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Detectable Neuropsychological Differences in Early Preclinical Alzheimer's Disease: A Meta-Analysis

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Abstract

The development of methods for *in vivo* detection of cerebral beta amyloid retention and tau accumulation have been increasingly useful in characterizing preclinical Alzheimer's disease (AD). While the association between these biomarkers and eventual AD has been demonstrated among cognitively intact older adults, the link between biomarkers and neurocognitive ability remains unclear. We conducted a meta-analysis to test the hypothesis that cognitively intact older adults would show statistically discernable differences in neuropsychological performance by amyloid status (amyloid negative=A-, amyloid positive=A+). We secondarily hypothesized a third group characterized by either CSF tau pathology or neurodegeneration, in addition to amyloidosis (A+/N+ or Stage 2), would show lower neuropsychology scores than the amyloid positive group (A+/N- or Stage 1) when compared to the amyloid negative group. Pubmed, PsychINFO, and other sources were searched for relevant articles, yielding 775 total sources. After review for inclusion/exclusion criteria, duplicates, and risk of bias, 61 studies were utilized in the final meta-analysis. Results showed A+ was associated with poorer performance in the domains of global cognitive function, memory, language, visuospatial ability, processing speed, and attention/working memory/executive functions when compared to A-. A+/N+ showed lower performances on memory measures when compared to A+/N- in secondary analyses based on a smaller subset of studies. Results support the notion that neuropsychological measures are sensitive to different stages of preclinical AD among cognitively intact older adults. Further research is needed to determine what constitutes meaningful differences in neuropsychological performance among cognitively intact older adults.

Keywords

cognition; preclinical Alzheimer's disease; biomarker; meta-analysis

INTRODUCTION

Alzheimer's disease (AD) is an age-related condition clinically characterized by a progressive deterioration of episodic memory and other cognitive abilities, and pathologically characterized by beta amyloid plaque and tau pathology accumulation in the brain. Many recent advances have been made in detecting abnormal beta amyloid and tau pathology levels in vivo, and these coupled with an interest in early AD intervention and prevention have emphasized the importance of better characterizing the preclinical AD phase through the identification of biomarkers (Sperling et al., 2011). The identification of AD biomarkers has also yielded theoretically-informed models of the temporal sequence of biomarker presentation in the preclinical phase (e.g., Jack et al., 2010, Jack et al., 2013), and these have had a significant impact upon the field of AD research.

While the search for potential AD biomarkers has yielded numerous promising possibilities, in vivo assessments of the presence of amyloid plaque and tau pathology remain arguably some of the most salient and clinically-relevant biomarkers utilized in the preclinical phase. Previous work has reliably shown cognitively intact persons who are deemed amyloid positive as high risk for progressing to AD (Villegmagne et al., 2013; Andreasen et al., 2001). However, the link between AD biomarkers and cognitive abilities is less clear. Models of biomarker sequencing based on the amyloid cascade hypothesis (Hardy and Higgins, 1992; Hardy and Selkoe, 2002) suggest accumulation of AD pathology occurs prior to cognitive impairment or even subtle cognitive decline (Jack et al., 2010). However, recent work supports the notion that neuropsychological performance may inversely correlate with amyloid load among cognitively intact older adults (Hedden et al., 2013). If meaningful differences in neuropsychological performance can be observed according to AD biomarker status (positive versus negative), then this has significant implications for proposed biomarker sequence models of AD and may provide additional avenues for early intervention and prevention of AD.

The preclinical phase of AD has recently been operationalized to consist of distinct stages reflecting increasing progression of the AD pathological process (Sperling et al., 2011; Dubois et al., 2016), which can be described as a series of stages: Stage 1) asymptomatic amyloidosis, Stage 2) amyloidosis + neuronal injury, and Stage 3) amyloidosis + neuronal injury + subtle cognitive decline. Characterizing the degree of cognitive decline detectable in older adults who are biomarker positive but do not meet threshold for current operational definitions of mild cognitive impairment (i.e., "cognitively normal" older adults) will help further efforts to define subtle cognitive decline. Additionally, further investigation into cognitive function during earlier preclinical AD stages will inform whether subtle decline or impairment is restricted to individuals with both amyloidosis and neurodegeneration or whether these may be detectable at an even earlier stage (i.e., Stage 1 or 2).

To the authors' knowledge, there has yet to be a systematic review of the literature to test whether differences in neuropsychological performance are perceivable at the biomarker positive and negative group level among those deemed cognitively intact by current standards. We therefore conducted a meta-analysis to test the hypothesis that cognitively intact older adults would show statistically discernable differences in neuropsychological

performance by biomarker status. Specifically, we hypothesized older adults deemed amyloid positive would show poorer scores than those deemed amyloid negative across specific domains of cognition. We secondarily tested the hypothesis that amyloid positive older adults who additionally show evidence of neuronal injury based on tau pathology or neurodegeneration as defined by MRI (A+/N+ or Stage 2) would show poorer neuropsychology scores than the amyloid positive group without evidence of neuronal injury (A+/N- or Stage 1) with respect to the amyloid negative group (A- or Stage 0). These hypotheses challenge the null hypothesis that there are no discernable differences in neuropsychological performance among persons deemed cognitively intact who differ with respect to preclinical AD biomarker status.

METHODS

Literature Search

Guidelines from the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) were utilized for this research project (Liberati et al, 2009). In accordance with PRISMA guidelines, systematic review criteria were documented with the international prospective register of systematic reviews PROSPERO system (registration number: CRD42016046527). Literature search was conducted on August 28, 2016. The range of dates for articles was not restricted. The search term “amyloid and (control or normal) and (cognition or neuropsychology) and (PET or CSF or cerebrospinal fluid)” was applied to the PubMed and PsychINFO databases. PET was used as a common abbreviation for positron emission tomography, and CSF was used a common abbreviation for cerebrospinal fluid.

Inclusion/Exclusion Criteria

The following were used as inclusion criteria: (1) mean age greater than 50 years old, (2) human participant studies, (3) participants with cognition in the normal range (i.e., determined to be “cognitively normal” by not meeting criteria for dementia, mild cognitive impairment (MCI) or subtle cognitive impairment characterizing stage 3 preclinical AD, when the latter was defined within the study), and (4) report of at least one neuropsychological measure. We instituted an age cut point to exclude studies of younger groups that may not be directly relevant to AD (e.g., traumatic brain injury studies). The following were used as exclusion criteria: (1) studies focused on animal studies, (2) studies focused on another topic (e.g., traumatic brain injury, Parkinson’s disease, HIV), (3) duplicate studies, (4) data not grouped as biomarker positive and negative, (5) citations that were not empirical, peer-reviewed scientific articles (e.g., dissertations, books, abstract only, case studies), and (6) the absence of neuropsychological or cognitive data reported among cognitively normal participants.

Data Extraction and Risk of Bias

An author (CPN) independently reviewed all individual titles and abstracts of citations yielded from searches and other sources per the inclusion and exclusion criteria. These were also reviewed by a second author (SDH). A third author (DAN) served as a tie-breaker if there was disagreement regarding a particular citation. Full-text articles were downloaded and reviewed whenever there was a question as to one of the selection criteria. Risk of bias

was assessed at the study level. Articles were assessed for selective reporting, incomplete outcome data, quality of experimental design, and undue influence of funding sources. Quality of experimental design entailed review of methods for parameters such as ensuring adequate numbers per biomarker group, consideration of basic demographic factors, and IRB approval for research procedures. Undue influence of funding sources was considered if a study's findings were viewed to be potentially influenced by funding institutions or organizations. If an article was judged to indicate a potential risk of bias, it was excluded from the review. As in the case for inclusion and exclusion criteria, each article was reviewed by at least two authors (CPN and SDH) for potential risk of bias, and a third author (DAN or NHS) served as a tie-breaker for any disagreements.

Data Analysis

The outcomes for the present study were neuropsychological performance scores on any neuropsychological measure by biomarker group (e.g., amyloid positive vs. negative). Neuropsychological measure scores were grouped to assess for any specific effects by domain. The following seven domains were assessed: global cognitive function, memory, language, visuospatial, processing speed, attention/working memory/executive functions, and premorbid function. Table 1 lists the neuropsychological measures that were observed in the articles and used in the present review according to each measure's corresponding cognitive domain. If more than one neuropsychological measure was reported in a single study for a given cognitive domain, outcomes were pooled across the study and the mean effect size was used as the study's contribution per meta-analysis convention. The principle summary measures were standard differences in means (Hedges' g ; Hedges, 1981) as calculated by random effects models. Random effects models assume that the true effect size might differ from study to study. Thus, results are weighted, and inferences may be extended beyond the studies included in the meta-analysis (Hedges and Vevea, 1998). Heterogeneity refers to variability or diversity of studies included in a systematic review, and may be considered at multiple levels, including outcomes, study design, bias, and statistical inference. This is important to consider in a meta-analysis because heterogeneity may impact the robustness and generalizability of results. Heterogeneity was considered via statistical calculation of Q , τ , τ^2 , and I^2 . Q provides a measure of absolute heterogeneity of effects with a corresponding p -value (Cochran, 1954). τ and τ^2 provide measures of the standard deviation and variance of true effects respectively (Borenstein et al., 2009). These provide a basis for comparison across studies. I^2 refers to a ratio of true effect variance to observed error variance (Higgins et al., 2003). In two-group analyses (amyloid positive vs. negative) that yielded significant results, method of biomarker assessment (CSF vs. PET) was explored as a possible moderating variable in post-hoc analyses. We also explored the impact of age differences in post-hoc meta-regression analyses. In our secondary analyses that included studies that also characterized subjects as tau or neurodegeneration positive, analyses were conducted using the amyloid negative group (A-) as a control group to test effects between (1) amyloid positive and tau/neurodegeneration negative (A+/N- or stage 1) and (2) amyloid positive and tau/neurodegeneration positive (A+/N+ or stage 2) groups. If fewer than five studies were available for a particular analysis, the analysis was not conducted due to lack of adequate data as a quality control measure. Meta-analyses were conducted using Comprehensive

Meta-Analysis (CMA) software, version 3.3.070 (Biostat, Englewood, NJ). Forest plots were visualized using CMA, and significance was determined using an alpha of $p < 0.05$.

RESULTS

Study Selection

Search of databases yielded 754 sources, and additional 21 articles were identified through other sources (e.g., articles known to co-authors). This yielded a total of 775 sources screened. Of these, 71 were identified as animal studies and 29 were identified as either an abstract only, review article, opinion article, case study, dissertation, or book. After exclusion of these, 675 sources remained. Of these, 252 were determined to be duplicates, 166 were determined to focus on another topic, 22 were found to have no cognitive data for a normal cognition group, and 164 did not have data grouped by biomarker group (positive or negative). After these exclusions, 71 articles remained in the qualitative synthesis. Further assessment of articles revealed 7 with data in a different format than could be used in the present study (e.g., cognitive data presented in median and IQR, or in regression models with multiple covariates). In an attempt to include these 7 articles, requests were sent via email to corresponding authors for data in the form needed to conduct meta-analyses, but data were not received by the date of preparation of this manuscript. Risk of bias was assessed for the remaining studies, and 2 studies were found to include persons with MCI in the reportedly cognitively normal group, and 1 study was found to have questionable data due to extremely low numbers of participants per group. After these exclusions, 61 studies remained for the quantitative meta-analysis. The flowchart for determination of the studies reviewed for this meta-analysis is presented in Figure 1.

Amyloid Positive Versus Negative

Demographic data per study are presented in Table 2. Meta-analyses of neuropsychological measure data revealed a significant difference such that amyloid positive persons scored poorer than amyloid negative persons in global cognitive function (57 studies: $H_g = -0.124$, $SE_g = 0.039$, 95% CI = -0.200 to -0.049 , $p = 0.001$), memory (34 studies: $H_g = -0.171$, $SE_g = 0.041$, 95% CI = -0.252 to -0.090 , $p < 0.001$), language (25 studies: $H_g = -0.152$, $SE_g = 0.039$, 95% CI = -0.229 to -0.075 , $p < 0.001$), visuospatial ability (16 studies: $H_g = -0.132$, $SE_g = 0.045$, 95% CI = -0.221 to -0.043 , $p = 0.004$), processing speed (12 studies: $H_g = -0.199$, $SE_g = 0.095$, 95% CI = -0.384 to -0.013 , $p = 0.036$), and attention/working memory/executive functions (22 studies: $H_g = -0.122$, $SE_g = 0.040$, 95% CI = -0.200 to -0.044 , $p = 0.002$). Heterogeneity was found to be within the low to moderate range for global cognitive function ($Q = 95.664$, $p = 0.001$, $I^2 = 41.462$, $\tau = 0.178$, $\tau^2 = 0.032$), memory ($Q = 48.154$, $p = 0.043$, $I^2 = 31.470$, $\tau = 0.127$, $\tau^2 = 0.016$), processing speed ($Q = 18.439$, $p = 0.072$, $I^2 = 40.345$, $\tau = 0.203$, $\tau^2 = 0.041$), language ($Q = 24.769$, $p = 0.418$, $I^2 = 3.105$, $\tau = 0.035$, $\tau^2 = 0.001$), visuospatial ability ($Q = 14.999$, $p = 0.451$, $I^2 < 0.001$, $\tau < 0.001$, $\tau^2 < 0.001$), and attention/working memory/executive functions ($Q = 16.992$, $p = 0.712$, $I^2 < 0.001$, $\tau < 0.001$, $\tau^2 < 0.001$). Amyloid positive persons scored higher on measures of premorbid functioning than amyloid negative persons (11 studies: $H_g = 0.171$, $SE_g = 0.061$, 95% CI = 0.051 to 0.291 , $p = 0.005$), and it should be noted that the heterogeneity for this analysis was found to be very low ($Q = 4.630$, $p = 0.915$, $I^2 < 0.001$, $\tau < 0.001$, $\tau^2 < 0.001$).

Forest plots are presented for the domains of global cognitive function (Figure 2), memory (Figure 3), language (Figure 4), visuospatial ability (Figure 5), processing speed (Figure 6), attention/working memory/executive functions (Figure 7), and premorbid functioning (Figure 8).

In a set of post-hoc analyses, we considered the method of amyloid grouping, specifically cerebrospinal fluid (CSF) and positron emission tomography (PET), as a potential moderator for results. For the language domain, there was a difference ($Q=4.304$, $p=0.038$) such that PET (20 studies: $H_g=-0.188$, $SE_g=0.043$, 95% CI= -0.272 to -0.103 , $p<0.001$) was significant over CSF (5 studies: ns). For global cognitive functioning, memory, visuospatial ability, and processing speed, there was no significant difference between method of amyloid grouping. All studies included in the premorbid functioning analysis were conducted using PET, therefore this consideration was not pursued. In another set of post-hoc analyses, we used a meta-regression approach to consider whether standardized difference in means of age between biomarker groups might explain the perceived differences in cognitive performance. Using this approach, results were non-significant for global cognitive function, visuospatial ability, premorbid functioning, and attention/working memory/executive functions. Results were significant for memory (Coef= -0.2279 , $SE=0.1081$, 95% CI= -0.4397 to -0.0161 , $z=-2.11$, $p=0.0350$), which accounted for 28% of the variance; language (Coef= -0.2327 , $SE=0.1139$, 95% CI= -0.4560 to -0.0093 , $z=-2.04$, $p=0.0412$), which accounted for 100% of the variance; and processing speed (Coef= -0.7111 , $SE=0.2938$, 95% CI= -1.2869 to -0.1352 , $z=-2.42$, $p=0.0155$), which accounted for 67% of the variance.

Amyloid Positive Versus Tau/Neurodegeneration Positive

Only 9 studies had sufficient data to investigate differences between amyloid positive (A+/N- or Stage 1) and tau/neurodegeneration positive (A+/N+ or Stage 2) groups. Because of the low number of studies, results from this analysis are presented with caution. One study (Vos et al., 2016), presented data separately for amyloid determined via CSF and PET, so this study was considered as two separate studies for this analysis, yielding a total of 10 studies. Demographic data per dataset is presented in Table 3. Only global cognitive function and memory were considered due to lack of sufficient datasets (less than 5) to pursue analyses in other cognitive domains. Considering global cognitive function, Stage 2 groups were lower than amyloid negative (A- or Stage 0) groups ($H_g=-0.348$, $SE_g=0.076$, 95% CI= -0.497 to -0.199 , $p<0.001$; Figure 10), but not Stage 1 groups (ns). Heterogeneity was found to be within the very low range ($Q=3.700$, $p=0.717$, $I^2<0.001$, $\tau<0.001$, $\tau^2<0.001$) for the Stage 2 vs. Stage 0 meta-analysis. Using amyloid negative participants (A-) as a control group, the overall model was significant for global cognitive function and showed that amyloid positive (A+/N-) and tau/neurodegeneration positive (A+/N+) performed lower ($H_g=-0.284$, $SE_g=0.052$, 95% CI= -0.386 to -0.182 , $p<0.001$) relative to amyloid negative; however, there was no significant difference between these biomarker positive groups. This is visualized in the forest plot in Figure 11. Considering memory, Stage 2 groups were lower than amyloid negative (A- or Stage 0) groups ($H_g=-0.469$, $SE_g=0.104$, 95% CI= -0.673 to -0.264 , $p<0.001$; Figure 12), and also Stage 1 groups ($H_g=-0.459$, $SE_g=0.070$, 95% CI= -0.596 to -0.322 , $p<0.001$; Figure 13). Heterogeneity was found to be within the moderate

range ($Q=19.084$, $p=0.004$, $I^2=68.560$, $\text{Tau}=0.223$, $\text{Tau}^2=0.050$) for the Stage 2 vs. Stage 0 meta-analysis, and within the low range ($Q=6.343$, $p=0.386$, $I^2=5.413$, $\text{Tau}=0.044$, $\text{Tau}^2=0.002$) for the Stage 2 vs. Stage 1 meta-analysis. Using amyloid negative (A-) participants as a control group, the overall model was significant for memory ($H_g=-0.173$, $\text{SE}_g=0.047$, 95% CI=-0.265 to -0.080, $p<0.001$), and there was a significant difference ($Q=10.146$, $df=1$, $p=0.001$) between biomarker positive groups such that the tau/neurodegeneration positive group (A+/N+) showed significantly lower performances (7 datasets: $H_g=-0.469$, $\text{SE}_g=0.104$, 95% CI=-0.673 to -0.264, $p<0.001$) than the amyloid positive group (A+/N-; ns) when compared to the amyloid negative group. This is visualized in the forest plot in Figure 14. Only 4 studies had sufficient data for consideration of Stage 3 participants. Because of this low number, Stage 3 meta-analyses were not conducted and these participants were not included in these analyses.

DISCUSSION

Using a standardized meta-analytic approach, we examined whether differences in neuropsychological performance could be detected according to specific cognitive domains among cognitively intact older adults who are considered positive for amyloidosis and those considered negative. Our findings suggest that small but significant differences are observable in neuropsychological measures of global cognitive function, memory, language, visuospatial ability, processing speed, and attention/working memory/executive functions. Furthermore, in a second set of meta-analyses where amyloid negative persons served as a reference group, cognitively normal older adults who are positive for tau pathology or neurodegeneration (A+/N+) showed lower performances on memory measures versus those who are only amyloid positive (A+/N-). Altogether these results suggest that neuropsychological measures are sensitive to different stages in preclinical AD among older adults considered to be in the normal cognitive range.

Previous models of biomarker sequencing suggest accumulation of AD pathology and neuroimaging structural and functional changes occur prior to cognitive impairment or significant cognitive decline (e.g., Jack et al., 2010). This understanding suggests that cognitively normal persons who differ with respect to preclinical AD biomarker status would not differ with respect to performances on neuropsychological measures, and some have supported this notion in previous empirical work (Goldman et al., 2001). This was the null hypothesis against which we tested our hypotheses, and the results of our meta-analysis study rejected this null. Our study thus adds to the growing cannon of literature (e.g., Hedden et al., 2012) that suggests detectable cognitive differences may occur earlier in the course of AD than previously considered, and these may be associated with increasing cerebral amyloid retention and tau accumulation. Widely used criteria for staging preclinical AD were used as the basis of the current study (Sperling et al., 2011), and these criteria are predicated on the amyloid cascade hypothesis (Hardy and Higgins, 1992; Hardy and Selkoe, 2002) that require the presence of amyloidosis to define the preclinical AD state. The results of our primary analyses may therefore be viewed as consistent with the amyloid hypothesis. More recently, an “A/T/N” (amyloid/tau/neurodegeneration) system was proposed to serve as an unbiased descriptive classification scheme that may better serve population-based studies of cognitive aging (Jack et al., 2013b). This was not proposed to be used to define

any specific diagnostic system (e.g., Alzheimer's disease), although this may better capture neuropathological models of AD that are not centered around amyloid as the fundamentally initiating pathological event. The A/T/N system also provides a mechanism for characterizing individuals who may show a neurodegeneration-first pathway to AD, such as individuals with suspected non-Alzheimer's pathology (SNAP, or A–N+) who were not included in the current meta-analysis. Studies using CSF biomarkers included in our secondary analyses looking at preclinical AD subgroups considered measures of CSF total tau (t-tau) and/or CSF phosphorylated tau (p-tau) as indicative of neuronal dysfunction or neurodegeneration (e.g., N+), but these were not considered separately in a way that would allow further examination of those meeting criteria for tau pathology (T+) as defined in the recent A/T/N system (p-tau or tau PET).

The results of our analyses that show that cognitive differences are detectable in biomarker positive cognitively normal individuals even when specifically excluding evidence of MCI. Given these results, we propose consideration of “cognition positive” (C+) as an additional important biomarker (in this case, a cognitive marker) that may capture important functional brain changes that may predate biomarker changes or occur outside of the sequence laid forth by the amyloid cascade hypothesis. Recent evidence indicates that AD-related neuropathological changes may occur well in advance of changes in CSF and PET markers, particularly for pre-tangle (Braak & Del Tradici, 2015) and beta amyloid oligomer (Viola & Klein, 2015) pathologies. Thus, cognitive markers may be of value in identifying the earliest changes in brain function related to pathophysiological events predating a change in amyloid or tau *in vivo* biomarker signal. The potential importance of defining individuals as cognition positive (C+) is further supported by studies showing memory decline may predate the emergence of *in vivo* markers of either tau or amyloid biomarkers (Jedynak et al., 2012; Iturria-Medina et al., 2016). The implications of our results are significant in that neuropsychological measures, which are of lower cost and are less invasive than CSF acquisition or PET scanning procedures, may be utilized to reliably detect AD pathological changes in the preclinical phase. Since all of the participants in our study were deemed to be within normal cognitive limits per standardized norms or other norming procedures, further research is needed to determine what may be considered a clinically significant difference in neuropsychological performance within what is commonly considered the normal range. To this end, longitudinal considerations may be particularly sensitive to changes in the preclinical AD phase, as changes over time may reflect growing neuropathology. The absence of practice effects may also serve as a potential preclinical marker of subtle cognitive impairment (Hassenstab et al., 2015; Machulda et al., in press; Duff et al., 2014), although baseline age of participants may be an important factor to consider (Lamar et al., 2003). Composite cognitive measure approaches may additionally yield promising psychometric properties for this purpose as these have been found to minimize potential Type I error (Langbaum et al., 2015) and have improved power to detect decline (Langbaum et al., 2014). Cognitive composites have been shown to be sensitive to cognitive decline in preclinical AD and will be used as primary outcome measures in secondary prevention trials (Ayutayanont et al., 2014; Donahue et al., 2014). It should be noted that the C+ conceptualization also presents challenges which are not readily addressable, and thus this remains more aspirational rather than practical. It would be most advantageous to have a

clinical cut-off score for cognitive measures with established sensitivity and specificity established for AD biomarkers. However, the values for these are likely to be low and there are a number of reasons other than AD that may result in low scores. More research is needed to determine if specific patterns of performances might be sensitive to biomarker status.

The subtle cognitive decline characterizing preclinical AD Stage 3 was not initially operationalized by the work group that defined preclinical AD stages by biomarker status, but was described as approaching the border zone of MCI (Sperling et al., 2011). Several groups have attempted to characterize this subtle cognitive impairment using various approaches, including use of a global cognitive domain score cut-off at the 10th percentile (Jack et al., 2012), a memory composite score cut-off at the 10th percentile (Vos et al., 2013), and having two out of six scores greater than one standard deviation below published normative data in two separate cognitive domains or a subtle decline in functional abilities defined as a Functional Assessment Questionnaire score of 6-8 (Edmonds et al., 2016). Only four of the ten studies divided A+N+ individuals into Stages 2 and 3 based upon the presence or absence of subtle cognitive impairment (Edmonds et al., 2016; Jack et al., 2012; Knopman et al., 2012; Vos et al., 2013). Thus, we believed we had an insufficient number of studies to adequately compare Stage 3 preclinical AD to earlier stages using meta-analytic approaches. Because of our goal to exclude all subjects with identified cognitive impairment (even subtle), we did not include participants identified as Stage 3 in the current study. This approach was selected to more robustly test our hypotheses, as it could be argued that any perceived differences may be driven by those who are found to have MCI, which would have been more represented in the biomarker positive groups. However, it should be acknowledged this approach may have attenuated the effect sizes observed. The remaining studies in these analyses did not operationally define subtle cognitive impairment and thus theoretically can be considered to include potentially both Stage 2 and Stage 3 individuals. Future work will need to link the subtle cognitive changes observed in Stage 3 with the cognitive differences observed in Stage 2 and Stage 1 in the present study.

Of the different cognitive domains considered, memory measures were most sensitive to preclinical AD biomarker stages. These showed differences not only between amyloid positive and negative groups, but also between amyloid positive and tau/neurodegeneration positive groups. Tau neuropathology has consistently shown associations with memory measures (Nelson et al., 2012), and memory measures have long been associated with clinically-relevant progression of AD. For these reasons, it is not surprising these measures may be most sensitive to preclinical AD stages. Future research is also needed to determine what specific components of memory might be most sensitive to accumulating neuropathology in preclinical AD, as these may be different than in clinically early AD. One potentially important consideration is subjective memory decline, as there seems to be some suggestion that subjective complaints may occur prior to objective memory impairment in the course of AD (Jessen et al., 2014). Efforts are currently underway to operationalize and quantify subjective memory decline for the goal of assessing its utility in preclinical AD. Despite the importance of our findings regarding memory as a key early domain of decline, the fact that all cognitive domains showed significant differences is also important. Memory is a particularly vulnerable domain in early AD, but it is increasingly recognized that many

cases of AD may initially present with other nonamnestic forms of cognitive impairment (Knopman et al., 2015). Thus, future studies should aim for comprehensive characterization of cognitive decline while still emphasizing the importance of memory.

We also made other observations that merit some further discussion. Our investigation of premorbid intellectual ability revealed that amyloid positive persons may have higher scores than amyloid negative persons. Although the significance of this perceived difference is unclear, a recent large meta-analytic study of cerebral amyloidosis has shown an association between higher educational attainment and cerebral amyloid levels (Jansen et al., 2015). This may be viewed as consistent with the cognitive reserve hypothesis since more highly educated individuals (who arguably have higher cognitive reserve, and by extension, higher premorbid intellectual functioning) can sustain greater amyloid pathology before developing signs of dementia. Thus, the higher premorbid intellectual functioning observed in biomarker positive non-cognitively impaired older adults may reflect greater cognitive reserve. We also observed in post-hoc analyses that PET was differentially and more strongly associated with language performance differences between amyloid positive and amyloid negative groups than CSF markers. While this finding might be driven in part by the low numbers of CSF studies relative to PET studies, the possibility that amyloid positivity as measured by PET may be more sensitive to language differences by biomarker status needs further exploration. Finally, we observed that the standard difference in means for age explained a portion of the variance for memory (28%), processing speed (67%), and language (100%) among amyloid positive and negative groups. Given that amyloid accumulation is strongly associated with age, it is difficult to determine the significance of these results. However, it is notable that with the exception of language abilities, age only explained a portion of the difference if at all among multiple cognitive domains considered.

The present study has a number of limitations which need to be acknowledged. First, the approach of grouping neuropsychological measures by broad cognitive domains may reduce sensitivity of specific measures over those that are not as sensitive. The approach we employed was chosen because it maximized incorporation of all neuropsychological data available; however, if sufficient data were provided to focus on episodic memory specifically, for example, this might have yielded more significant findings. Second, our strict exclusion criteria may have prevented the inclusion of some studies that may have been relevant to the hypotheses addressed. We attempted to obtain data in the form needed for meta-analysis by directly contacting authors, but attempts to obtain these data for some studies were unsuccessful. Third, our analyses could not fully account for factors that might explain neuropsychological performance differences between groups. Although we considered certain factors in our approach, we cannot account for other factors that might explain differences in cognition, such as cardiovascular risk and socioeconomic status. Fourth, some cognitive domain analyses (language, visuospatial, processing speed, premorbid functioning) had fewer studies included in analyses than others (global cognitive functioning, memory, attention/working memory/executive functions), and the analyses considering amyloid positive and tau/neurodegeneration positive groups had only very few studies. For these reasons, results for these specific analyses should be interpreted with caution. Fifth, it should be noted that our goal of including participants without cognitive impairment was dependent on appropriate characterization of cognitive abilities by

investigators. There is variability in how cognitive abilities are measured and what is deemed cognitive impairment among research groups, therefore this variability may impact the generalizability of our results. Sixth, we acknowledge that studies that were not published but may have had an impact upon our results were not included in the present study. Seventh, we note that the reviewers were not blinded to the institution or authors of studies. We do not believe this impacted study selection; however, we acknowledge this as a possible limitation. Eighth, while we attempted to contact some study authors to obtain reported cognitive data in the form necessary for our analyses, we did not contact all study authors of rejected studies to determine if cognitive data were available in studies that did not originally include cognition as an outcome. This might have significantly increased our numbers for analysis. Finally, relatively few AD research laboratories and centers have the means to characterize preclinical AD biomarkers. For this reason, multiple studies may use data from the same research cohorts. The degree to which individual studies used the same participants could not be determined, and this may have had an impact on the effects observed in these studies. More specifically, if multiple studies were drawn from the same participant pool, then this would have the effect of overgeneralizing our findings.

Despite these limitations, the implications of the present study are consequential. Our meta-analytic review of the literature supports the notion that neuropsychological measures are sensitive to different stages of preclinical AD among older adults considered cognitively intact. It is striking that these differences are perceived across multiple different research sites, groups, and cohorts. It is also striking that these differences occurred despite the exclusion of participants identified as having subtle cognitive declines (Stage 3). Further research is needed to determine what constitutes meaningful differences in neuropsychological performance among cognitively intact older adults and how these may correlate with preclinical AD biomarkers.

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Figure 1.
Meta-Analysis Flow Diagram

Figure 2. Forrest plot for global cognitive function for amyloid positive and negative
 Difference in means reflects amyloid positive minus amyloid negative. Rhombus midpoint is the standard difference in means and the left and right points span the lower and upper limit.

Memory

Figure 3. Forrest plot for memory for amyloid positive and negative

Difference in means reflects amyloid positive minus amyloid negative. Rhombus midpoint is the standard difference in means and the left and right points span the lower and upper limit.

Figure 4. Forrest plot for language for amyloid positive and negative
 Difference in means reflects amyloid positive minus amyloid negative. Rhombus midpoint is the standard difference in means and the left and right points span the lower and upper limit.

Figure 5. Forrest plot for visuospatial for amyloid positive and negative

Difference in means reflects amyloid positive minus amyloid negative. Rhombus midpoint is the standard difference in means and the left and right points span the lower and upper limit.

Figure 6. Forrest plot for processing speed for amyloid positive and negative

Difference in means reflects amyloid positive minus amyloid negative. Rhombus midpoint is the standard difference in means and the left and right points span the lower and upper limit.

Attention, Working Memory, Executive Functions

Figure 7. Forrest plot for attention/working memory/executive functions for amyloid positive and negative

Difference in means reflects amyloid positive minus amyloid negative. Rhombus midpoint is the standard difference in means and the left and right points span the lower and upper limit.

Figure 8. Forrest plot for premorbid functioning for amyloid positive and negative
 Difference in means reflects amyloid positive minus amyloid negative. Rhombus midpoint is the standard difference in means and the left and right points span the lower and upper limit.

Figure 9. Forest plot for language with CSF/PET as moderator for amyloid positive and negative
 Difference in means reflects amyloid positive minus amyloid negative. Rhombus midpoint is the standard difference in means and the left and right points span the lower and upper limit.

Figure 10.
Meta-regression of standardized mean difference in age and memory in amyloid positive and negative

Figure 11.
Meta-regression of standardized mean difference in age and language in amyloid positive and negative

Figure 12.
Meta-regression of standardized mean difference in age and processing speed in amyloid positive and negative

Global Cognitive Function (Stage 0 vs. Stage 2)

Figure 13. Forrest plot for global cognitive function amyloid negative (A– or Stage 0) versus tau/neurodegeneration positive (A+/N+ or Stage 2)

Difference in means reflects tau/neurodegeneration minus amyloid negative. Rhombus midpoint is the standard difference in means and the left and right points span the lower and upper limit.

Figure 14. Forrest plot for global cognitive function amyloid positive (A+/N- or Stage 1) versus tau/neurodegeneration positive (A+/N+ or Stage 2) using amyloid negative (A- or Stage 0) as a control group

Difference in means reflects tau/neurodegeneration minus amyloid positive using amyloid negative as a control group. Rhombus midpoint is the standard difference in means and the left and right points span the lower and upper limit.

Figure 15. Forrest plot for memory amyloid negative (A– or Stage 0) versus tau/neurodegeneration positive (A+/N+ or Stage 2)

Difference in means reflects tau/neurodegeneration minus amyloid negative. Rhombus midpoint is the standard difference in means and the left and right points span the lower and upper limit.

Figure 16. Forrest plot for memory amyloid positive (A+/N- or Stage 1) versus tau/neurodegeneration positive (A+/N+ or Stage 2)

Difference in means reflects tau/neurodegeneration minus amyloid positive. Rhombus midpoint is the standard difference in means and the left and right points span the lower and upper limit.

Figure 17. Forest plot for memory amyloid positive (A+/N- or Stage 1) versus tau/neurodegeneration positive (A+/N+ or Stage 2) using amyloid negative (A- or Stage 0) as a control group

Difference in means reflects tau/neurodegeneration minus amyloid positive using amyloid negative as a control group. Rhombus midpoint is the standard difference in means and the left and right points span the lower and upper limit.

TABLE 1

Neuropsychological Measures by Domain

<u>Domain</u>	<u>Abbreviation</u>	<u>Test</u>
Global	ADAS-Cog	Alzheimer's Disease Assessment Scale cognitive subscale
	Cognitive composite	Calculated Z-score from cognitive domains (i.e. episodic, semantic, working, and visuospatial memory)
	Global	Composite Global Cognition Score
	MDRS	Mattis Dementia Rating Scale
	MMSE	Mini Mental State Examination
	Non-Memory	Composite Non-Memory Score
	WMS Mental Control	Wechsler Memory Scale – Mental Control
	STMS	Short Test of Mental Status
Memory	AVLT Delayed Recall	Auditory Verbal Learning Test – Delayed Recall
	AVLT Recall	Auditory Verbal Learning Test – Recall
	AVLT Recognition	Auditory Verbal Learning Test – Recognition
	BVRT Delayed	Benton Visual Retention Test – Delayed
	CVLT-II Delayed Recall	California Verbal Learning Test, second edition – Delayed Recall
	CVLT-II Immediate Recall	California Verbal Learning Test, second edition – Immediate Recall
	CVLT-II Learning	California Verbal Learning Test, second edition – Sum of Learning Trials
	CVLT-II Recognition	California Verbal Learning Test, second edition – Recognition
	Detail Accuracy	Detail Accuracy (per trial)
	Episodic Memory	Composite Episodic Memory Score
	FCSRT	Free and Cued Selective Reminding Test
	FCsrt	Free and Cued Selective Reminding Test—Cued Recall subtest
	FCSRT-L	Free and Cued Selective Reminding Test – Learning
	FCSRT-R	Free and Cued Selective Reminding Test – Recall
	FCSRT-TL	Free and Cued Selective Reminding Test – Total Learning
	FCSRT-TR	Free and Cued Selective Reminding Test – Total Recall
	F-Name letter	Rentz Face-Name Task
	FRsrt	Free and Cued Selective Reminding Test—Free Recall subtest
	Gist correct rejection rate	Gist Memory Task – correct rejection rate
	Gist hit rate	Gist Memory Task – items remembered
	Gist sensitivity d'	Gist Memory Task – sensitivity d'
	ISLT	International Shopping List Task
	M@T	Memory Alteration Test
	Mem Factor Score	Memory Factor Score
	Memory	Composite Memory Score
	One Card Learning Task	Cogstate One Card Learning task
	Rey-3' Recall	Rey-Osterrieth Complex Figure 3-Minute Recall
	Rey-30' Recall	Rey-Osterrieth Complex Figure 30-Minute Recall
	RCFT Immediate	Rey-Osterrieth Complex Figure – Immediate Recall
	RCFT Delayed	Rey-Osterrieth Complex Figure – Delayed Recall

Domain	Abbreviation	Test
	SRT (6-Trial Selective Reminding Test): total recall	6-Trial Selective Reminding Test
	SRT: long delayed recall	Selective Reminding Test: Long Delayed Recall
	SRT: short delayed recall	Selective Reminding Test: Short Delayed Recall
	Verbal Memory	Verbal Episodic Memory (included CVLT-II long delay free recall and CVLT-II d' recognition scores, and Logical Memory delayed recall)
	Visual Memory	Visual Episodic Memory (included Rey Complex Figure Test 30-minute delayed recall, Cogstate One Card Learning task, and Cogstate One Back task)
	WMS Associate Learning	Wechsler Memory Scale – Associate Learning
	WMS Delayed Recall	Wechsler Memory Scale – Delayed Recall Index Score
	WMS Immediate Recall	Wechsler Memory Scale – Immediate Recall Index Score
	WMS-R Logical Memory Delayed	Wechsler Memory Scale, Revised – Logical Memory Delayed
	WMS-R Logical Memory Immediate	Wechsler Memory Scale, Revised – Logical Memory Immediate
	WMS-R Mem	Wechsler Memory Scale, Revised – Logical Memory Story A
	WMS-R Paired Associates Immediate Recall	Wechsler Memory Scale, Revised – Paired Associates Immediate Recall
	WMS VR Delayed Recall	Wechsler Memory Scale – Visual Reproduction Delayed Recall
	WMS VR Immediate Recall	Wechsler Memory Scale – Visual Reproduction Immediate Recall
	Word List Delayed Recall score	Consortium to Establish a Registry for Alzheimer's Disease Word List Learning – Delayed Recall Score
Language	BNT	Boston Naming Test
	CAT	Category Generation – Animals, Vegetables, and Fruits
	CF	Categorical Fluency
	FAS	Controlled Oral Word Fluency to the letters F-A-S
	Language	Composite Language Score
	LF	Letter Fluency
	Phonemic Fluency	Verbal Fluency – Phonemic
	Semantic Fluency	Verbal Fluency – Semantic
	SM	Composite Semantic Memory Score
	Verbal Fluency – Animals	Category Generation – Animals
	Verbal Fluency – Vegetables	Category Generation – Vegetables
	Vocabulary	Composite Vocabulary Score
	WAIS Information	Wechsler Adult Intelligence Scale
Visuospatial	BPSO	Behavioral Pattern Separation-Object Task
	GMLT composite	Groton Maze Learning Task – Composite score
	GMLT moves/s (MPS)	Groton Maze Learning Task – Moves Per Second
	GMLT Total Errors (TER)	Groton Maze Learning Task – Total Number of Errors
	Perceptual comparison, ms	Perceptual Comparison Task (milliseconds)
	PDT	Perceptual Digital Test
	RCFT Copy	Rey-Osterrieth Complex Figure – Copy
	Rey	Modified Rey Osterrieth Figure Recalls
	VFDT	Visual Form Discrimination Test
	Visuospatial	Composite Visuospatial Score

Domain	Abbreviation	Test
	VOSP Numbers	Visual Object and Space Perception Battery Number Location Task
	WAIS Block	Wechsler Adult Intelligence Scale – Modified Block Design Subtest
	WAIS-R Block	Wechsler Adult Intelligence Scale, Revised – Modified Block Design Subtest
Processing Speed	DSST	Digit Symbol Substitution Test
	Motor speed, tap/second, left hand	Basic motor speed
	Sensorimotor speed, ms	Sensorimotor speed mean (milliseconds)
	Speed	Composite Processing Speed/Attention Score
	WAIS-III Digital Symbol	Wechsler Adult Intelligence Scale, third edition – Digital Symbol
	WAIS-III Symbol Search	Wechsler Adult Intelligence Scale, third edition – Symbol Search
	WMS-R Digit Symbol Coding	Wechsler Memory Scale, Revised – Digit Symbol Coding
Premorbid	AMNART	American National Adult Reading Test
	WTAR IQ	Premorbid Intelligence Quotient – Wechsler Test of Adult Reading
	VIQ	Verbal Intelligence Quotient
Attention/WM/EF	Attention	Composite Attention Score
	CAT	Category Generation (60 seconds to 3 categories, animals, vegetables, and fruit)
	Clock Drawing	Spontaneous Clock Drawing
	Conceptual comparison, ms	Conceptual Comparison Task (milliseconds)
	Digit Span	Wechsler Adult Intelligence Scale, third edition – Digit Span
	DSB	Digit Span Backward
	DSF	Digit Span Forward
	Executive Function	Composite Executive Function Score
	Hayling incongruent- congruent conditions, ms	Hayling Test – incongruent-congruent conditions (milliseconds)
	Letter Sternberg Task RT	Letter Sternberg Task Response Time
	Letter Sternberg Task Accuracy	Letter Sternberg Task Proportion Correct
	Letter Sternberg Task d'	Letter Sternberg Task d' scores
	LNS	Wechsler Adult Intelligence Scale, third edition – Letter-Number Sequencing
	LS	Listening Span Task
	Matrix Reasoning	Wechsler Adult Intelligence Scale, third edition – Matrix Reasoning
	N-back	N-back Task Score
	One Back Task	Cogstate One Back Task
	RPM	Raven's Progressive Matrices (range 0–36)
	Stroop Test incongruent-neutral conditions, ms	Stroop Color-Word Interference – incongruent-neutral conditions (milliseconds)
	Stroop Test no. of intrusions	Stroop Color-Word Interference – number of intrusions
	Stroop Test response time differences	Stroop Color-Word Interference – response time differences
	TMT A	Trail Making Test A
	TMT B	Trail Making Test B
	WMS-R DSB	Wechsler Memory Scale, Revised – Digit Span Backward
	WMS-R DSF	Wechsler Memory Scale, Revised – Digit Span Forward
	Working Memory	Composite Working Memory Score

Table 2

Demographic data for participants in amyloid positive versus amyloid negative analysis

Study	Biomarker	N		Age				Education				Sex	
		Amyloid−	Amyloid+	Amyloid−		Amyloid+		Amyloid−		Amyloid+		Amyloid−	Amyloid+
				M	SD	M	SD	M	SD	M	SD	%F	%F
Aizenstein et al. (2008)	PET	29	9	73.4	6	74.2	5.4	14.9	2.6	14.3	2.8	69	56
Alcolea et al. (2015)	CSF	203	26	57.3	6.5	60.6	7.9	—	—	—	—	59.1	69.2
Amariglio et al. (2012)	PET	97	34	72.7	5.9	75.5	6	16.3	2.9	15.6	1	51.5	57.1
Amariglio et al. (2015)	PET	122	32	71.6	5.7	73.1	5	15.9	3	16.4	2.7	63.1	59.4
Besson et al. (2015)	CSF	46	8	64.5	8	73.1	6.9	11.9	3.7	11	3.7	46	75
Besson et al. (2015)	PET	42	12	66	8.7	65	7.3	11.8	3.8	11.4	3.5	52	42
Buckley et al. (2016)	PET	230	58	69	5.9	72	7.2	—	—	—	—	54	50
Chen et al. (2015)	PET	88	26	77.7	6.5	77.2	4.6	16.6	3	16	2.5	45	38
Chetelat et al. (2010)	PET	31	13	73.1	7.1	78.8	5.5	14	3.3	14.3	3	65	31
Chetelat et al. (2012)	PET	54	20	72.7	7.3	76.6	6.4	14.2	3.2	14.1	3.4	52	40
Donohue et al. (2014)	PET	60	37	74.8	5.4	77.5	4.7	15.2	2.9	15.5	3.2	50	32
Doraiswamy et al. (2012)	PET	59	10	68.5	11.3	77.3	8	15.2	2.4	15.9	0.7	62.7	40
Doraiswamy et al. (2014)	PET	57	10	68.7	11.3	77.3	8	15.2	2.4	15.9	0.7	63.2	40
Edmonds et al. (2015)	CSF	142	48	72.3	6.8	71.8	6.7	16.2	2.6	16.1	3	48.6	54.2
Elman et al. (2014)	PET	33	16	76.8	5.3	75.6	4.7	16.7	1.7	16.4	2.3	61	56
Fortea et al. (2011)	CSF	18	15	68.3	6.4	72.7	7.9	10.4	4.6	9.7	3.9	56	53
Frapp et al. (2008)	PET	10	5	70.3	8.2	76	2.7	—	—	—	—	40	80
Gidycz et al. (2015)	PET	140	46	73.7	5.9	76.6	6.1	16.2	2.7	16.3	2.8	53	61
Gietl et al. (2015)	PET	74	11	67.7	5.5	72.1	5.7	15.1	2.8	14.6	2.4	—	—
Gu et al. (2015)	PET	75	41	83.8	4.4	85.9	4.7	12.6	3.5	12.8	4.1	60	71
Harrington et al. (2016)	PET	278	81	68.7	6.1	73.5	7.3	—	—	—	—	53	53
Hassenstab et al. (2016)	PET	177	87	71.6	5	73.1	6.2	15.3	2.6	15.9	3	58.2	40.2
Hatashita et al. (2010)	PET	74	17	64.2	8.9	69.2	7.9	—	—	—	—	48	53
Holland et al. (2012)	CSF	58	39	75.5	5.3	77	5.3	—	—	—	—	52	46
Hsu et al. (2014)	PET	56	18	67.4	5.7	69.6	7.4	15.5	2.6	16.7	1.8	73	61
Huijbers et al. (2014)	PET	24	24	74.4	1.2	76.8	1.3	16.8	0.6	16.9	0.5	58	42

Study	Biomarker	N		Age				Education				Sex	
		Amyloid−	Amyloid+	Amyloid−		Amyloid+		Amyloid−		Amyloid+		Amyloid− %F	Amyloid+ %F
				M	SD	M	SD	M	SD	M	SD		
Jack et al. (2012)	PET	193	70	77	5	79	5	14	3	14	3	49	50
Jack et al. (2013)	PET	67	80	78	5	80	5	14	3	14	3	45	37
Jack et al. (2014)	PET	503	213	69	9	75	7	15	3	15	3	47	53
Knopman et al. (2012)	PET	127	44	77	4	79	5	14	3	14	2	49	45
Lim et al. (2014)	PET	29	27	75.3	6.4	76.3	5.8	14.8	2.4	14.3	2.4	69	63
Lim et al. (2015)	PET	48	15	63.9	6.3	62.8	5.4	17.5	3.5	17.2	2.8	58.3	73.3
Lim et al. (2016)	PET	326	33	68.3	6	73.1	7.1	−	−	−	−	54.9	66.7
Llado-Saz et al. (2015)	CSF	60	60	68.4	3.4	69.3	4	11	4.6	11.1	4.7	40	52
Marchant et al. (2013)	PET	32	29	76.6	7.5	79	6.3	13.8	2.9	14.1	2.5	41	17
Mathis et al. (2013)	PET	74	78	85.5	2.6	85.4	3.1	14.8	2.7	14.8	2.6	40.5	43.6
Molinuevo et al. (2014)	CSF	19	19	69.2	5.6	69.9	7.6	9.9	4	10.3	4.4	63.1	68.4
Mormino et al. (2012)	PET	49	11	75.1	6.6	79.2	8	17.2	2	16.5	2.1	59	73
Oh et al. (2010)	PET	33	19	73.9	5.7	74.4	6.6	17.5	1.8	16.8	2.1	61	74
Oh et al. (2012)	PET	34	18	73.8	5.8	74.8	6.6	17.5	1.9	16.7	2	59	78
Oh et al. (2015)	PET	41	12	64.7	2.9	64.2	3.4	16.7	2.5	16.8	2.2	54	57
Oh et al. (2016)	PET	50	12	64.7	2.9	64.2	3.5	16.9	2.4	16.8	2.3	54	50
Ossenkoppele et al. (2014)	PET	53	15	74.8	6.2	78.1	7	17.2	1.8	16.5	1.8	64	67
Petersen et al. (2016)	PET	385	179	78	5	80	5	14	3	14	3	45	42
Pike et al. (2011)	PET	119	58	69.8	7	75.2	7.1	−	−	−	−	50	50
Rentz et al. (2010)	PET	28	55	73.6	9.6	71.7	9.1	15.8	3.1	15.9	2.5	61	62
Schott et al. (2010)	CSF	40	65	76.3	5.1	74.9	5.1	−	−	−	−	45	49.2
Snitz et al. (2013)	PET	87	107	85.2	2.5	85.7	3	14.7	2.8	14.7	2.5	36.8	44.9
Soldan et al. (2016)	CSF	102	46	54.8	10.3	56.8	8.1	17.2	2.4	16.9	2.4	60.8	58.7
Sperling et al. (2013)	PET	67	11	68.4	11.1	75.6	9.4	15.2	2.4	15.5	1.4	58.2	45.5
Stark et al. (2013)	PET	101	18	74.4	5.9	74.4	4.5	15.5	2.7	15.3	2.7	64.4	66.7
Susanto et al. (2014) – ADNI-1 cohort	CSF	66	37	75.1	5.3	76.1	5	15.6	2.7	16	3.2	52	43
Susanto et al. (2014) – ADNI-2 cohort	CSF	37	41	75.8	5.1	77.1	6.2	16.6	2.8	16.4	2.6		
Thai et al. (2015)	PET	182	31	68.8	6	76	7.2	−	−	−	−	51.1	54.8
Vemuri et al. (2015)	PET	178	81	77	5	78	4	14	3	15	3	48	41

Study	Biomarker	N		Age				Education				Sex	
		Amyloid−	Amyloid+	Amyloid−		Amyloid+		Amyloid−		Amyloid+		Amyloid− %F	Amyloid+ %F
				M	SD	M	SD	M	SD	M	SD		
Villemagne et al. (2013)	PET	33	112	72	6.7	71.2	7.2	14	3.5	13.6	3.8	52	48
Villeneuve et al. (2014)	CSF	45	22	77.5	6.9	80.1	5.9	14.8	3	15	2.8	36	14
Vlassenko et al. (2016)	PET	123	21	63.1	9.4	69.5	5.6	16	2.4	16.1	2.3	65	61.9
Voevodskaya et al. (2016)	CSF	156	59	72.6	4.7	72.7	4.7	12.1	3.7	11.7	3.8	61	61
Vos et al. (2013)	CSF	129	47	70.6	4.6	73.8	6.9	15.2	2.6	16.9	3.2	57	49
Vos et al. (2016)	CSF	127	26	63.4	9	68.1	9.6	15.9	2.5	14.8	3	63	58
Vos et al. (2016)	PET	114	42	64	9.4	70.6	5.9	16	2.4	16.4	2.6	68	45
Wirth et al. (2013a)	PET	25	13	74.2	7	71.5	6.9	17.6	2.1	16.3	2.1	56	77
Wirth et al. (2013b)	PET	47	25	74.9	5.5	75	6.1	17.3	1.7	16.4	2.1	66	68

Table 3
Demographic data for participants in three group amyloid positive (A– or Stage 0), amyloid positive (A+/N– or Stage 1), and tau/neurodegeneration positive (A+/N+ or Stage 2) analysis

Study	N			Age						Education						Sex	
	A–			A+/N–			A+/N+			A–			A+/N–			A+/N+	
	M	SD	%F	M	SD	%F	M	SD	%F	M	SD	%F	M	SD	%F	M	%F
Alcolea et al. (2015)	203	26	10	57.3	6.5	60.6	7.9	66.3	6.7	–	–	–	–	–	–	–	40
Amariglio et al. (2015)	122	32	36	71.6	5.7	73.1	5	77.1	6.4	15.9	3	16.4	2.7	16.2	2.8	63.1	61.1
Edmonds et al. (2015)	142	48	173	72.3	6.8	71.8	6.7	74.6	6.9	16.2	2.6	16.1	3	16.2	2.5	48.6	46.8
Jack et al. (2012)	193	70	56	77	5	79	5	80	4	14	3	14	3	15	3	49	50
Jack et al. (2014)	503	213	139	69	9	75	7	80	5	15	3	15	3	15	3	47	53
Knopman et al. (2012)	127	44	39	77	4	79	5	80	4	14	3	14	2	15	3	49	45
Soldan et al. (2016)	102	46	28	54.8	10.3	56.8	8.1	63.6	9.9	17.2	2.4	16.9	2.4	17.1	2.1	60.8	57.1
Vos et al. (2013)	129	47	36	70.6	4.6	73.8	6.9	74.4	5.8	15.2	2.6	16.9	3.2	15.3	2.7	57	49
Vos et al. (2016)	127	26	19	63.4	9	68.1	9.6	73.5	5.6	15.9	2.5	14.8	3	16.5	2.5	63	58
Vos et al. (2016)	114	42	16	64	9.4	70.6	5.9	74	6.9	16	2.4	16.4	2.6	14.1	3.4	68	45