed steeper cognitive decline and risk of dementia than biomarker-negative individuals (Ebenau et al., 2020). However, Levine and colleagues (2022) did not observe an association between AD biomarkers or presence of an APOE ε4 allele and self-reported change in spatial navigation ability. Given the small number of existing studies, there is a need to further examine the relationship between AD biomarkers and longitudinal subjective change in cognition to assess whether questionnaire-based measures have utility in tracking subtle change in everyday cognition beginning in the earliest stages of the AD continuum.

The goal of the current study was to expand the existing body of research examining longitudinal change in subjective cognition by assessing whether self- or informant-reported change in memory, attention, or spatial navigation may be useful in monitoring everyday cognition in clinically normal adults and clinical progression. We first examined whether increased AD biomarker burden (CSF p-tau$_{181}$/A$\beta_{42}$ ratio and hippocampal volume) at baseline was associated with subsequent decline in subjective memory, attention, and spatial navigation ability, hypothesizing that increased biomarker burden would predict subjective decline in cognitive functioning. Then, we examined whether clinical progression to symptomatic stages of MCI or AD moderated the relationship between change in subjective cognitive ability and biomarker burden, hypothesizing that clinical progression in conjunction with greater biomarker burden would be associated with greater subjective decline. The goal of this aim was to examine whether slopes of self- and/or informant-reported cognitive change could be used to assess for risk of progression from clinical normality to symptomatic MCI/AD.

## Methods

### Participants

Data were downloaded from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database on January 10, 2021 (adni.loni.use.edu). The ADNI was established in 2003 as a public-private partnership, led by Principal Investigator Michael W. Weiner. The primary goal of ADNI is to test whether serial MRI, PET, other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of AD. All procedures were approved by local IRBs and participants provided informed consent to all procedures in accordance with the Helsinki Declaration. For further information, see www.adni-info.org. The current study included all clinically normal participants (Clinical Dementia Rating Scale (CDR®) = 0) at baseline and their informants who completed the ECog at least twice, as well as had CSF data available within 2 years of completing the baseline ECog. The final sample consisted of 320 participants and informant dyads (Table 1).

### Study duration-matched sample for sensitivity analyses

The 66 participants who progressed to symptomatic MCI/AD (progressors) and did not have biomarker values considered outliers were in the study significantly longer than the 250 participants who did not progress to symptomatic MCI/AD (non-progressors). As such, it is possible that any differences observed between progressors and non-progressors are a result of the progressors being in the study longer, thus having more opportunity to evidence cognitive change. To address this possibility, we randomly sampled 66 non-progressors and compared the total time spent in study to the 66 progressors, excluding four participants with CSF p-tau$_{181}$/A$\beta_{42}$ ratio outliers, using a *t*-test. This process was repeated until the p-value of the test reached above a .25, as this would provide a mean and standard deviation of the time spent in study by the randomly selected non-progressors of at least 90% of that of the progressors. While the original sample of 250 non-progressors had a significantly lower number of years spent in the study ($M = 3.70$, $SD = 2.44$) compared to progressors ($M = 5.30$, $SD = 2.65$; $t(318) = 4.74$, $p < .001$), the average years spent by the randomly selected subsample of non-progressors ($M = 4.87$, $SD = 2.57$) did not significantly differ from progressors ($t(130) = 1.2$, $p = .27$; Table 2).

### Clinical progression

The Clinical Dementia Rating (CDR®) score was used to determine absence or presence, as well as severity, of dementia with a CDR = 0 indicative of clinical normality (Morris, 1997). For CDR = 0.5 individuals, clinical diagnoses of MCI or probable AD were made in accordance with the Petersen criteria (Petersen et al., 2010) or with the criteria reported by National Institute of

https://doi.org/10.1017/S135561772300070X Published online by Cambridge University Press

**Table 1.** Sample characteristics for primary analyses

| | Total sample | Non-progressors | Progressors |
|---|---|---|---|
| *N* | 320 | 250 | 70 |
| Sex (M/F) | 135/185 | 102/148 | 33/37 |
| Age (years) (*M*, *SD*)* | 73.36 (6.78) | 72.74 (6.72) | 75.58 (6.57) |
| Age range | 56.32–93.76 | 56.67–93.76 | 56.32–89.16 |
| Education (years) (*M*, *SD*)* | 16.59 (2.43) | 16.74 (2.44) | 16.04 (2.32) |
| Education (range) | 6–20 | 6–20 | 12–20 |
| Race (White/Black/American Indian/Asian/More than one race) | 292/15/1/3/9 | 230/10/1/2/7 | 62/5/0/1/2 |
| Ethnicity (% Non-Hispanic) | 95.63% | 94.40% | 100% |
| Time in study (years) (*M*, *SD*)* | 4.05 (2.57) | 3.70 (2.44) | 5.30 (2.65) |
| Time in study (range) | .46–10.39 | .46–9.97 | .46–10.39 |
| Hippocampus ($cm^3$) (*N*, *M*, *SD*)* | 280, 7470.36, 789.79 | 216, 7586.38, 756.88 | 64, 7078.82, 778.14 |
| $ptau_{181}/A\beta_{42}$ (*N*, *M*, *SD*)* | 320, .025, .019 | 250, .022, .016 | 70, .037, .024 |

*Notes.* *M* = mean; *SD* = standard deviation. * indicates difference between groups $p < .05$. Time in study = years between baseline and final ECog assessment available at time of data download. All participants had Clinical Dementia Rating Scale = 0 at baseline. "No Progression" refers to the subsample that remained CDR = 0 at time of final ECog assessment. "Yes Progression" refers to the subsample that was CDR > 0 at time of final ECog assessment.

**Table 2.** Sample characteristics for sensitivity analyses

| | Total sample | Non-progressors | Progressors |
|---|---|---|---|
| *N* | 132 | 66 | 66 |
| Sex (M/F) | 59/73 | 28/38 | 31/35 |
| Age (years) (*M*, *SD*)* | 73.84 (6.99) | 72.07 (6.89) | 75.61 (6.69) |
| Age range | 56.32–93.76 | 60.07–93.76 | 56.32–89.16 |
| Education (years) (*M*, *SD*) | 16.32 (2.41) | 16.56 (2.45) | 16.08 (2.37) |
| Education (range) | 12–20 | 12–20 | 12–20 |
| Race (White/Black/American Indian/Asian/More than one race) | 118/8/1/2/3 | 59/4/1/1/1 | 59/4/0/1/2 |
| Ethnicity (% Non-Hispanic) | 97.72% | 95.46% | 100% |
| Time in study (years) (M, SD) | 5.12 (2.58) | 4.87 (2.57) | 5.37 (2.59) |
| Time in study (range) | .46–10.39 | .46–9.97 | .46–10.39 |
| Hippocampus ($cm^3$) (*N*, *M*, *SD*)* | 121, 7368.07, 831.85 | 62, 7633.12, 789.86 | 61, 7098.61, 791.50 |
| $ptau_{181}/A\beta_{42}$ (*N*, *M*, *SD*)* | 132, .027, .017 | 66, .020, .012 | 66, .033, .018 |

*Notes.* *M* = mean; *SD* = standard deviation. * indicates difference between groups $p < .05$. Time in study = years between baseline and final ECog assessment available at time of data download. All participants had Clinical Dementia Rating Scale = 0 at baseline. "No Progression" refers to the subsample that remained CDR = 0 at time of final ECog assessment. "Yes Progression" refers to the subsample that was CDR > 0 at time of final ECog assessment.

Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADRDA; McKhann et al., 1984), respectively. CDR > 0.5 individuals were diagnosed with probable AD in accordance with the NINCDS-ADRDA criteria (McKhann et al., 1984).

All participants were rated clinically normal within (±) 1 year of baseline assessment (CDR = 0; time difference from first ECog *M* = 38 days, *SD* = 35 days, range = 0–271 days). Participants were considered to have clinically progressed to symptomatic stages of the disease process (i.e., MCI or AD) if their closest CDR measurement within (±) 1 year of final ECog (*M* = 4 days, *SD* = 37 days, range = 0–365 days) was greater than 0. Based on CDR rating, 250 participants did not clinically progress (CDR = 0 at final ECog) and 70 participants clinically progressed to symptomatic MCI/AD (CDR > 0 at final ECog). Of the 70 progressors, 62 had a CDR = .5, 5 CDR = 1, and 3 CDR = 3.

### *Cerebrospinal fluid*

CSF collected by ADNI were analyzed using Elecsys immunoassays, following the Roche Study Protocol at the UPenn/ADNI Biomarker Laboratory as previously described (Bittner et al., 2016). CSF data were included if collected within 2 years of completing the ECog (*M* = 32 days, *SD* = 90 days, range = 0–688 days). The ratio between p-$tau_{181}$ and $A\beta_{42}$ was used as the primary CSF biomarker measure of interest because it has been found to best map onto PET imaging results (Santangelo et al., 2019; Schindler et al., 2018).

### *Structural MRI*

ADNI 3T MRI acquisition and pre-processing methods have been previously described (http://adni-info.org; Jack et al., 2008). MRI data were used if collected within 2 years of completing the ECog (*M* = 44 days, *SD* = 96 days, range = 0–728 days). The hippocampus was the region-of-interest for the current study given that this region is impacted in preclinical AD (Csernansky et al., 2005). The FreeSurfer image analysis was used for image processing and delineation of the hippocampus (Fischl et al., 2002). FreeSurfer implements an automated probabilistic labeling procedure where individual voxels in an image are assigned to a neuroanatomical label based on data from a manually labeled training set. Volumetric data obtained through this procedure are highly correlated with manually generated volumes (Desikan et al., 2006; Fischl et al., 2002). Volumes were summed across hemispheres and estimated intracranial volume was used to adjust volumes for body size differences using an analysis of covariance approach (Buckner et al., 2004).

### *Everyday cognition scale*

The ECog is a 39-item self- and informant-reported measure that assesses changes in everyday cognitive functioning across six cognitive domains (memory, language, visuospatial abilities,

https://doi.org/10.1017/S135561772300070X Published online by Cambridge University Press

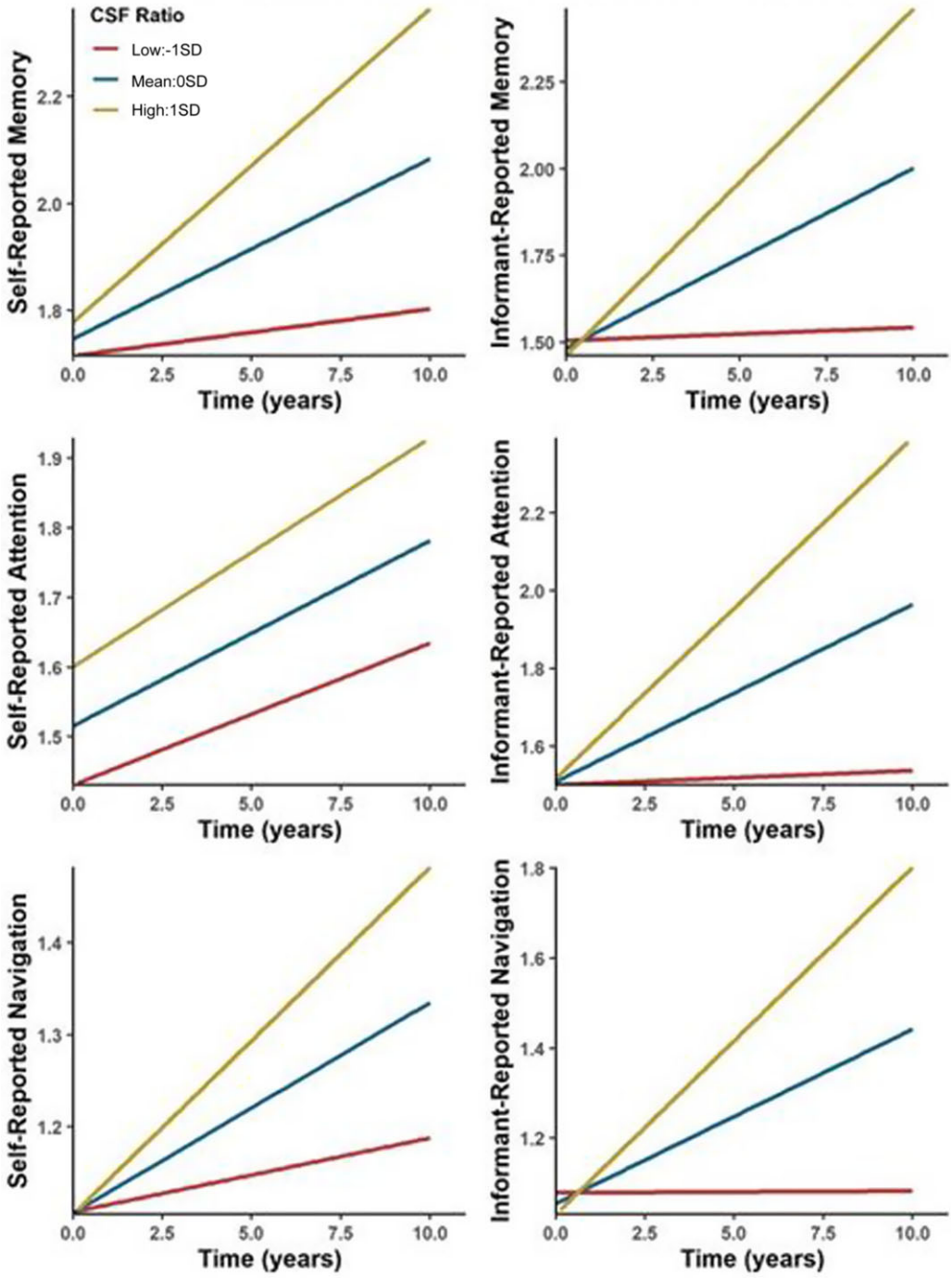


**Figure 1.** Change in self- and informant-reported memory, attention, and spatial navigation ability based on baseline CSF p-tau$_{181}$/A$\beta_{42}$ ratio.

planning, organization, and divided attention) compared to 10 years ago using a four-point Likert scale with higher ratings indicating greater change (1 = better or no change compared to 10 years earlier, 2 = questionable/occasionally worse, 3 = consistently a little worse, 4 = consistently much worse; Farias et al., 2008). The participant and informant ECog memory (eight items), divided attention (four items), and visuospatial abilities (seven items which assess spatial navigation ability) subsections were considered for the purposes of this study given that these cognitive domains are impacted by preclinical AD (Allison et al., 2019; Aschenbrenner et al., 2015; Hedden et al., 2013). Notably, these subsections have been associated with hippocampal volume cross-sectionally and with significantly greater risk of clinical progression from cognitive normality (Farias et al., 2013; Farias et al., 2017). Items were averaged within each domain to include participants and informants who skipped items and, therefore, maximized the sample size.

### *Statistical analyses*

Linear mixed-effects models were used to examine longitudinal change in ECog subsections. These models were conducted using

https://doi.org/10.1017/S135561772300070X Published online by Cambridge University Press

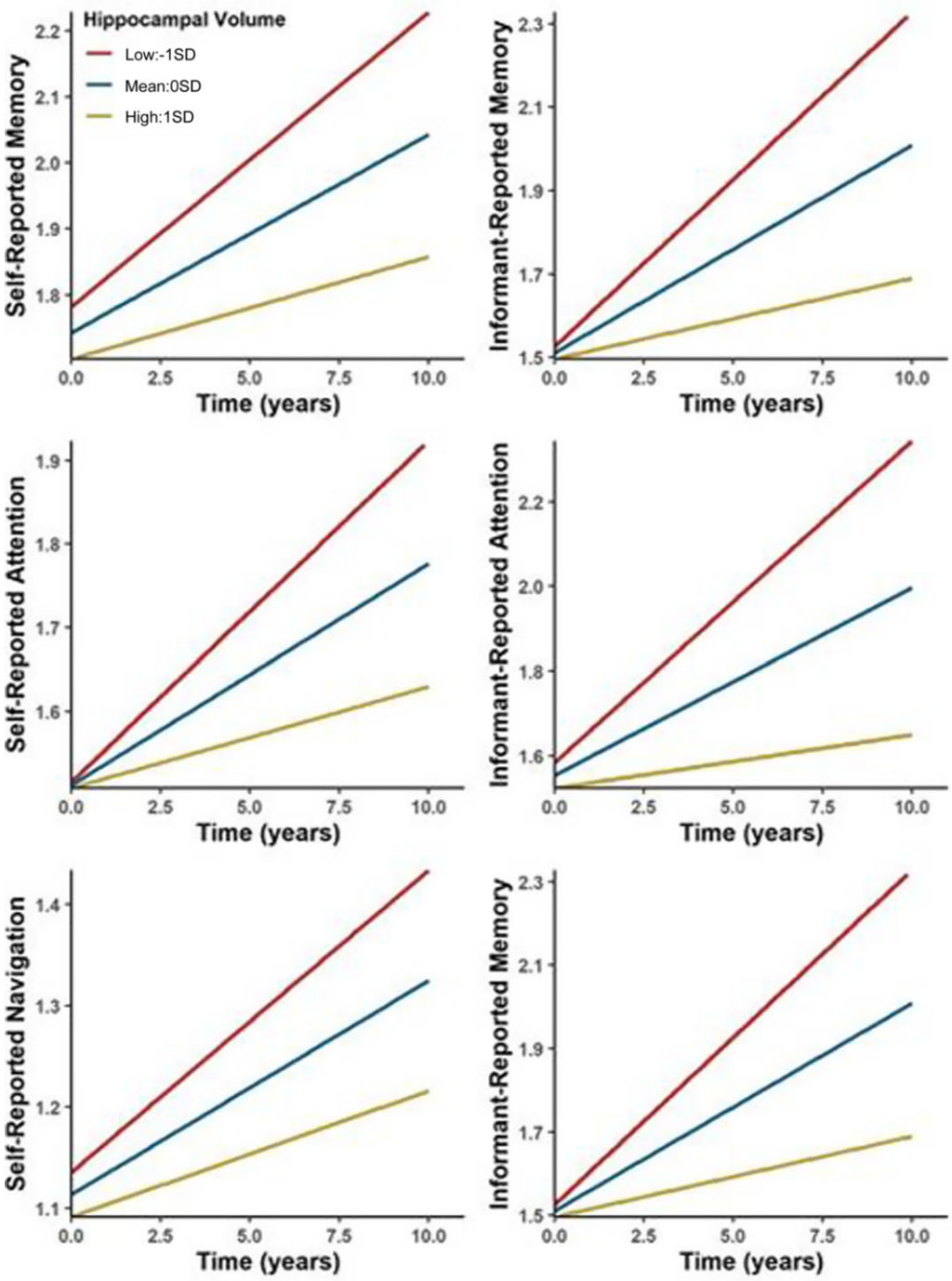


**Figure 2.** Change in self- and informant-reported memory, attention, and spatial navigation ability based on baseline hippocampal volume.

the nlme package in R version 4.1.3 (Pinheiro et al., 2022). Age, sex, and education were controlled for in all analyses. Time (years in study) and intercept were random effects. Time was the predictor of interest in the initial models to examine longitudinal change in the ECog subsection scores. Next, a model was conducted to examine if AD biomarkers (i.e., CSF p-tau$_{181}$/A$\beta_{42}$ ratio and hippocampal volume) at baseline predicted change in ECog subsection scores where the variable of interest was the AD biomarker × Time interaction. Then, whether the participant clinically progressed to symptomatic MCI/AD was added to the model (coded as 0/1) along with the AD biomarker × Time × Progression interaction to assess whether clinical progression moderated the effects of AD biomarkers on ECog subsection scores over time.

Univariate outliers were defined as values >3 standard deviations from the group mean at baseline. Unless otherwise specified, results were unchanged when outliers were omitted from analyses.

## Results

### *Primary analyses*

Self-reported memory, attention, and spatial navigation significantly declined over time ($ps < .001$; Supplemental Figures 1 and 2).

https://doi.org/10.1017/S135561772300070X Published online by Cambridge University Press

**Table 3.** Self-report primary analyses

| | *Standardized β* | *SE* | *T* | *p-value* |
|---|---|---|---|---|
| *ECog memory* | | | | |
| Base model | | | | |
| Time | 0.032 | 0.006 | 4.917 | <0.001* |
| CSF p-tau$_{181}$/Aβ$_{42}$ models | | | | |
| p-tau$_{181}$/Aβ$_{42}$*time | 0.025 | 0.007 | 3.880 | <0.001* |
| p-tau$_{181}$/Aβ$_{42}$*progression | −0.018 | 0.064 | −0.281 | 0.779 |
| Progression*time | 0.046 | 0.014 | 3.349 | 0.001* |
| p-tau$_{181}$/Aβ$_{42}$*time*progression | 0.009 | 0.014 | 0.666 | 0.505 |
| Hippocampal volume models | | | | |
| Hippocampus*time | −0.015 | 0.006 | −2.265 | 0.024* |
| Hippocampus*progression | 0.004 | 0.076 | 0.050 | 0.960 |
| Progression*time | 0.059 | 0.014 | 4.150 | <0.001* |
| Hippocampus*time*progression | −0.019 | 0.014 | −1.421 | 0.156 |
| *ECog attention* | | | | |
| Base model | | | | |
| Time | 0.026 | 0.007 | 3.934 | <0.001* |
| CSF p-tau$_{181}$/Aβ$_{42}$ models | | | | |
| p-tau$_{181}$/Aβ$_{42}$*time | 0.006 | 0.007 | 0.908 | 0.364 |
| p-tau$_{181}$/Aβ$_{42}$*progression | −0.061 | 0.071 | −0.861 | 0.390 |
| Progression*time | 0.020 | 0.015 | 1.319 | 0.187 |
| p-tau$_{181}$/Aβ$_{42}$*time*progression | 0.018 | 0.015 | 1.230 | 0.216 |
| Hippocampal volume models | | | | |
| Hippocampus*time | −0.014 | 0.007 | −2.186 | 0.029* |
| Hippocampus*progression | −0.126 | 0.086 | −1.473 | 0.142 |
| Progression*time | 0.020 | 0.015 | 1.318 | 0.188 |
| Hippocampus*time*progression | 0.002 | 0.014 | 0.110 | 0.912 |
| *ECog spatial navigation* | | | | |
| Base model | | | | |
| Time | 0.022 | 0.004 | 5.384 | <0.001* |
| CSF p-tau$_{181}$/Aβ$_{42}$ models | | | | |
| p-tau$_{181}$/Aβ$_{42}$*time | 0.015 | 0.004 | 3.689 | <0.001* |
| p-tau$_{181}$/Aβ$_{42}$*progression | −0.017 | 0.029 | −0.605 | 0.546 |
| Progression*time | 0.024 | 0.009 | 2.746 | 0.006* |
| p-tau$_{181}$/Aβ$_{42}$*time*progression | 0.014 | 0.009 | 1.576 | 0.115 |
| Hippocampal volume models | | | | |
| Hippocampus*time | −0.009 | 0.004 | −2.171 | 0.030* |
| Hippocampus*progression | −0.007 | 0.034 | −0.193 | 0.847 |
| Progression*time | 0.030 | 0.009 | 3.401 | 0.001* |
| Hippocampus*time*progression | −0.016 | 0.009 | −1.868 | 0.062# |

*Notes.* *$p < .05$; #$p < .10$. See text for details regarding the analyses.

Baseline CSF p-tau$_{181}$/Aβ$_{42}$ ratio and hippocampal volume predicted decline in self-reported memory and spatial navigation ($ps < .030$; Figures 1 and 2). Baseline hippocampal volume, but not CSF p-tau$_{181}$/Aβ$_{42}$ ratio, predicted decline in self-reported attention ($p = .029$ and $p = .364$, respectively; Figures 1 and 2). Clinical progression did not significantly moderate the relationship between biomarkers and domain-specific cognitive change ($ps > .062$). See Table 3 for detailed results.

Informant-reported memory, attention, and spatial navigation significantly declined over time ($ps < .001$; Supplemental Figures 3 and 4). Baseline CSF p-tau$_{181}$/Aβ$_{42}$ ratio and hippocampal volume predicted decline in informant-reported memory, attention, and spatial navigation ($ps \leq .001$; Figures 1 and 2). Clinical progression did not significantly moderate the association of CSF p-tau$_{181}$/Aβ$_{42}$ ratio or hippocampal volume with informant-reported cognitive change when outliers were removed ($ps > .183$). See Table 4 for detailed results.

### *Sensitivity analyses*

The sensitivity analyses were specifically conducted to determine whether the difference in study duration between progressors and non-progressors impacted our ability to detect a moderating effect of clinical progression in the primary analyses. However, as with the primary analyses, clinical progression did not moderate the relationship between AD biomarkers and self- and informant-reported cognitive change ($ps > .089$). See Tables 5 and 6 for detailed results.

### *Post-hoc analyses*

A series of post-hoc analyses were conducted to further investigate our primary results. This included analysis of individual CSF biomarkers, comparison of self- and informant-reported decline, and the relationship between biomarkers and total ECog.

#### *Individual CSF biomarkers*

In addition to our *a priori* analyses, we examined baseline CSF Aβ$_{42}$ and p-tau$_{181}$ separately. Baseline CSF Aβ$_{42}$ and p-tau$_{181}$ were significant predictors of change in self-reported memory and spatial navigation ($ps < .046$), but not self-reported attention ($ps > .199$; Figures 3 and 4). Clinical progression did not significantly moderate the relationship between biomarkers and domain-specific cognitive change ($ps > .137$). These results were consistent with CSF p-tau$_{181}$/Aβ$_{42}$ ratio results. See Table 7 for detailed results.

Baseline CSF Aβ$_{42}$ and p-tau$_{181}$ were significant predictors of all informant-reported subsections ($ps < .016$; Figures 3 and 4). This was consistent with CSF p-tau$_{181}$/Aβ$_{42}$ ratio results. However, significant three-way interactions were observed in post-hoc

https://doi.org/10.1017/S135561772300070X Published online by Cambridge University Press

**Table 4.** Informant-report primary analyses

| | *Standardized β* | *SE* | *T* | *p-value* |
|---|---|---|---|---|
| *ECog memory* | | | | |
| Base model | | | | |
| Time | 0.049 | 0.009 | 5.643 | <0.001* |
| CSF p-tau$_{181}$/Aβ$_{42}$ models | | | | |
| p-tau$_{181}$/Aβ$_{42}$*time | 0.048 | 0.008 | 5.809 | <0.001* |
| p-tau$_{181}$/Aβ$_{42}$*progression | −0.030 | 0.051 | −0.592 | 0.554 |
| Progression*time | 0.102 | 0.017 | 6.069 | <0.001* |
| p-tau$_{181}$/Aβ$_{42}$*time*progression | 0.042/0.020 | 0.016/0.018 | 2.639/1.131 | 0.009*/0.258 |
| Hippocampal volume models | | | | |
| Hippocampus*time | −0.030 | 0.009 | −3.458 | 0.001* |
| Hippocampus*progression | −0.099 | 0.060 | −1.644 | 0.101 |
| Progression*time | 0.120 | 0.018 | 6.560 | <0.001* |
| Hippocampus*time*progression | −0.023 | 0.017 | −1.313 | 0.190 |
| *ECog attention* | | | | |
| Base model | | | | |
| Time | 0.043 | 0.010 | 4.498 | <0.001* |
| CSF p-tau$_{181}$/Aβ$_{42}$ models | | | | |
| p-tau$_{181}$/Aβ$_{42}$*time | 0.042 | 0.009 | 4.470 | <0.001* |
| p-tau$_{181}$/Aβ$_{42}$*progression | −0.010 | 0.063 | −0.163 | 0.870 |
| Progression*time | 0.092 | 0.020 | 4.706 | <0.001* |
| p-tau$_{181}$/Aβ$_{42}$*time*progression | 0.051/0.023 | 0.019/0.021 | 2.770/1.102 | 0.006*/0.271 |
| Hippocampal volume models | | | | |
| Hippocampus*time | −0.032 | 0.010 | −3.261 | 0.001* |
| Hippocampus*progression | −0.199 | 0.077 | −2.583 | 0.010* |
| Progression*time | 0.107 | 0.021 | 5.029 | <0.001* |
| Hippocampus*time*progression | 0.001 | 0.020 | 0.053 | 0.958 |
| *ECog spatial navigation* | | | | |
| Base model | | | | |
| Time | 0.037 | 0.008 | 4.899 | <0.001* |
| CSF p-tau$_{181}$/Aβ$_{42}$ models | | | | |
| p-tau$_{181}$/Aβ$_{42}$*time | 0.038 | 0.007 | 5.289 | <0.001* |
| p-tau$_{181}$/Aβ$_{42}$*progression | −0.019 | 0.023 | −0.837 | 0.404 |
| Progression*time | 0.085 | 0.015 | 5.523 | <0.001* |
| p-tau$_{181}$/Aβ$_{42}$*time*progression | 0.040/0.006 | 0.014/0.016 | 2.788/0.381 | 0.005*/0.703 |
| Hippocampal volume models | | | | |
| Hippocampus*time | −0.027 | 0.008 | −3.535 | <0.001* |
| Hippocampus*progression | <−0.001 | 0.028 | −0.009 | 0.993 |
| Progression*time | 0.095 | 0.017 | 5.573 | <0.001* |
| Hippocampus*time*progression | −0.022 | 0.016 | −1.333 | 0.183 |

*Notes.* *$p < .05$. See text for details regarding the analyses.

analyses that were not in CSF p-tau$_{181}$/Aβ$_{42}$ ratio analyses. Clinical progression significantly moderated the association of CSF Aβ$_{42}$ with informant-reported memory ($p = .023$) and spatial navigation ($p = .022$), and the association of CSF p-tau$_{181}$ with informant-reported memory with outliers removed ($p = .013$), attention ($p = .027$), and spatial navigation with outliers removed ($p = .010$). The observed moderation effects were such that the association between CSF Aβ$_{42}$ and p-tau$_{181}$ and informant-reported cognitive change was stronger in progressors relative to non-progressors. See Table 8 for detailed results.

### *Comparison of self- and informant-reported change over time*

We compared self- and informant-reported change over time as predicted by baseline biomarkers using the ghlt function from the multcomp package in R with Holm's procedure to correct for multiple comparisons (Hothorn et al., 2008). CSF p-tau$_{181}$/Aβ$_{42}$ ratio and CSF p-tau$_{181}$ predicted greater decline in informant-reported than self-reported memory, attention, and spatial navigation ($ps < .023$). Hippocampal volume predicted greater decline in informant-reported than self-reported memory and spatial navigation ($ps < .022$), but not attention ($p = .125$). CSF Aβ$_{42}$ did not predict significantly different declines in self- and informant-reported memory, attention, and spatial navigation ($ps > .566$). See Supplementary Table 1 for detailed results.

### *Total ECog*

Post-hoc examination of total ECog score was conducted to examine whether observed relationships between ECog subsection change and AD-related biomarkers (CSF p-tau$_{181}$/Aβ$_{42}$ ratio and hippocampal volume) were domain-specific or if similar relationships were observed when examining change in total ECog over time. Indeed, baseline biomarker burden predicted self- and informant-reported decline in total ECog ($ps < .002$). Clinical progression did not significantly moderate the relationship between biomarkers and total ECog ($ps > .299$). See Table 9 for detailed results.

We also compared total score change to subsection change using the ghlt function from the multcomp package in R with Holm's procedure to correct for multiple comparisons (Hothorn et al., 2008). CSF p-tau$_{181}$/Aβ$_{42}$ ratio predicted greater decline in informant-reported attention than informant-reported total score ($p = .005$) but greater decline in self-reported total score than self-reported attention ($p = .049$). See Supplementary Table 2 for detailed results.

### *Potential impact of time delays between measurements*

Of note, when primary analyses were rerun to include the delay between ECog and CDR, the delay between the two measures was not a significant predictor of subjective decline and did not change the results. Additionally, when the sample was limited to

https://doi.org/10.1017/S135561772300070X Published online by Cambridge University Press

**Table 5.** Self-report sensitivity analyses

| | *Standardized β* | *SE* | *T* | *p-value* |
|---|---|---|---|---|
| *ECog memory* | | | | |
| Base model | | | | |
| Time | 0.040 | 0.009 | 4.396 | <0.001* |
| CSF p-tau$_{181}$/Aβ$_{42}$ models | | | | |
| p-tau$_{181}$/Aβ$_{42}$*time | 0.032 | 0.011 | 3.018 | 0.003* |
| p-tau$_{181}$/Aβ$_{42}$*progression | <−0.001 | 0.133 | <−0.001 | 0.999 |
| Progression*time | 0.044 | 0.020 | 2.184 | 0.029* |
| p-tau$_{181}$/Aβ$_{42}$*time*progression | −0.010 | 0.027 | −0.381 | 0.704 |
| Hippocampal volume models | | | | |
| Hippocampus*time | −0.011 | 0.009 | −1.236 | 0.217 |
| Hippocampus*progression | 0.083 | 0.100 | 0.825 | 0.411 |
| Progression*time | 0.061 | 0.019 | 3.219 | 0.001* |
| Hippocampus*time*progression | −0.030 | 0.018 | −1.654 | 0.099 |
| *ECog attention* | | | | |
| Base model | | | | |
| Time | 0.028 | 0.008 | 3.498 | 0.001* |
| CSF p-tau$_{181}$/Aβ$_{42}$ models | | | | |
| p-tau$_{181}$/Aβ$_{42}$*time | 0.009 | 0.010 | 0.886 | 0.376 |
| p-tau$_{181}$/Aβ$_{42}$*progression | −0.038 | 0.150 | −0.254 | 0.780 |
| Progression*time | 0.016 | 0.019 | 0.846 | 0.398 |
| p-tau$_{181}$/Aβ$_{42}$*time*progression | 0.012 | 0.026 | −0.462 | 0.644 |
| Hippocampal volume models | | | | |
| Hippocampus*time | −0.011 | 0.008 | −1.374 | 0.170 |
| Hippocampus*progression | −0.061 | 0.113 | −0.538 | 0.591 |
| Progression*time | 0.015 | 0.017 | 0.870 | 0.385 |
| Hippocampus*time*progression | 0.006 | 0.016 | 0.346 | 0.729 |
| *ECog spatial navigation* | | | | |
| Base model | | | | |
| Time | 0.026 | 0.005 | 4.843 | <0.001* |
| CSF p-tau$_{181}$/Aβ$_{42}$ models | | | | |
| p-tau$_{181}$/Aβ$_{42}$*time | 0.017 | 0.006 | 2.737 | 0.006* |
| p-tau$_{181}$/Aβ$_{42}$*progression | −0.070 | 0.062 | −1.131 | 0.260 |
| Progression*time | 0.022 | 0.012 | 1.858 | 0.064# |
| p-tau$_{181}$/Aβ$_{42}$*time*progression | −0.001 | 0.016 | −0.086 | 0.932 |
| Hippocampal volume models | | | | |
| Hippocampus*time | −0.007 | 0.005 | −1.371 | 0.171 |
| Hippocampus*progression | −0.040 | 0.047 | −0.854 | 0.395 |
| Progression*time | 0.028 | 0.011 | 2.525 | 0.012* |
| Hippocampus*time*progression | −0.018 | 0.011 | −1.703 | 0.089# |

*Notes.* *$p < .05$; #$p < .10$. See text for details regarding the analyses.

participants who only had 1-year maximum delay between ECog and biomarker measures, results remained the same (results not presented).

## Discussion

In a clinically normal sample, baseline CSF p-tau$_{181}$/Aβ$_{42}$ ratio predicted decline in self-reported memory and spatial navigation and in informant-reported memory, attention, and spatial navigation. Post-hoc analyses examining CSF Aβ$_{42}$ and CSF p-tau$_{181}$ separately generally replicated these results. In addition, baseline hippocampal volume predicted decline in self- and informant-reported memory, attention, and spatial navigation. Clinical progression did not robustly moderate the relationship between biomarkers and subjective cognitive change with significant effects only seen in post-hoc analyses examining individual CSF biomarkers.

The results from this study suggest that subjective changes in memory, attention, and spatial navigation ability have the potential to be used by clinicians to monitor subtle cognitive changes associated with early AD biomarker burden to aid in identifying individuals who may benefit from more diagnostic procedures (e.g., lumbar puncture or PET). The observed association between baseline AD biomarkers and decline in subjective domain-specific cognitive ability is consistent with the existing literature supporting the relationship between AD biomarkers and objectively measured memory, attention, and spatial navigation (Allison et al., 2016; Balota et al., 2010; Hedden et al., 2013; Hutchison et al., 2010; Langbaum et al., 2014; Levine et al., 2020). This suggests that both subjective and objective measures of memory, attention, and spatial navigation can be used to assess disease progression in the preclinical phase. Using questionnaire-based measures to track cognitive decline has several advantages relative to objective tasks. For example, questionnaires tend to be more time- and cost-effective and have demonstrated fewer practice effects (Allison et al., 2019; Jessen, 2014). The ECog may have particular utility in clinical trials for monitoring everyday cognition, as these subsections are brief, easily administered, and can be repeated annually without practice effects. Thus, the ECog subsections represent a brief assessment that can be used to track subtle change in everyday cognition and may mitigate research-related burden for participants and their informants.

Notably, estimated slopes of decline of informant-reported cognitive change were steeper than self-reported cognitive change for most models, suggesting that informant-reports may be better suited for monitoring cognitive change across the AD continuum

https://doi.org/10.1017/S135561772300070X Published online by Cambridge University Press

**Table 6.** Informant-report sensitivity analyses

| | *Standardized β* | *SE* | *T* | *p-value* |
|---|---|---|---|---|
| *ECog memory* | | | | |
| Base model | | | | |
| Time | 0.075 | 0.013 | 5.894 | <0.001* |
| CSF p-tau$_{181}$/Aβ$_{42}$ model | | | | |
| p-tau$_{181}$/Aβ$_{42}$*time | 0.054 | 0.015 | 3.711 | <0.001* |
| p-tau$_{181}$/Aβ$_{42}$*progression | −0.041 | 0.100 | −0.409 | 0.683 |
| Progression*time | 0.111 | 0.026 | 4.314 | <0.001* |
| p-tau$_{181}$/Aβ$_{42}$*time*progression | 0.022 | 0.035 | 0.639 | 0.523 |
| Hippocampal volume model | | | | |
| Hippocampus*time | −0.023 | 0.012 | −1.900 | 0.058# |
| Hippocampus*progression | −0.063 | 0.071 | −0.887 | 0.377 |
| Progression*time | 0.118 | 0.024 | 4.983 | <0.001* |
| Hippocampus*time*progression | −0.019 | 0.023 | −0.837 | 0.403 |
| *ECog attention* | | | | |
| Base model | | | | |
| Time | 0.059 | 0.014 | 4.253 | <0.001* |
| CSF p-tau$_{181}$/Aβ$_{42}$ model | | | | |
| p-tau$_{181}$/Aβ$_{42}$*time | 0.050 | 0.016 | 3.129 | 0.002* |
| p-tau$_{181}$/Aβ$_{42}$*progression | 0.113 | 0.143 | 0.796 | 0.428 |
| Progression*time | 0.095 | 0.029 | 3.230 | 0.001* |
| p-tau$_{181}$/Aβ$_{42}$*time*progression | −0.006 | 0.039 | −0.144 | 0.885 |
| Hippocampal volume model | | | | |
| Hippocampus*time | −0.022 | 0.014 | −1.655 | 0.099# |
| Hippocampus*progression | −0.245 | 0.104 | −2.348 | 0.021* |
| Progression*time | 0.112 | 0.028 | 4.056 | <0.001* |
| Hippocampus*time*progression | 0.011 | 0.027 | 0.419 | 0.676 |
| *ECog spatial navigation* | | | | |
| Base model | | | | |
| Time | 0.054 | 0.012 | 4.659 | <0.001* |
| CSF p-tau$_{181}$/Aβ$_{42}$ model | | | | |
| p-tau$_{181}$/Aβ$_{42}$*time | 0.032 | 0.014 | 2.371 | 0.018* |
| p-tau$_{181}$/Aβ$_{42}$*progression | −0.021 | 0.056 | −0.365 | 0.716 |
| Progression*time | 0.100 | 0.025 | 4.052 | <0.001* |
| p-tau$_{181}$/Aβ$_{42}$*time*progression | 0.021 | 0.033 | 0.629 | 0.530 |
| Hippocampal volume model | | | | |
| Hippocampus*time | −0.020 | 0.012 | −1.756 | 0.080# |
| Hippocampus*progression | −0.004 | 0.041 | −0.097 | 0.923 |
| Progression*time | 0.098 | 0.024 | 4.158 | <0.001* |
| Hippocampus*time*progression | −0.020 | 0.023 | −0.887 | 0.376 |

*Notes.* *$p < .05$; #$p < .10$. See text for details regarding the analyses.

than self-reports (Supplementary Table 1). Our results are consistent with a recent publication by Numbers and collogues (2023) which reported that informant-reported change in subjective cognitive complaint reporting was associated with clinical progression to dementia from cognitive normality, whereas self-reported change in subjective cognitive complaint reporting was not. Broadly the current literature suggests that informant-reported change may be particularly useful in detecting AD-related pathological change and clinical progression in individuals farther along the AD continuum (i.e., MCI or symptomatic AD), whereas self-reported cognitive change may have more utility in the preclinical stage (for review see Rabin et al., 2017). However, from a longitudinal perspective, our results suggest that there may be an advantage of informant-reported cognitive change in tracking subtle decline as disease progresses even within the preclinical stage. It may be the case that informants are better able to observe and report changes in cognitive ability between time points due to participants slowly habituating to their changing cognitive abilities and therefore not readily noticing subtle cognitive change.

Post-hoc examination of total ECog score found generally similar relationships between total ECog and AD-related biomarkers to what was observed within ECog subsections. While the total ECog could be used to monitor subtle change in everyday cognition, these data support the notion that the 39-item full questionnaire could be abbreviated to focus on specific domains of cognition, thus significantly shortened, and the ability to track longitudinal change would not be meaningfully impacted. A short form of the ECog has been previously validated (Farias et al., 2011). Future work could compare the association of ECog subsections and total ECog short form to determine whether there is benefit of domain-specific measurement compared to the global short form scale.

The lack of observed moderating effect is not consistent with a recent review and meta-analysis of the literature, which both suggest that increased amyloid pathology or the combination of increased amyloid and tau results in increased risk of clinical progression in individuals with subjective cognitive decline (Rostamzadeh et al., 2022; Scarth et al., 2021). Individuals who progressed to symptomatic MCI/AD did generally demonstrate greater change in self- and informant-reported abilities regardless of biomarker burden, except in the case of self-reported attention (see Tables 3 and 4). However, there was some inconsistency in terms of moderating effects of clinical progression on the relationship between biomarkers and subjective cognitive change with null findings across self-reported models and mixed results in informant models. Some observed differences between results with

https://doi.org/10.1017/S135561772300070X Published online by Cambridge University Press

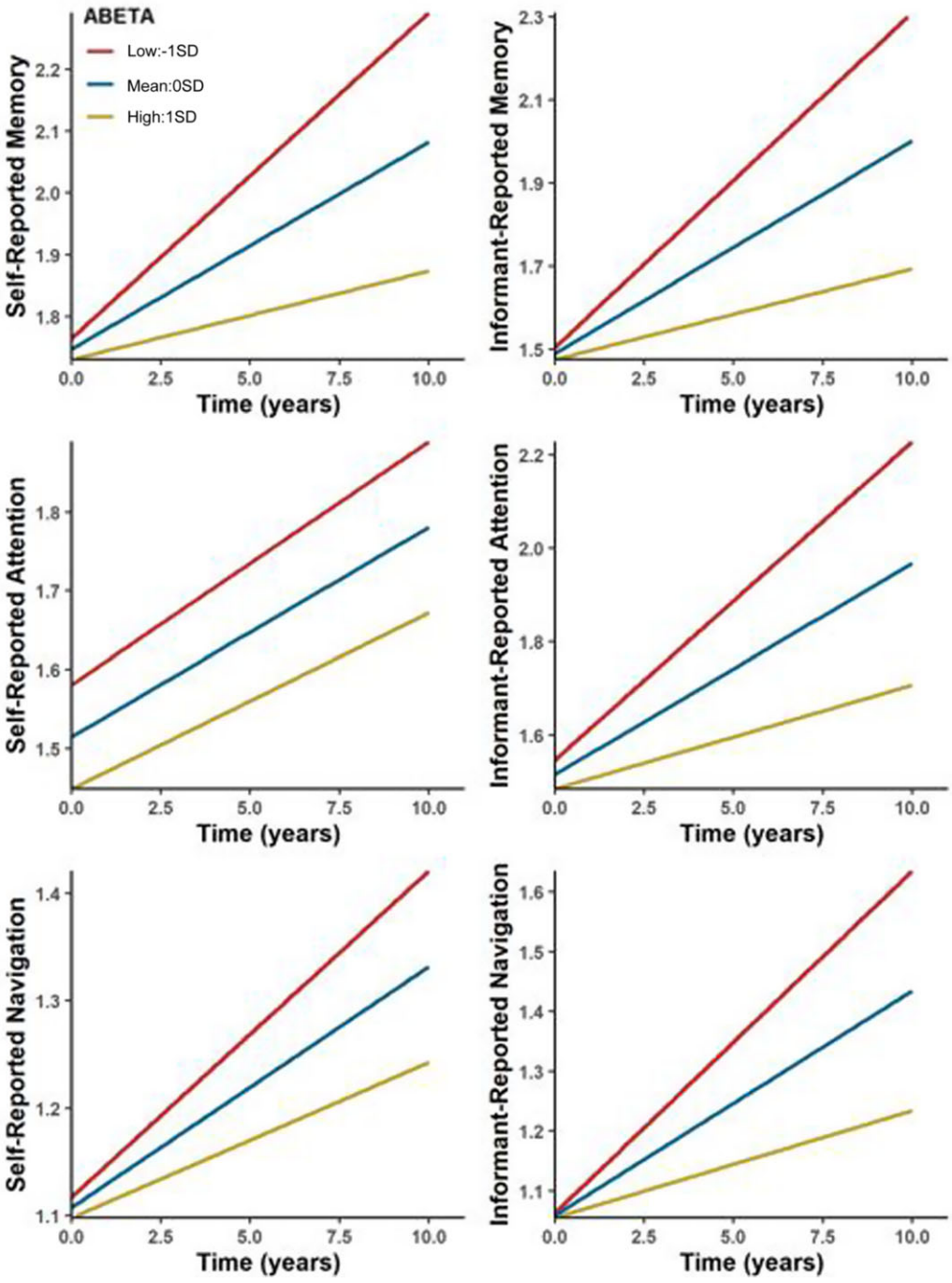


**Figure 3.** Change in self- and informant-reported memory, attention, and spatial navigation ability based on baseline CSF $A\beta_{42}$.

the ratio vs the individual markers could have been related to outliers, as inclusion/exclusion of outliers changed the results of several interactions. Notably, there was no overlap between participants with CSF p-$tau_{181}$/$A\beta_{42}$ ratio outliers and participants with CSF p-$tau_{181}$ outliers. Significant results in the CSF $A\beta_{42}$ models may be explained by the hypothesis that cerebral amyloidosis is the first neuropathological change to occur on the AD continuum (Jack et al., 2018). The current samples consisted entirely of clinically normal participants, and it is possible that as a group we capture a greater range of CSF $A\beta_{42}$ burden in comparison to CSF p-$tau_{181}$ burden. It is possible that individual CSF biomarker-related subjective decline might be more sensitive to distinguish clinically normal adults who are at risk of progressing to symptomatic MCI/AD relative to the CSF p-$tau_{181}$/$A\beta_{42}$ ratio. However, these current post-hoc analyses should be interpreted with caution and require replication. At this time, taken together, the ECog subsections were robustly able to detect biomarker-related subjective decline overall, but it is unclear

https://doi.org/10.1017/S135561772300070X Published online by Cambridge University Press

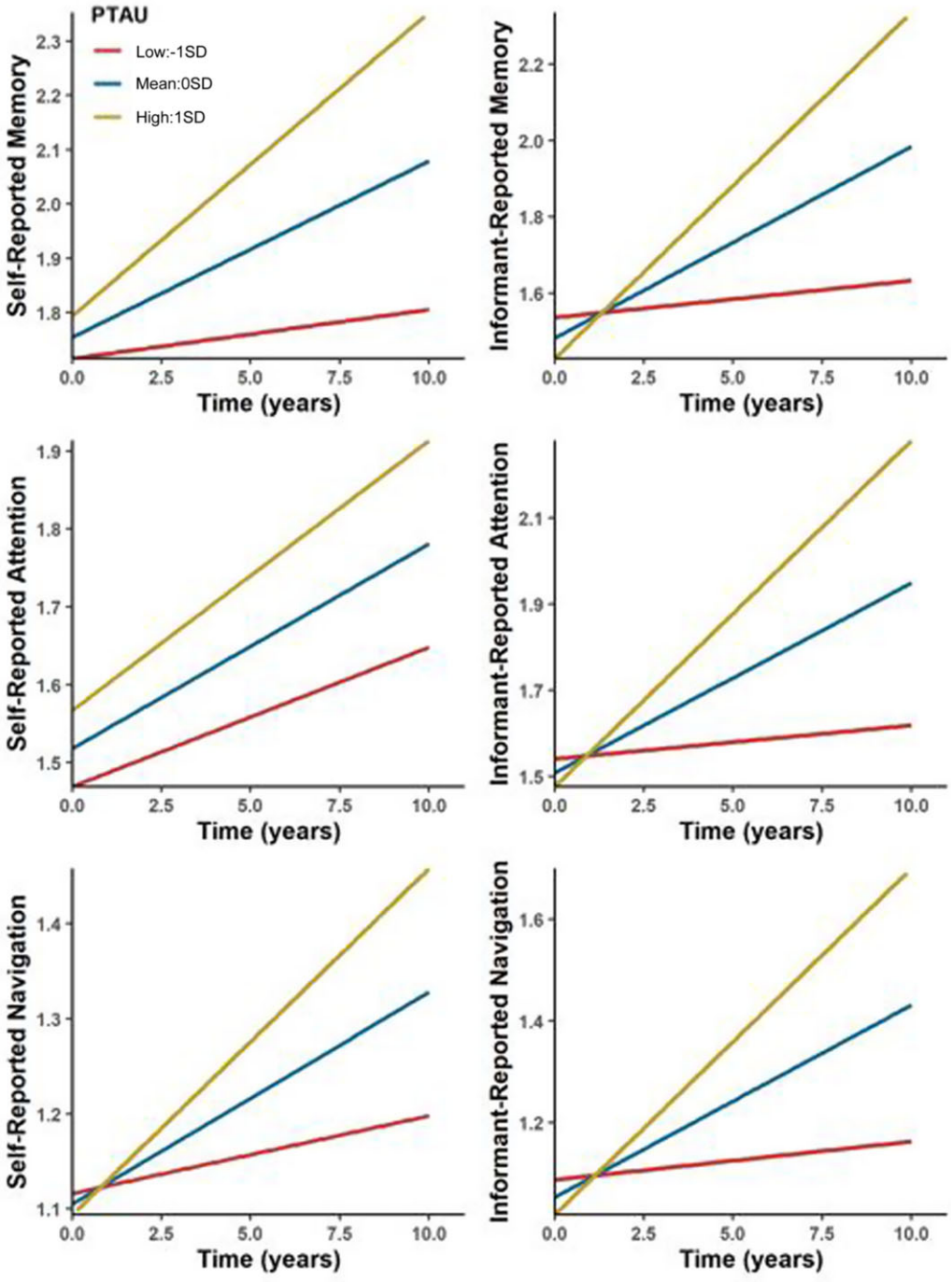


**Figure 4.** Change in self- and informant-reported memory, attention, and spatial navigation ability based on baseline CSF p-tau$_{181}$.

whether they are sufficiently sensitive to distinguish participants who went on the develop symptomatic MCI/AD and those who remained clinically normal.

There are several limitations to this study. First, ADNI participants are predominately Non-Hispanic White. Thus, approximately 96% of our sample with CSF data and 98% of our sample with hippocampal volume data was Non-Hispanic White. The lack of racial and ethnic representation in our sample limits generalizability of our findings and precludes examination of group differences (for review see Gleason et al., 2022). Second, by nature of using previously collected data through ADNI, we were unable to control the timing of ECog, clinical, and biomarker data collection. As a result, these variables were not measured on the same date, and we had to determine cutoff points for inclusion or exclusion of data. We attempted to balance the need for a relatively large sample size and the aim to restrict meaningful status change at baseline by limiting the delay between ECog and CDR to 1 year and ECog and biomarker measures to 2 years; however, this does not guarantee that there was not an impact of time delay between measures.

https://doi.org/10.1017/S135561772300070X Published online by Cambridge University Press

**Table 7.** Self-report post-hoc analyses

| | *Standardized β* | *SE* | *T* | *p-value* |
|---|---|---|---|---|
| *ECog memory* | | | | |
| CSF $A\beta_{42}$ models | | | | |
| $A\beta_{42}$*time | −0.019 | 0.006 | −3.056 | <0.001* |
| $A\beta_{42}$*progression | 0.108 | 0.070 | 1.542 | 0.124 |
| Progression*time | 0.051 | 0.013 | 3.852 | <0.001* |
| $A\beta_{42}$*time*progression | −0.020 | 0.013 | −1.487 | 0.137 |
| CSF p-$tau_{181}$ models | | | | |
| p-$tau_{181}$*time | 0.024 | 0.006 | 3.848 | <0.001* |
| p-$tau_{181}$*progression | 0.104 | 0.065 | 1.603 | 0.110 |
| Progression*time | 0.049 | 0.014 | 3.493 | 0.001* |
| p-$tau_{181}$*time*progression | −0.011 | 0.013 | −0.844 | 0.399 |
| *ECog attention* | | | | |
| CSF $A\beta_{42}$ models | | | | |
| $A\beta_{42}$*time | −0.004 | 0.007 | −0.649 | 0.517 |
| $A\beta_{42}$*progression | 0.070 | 0.078 | 0.904 | 0.367 |
| Progression*time | 0.021 | 0.014 | 1.475 | 0.141 |
| $A\beta_{42}$*time*progression | −0.011 | 0.014 | −0.758 | 0.449 |
| CSF p-$tau_{181}$ models | | | | |
| p-$tau_{181}$*time | 0.009 | 0.007 | 1.287 | 0.199 |
| p-$tau_{181}$*progression | 0.013 | 0.072 | 0.176 | 0.860 |
| Progression*time | 0.019 | 0.015 | 1.244 | 0.214 |
| p-$tau_{181}$*time*progression | 0.002 | 0.014 | 0.137 | 0.891 |
| *ECog spatial navigation* | | | | |
| CSF $A\beta_{42}$ models | | | | |
| $A\beta_{42}$*time | −0.008 | 0.004 | −2.000 | 0.046* |
| $A\beta_{42}$*progression | 0.016 | 0.031 | 0.496 | 0.620 |
| Progression*time | 0.029 | 0.008 | 3.465 | 0.001* |
| $A\beta_{42}$*time*progression | −0.012 | 0.008 | −1.466 | 0.143 |
| CSF p-$tau_{181}$ models | | | | |
| p-$tau_{181}$*time | 0.014 | 0.004 | 3.671 | <0.001* |
| p-$tau_{181}$*progression | 0.023 | 0.029 | 0.778 | 0.437 |
| Progression*time | 0.025 | 0.009 | 2.866 | 0.004* |
| p-$tau_{181}$*time*progression | −0.005 | 0.008 | −0.619 | 0.536 |

*Notes.* $^{*}p < .05$. See text for details regarding the analyses.

**Table 8.** Informant-report post-hoc analyses

| | *Standardized β* | *SE* | *T* | *p-value* |
|---|---|---|---|---|
| *ECog memory* | | | | |
| CSF $A\beta_{42}$ models | | | | |
| $A\beta_{42}$*time | −0.029 | 0.009 | −3.442 | 0.001* |
| $A\beta_{42}$*progression | <0.001 | 0.056 | 0.003 | 0.998 |
| Progression*time | 0.118 | 0.017 | 7.061 | <0.001* |
| $A\beta_{42}$*time*progression | −0.038 | 0.017 | −2.282 | 0.023* |
| CSF p-$tau_{181}$ models | | | | |
| p-$tau_{181}$*time | 0.041 | 0.008 | 4.992 | <0.001* |
| p-$tau_{181}$*progression | −0.023 | 0.051 | −0.455 | 0.649 |
| Progression*time | 0.106 | 0.017 | 6.170 | <0.001* |
| p-$tau_{181}$*time*progression | 0.029/0.041 | 0.016/0.017 | 1.845/2.483 | $0.065^{\#}$/0.013* |
| *ECog attention* | | | | |
| CSF $A\beta_{42}$ models | | | | |
| $A\beta_{42}$*time | −0.023 | 0.010 | −2.404 | 0.016* |
| $A\beta_{42}$*progression | −0.025 | 0.069 | −0.359 | 0.720 |
| Progression*time | 0.109 | 0.020 | 5.582 | <0.001* |
| $A\beta_{42}$*time*progression | −0.035 | 0.019 | −1.826 | $0.068^{\#}$ |
| CSF p-$tau_{181}$ models | | | | |
| p-$tau_{181}$*time | 0.036 | 0.009 | 3.923 | <0.001* |
| p-$tau_{181}$*progression | −0.022 | 0.064 | −0.341 | 0.734 |
| Progression*time | 0.095 | 0.020 | 4.686 | <0.001* |
| p-$tau_{181}$*time*progression | 0.041 | 0.019 | 2.218 | 0.027* |
| *ECog spatial navigation* | | | | |
| CSF $A\beta_{42}$ models | | | | |
| $A\beta_{42}$*time | −0.020 | 0.007 | −2.657 | 0.008* |
| $A\beta_{42}$*progression | −0.014 | 0.025 | −0.547 | 0.585 |
| Progression*time | 0.099 | 0.015 | 6.495 | <0.001* |
| $A\beta_{42}$*time*progression | −0.035 | 0.015 | −2.299 | 0.022* |
| CSF p-$tau_{181}$ models | | | | |
| p-$tau_{181}$*time | 0.030 | 0.007 | 4.218 | <0.001* |
| p-$tau_{181}$*progression | −0.025 | 0.023 | −1.098 | 0.273 |
| Progression*time | 0.092 | 0.016 | 5.758 | <0.001* |
| p-$tau_{181}$*time*progression | 0.027/0.039 | 0.014/0.015 | 1.882/2.596 | $0.060^{\#}$/0.010* |

*Notes.* $^{*}p < .05$; $^{\#}p < .10$. See text for details regarding the analyses.

https://doi.org/10.1017/S135561772300070X Published online by Cambridge University Press

**Table 9.** Post-hoc analyses examining total ECog score and primary biomarkers of interest

| | *Standardized β* | *SE* | *T* | *p-value* |
|---|---|---|---|---|
| *Self-reported total* | | | | |
| Base model | | | | |
| Time | 0.030 | 0.005 | 5.622 | <0.001* |
| CSF p-tau$_{181}$/Aβ$_{42}$ models | | | | |
| p-tau$_{181}$/Aβ$_{42}$*time | 0.021 | 0.006 | 3.744 | <0.001* |
| p-tau$_{181}$/Aβ$_{42}$*progression | −0.017 | 0.044 | −0.378 | 0.705 |
| Progression*time | 0.041 | 0.012 | 3.534 | <0.001 |
| p-tau$_{181}$/Aβ$_{42}$*time*progression | 0.008 | 0.012 | 0.724 | 0.469 |
| Hippocampal volume models | | | | |
| Hippocampus*time | −0.016 | 0.005 | −3.095 | 0.002* |
| Hippocampus*progression | −0.041 | 0.052 | −0.782 | 0.435 |
| Progression*time | 0.051 | 0.012 | 4.389 | <0.001* |
| Hippocampus*time*progression | −0.012 | 0.011 | −1.040 | 0.299 |
| *Informant-reported total* | | | | |
| Base model | | | | |
| Time | 0.039 | 0.007 | 5.303 | <0.001* |
| CSF p-tau$_{181}$/Aβ$_{42}$ models | | | | |
| p-tau$_{181}$/Aβ$_{42}$*time | 0.041 | 0.007 | 5.945 | <0.001* |
| p-tau$_{181}$/Aβ$_{42}$*progression | −0.031 | 0.033 | −0.938 | 0.349 |
| Progression*time | 0.092 | 0.014 | 6.364 | <0.001 |
| p-tau$_{181}$/Aβ$_{42}$*time*progression | 0.044/0.014 | 0.013/0.015 | 3.323/0.934 | 0.001*/0.351 |
| Hippocampal volume models | | | | |
| Hippocampus*time | −0.026 | 0.008 | −3.525 | <0.001* |
| Hippocampus*progression | −0.103 | 0.040 | −2.577 | 0.011* |
| Progression*time | 0.108 | 0.016 | 6.687 | <0.001* |
| Hippocampus*time*progression | −0.014 | 0.015 | −0.946 | 0.345 |

*Notes.* *$p < .05$. See text for details regarding the analyses.

Taken together, the results of this study indicate that baseline AD biomarker burden was associated with decline of both self- and informant-reported memory, attention, and spatial navigation abilities. Cross-sectional work from our group demonstrated that the self-reported ECog memory, attention, and spatial navigation subsections were not robust predictors of AD-related biomarker positivity (Levine et al., 2023). These findings highlight the potential to use these ECog subsections to monitor subtle cognitive change occurring in the preclinical phase of AD and suggest that the ECog subsections may provide greater longitudinal utility than cross-sectional.

Future research would benefit from comparing the performance of the ECog subsections, or other subjective measures, in tracking cognitive change with objective neuropsychological tasks in clinically normal individuals. Additionally, it would be beneficial to compare the ECog with other brief and accessible cognitive measures, such as automated online neuropsychological assessments and phone screens, as these methods have also demonstrated utility in the preclinical stage (Öhman et al., 2021; Harrington et al., 2022). These comparisons would aid in identifying the optimal methods for tracking subtle cognitive change associated with AD pathology.

**Supplementary material.** The supplementary material for this article can be found at https://doi.org/10.1017/S135561772300070X

**Funding statement.** T.F. Levine and S.J. Dessenberger were funded by the National Science Foundation DGE-1745038. Data collection and sharing for this project was funded by the Alzheimer's Disease Neuroimaging Initiative (ADNI) (National Institutes of Health Grant U01 AG024904) and DOD ADNI (Department of Defense award number W81XWH-12-2-0012). ADNI is funded by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, and through generous contributions from the following: AbbVie, Alzheimer's Association; Alzheimer's Drug Discovery Foundation; Araclon Biotech; BioClinica, Inc.; Biogen; Bristol-Myers Squibb Company; CereSpir, Inc.; Cogstate; Eisai Inc.; Elan Pharmaceuticals, Inc.; Eli Lilly and Company; EuroImmun; F. Hoffmann-La Roche Ltd and its affiliated company Genentech, Inc.; Fujirebio; GE Healthcare; IXICO Ltd.; Janssen Alzheimer Immunotherapy Research & Development, LLC.; Johnson & Johnson Pharmaceutical Research & Development LLC.; Lumosity; Lundbeck; Merck & Co., Inc.; Meso Scale Diagnostics, LLC.; NeuroRx Research; Neurotrack Technologies; Novartis Pharmaceuticals Corporation; Pfizer Inc.; Piramal Imaging; Servier; Takeda Pharmaceutical Company; and Transition Therapeutics. The Canadian Institutes of Health Research is providing funds to support ADNI clinical sites in Canada. Private sector contributions are facilitated by the Foundation for the National Institutes of Health (www.fnih.org). The grantee organization is the Northern California Institute for Research and Education, and the study is coordinated by the Alzheimer's Therapeutic Research Institute at the University of Southern California. ADNI data are disseminated by the Laboratory for Neuro Imaging at the University of Southern California.

**Competing interests.** None.

## References

Allison, S. L., Fagan, A. M., Morris, J. C., & Head, D. (2016). Spatial navigation in preclinical Alzheimer's disease. *Journal of Alzheimer's Disease*, *52*(1), 77–90.

Allison, S., Babulal, G. M., Stout, S. H., Barco, P. P., Carr, D. B., Fagan, A. M., Morris, J. C., Roe, C. M., & Head, D. (2018). Alzheimer's disease biomarkers and driving in clinically normal older adults: Role of spatial navigation abilities. *Alzheimer Disease and Associated Disorders*, *32*(2), 101.

Allison, S. L., Rodebaugh, T. L., Johnston, C., Fagan, A. M., Morris, J. C., & Head, D. (2019). Developing a spatial navigation screening tool sensitive to the preclinical Alzheimer Disease Continuum. *Archives of Clinical Neuropsychology*, *34*(7), 1138–1155.

Aschenbrenner, A. J., Balota, D. A., Fagan, A. M., Duchek, J. M., Benzinger, T. L., & Morris, J. C. (2015). Alzheimer disease cerebrospinal fluid biomarkers moderate baseline differences and predict longitudinal change in attentional

control and episodic memory composites in the adult children study. *Journal of the International Neuropsychological Society*, *21*(8), 573–583.

Balota, D. A., Tse, C. S., Hutchison, K. A., Spieler, D. H., Duchek, J. M., & Morris, J. C. (2010). Predicting conversion to dementia of the Alzheimer's type in a healthy control sample: The power of errors in stroop color naming. *Psychology and Aging*, *25*(1), 208.

Baker, J. E., Lim, Y. Y., Pietrzak, R. H., Hassenstab, J., Snyder, P. J., Masters, C. L., & Maruff, P. (2017). Cognitive impairment and decline in cognitively normal older adults with high amyloid-β: A meta analysis. *Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring*, *6*, 108–121.

Bittner, T., Zetterberg, H., Teunissen, C. E., Ostlund Jr., R. E., Militello, M., Andreasson, U., Hubeek, I., Gibson, D., Chu, D. C., Eichenlaub, U., Heiss, P., Kobold, U., Leinenbach, A., Madin, K., Manuilova, E., Rabe, C., & Blennow, K. (2016). Technical performance of a novel, fully automated electro-chemiluminescence immunoassay for the quantitation of β-amyloid (1-42) in human cerebrospinal fluid. *Alzheimer's & Dementia*, *12*(5), 517–526.

Buckner, R. L., Head, D., Parker, J., Fotenos, A. F., Marcus, D., Morris, J. C., & Snyder, A. Z. (2004). A unified approach for morphometric and functional data analysis in young, old, and demented adults using automated atlas-based head size normalization: Reliability and validation against manual measurement of total intracranial volume. *Neuroimage*, *23*(2), 724–738.

Cantero, J. L., Iglesias, J. E., Van Leemput, K., & Atienza, M. (2016). Regional hippocampal atrophy and higher levels of plasma amyloid-beta are associated with subjective memory complaints in nondemented elderly subjects. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences*, *71*(9), 1210–1215.

Csernansky, J. G., Wang, L., Swank, J., Miller, J. P., Gado, M., McKeel, D., Miller, M. I., & Morris, J. C. (2005). Preclinical detection of Alzheimer's disease: Hippocampal shape and volume predict dementia onset in the elderly. *Neuroimage*, *25*(3), 783–792.

Daugherty, A. M., & Raz, N. (2017). A virtual water maze revisited: Two-year changes in navigation performance and their neural correlates in healthy adults. *NeuroImage*, *146*, 492–506.

Desikan, R. S., Ségonne, F., Fischl, B., Quinn, B. T., Dickerson, B. C., Blacker, D., Buckner, R. L., Dale, A. M., Maguire, R. P., Hyman, B. T., Albert, M. S., & Killiany, R. J. (2006). An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. *Neuroimage*, *31*(3), 968–980.

Ebenau, J. L., Timmers, T., Wesselman, L. M. P., Verberk, I. M. W., Verfaillie, S. C. J., Slot, R. E. R., van Harten, A. C., Teunissen, C. E., Barkhof, F., van den Bosch, K. A., van Leeuwenstijn, M., Tomassen, J., Braber, A., Visser, P. J., Prins, N. D., Sikkes, S. A. M., Scheltens, P., van Berckel, B. N. M., & van der Flier, W. M. (2020). ATN classification and clinical progression in subjective cognitive decline: The SCIENCe project. *Neurology*, *95*(1), e46–e58.

Farias, S. T., Mungas, D., Reed, B. R., Cahn-Weiner, D., Jagust, W., Baynes, K., & DeCarli, C. (2008). The measurement of everyday cognition (ECog): Scale development and Psychometric properties. *Neuropsychology*, *22*(4), 531–544.

Farias, S. T., Mungas, D., Harvey, D. J., Simmons, A., Reed, B. R., & DeCarli, C. (2011). The measurement of everyday cognition: Development and validation of a short form of the Everyday Cognition scales. *Alzheimer's & Dementia*, *7*(6), 593–601.

Farias, S. T., Park, L. Q., Harvey, D. J., Simon, C., Reed, B. R., Carmichael, O., & Mungas, D. (2013). Everyday cognition in older adults: Associations with neuropsychological performance and structural brain imaging. *Journal of the International Neuropsychological Society*, *19*(4), 430–441.

Farias, S. T., Lau, K., Harvey, D., Denny, K. G., Barba, C., & Mefford, A. N. (2017). Early functional limitations in cognitively normal older adults predict diagnostic conversion to mild cognitive impairment. *Journal of the American Geriatrics Society*, *65*(6), 1152–1158.

Fischl, B., Salat, D. H., Busa, E., Albert, M., Dieterich, M., Haselgrove, C., van der Kouwe, A., Killiany, R., Kennedy, D., Klaveness, S., Montillo, A., Makris, N., Rosen, B., & Dale, A. M. (2002). Whole brain segmentation: Automated labeling of neuroanatomical structures in the human brain. *Neuron*, *33*(3), 341–355.

Gleason, C. E., Zuelsdorff, M., Gooding, D. C., Kind, A. J. H., Johnson, A. L., James, T. T., Lambrou, N. H., Wyman, M. F., Ketchum, F. B., Gee, A., Johnson, S. C., Bendlin, B. B., & Zetterberg, H. (2022). Alzheimer's disease biomarkers in Black and non-Hispanic White cohorts: A contextualized review of the evidence. *Alzheimer's & Dementia*, *18*(8), 1545–1564.

Goldberg, T. E., Harvey, P. D., Wesnes, K. A., Synder, P. J., & Schneider, L. S. (2015). Practice effects due to serial cognitive assessment: Implications for preclinical Alzheimer's disease randomized control trials. *Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring*, *1*(1), 103–111.

Gordon, B. A., Blazey, T., Su, Y., Fagan, A. M., Holtzman, D. M., Morris, J. C., & Benzinger, T. L. (2016). Longitudinal β-amyloid deposition and hippocampal volume in preclinical Alzheimer disease and suspected non-Alzheimer disease pathophysiology. *JAMA Neurology*, *73*(10), 1192–1200.

Harrington, K. D., Roque, N. A., Strenger, J., Correia, S., Salloway, S. P., Sliwinski, M. J., & Thompson, L. I. (2022). Loneliness and subjective cognitive impairment in preclinical Alzheimer's disease and healthy aging. *Alzheimer's & Dementia*, *18*, e069279.

Hedden, T., Oh, H., Younger, A. P., & Patel, T. A. (2013). Meta-analysis of amyloid-cognition relations in cognitively normal older adults. *Neurology*, *80*(14), 1341–1348.

Hothorn, T., Bretz, F., & Westfall, P. (2008). Simultaneous inference in general parametric models. *Biometrical Journal*, *50*(3), 346–363.

Hutchison, K. A., Balota, D. A., & Ducheck, J. M. (2010). The utility of Stroop task switching as a marker for early-stage Alzheimer's disease. *Psychology and Aging*, *25*(3), 545.

Jack Jr., C. R., Bernstein, M. A., Fox, N. C., Thompson, P., Alexander, G., Harvey, D., Borowski, B., Britson, P. J., Whitwell, J. L., Ward, C., Dale, A. M., Felmlee, J. P., Gunter, J. L., Hill, D. L. G., Killiany, R., Schuff, N., Fox-Bosetti, S., Lin, C., Studholme, C., . . . Weiner, M. W. (2008). The Alzheimer's disease neuroimaging initiative (ADNI): MRI methods. *Journal of Magnetic Resonance Imaging: An Official Journal of the International Society for Magnetic Resonance in Medicine*, *27*(4), 685–691.

Jack Jr., C. R., Bennett, D. A., Blennow, K., Carrillo, M. C., Dunn, B., Haeberlein, S. B., Holtzman, D. M., Jagust, W., Jessen, F., Karlawish, J., Liu, E., Molinuevo, J. L., Montine, T., Phelps, C., Rankin, K. P., Rowe, C. C., Scheltens, P., Siemers, E., Snyder, H. M., . . . Silverberg, N. (2018). NIA-AA research framework: Toward a biological definition of Alzheimer's disease. *Alzheimer's & Dementia*, *14*(4), 535–562.

Jessen, F. (2014). Subjective and objective cognitive decline at the pre-dementia stage of Alzheimer's disease. *European Archives of Psychiatry and Clinical Neuroscience*, *264*(1), 3–7.

Korthauer, L. E., Nowak, N. T., Moffat, S. D., An, Y., Rowland, L. M., Barker, P. B., Resnick, S. M., & Driscoll, I. (2016). Correlates of virtual navigation performance in older adults. *Neurobiology of Aging*, *39*, 118–127.

Langbaum, J. B., Hendrix, S. B., Ayutyanont, N., Chen, K., Fleisher, A. S., Shah, R. C., Barnes, L. L., Bennett, D. A., Tariot, P. N., & Reiman, E. M. (2014). An empirically derived composite cognitive test score with improved power to track and treatments for preclinical Alzheimer's disease. *Alzheimer's & Dementia*,*10*(6), 666–674.

Levine, T. F., Allison, S. L., Stojanovic, M., Fagan, A. M., Morris, J. C., & Head, D. (2020). Spatial navigation ability predicts progression of dementia symptomatology. *Alzheimer's & Dementia*, *16*(3), 491–500.

Levine, T. F., Roe, C. M., Babulal, G. M., Fagan, A. M., & Head, D. (2022). Limited longitudinal change in self-reported spatial navigation ability in preclinical alzheimer disease. *Alzheimer Disease & Associated*, *36*(1), 15–21.

Levine, T. F., Allison, S. L., Dessenberger, S. J., Head, D., & Alzheimer's Disease Neuroimaging Initiative (2023). Clinical utility of self- and informant-reported memory, attention, and spatial navigation in detecting biomarkers associated with Alzheimer disease in clinically normal adults. *Journal of the International Neuropsychological Society*, 1–12.

McKhann, G., Drachman, D., Folstein, M., Katzman, R., Price, D., & Stadlan, E. M. (1984). Clinical diagnosis of Alzheimer's disease: Report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology*, *34*(7), 939–939.

Millar, P. R., Balota, D. A., Maddox, G. B., Duchek, J. M., Aschenbrenner, A. J., Fagan, A. M., Benzinger, T. L. S., & Morris, J. C. (2017). Process dissociation analyses of memory changes in healthy aging, preclinical, and very mild Alzheimer disease: Evidence for isolated recollection deficits. *Neuropsychology*, *31*(7), 708.

https://doi.org/10.1017/S135561772300070X Published online by Cambridge University Press

Morris, J. C. (1997). Clinical dementia rating: A reliable and valid diagnostic and staging measure for dementia of the Alzheimer type. *International Psychogeriatrics*, *9*(S1), 173–176.

Numbers, K., Lam, B. C., Crawford, J. D., Kochan, N. A., Sachdev, P. S., & Brodaty, H. (2023). Longitudinal changes in participant and informant reports of subjective cognitive complaints are associated with dementia risk. *Frontiers in Aging Neuroscience*, *15*, 1044807.

Öhman, F., Hassenstab, J., Berron, D., Schöll, M., & Papp, K. V. (2021). Current advances in digital cognitive assessment for preclinical Alzheimer's disease. *Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring*, *13*(1), e12217.

Petersen, R. C., Aisen, P. S., Beckett, L. A., Donohue, M. C., Gamst, A. C., Harvey, D. J., Jack, C. R., Jagust, W. J., Shaw, L. M., Toga, A. W., Trojanowski, J. Q., & Weiner, M. W. (2010). Alzheimer's disease neuroimaging initiative (ADNI): Clinical characterization. *Neurology*, *74*(3), 201–209.

Pinheiro, J., Bates, D., & R Core Team (2022). nlme: Linear and Nonlinear Mixed Effects Models. R package version 3.1-159. http://CRAN.R-project.org/package=nlme

Rabin, L. A., Smart, C. M., & Amariglio, R. E. (2017). Subjective cognitive decline in preclinical Alzheimer's disease. *Annual Review of Clinical Psychology*, *13*(1), 369–396.

Roebuck-Spencer, T. M., Glen, T., Puente, A. E., Denney, R. L., Ruff, R. M., Hostetter, G., & Bianchini, K. J. (2017). Cognitive screening tests versus comprehensive neuropsychological test batteries: A national academy of neuropsychology education paper. *Archives of Clinical Neuropsychology*, *32*(4), 491–498.

Rostamzadeh, A., Bohr, L., Wagner, M., Baethge, C., & Jessen, F. (2022). Progression of subjective cognitive decline to MCI or dementia in relation to biomarkers for Alzheimer disease: A meta analysis. *Neurology*, *99*(17), e1866–e1874.

Santangelo, R., Dell'Edera, A., Sala, A., Cecchetti, G., Masserini, F., Caso, F., Pinto, P., Leocani, L., Falautano, M., Passerini, G., Martinelli, V., Comi, G., Perani, D., & Magnani, G. (2019). The CSF p-tau181/Aβ42 ratio offers a good accuracy "in vivo" in the differential diagnosis of Alzheimer's dementia. *Current Alzheimer Research*, *16*(7), 587–595.

Scarth, M., Rissanen, I., Scholten, R. J., & Geerlings, M. I. (2021). Biomarkers of Alzheimer's disease and cerebrovascular lesions and clinical progression in patients with subjective cognitive decline: A systematic review. *Journal of Alzheimer's Disease*, *83*(3), 1089–1111.

Schindler, S. E., Gray, J. D., Gordon, B. A., Xiong, C., Batrla-Utermann, R., Quan, M., Wahl, S., Benzinger, T. L. S., Holtzman, D. M., Morris, J. C., & Fagan, A. M. (2018). Cerebrospinal fluid biomarkers measured by Elecsys assays compared to amyloid imaging. *Alzheimer's & Dementia*, *14*(11), 1460–1469.

Sperling, R. A., Aisen, P. S., Beckett, L. A., Bennett, D. A., Craft, S., Fagan, A. M., Iwatsubo, T., Jack Jr, C. R., Kaye, J., Montine, T. J., Park, D. C., Reiman, E. M., Rowe, C. C., Siemers, E., Stern, Y., Yaffe, K., Carrillo, M. C., Thies, B., Morrison-Bogorad, M., … Phelps, C. H. (2011). 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 & Dementia*, *7*(3), 280–292.

Storandt, M., Mintun, M. A., Head, D., & Morris, J. C. (2009). Cognitive decline and brain volume loss as signatures of cerebral amyloid-β peptide deposition identified with Pittsburgh compound B: cognitive decline associated with Aβ deposition. *Archives of Neurology*, *66*(12), 1476–1481.

Tong, T., Thokala, P., McMillan, B., Ghosh, R., & Brazier, J. (2017). Cost effectiveness of using cognitive screening tests for detecting dementia and mild cognitive impairment in primary care. *International Journal of Geriatric Psychiatry*, *32*(12), 1392–1400.

Weintraub, S., Carrillo, M. C., Farias, S. T., Goldberg, T. E., Hendrix, J. A., Jaeger, J., Knopman, D. S., Langbaum, J. B., Park, D. C., Ropacki, M. T., Sikkes, S. A. M., Welsh-Bohmer, K. A., Bain, L. J., Brashear, R., Budur, K., Graf, A., Martenyi, F., Storck, M. S., & Randolph, C. (2018). Measuring cognition and function in the preclinical stage of Alzheimer's disease. *Alzheimer's & Dementia: Translational Research & Clinical Interventions*, *4*(1), 64–75.

https://doi.org/10.1017/S135561772300070X Published online by Cambridge University Press