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Cross-sectional associations of tau protein biomarkers with semantic and episodic memory in older adults without dementia: A systematic review and meta-analysis

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ABSTRACT

Pathological tau is suggested to play a role in cognitive deterioration in the preclinical phase of Alzheimer's disease. We investigated cross-sectional associations of tau burden with episodic and semantic memory performance in older adults without dementia. A systematic search in MEDLINE (via PubMed), PsychINFO, and Embase resulted in 24 eligible studies for meta-analysis. Tau burden was assessed using CSF, PET, or histopathological measures. All studies evaluated associations of tau with episodic memory: weighted effect sizes were -0.46 (95 % CI [-0.73; -0.20], $p < .001$) for episodic composite scores, -0.19 ([-0.36; -0.03], $p = .024$) for delayed word list recall, and -0.05 ([-0.14; 0.04], $p = .257$) for logical memory. Fourteen studies evaluated associations of tau with semantic memory: weighted effect sizes were -0.28 ([-0.52; -0.04], $p = .023$) for semantic composite scores, -0.06 ([-0.16; 0.03], $p = .194$) for semantic fluency, and 0.06 ([-0.06; 0.18], $p = .319$) for picture naming. Our findings indicate that tau burden related to both episodic and semantic memory impairment in older individuals without a diagnosis of mild cognitive impairment or manifest dementia, with episodic composite scores showing the strongest association with tau burden. Future potential lies in developing more sensitive scores to detect this subtle cognitive impairment, which could contribute to early identification of individuals in the preclinical phase of Alzheimer's disease, thereby improving early diagnosis and timely intervention.

1. Introduction

Alzheimer's disease is the most common neurodegenerative disease worldwide (Ferri et al., 2005). Before the onset of clinical dementia and manifest cognitive impairment, Alzheimer's disease involves a long preclinical stage with various pathological changes and biomarker abnormalities (Holtzman et al., 2011). Among these, neurofibrillary tangles containing tau and amyloid β (Aβ) plaques are considered the most pathological hallmarks of Alzheimer's disease (Mandelkow and Mandelkow, 1998; Olsson et al., 2016). Pathogenic tau is suggested to be one of the earliest pathophysiological changes in preclinical Alzheimer's disease (Jack et al., 2013), making it a key biomarker and possible clinical target for early intervention.

Tau is a microtubule-associated protein and has an important function in the assembly and stabilization of microtubules in the brain (Mandelkow and Mandelkow, 1998). When hyperphosphorylated, however, tau detaches from the microtubes, leading to misfolding and accumulation of tau as it aggregates into neurofibrillary tangles (Arriagada et al., 1992; Mandelkow and Mandelkow, 1998; Villemagne et al., 2015). The pathological process of tau deposition is detectable in a preclinical stage of Alzheimer's disease, long before the first clinical symptoms appear (Schmand et al., 2010). Tau pathology can be visualized using a variety of measurements, such as by analyzing abnormal composition of cerebrospinal fluid (CSF) (Olsson et al., 2016) or

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visualizing the distribution of these pathologies using positron emission tomography (PET) imaging (Ossenkoppele et al., 2015; Villemagne et al., 2015). Previous studies have revealed that in contrast to a diffuse accumulation of Aβ in preclinical Alzheimer's disease (Gordon et al., 2016; Ingelsson et al., 2004; Nordberg, 2004), tau accumulation occurs more focally, often starting from brain regions in the medial temporal lobe, including the anterolateral entorhinal cortex and the hippocampus (Braak and Braak, 1997). Tau pathology in these brain areas have been associated with episodic memory dysfunction in both Alzheimer's disease (Reijs et al., 2017) and normal aging (Crary et al., 2014).

Even in absence of cognitive deterioration, an accumulation of tau is repeatedly detected in cognitively unimpaired individuals (Nelson et al., 2012; Ziontz et al., 2019). As tau pathology in cognitively normal adults starts in the entorhinal cortex and hippocampus (Braak and Braak, 1997), it is hypothesized that early tau deposition evokes hippocampal dysfunction, leading to the memory impairment prevalent in aging (Marks et al., 2017). Levels of entorhinal tau increase with age (Braak et al., 2011) and are found in individuals without any Aβ pathology (Braak et al., 2011; Nelson et al., 2012). Additionally, tau aggravation in the entorhinal cortex is also associated with memory impairment in healthy participants, independently of Aβ accumulation (Lowe et al., 2019; Maass et al., 2018). This observation suggests that Aβ-independent tau pathology is associated with memory decline in normal aging and localized in the medial temporal lobe (Ziontz et al., 2019). However, studies have also shown that Aβ is a promotor of endogenous tau hyperphosphorylation (Zempel and Mandelkow, 2012) and facilitates the distribution of tau outside the entorhinal cortex to other limbic areas and association cortices (Pooler et al., 2015). It is suggested that tau deposition outside the entorhinal cortex initiates memory decline in relation to Alzheimer's disease pathology (Chen et al., 2020).

Memory domains affected in Alzheimer's disease include episodic memory (the conscious recollection of specific events), semantic memory (the conceptual knowledge of facts) and working memory (temporary storage and manipulation of stimuli) (Hodges, 2000; Verma and Howard, 2012). Memory assessment is a useful and reliable tool in the early detection and tracking of disease progression of Alzheimer's disease (Drago et al., 2011; Reijs et al., 2017). Many studies have shown that individuals in the preclinical phase of Alzheimer's disease exhibit a profound deficit in episodic memory (Gallagher and Koh, 2011; Greene et al., 1996; Zakzanis, 1998) and, although to a lesser extent, a decline in semantic memory (Tchakoute et al., 2017; Vonk et al., 2019b). Recently, there has been a shift of focus in research from a decline in episodic memory towards semantic memory as a more reliable early biomarker for Alzheimer's disease (Venneri et al., 2018), as the presence of semantic impairment is more restricted to the preclinical phase of Alzheimer's disease (Lovden et al., 2004; Papp et al., 2016; Vonk et al., 2020a), whereas episodic memory decline is present in normal aging as well (Hänninen et al., 1996). Aβ burden has been associated, although relatively weakly, with both semantic and episodic memory in healthy aging (Baker et al., 2017; Hedden et al., 2013; Vonk et al., 2020b). However, the association between tau burden and these memory domains remains unclear. Assessing this relationship may offer insights for cognitive impairment in the presence of biomarkers as an early diagnostic target for Alzheimer's disease.

This systematic review and meta-analysis aimed to summarize, compare, and contrast the available studies on the cross-sectional association of tau burden with episodic and semantic memory performance in older adults without the diagnosis dementia. Neuropsychological assessment of cognition in individuals without dementia is possible using well-validated clinical tasks (Wilson et al., 2011), but the wide variability in tasks available could lead to discrepancy in results (Vonk et al., 2020b). Therefore, we investigated the relation between tau burden and various tasks of episodic memory (e.g., delayed recall and complex figure tasks) and semantic memory (e.g., category fluency and picture naming tasks), as well as composite scores of these domains. We hypothesized to find negative associations of tau burden with both episodic and semantic task performance in older adults without dementia. As episodic memory impairment may be more common than semantic memory impairment in normal aging, we expected larger effect estimates for episodic tasks in relation to tau burden across these samples of individuals without dementia.

2. Methods

This systematic review was conducted in accordance with the PRISMA guidelines for systematic reviews (Moher et al., 2009). We registered the protocol of this systematic review on PROSPERO under registration number CRD42021224113 (see Supplementary Materials).

2.1. Literature searches

Three electronic databases—PubMed, PsychINFO, and Embase—were subjected to systematic searches on December 3rd, 2020. Search strategies were developed by two authors (JV and TP) in consultation with a professional librarian (PW, acknowledgments). The search string was built for PubMed and subsequently translated for PsychINFO and Embase. The full electronic search strings are outlined in Supplementary Table S1. The search was performed without date or language restrictions. We included peer-reviewed articles, while unpublished materials, conference abstracts, and grey literature were excluded.

Duplicates were removed in EndNote reference manager, then transferred into Rayyan (Ouzzani et al., 2016), where a final duplicate removal was performed. Screening was carried out using Rayyan, in which screening decisions were recorded. Two reviewers (MB and TP) independently screened all titles and abstracts for eligibility while being blinded from each other's decisions. Differences in study selection were resolved by discussion between the reviewers. The full texts of the selected articles were extracted and independently examined by the two reviewers to confirm eligibility. Snowballing and reverse snowballing was performed to identify additional articles. The reference lists of the selected articles were searched for secondary references that might be of interest (i.e., snowballing) and articles that have cited the selected articles were screened using Scopus (i.e., reverse snowballing).

2.2. Study selection

Articles were included for this systematic review if (1) a cross-sectional or longitudinal observational design was used, (2) associations between tau pathology and episodic and semantic memory were reported, (3) tau pathology and memory tasks were measured within one year from each another, (4) information was reported for older participants without dementia with an average age of >50 years, and (5) sufficient information was provided to compute effect sizes. We were interested in investigating the cross-sectional relationship between memory performance and tau in older adults (>65 years) as opposed to mid-life. Pathogenic tau is suggested to be one of the earliest pathophysiological changes in preclinical Alzheimer's disease (Jack et al., 2013), starting to accumulate approximately 10–15 years before symptom onset (Bateman et al., 2012). As such, we chose a to include studies in which individuals had an average age of >50 years.

Studies were excluded if the study population was limited to participants with a diagnosis of neurodegenerative disease or mild cognitive impairment (MCI), or all participants were classified with the same tau-status (i.e., either all tau positive or negative). Studies were excluded if only non-domain specific composite scores were reported (e.g., a score for cognition or multi-domain memory), as we aimed to investigate the role of specific memory domains (episodic and semantic) in relation to tau. We excluded articles that did not report scores of memory or tau for a cognitively normal group but only for a disease group, and articles that were written in any other languages than Dutch, English, or German. In

the case of multiple studies reporting the same tasks from the same cohort study, only the study with the largest sample was included to represent the data of a specific semantic or episodic task in order to avoid overestimation of effects due to inclusion of duplicated data (following e.g., Hedden et al., 2013).

2.3. Determinant and outcome measures

Tau burden, the determinant of interest, was defined in one of two ways; either as continuous (i.e., on a scale from no or low tau protein levels to high tau protein levels) or categorical variables (i.e., as a presence or absence of tau protein based on an established cut-off value). Tau levels were measured through CSF or blood plasma arrays (total-tau, phosphorylated-tau), PET ligands, or via histopathology.

The outcome of interest was performance on episodic and/or semantic cognition tasks, defined as continuous outcome scores. Studies that assessed the following episodic tasks were included: (1) delayed recall on word-list learning tasks, including Rey Auditory Verbal Learning test (RAVLT), California Verbal Learning Test (CVLT), Auditory Verbal Learning Test (AVLT) and other word-list learning tasks, (2) delayed recall on the Rey–Osterrieth Complex Figure (RCFT), Benson Complex Figure (BCF), Benton Visual Retention Test and other complex figure tests, and (3) delayed recall on the Logical Memory (LM) subtest of the Wechsler Memory Scale (WMS), Craft Story 21, and other story memory tests. The following semantic tasks were included: (1) Boston Naming Test, Action Naming Test, and other picture naming tasks or object naming tasks, (2) category fluency, also called semantic fluency or animal fluency, and (3) WAIS Vocabulary or other vocabulary tasks. Besides individual task performance, we also considered studies that assessed composite scores of episodic and/or semantic memory, combining multiple different tasks of that memory domain. Outcome scores of task performance in cross-sectional studies and at baseline in longitudinal studies were included; however, change from baseline to follow-up (i.e., memory rate, decline) was not considered in this review.

2.4. Data extraction

Two reviewers (MB and TP) independently extracted and recorded the data from the eligible studies in an Excel spreadsheet. We extracted (1) information about study design and methodology, (2) study sample characteristics, (3) tau detection methods (PET, CSF, blood plasma, or histopathology), (4) tau levels, (5) performance on individual or composite episodic and/or semantic tasks, and (6) associations between tau and cognition tasks. Disagreements in data extraction were resolved by discussion between the reviewers. If studies reported both values corrected for demographic covariates and unadjusted values, we included the adjusted values. If PET studies reported associations with multiple brain regions, we included effect sizes for one of the following reported regions: the medial temporal lobe, Braak III/IV, or hippocampus. If CSF studies reported associations with total-tau (t-tau) and phosphorylated-tau (p-tau) levels, p-tau associations were included as this is more specific for neurofibrillary tangles than t-tau and more clinically relevant for Alzheimer's' disease (Thijssen et al., 2020).

2.5. Bias and quality assessment

The Newcastle-Ottawa Quality Assessment Scale for Cohort Studies was modified (see Vonk et al., 2020b) and used to assess the risk of bias of the included studies (Wells et al., 2014). The first six studies were independently assessed by two reviewers (MB and TP). Results were compared and Cohen's kappa (κ) was computed to detect the inter-rater reliability. As there was very high agreement (Cohen's $\kappa = 0.959$), the remaining studies were divided among reviewers. If a specific task had a sufficient number of studies (>10), publication bias was assessed using funnel plots, and significance of asymmetry was tested using Egger's test.

2.6. Data synthesis

To evaluate the effects of tau on our outcome of interest, we computed effect sizes using the statistics reported in the included studies (e.g., mean and standard deviation or standard error, or results from analyses including t-tests, analysis of variance, correlations, regressions, and linear mixed effects models). We transformed effect sizes into standardized mean differences (Cohen's d), i.e., the mean difference/pooled standard for dichotomous variables and standardized regression coefficients for continuous variables. Greater tau pathology associated with lower episodic or semantic cognitive performance was coded as a negative effect size. Studies that evaluated semantic or episodic cognition in individuals with high levels of tau protein (categorized as tau-positive) were contrasted to individuals with low levels of tau protein (categorized as tau-negative subjects). We computed pooled estimates using random-effects models with inverse variance weighing if a specific cognitive task was reported in 5 or more studies. If between 2 and 4 studies were identified for a task, we applied a fixed-effects model with inverse variance weighting, although we recognize the result may be too optimistic when using the fixed-effects model (Vonk et al., 2020b).

Heterogeneity of the results were examined using Cochran's Q test, visual inspection of confidence intervals in the forest plots, and I-squared statistic. The models used a DerSimonian-Laird estimator for $\tau 2$, in order to detect between-study variance. Heterogeneity was investigated by performing subgroup analyses. These subgroup analyses were performed to detect effects of method of tau assessment (PET, CSF, plasma, or histopathology), mean sample age above or below 70 years, studies controlling for demographic data (e.g., age, sex/gender, or other covariates), studies using continuous or categorical scales of tau, and studies only including participants with subjective cognitive complaints (SC). To investigate whether there are differences in strength of associations across tasks, we included subgroup analyses comparing pairs of episodic and semantic tasks. We evaluated the difference in strength between all episodic and all semantic tasks, between episodic and semantic composites, and between word list learning and semantic fluency, as the number of studies of these tasks were sufficient.

P-values below .05 were considered as statistically significant. For subgroup analyses, *p*-value threshold of the Q-test was set at $p = .10$ (Pereira et al., 2010). All analyses and subsequent generation of figures were conducted in R Version 4.0.2 (Rstudio, 2020), using the *meta*, *metafor* and *dplyr* packages (Balduzzi et al., 2019; Viechtbauer, 2010; Wickham et al., 2021).

3. Results

3.1. Data collection process

The results of our literature search and screening process are depicted in the PRISMA flowchart in Fig. 1. We retrieved a total of 4271 titles from MEDLINE, PsychINFO, and Embase databases, followed by the removal of 1631 duplicates. During the first screening, 2425 articles were excluded based on title and abstract, leaving 215 articles for full-text evaluation. During full-text screening, studies were omitted for the following reasons: no semantic or episodic tasks, no association between tau and cognition reported, no tau or cognition metrics reported for cognitively healthy participants, period between tau and cognitive assessment >1 year, only longitudinal associations reported, part of a series of publications from the same cohort, mean sample age <50 years, or insufficient information reported for effect size computation. After excluding 192 studies during the full-text screening, 24 studies met the inclusion criteria for the meta-analysis.

3.2. Study characteristics

Study characteristics are presented in Table 1. Articles originated from publications between 2012 (Bennett et al., 2012) to 2021 (Radestig

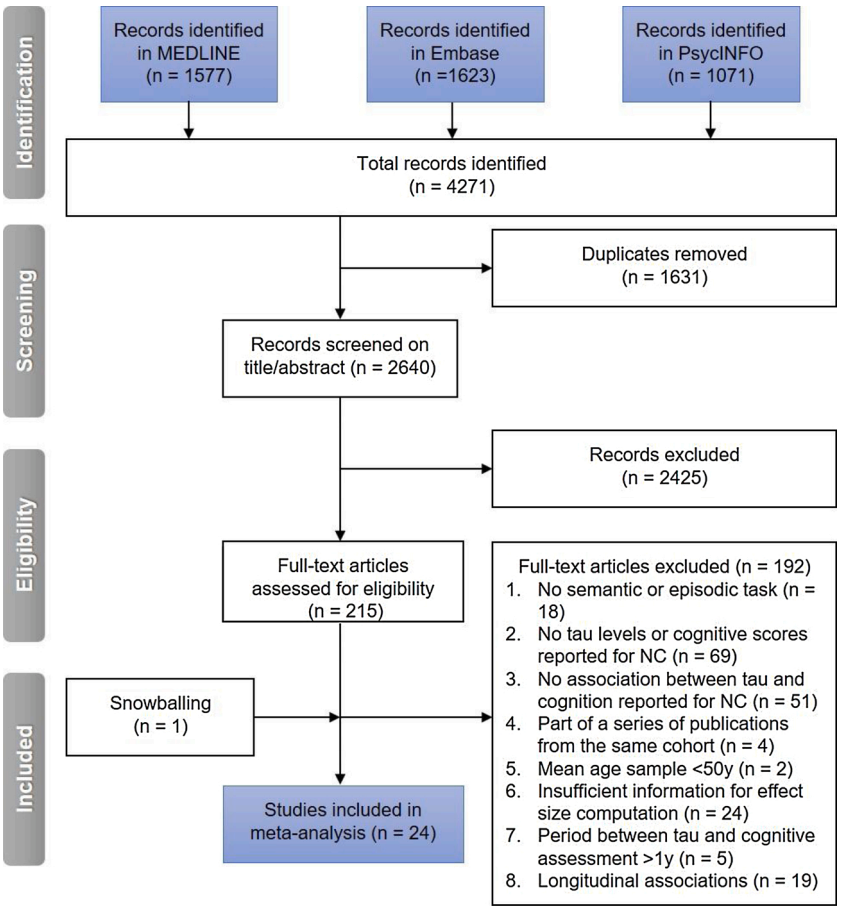

Fig. 1. PRISMA flowchart for study selection.

et al., 2021). Of these selected studies, the sample size ranged between 10 (Villemagne et al., 2014) and 579 individuals (Lowe et al., 2019), and the total number of included participants was 4,466. In 18 studies (75.0 %), the sample size included 50 or more participants, which increased power to detect the presence of an association. Mean age ranged from 57.4 years (Li et al., 2014) to 85.0 years (Bennett et al., 2012) and the percentage female participants ranged from 46.0 % (Lowe et al., 2019) to 73.9 % (McSweeney et al., 2020). The association between tau and cognition was controlled for age, sex/gender, education, and/or other variables in 19 studies (79.2 %). Tau was analyzed as a continuous determinant in 19 studies (79.2 %). Thirteen studies (54.2 %) used CSF measures to detect tau burden, ten studies (41.7 %) used PET ligands, and one study via histopathology (4.2 %; Bennett et al., 2012). None of the included studies measured tau levels in blood plasma. Almost all CSF studies evaluated levels of p-tau (n = 12/13, 92.3 %), except one study that solely investigated levels of t-tau (n = 1/13, 7.7 %). The study that measured tau burden using histopathology used antibodies for p-tau (Bennett et al., 2012). Eight of ten PET studies (80.0 %) targeted tau using [18 F] AV-1451, one study (10.0 %) used [18 F] THK53511, and one study (10.0 %) [18 F] THK523 as PET ligands. Of these, two studies assessed tau retention in Braak stage III/IV (Maass et al., 2018; Snitz et al., 2020), three studies the medial temporal lobe (which corresponds to Braak III/IV; Groot et al., 2020; Kang et al., 2017; Weigand et al., 2020), one study limbic regions (Wolters et al., 2020), and one study the entorhinal region (Lowe et al., 2019).

Of 24 included studies, all incorporated episodic memory tasks and 14 studies (58.3 %) additionally included tasks of semantic memory. All tasks are presented in Table 1. Most studies that evaluated episodic tasks involved, either individual or as part of domain scores, delayed recall on various word-lists tasks, generally the Rey Auditory Verbal Learning test (RAVLT; n = 6/24; 25.0 %), or the California Verbal Learning Test (CVLT; n = 6/24; 25.0 %). Story memory tests used the Logical Memory subtest of the Wechsler Memory Scale (WMS; n = 13/24; 54.2 %). One study assessed individual scores of the Rey Complex Figure Task (Kang et al., 2017). The most evaluated semantic tasks were semantic fluency (predominantly Animal Fluency, n = 13/14; 92.9 %) and naming tasks (Boston Naming Test; n = 8/14; 57.2 %). Twelve studies computed episodic composite scores (n = 12/24, 50.0 %) and seven computed semantic composite scores (n = 7/14, 50.0 %). Tasks incorporated in domain scores varied between studies. Higher scores reflected better cognitive function for all tasks.

3.3. Publication bias

Using an adjusted version of the the Newcastle-Ottawa Quality Assessment Scale, quality assessment for risk of bias for included studies was performed (Table 2). Twelve studies (48 %) lost stars on account of using a non-representative sample, as they only included volunteers or individuals with subjective cognitive complaints. Only a few studies (n = 5; 20 %) lost stars as a result of not controlling for age, sex/gender, education and/or other covariates in their analyses. Three studies lost stars because they categorized tau on non-established cut-offs. Every study received the maximum number of stars on the assessment of outcome, as we only included studies that assessed cognition using independent neuropsychological tasks.

As the number of studies was too small to compute the Egger's test for asymmetry for each individual task, all tasks were pooled for each cognitive domain. Funnel plots for both episodic tasks and semantic tasks indicated asymmetry (Fig. 2A-B). The Egger's t statistic confirmed this asymmetry for episodic tasks (b for bias = -1.801, SE = 0.806; t(22)

Table 1
Study characteristics of included studies. Population characteristics (cognitive distribution, sample size, cohort); sex/gender; age; education; tau measures (method, definition of tau burden); neuropsychological assessments (domain, tasks).

Study	Population			Sex/ gender	Age		Education		Tau		Cognition	
	NC or SCD	*N*	*Cohort/Sample origin*	*% female*	*Mean*	*±SD*	*Mean*	*±SD*	*Method*	*p-tau or t-tau; PET tracer*	*Domain*	*Tasks*
Alm et al. (2020)	NC	109	BIOCARD	60.6 %	69.2	±8.6	17.5	±2.1	CSF	t-tau	Episodic	*EC* = delay free recall on CVLT and LM
Aschenbrenner et al. (2020)	NC	255	Healthy Aging and Senile Dementia (HASD) study and Adult Children Study (ACS)	62.0 %	66.2	±5.5	16.1	±2.5	CSF	p-tau	Episodic	*EC* = free recall on FCSRT, delayed recall on LM, and associate learning tests
Bennett et al. (2012)	NC	296	Religious Order Study and Memory and Aging Project	62.2 %	85.0	±6.6	16.5	±3.8	histopathology	p-tau $_{f}$	Episodic & Semantic	*EC* = immediate and delayed recall on LM, East Boston Story, word List, and recognition; *SC* = BNT, CAT, reading test, complex Ideational Material, Digit Span Forward, Digit Span Backward, and Digit ordering
Bruno et al. (2019)	NC	110	Wisconsin ADRC	72.0 %	62.5	±9.2	16.1	±2.5	CSF	p-tau	Episodic	Delayed recall on RAVLT
Casaletto et al. (2017)	NC	132	Wisconsin Registry for Alheimer's Prevention study and Wisconsin ADRC	65.2 %	64.5	±7.4	16.0	(14−18)$_{a}$	CSF	p-tau	Episodic	Delayed recall on RAVLT
Groot et al. (2020)	NC	47	Australian Imaging Biomarkers and Lifestyle (AIBL)	53.2 %	73.3	±5.5	13.0	±2.9	PET	[18 F] AV-1451	Episodic	*EC* = delayed recall on CVLT, RCFT, and LM
Ho and Nation (2018)	NC	518	Alzheimer's Disease Neuroimaging Initiative (ADNI)	51.2 %	71.3	±6.9	16.3	±2.6	CSF	p-tau	Episodic & Semantic	Delayed recall on RAVLT; CAT-A; BNT
Ihara et al. (2018)	NC	12	Japanese Alzheimer's Disease Neuroimaging Initiative (J-ADNI)	48.9 %	67.81	$_{b}$	13.4	±1.6$_{c}$	CSF	p-tau	Episodic	Delayed recall on LM
Insel et al. (2015)	NC	220	Alzheimer's Disease Neuroimaging Initiative (ADNI) 1 + 2	47.7 %	75.2	±5.5	16.1	±2.7	CSF	p-tau	Episodic	Delayed recall on LM
Kang et al. (2017)	NC	43	Memory Disorder Clinic of Gil Medical Center, community and volunteers	68.6 %	66.4	±7.9	11.1	±4.9	PET	[18 F] THK5351	Episodic & Semantic	Delayed recall on SVLT; RCFT; BNT
Li et al. (2014)	NC	315	Community, University of Washington Alzheimer's Disease Research center and collaborating AD centers	54.0 %	57.4	±18.1	16.1	±2.6	CSF	p-tau	Episodic & Semantic	Delayed recall on LM; CAT-A
Lowe et al. (2019)	NC	579	Mayo Clinic Study of Aging (MCSA)	46.0 %	70$_{d}$	(63, 79)$_{e}$	16$_{d}$	(13, 16)$_{e}$	PET	[18 F] AV-1451	Episodic & Semantic	*EC* = Delayed Recall on RAVLT and LM, and Visual Reproduction II subtests; *SC* = BNT and CAT
Maass et al. (2018)	NC	83	Berkeley Aging Cohort Study (BACS)	58.0 %	77	±6	17	±2.0	PET	[18 F] AV-1451	Episodic	*EC* = delayed recall on CVLT and VR tests
Matura et al. (2019)	NC	30	Frankfurt	63.0 %	66.4	±4.1	15.2	±3.0	CSF	p-tau	Episodic	Delayed recall on CVLT
McSweeney et al. (2020)	NC	119	Presymptomatic Evaluation of Experimental or Novel Treatments for Alzheimer's Disease	73.9 %	67.5	±4.8	15.1	±3.2	PET	[18 F] AV-1451	Episodic & Semantic	*EC* = RBANS List recall, list recognition, story recall, and figure recall; *SC* = RBANS

(*continued on next page*)

Table 1 (*continued*)

Study	Population			Sex/ gender	Age		Education		Tau		Cognition	
	NC or SCD	*N*	*Cohort/Sample origin*	*% female*	*Mean*	*±SD*	*Mean*	*±SD*	*Method*	*p-tau or t-tau; PET tracer*	*Domain*	*Tasks*
			(PREVENT-AD) cohort									Picture naming, and CAT
Radestig et al. (2021)	NC	259	Gothenburg H70 Birth Cohort Studies	49.8 %	70.6	±0.3	13.1	±3.9	CSF	p-tau	Episodic & Semantic	12 Object Delayed recall; CAT
Schindler et al. (2017)	NC	233	Adult Children Study (ACS)	64.0 %	60.7	±8.4	16.1	±2.5	CSF	p-tau	Episodic & Semantic	Delayed recall on LM; CAT-A
Snitz et al. (2020)	NC	118	Monongahela-Youghiogheny Healthy Aging Team Neuroimaging (MYHAT-NI) and Heart Strategies Concentrating on Risk Evaluation (Heart SCORE) parent study	57.6 %	76.3	±5.7	[f]		PET	[18 F] AV-1451	Episodic & Semantic	Delayed recall on LM; CAT-A
Verberk et al. (2020)	SCD	241	SCIENCe project and Amsterdam Dementia Cohort	40.0 %	61.0	±9.0	5.0	±1.0	CSF	p-tau	Episodic & Semantic	Delayed recall on RAVLT; BNT; CAT-A
Villemagne et al. (2014)	NC	10	Australia community	70.0 %	77.4	±10.0	14.7	±2.7	PET	[18 F] THK523	Episodic	*EC* = delayed recall on CVLT, RCFT, and LM
Weigand et al. (2020)	NC	209	Alzheimer's Disease Neuroimaging Initiative (ADNI) Cohort	51.4 %	75.1	±0.5	16.9	±0.2	PET	[18 F] AV-1451	Episodic & Semantic	*EC* = immediate and delayed recall on LM; *SC* = BNT and CAT-A
Wolfsgruber et al. (2020)	SCD	449	German Center for Neurodegenerative Diseases (DZNE) and Longitudinal Cognitive Impairment and Dementia Study (DELCODE)	53.7 %	70.0	±5.6	14.8	±2.9	CSF	p-tau	Episodic & Semantic	*EC* = delayed recall on LM, FCSRT recognition, free recall, cue efficiency; Figure Savings, Word list trials (x3), Word list delayed recall, FNART, and SDMT; *SC* = BNT, CAT-A, CAT-G, FCSRT naming
Wolters et al. (2020)	SCD	25	Amsterdam Dementia Cohort	60.0 %	65.0	±6.0	6.0	(2–7)[a]	PET	[18 F] AV-1451	Episodic & Semantic	*EC* = immediate and delayed recall on RAVLT, VAT-A; *SC* = VAT- A naming, CAT-A
Ziontz et al. (2019)	NC	54	Baltimore Longitudinal Study of Aging (BLSA)	55.5 %	77.4	±8.9	17.6	±2.2	PET	[18 F] AV-1451	Episodic & Semantic	*EC* = immediate and delayed recall CVLT; *SC* = CAT and Letter Fluency

Note. [a] = range; [b] = not specified; [c] = not specified for p-tau group, as all p-tau participants (n = 12) were amyloid β positive, we used the mean for amyloid β group; [c] = median, [e] = interquartile range (IQR), [f] = education was specified as high school or less (25.6 %), some college (24.8 %), 4-year college (18.8 %), greater than college (30.8 %); f = study used antibodies for phosphorylated tau.

Abbreviations: NC = normal cognition; SCD = subjective cognitive decline; SD = standard deviation; PET = positron emission tomography; CSF = cerebrospinal fluid; t-tau = total tau; p-tau = phosphorylated tau; EC = episodic composite score; SC = semantic composite score; BNT = Boston Naming Test; CAT = Category Fluency; CAT-A = Category Fluency Animals; CAT-G = Category Fluency Groceries, CVLT = California Verbal Learning Test; RCFT = Rey Complex Figure Test; RAVLT = Rey Auditory Verbal Learning Test; LM = Wechsler Logical Memory; VR = Virtual Reality; SVLT = Seoul verbal learning test; RBANS = Repeatable Battery for the Assessment of Neuropsychological Status; WMS-R = Wechsler Memory Scale-Revised; FCSRT = free and cued selective reminding test; FNART = Face Name Associatijve Recognition Test; SDMT = Symbol Digits Modality Test; VAT-A = Visual Association Test version A.

= -2.24, p = .036) and for semantic tasks (b for bias = -1.450, SE = 0.629; t(15) = -2.31, p = .036). Additionally, for episodic composite scores, the funnel plot also depicted asymmetry (Fig. 2C), but the Egger's t statistic was not significant (b for bias = -3.292, SE = 1.489; t(10) = -2.21, p = .052).

3.4. Meta-analysis of association tau and cognition

Analysis of the pooled cognitive tasks of episodic and semantic cognitive domain revealed that an increased tau burden is associated with lower performance on both episodic tasks (overall effect size = -0.27, 95 % CI [-0.41; -0.13], p < .001) and semantic tasks (overall

Table 2
Adjusted Newcastle-Ottawa scale for assessment of quality of included studies.

Study	Selection			Comparability				Outcome		Overall
	1. Representative	2. Selection	3. Exposure	Age	Sex/ gender	Education	Other factors	1. Outcome	2. Same method	(max. 9)
Alm et al. (2020)	✶	✶	✶	✶	✶	✶	✶	✶	✶	9
Aschenbrenner et al. (2020)	–	✶	✶	✶	–	–	✶	✶	✶	6
Bennett et al. (2012)	–	✶	✶	✶	✶	✶	–	✶	✶	7
Bruno et al. (2019)	–	✶	✶	✶	✶	✶	–	✶	✶	7
Casaletto et al. (2017)	–	✶	✶	✶	✶	–	–	✶	✶	6
Groot et al. (2020)	✶	✶	✶	✶	✶	✶	✶	✶	✶	9
Ho and Nation (2018)	✶	✶	✶	✶	✶	✶	✶	✶	✶	9
Ihara et al. (2018)	✶	✶	–	–	–	–	–	✶	✶	4
Insel et al. (2015)	✶	✶	–	✶	✶	✶	–	✶	✶	7
Kang et al. (2017)	–	–	✶	–	–	–	–	✶	✶	3
Li et al. (2014)	–	✶	✶	✶	✶	✶	✶	✶	✶	8
Lowe et al. (2019)	✶	✶	–	✶	✶	✶	✶	✶	✶	8
Maass et al. (2018)	✶	✶	✶	–	–	–	–	✶	✶	5
Matura et al. (2019)	–	–	✶	✶	–	✶	–	✶	✶	5
McSweeney et al. (2020)	✶	✶	✶	–	✶	✶	–	✶	✶	7
Radestig et al. (2021)	✶	✶	–	–	–	–	–	✶	✶	4
Schindler et al. (2017)	–	✶	✶	✶	✶	✶	✶	✶	✶	8
Snitz et al. (2020)	✶	✶	✶	✶	✶	✶	✶	✶	✶	9
Verberk et al. (2020)	–	✶	✶	✶	✶	✶	–	✶	✶	7
Villemagne et al. (2014)	–	✶	✶	✶	–	–	–	✶	✶	5
Weigand et al. (2020)	✶	✶	✶	✶	✶	✶	✶	✶	✶	9
Wolfsgruber et al. (2020)	✶	✶	✶	–	–	–	–	✶	✶	5
Wolters et al. (2020)	–	✶	✶	✶	✶	✶	✶	✶	✶	8
Ziontz et al. (2019)	–	✶	✶	✶	✶	✶	✶	✶	✶	8

Note. Each star represents whether the above-mentioned criterion within the subsection was fulfilled.

effect size = -0.13, 95 % CI [-0.22; -0.04], $p = .005$), depicted in Fig. 3.

Effect sizes (Cohen's d) computed for the individual cognitive tasks (i.e., semantic fluency, picture naming, delayed recall on word lists, and logical memory) and composite scores of the episodic and semantic domain are presented in Table 3. Figs. 4 and 5 show the forest plots per episodic and semantic task including effect sizes per study with 95 % confidence intervals (CI) and the pooled results. The overall weighted effect size of the association between tau burden and episodic performance was -0.46 (95 % CI [-0.73; -0.20], $p < .001$) for episodic composite scores, -0.19 (95 % CI [-0.36; -0.03], $p = .024$) for word-list learning and -0.05 (95 % CI [-0.14; 0.04], $p = .257$) for logical memory. The effect sizes for semantic tasks were -0.28 (95 % CI [-0.52; -0.04], $p = .023$) for semantic composite scores, -0.06 (95 % CI [-0.16; 0.03], $p = .194$) for semantic fluency, and 0.06 (95 % CI [-0.06; 0.18], $p = .319$) for picture naming. These effect sizes are considered to be between small and medium, as effect sizes of d = 0.20 are treated as small effects, d = 0.50 medium, and d = 0.80 large (Cohen, 1988). The Rey–Osterrieth Complex Figure test was not meta-analyzed, as only one study reported an effect size of 0.4104 (95 % CI [-0.19; 1.01] (Kang et al., 2017). We detected considerable heterogeneity for episodic composite scores (Q = 296.51, $p < .0001$, $I^2 = 96.3$ %) and semantic composite scores (Q = 68.00, $p < .0001$, $I^2 = 91.1$ %), moderate heterogeneity for semantic fluency (Q = 11.64, $p = .040$, $I^2 = 57.0$ %) and word-list learning, (Q = 13.50, $p = .036$, $I^2 = 55.6$ %), and low heterogeneity for logical memory (Q = 2.18, $p = .703$, $I^2 = 0.0$ %) and picture naming (Q = 0.67, $p = .717$, $I^2 = 0.0$ %).

To examine the difference in strength of associations between tau and semantic tasks or episodic tasks, we compared pairs of episodic and semantic tasks. No difference was found when pooling all tasks of the episodic domain compared to all tasks of the semantic domain (Q = 3.00, $p = 0.083$). Additionally, we found no difference in associations between episodic composite and semantic composite (Q = 1.00, $p = 0.318$), and between semantic fluency and word-list learning (Q = 1.74, $p = 0.187$).

3.5. Subgroup analyses

To address the heterogeneity within our results, we included subgroup analyses investigating the role of age, method of tau assessment, controlling for demographics, using either continuous or categorical tau scales, and studies including only participants with subjective cognitive complaints (Table 4). The number of studies for picture naming (n = 3) and logical memory (n = 5) was too low to allow for a stratified analysis.

When combining all tasks for each domain, we found an effect of tau method for both episodic and semantic tasks, as well as an effect of age for episodic tasks. The association between tau and episodic tasks was greater when studies had a mean sample age above 70 years (14 vs. 10 studies; Q = 3.05, df = 1, $p = .081$) and when studies used PET tracers to detect tau burden (13 vs. 10 vs. 1 studies; Q = 9.43, df = 2, $p = .009$). The association was similarly moderated by method of tau burden for semantic tasks, as the association was greater when PET was used (8 vs. 8 vs. 1 studies; Q = 5.94, df = 2, $p = .051$).

For episodic composite scores, the association between tau and cognition was stronger in studies using categorical tau measures (1 vs. 11 studies; Q = 145.93, df = 1, $p < .001$) and studies using PET, as opposed to CSF or histopathology, as tau method (3 vs. 8 vs. 1 studies; Q = 6.09, df = 2, $p = .048$). The association between tau and delayed recall on word lists was stronger when studies used categorical measures of tau (2 vs. 5 studies; Q = 5.76, df = 1, $p = .016$), had a mean sample age above 70 years (5 vs. 2 studies; Q = 5.76, df = 1, $p = .016$), and in study samples who were not selected on subjective cognitive complaints (6 vs. 1 studies; Q = 12.37, df = 1, $p < .001$). For semantic cognition, we found that the association between tau and semantic composite scores was greater in studies using categorical tau (1 vs. 6; Q = 18.19, df = 1, $p < .0001$) and in studies using PET as tau measurement (1 vs. 5 vs. 1 studies; Q = 12.47, df = 2, $p < .001$). The association between tau and semantic fluency was stronger in study samples who were not selected on subjective cognitive complaints (5 vs. 1 studies ; Q = 10.84, df = 1, $p = .001$). Subgroup results are depicted in forest plots in Supplementary Figures. However, these results should be interpreted with caution due to sample size as subgroup analyses were performed among a

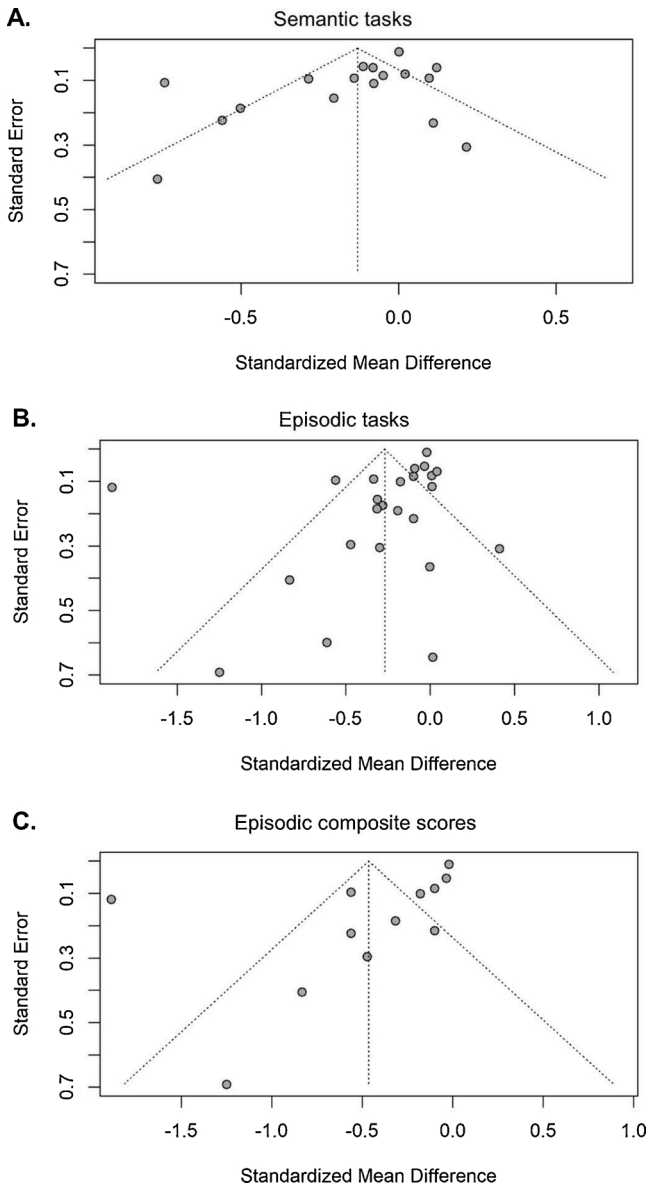

Fig. 2. Funnel plots to assess publication bias for (**A.**) all semantic tasks, (**B.**) all episodic tasks, (**C.**) episodic composite scores.

smaller subset of studies.

4. Discussion

This paper systematically reviewed and meta-analyzed the cross-sectional relationship of tau burden with episodic and semantic cognition in older adults without dementia. We included 24 studies, all of which investigated tau in relation to episodic tasks, and 14 studies additionally examined its relation to semantic tasks. We found that greater tau burden was associated with both lower episodic and semantic memory performance when pooling different tasks of each domain. We further found that higher tau levels were associated with lower episodic and semantic composite scores and lower performance on word-list delayed recall, but not on logical memory, picture naming, and semantic fluency. Large heterogeneity was found within the results, indicating effect modification across studies. Subgroup analyses revealed that categorical versus continuous tau scales modified effects on episodic and semantic domain scores and word-list learning, and tau detection method (PET, CSF, histopathology) additionally modified the effect on domain scores. Effects on word-list learning and semantic fluency were influenced by studies including only participants with subjective cognitive impairment. Our findings indicate that tau-associated memory impairment is already present and detectable in older adults without dementia, which warrants further study of tau as a potential early biomarker of Alzheimer's disease.

The meta-analytic results indicated a cross-sectional relationship between tau burden and episodic memory performance in older adults without dementia, as increased tau levels were associated with lower performance on episodic tasks. These findings resonate with longitudinal studies reporting associations between an increase of tau levels and decline in episodic performance over time (Aschenbrenner et al., 2018; Mitchell et al., 2002; Ziontz et al., 2019). Episodic composite scores had a medium-sized effect estimate, whereas smaller effect sizes were found for individual episodic tasks, like delayed recall on word lists and logical memory. While the effect was present for episodic domain scores and delayed recall on word lists, no effect was found for logical memory. This finding could be attributed to the low number of studies evaluating logical memory tasks (n = 5). Although most studies (n = 19) reported negative effect estimates, the vast majority of these (n = 14) were not significant. This discrepancy between the pooled overall effect sizes and effect sizes reported by individual studies might result from high variance between-studies and poor statistical power within individual studies. When pooling effect sizes, the high variance between studies is reduced, thus generating more statistical power to detect smaller effect estimates, as shown in the meta-analysis. The lack of study results could also be attributed to low sample sizes in some of the studies. Another explanation may be possible ceiling effects, due to a generally high cognitive performance in a cognitively normal population.

We also observed a cross-sectional association between tau and semantic memory, as higher levels of tau were associated with lower performance on semantic memory tasks. In line with our hypothesis, we found a smaller effect between tau and semantic cognition compared to episodic cognition, and the effect was only observed for semantic domain scores but not for individual tasks of semantic fluency and picture naming. These findings suggest that these individual tasks may not be sensitive enough to detect the subtle semantic impairment that is expected in a cognitively healthy older population, indicating that the traditional metrics of semantic tasks are too coarse to measure subtle semantic impairment cross-sectionally (Vonk et al., 2020b). As relatively few studies have evaluated tau burden in relation to semantic composite scores (n = 7), semantic fluency (n = 6), and picture naming (n = 3), more studies are needed to qualify these observations. Our results indicate that semantic cognition is associated with increased tau accumulation in healthy aging and emphasizes the need for more sensitive neuropsychological tasks to detect these subtle cognitive effects.

For both episodic and semantic memory, domain composite scores depicted the largest effect sizes in the association with tau burden. Composite scores are suggested to be useful as cognitive measures, assuming that the individual tasks of a certain cognitive domain measure similar aspects of that specific domain (Hedden et al., 2013). However, this premise is difficult to uphold as the neuropsychological tasks that are used to compute composite scores for each cognitive domain vary between studies, and not all tasks may be equally related to a specified cognitive domain (Vonk et al., 2020b). Additionally, composite scores may include tests that do not measure that specific cognitive domain; for example, one study included measures of working memory (i.e., digit-span task) as part of their semantic composite score (Bennett et al., 2012). Nonetheless, we found that the domain scores of episodic and semantic memory were able to detect an effect between tau burden and memory performance, in contrast to individual tasks that had lower effect sizes (e.g., word-list delayed recall) or non-significant effect sizes (e.g., logical memory, semantic fluency and picture naming). The diversity in tasks that are included in composite scores makes it difficult to pinpoint which types of tasks may be more sensitive than others to capture early cognitive impairment that tracks with biomarkers of Alzheimer's disease. For this reason, we investigated both

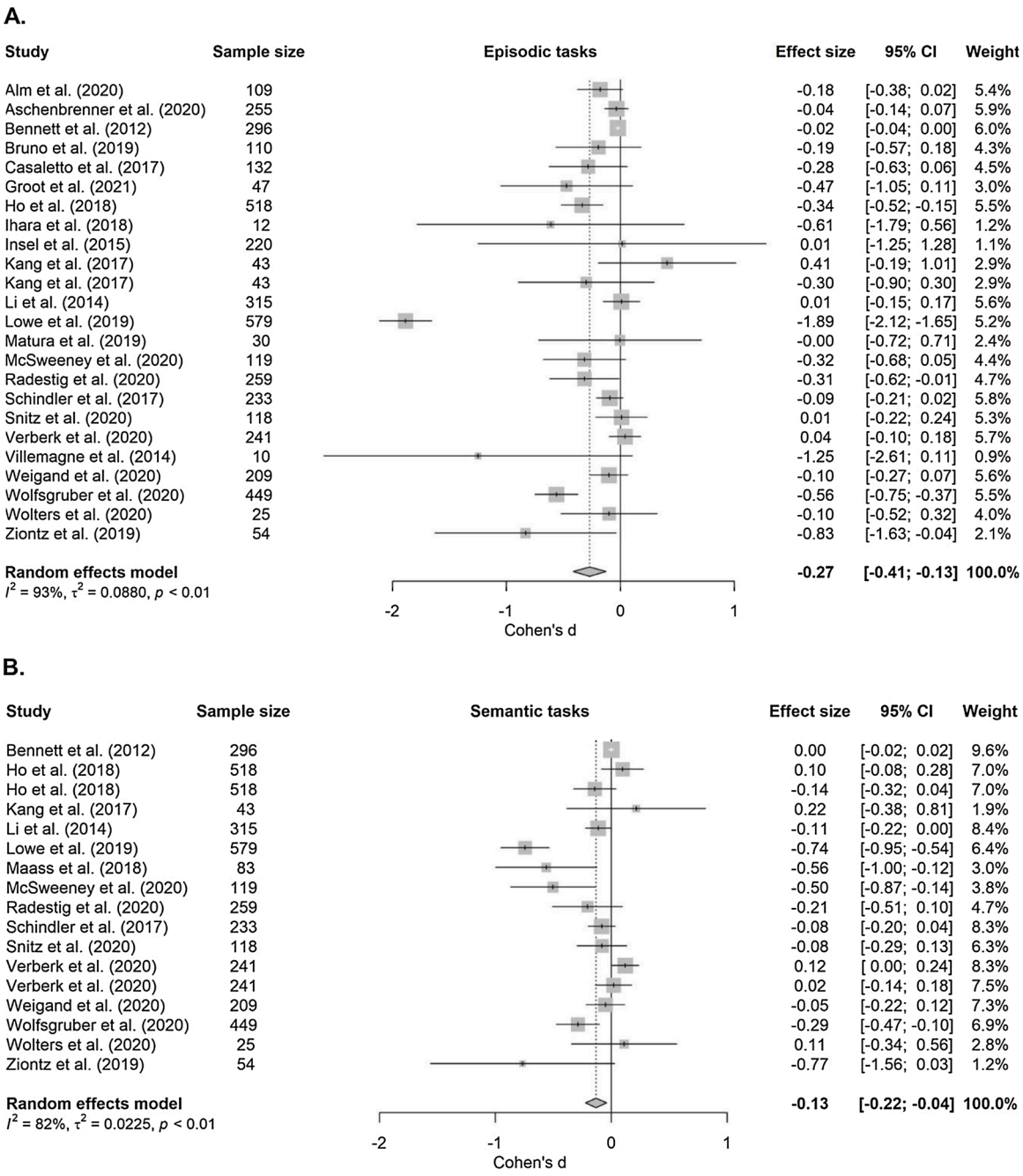

Fig. 3. Forest plots of association between tau burden and pooled tasks of the (**A.**) episodic domain and (**B.**) semantic domain. Greater tau burden associated with lower task performance is represented by negative effect sizes. Study weight is represented by size of the squares.

domain composite scores as well as separate tasks. Based on our results, we did not find a semantic memory measure that seems particularly sensitive, but among the episodic memory measures the word list learning tasks seems to be more strongly associated with tau than the logical memory tasks. It is important to note that the number of studies evaluating these individual tasks were also lower than studies investigating domain scores, thus possessing less power to detect an effect.

Our findings indicate that the literature on preclinical Alzheimer's disease biomarkers and cognition is posed to publication bias, suggesting that non-significant findings are less likely to be published in this field. Publication bias poses a threat to the validity of meta-analyses, as it potentially leads to overestimation of effect sizes (Van Aert et al., 2019). In order to diminish this overestimation, we contacted authors of studies that did not report the statistical data of non-significant associations. Although we were able to include two additional studies in this manner, the risk of bias is still present and should be taken into account when evaluating our findings.

The meta-analysis indicated substantial heterogeneity across tasks between studies investigating the relationship between tau burden and cognition. Subgroup analyses identified various moderators that influenced the meta-analytic results. A mean sample age of >70 years seemed to influence the results of delayed recall on word lists, suggesting that the effect of tau-associated cognitive impairment is stronger in older populations. We did not find this effect for the other cognitive tasks, and as a large proportion of studies corrected for age in their analysis, this effect may be diminished. For word-list learning and semantic fluency, the inclusion of individuals with subjective cognitive complaints moderated the meta-analytic results. A smaller effect size was found

Table 3
Study analytic specifications (effect sizes with standard error).

Author	N	Tau metric	Tau method	SCD only	Covariates	Semantic composite		Semantic fluency		Picture naming task		Episodic composite		Delayed recall word list		*Delayed recall complex figure task*		*Logical memory*	
Alm et al. (2020)	109	con	CSF	no	yes	–		–		–		−0.178	(0.101)	–		–		–	
Aschenbrenner et al. (2020)	255	con	CSF	no	yes	–		–		–		−0.035	(0.053)	–		–		–	
Bennett et al. (2012)	296	con	histo	no	yes	0.001	(0.011)	–		–		−0.021	(0.010)	–		–		–	
Bruno et al. (2019)	110	con	CSF	no	yes	–		–		–		–		−0.193	(0.191)	–		–	
Casaletto et al. (2017)	132	con	CSF	no	yes	–		–		–		–		−0.283	(0.175)	–		–	
Groot et al. (2020)	47	con	PET	no	yes	–		–		–		−0.473	(0.296)	–		–		–	
Ho and Nation (2018)	518	cat	CSF	no	yes	–		–		−0.142	(0.092)	–		−0.336	(0.093)	–		–	
Ihara et al. (2018)	12	cat	CSF	no	no	–		–		–		–		–		–		−0.613	(0.599)
Insel et al. (2015)	220	cat	CSF	no		–		–		–		–		–[a]		–		0.014	(0.636)
Kang et al. (2017)	43	con	PET	no	no	–		0.215	(0.306)	–		–		−0.3	(0.305)	0.410	(0.308)	–	–
Li et al. (2014)	315	con	CSF	no	yes	–		–		−0.113	(0.056)	–		–		–		0.008	(0.082)
Lowe et al. (2019)	579	cat	PET	no	yes	−0.744	(0.106)	–		–		−1.886	(0.118)	–		–		–	
Maass et al. (2018)	83	con	PET	no	no	–		–		–		−0.561	(0.224)	–		–		–	
Matura et al. (2019)	30	con	CSF	no	yes	–		–		–		–		−0.004	(0.365)	–		–	
McSweeney et al. (2020)	119	con	PET	no	yes	−0.503	(0.186)	–		–		−0.316	(0.185)	–		–		–	
Radestig et al. (2021)	259	cat	CSF	no	no	–		–		−0.206	(0.154)	–		−0.315	(0.155)	–		–	
Schindler et al. (2017)	233	con	CSF	no	yes	–		–		−0.082	(0.06)	–		–		–		−0.093	(0.060)
Snitz et al. (2020)	118	con	PET	no	yes	–		–		−0.08	(0.109)	–		–		–		0.010	(0.116)
Verberk et al. (2020)	241	con	CSF	yes	yes	–		0.020	(0.08)	0.120	(0.060)	–		0.040	(0.070)	–		–	
Villemagne et al. (2014)	10	con	PET	no	yes	–		–		–		−1.250	(0.691)	–		–		–	
Weigand et al. (2020)	209	con	PET	no	yes	−0.050	(0.085)	–		–		−0.100	(0.085)	–		–		–	
Wolfsgruber et al. (2020)	449	con	CSF	yes	no	−0.287	(0.095)	–		–		−0.561	(0.096)	–		–		–	
Wolters et al. (2020)	25	con	PET	yes	yes	0.110	(0.232)	–		–		−0.100	(0.215)	–		–		–	
Ziontz et al. (2019)	54	con	PET	no	yes	−0.766	(0.405)	–		–		−0.833	(0.405)	–		–		–	

Note. Cohen's D (Standard Error).
Abbreviations: con = continuous; cat = categorical.

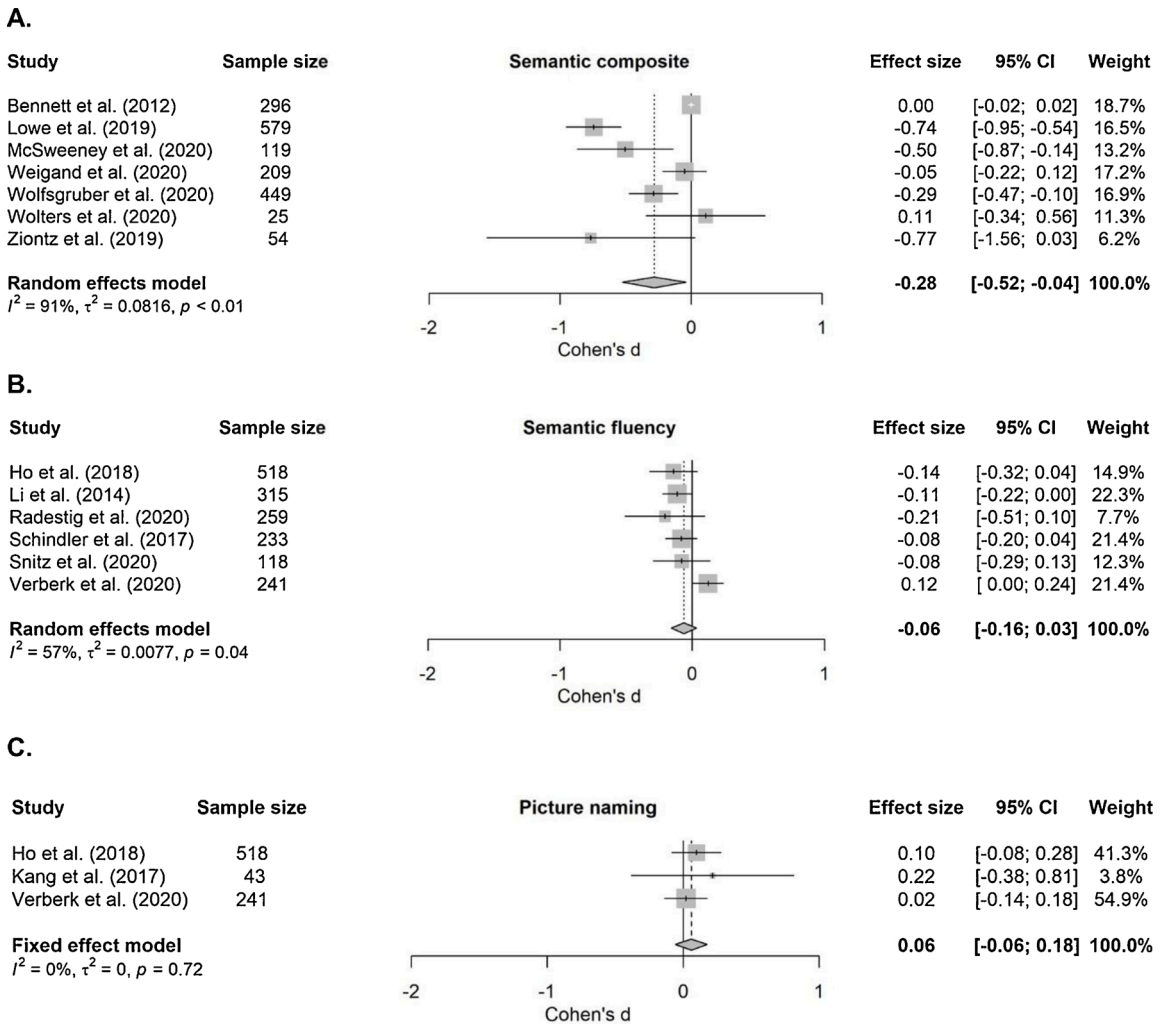

Fig. 4. Forest plots of association between tau burden and semantic memory tasks, (**A.**) semantic composite scores, (**B.**) semantic fluency, and (**C.**) picture naming tasks. Greater tau burden associated with lower task performance is represented by negative effect sizes. Study weight is represented by size of the squares.

when solely individuals with subjective cognitive complaints were included. When all participants have subjective cognitive complaints, instead of only part of the study sample, it is more difficult to detect a cross-sectional association because the distribution of the subject population is less variable which may explain these findings. However, as only one study evaluated individuals with subjective complaints for semantic fluency and delayed recall on word lists (Verberk et al., 2020), more studies are needed to substantiate this finding. Another factor that moderated the results was using categorical versus continuous metrics for tau burden, as the effect was stronger when categorical metrics were used for episodic domain scores, word-list learning and semantic domain scores. When using continuous metrics, a linear relationship with cognitive impairment is expected, which might suggest that the relationship between tau accumulation and cognitive deterioration is non-linear. The results of the subgroup analyses should be interpreted with caution, as smaller subsets of studies were compared.

The method of tau assessment influenced the meta-analytic results, as PET studies reported greater effect estimates compared to CSF or histopathology. Tau accumulates locally, starting in the mesial temporal lobe, including the anterolateral entorhinal cortex and then spreading to other regions, such as the hippocampus (Braak and Braak, 1997). In contrast to CSF studies, PET studies have the capacity to assess focal tau concentrations, as the retention of tau ligands are measured in specific, pre-determined brain areas (Ossenkoppele et al., 2015; Villemagne et al., 2015). Our findings resonate with previous findings of an aggravation of tau in these specific areas that is associated with memory dysfunction in individuals without dementia (Crary et al., 2014), and also individuals with Alzheimer's disease (Reijs et al., 2017). As CSF methods are limited to measuring only global levels of tau, the assessment of tau through CSF may not be sensitive enough to detect the more localized elevations of tau, and thus unable to examine its relation with cognition. Future studies should measure tau burden using tau PET tracers when assessing its relation to cognition, as this is more sensitive to the focal characteristic of tau accumulation. This regional accumulation may be more sensitive to some cognitive domains than others, depending on the localization. For example, our focus on medial temporal lobe and limbic regions in the current analysis may be more sensitive to episodic memory than semantic impairment, as semantic memory has been linked more strongly to temporal-parietal regions and the anterior temporal lobe (Binder et al., 2009; Vonk et al., 2019a). As such, future work should investigate if the differential strength of associations of tau with episodic versus semantic memory changes depending on the progression of tau accumulation towards temporal-parietal regions in individuals without dementia.

Strengths of this study include identification of risk of bias using a validated quality assessment tool, consideration of publication bias, investigation of individual task effects, and exploration of potential moderator factors. We also acknowledge several limitations of this systematic review and meta-analysis. We limited our inclusion criteria to cross-sectional associations; as exposure and outcome are

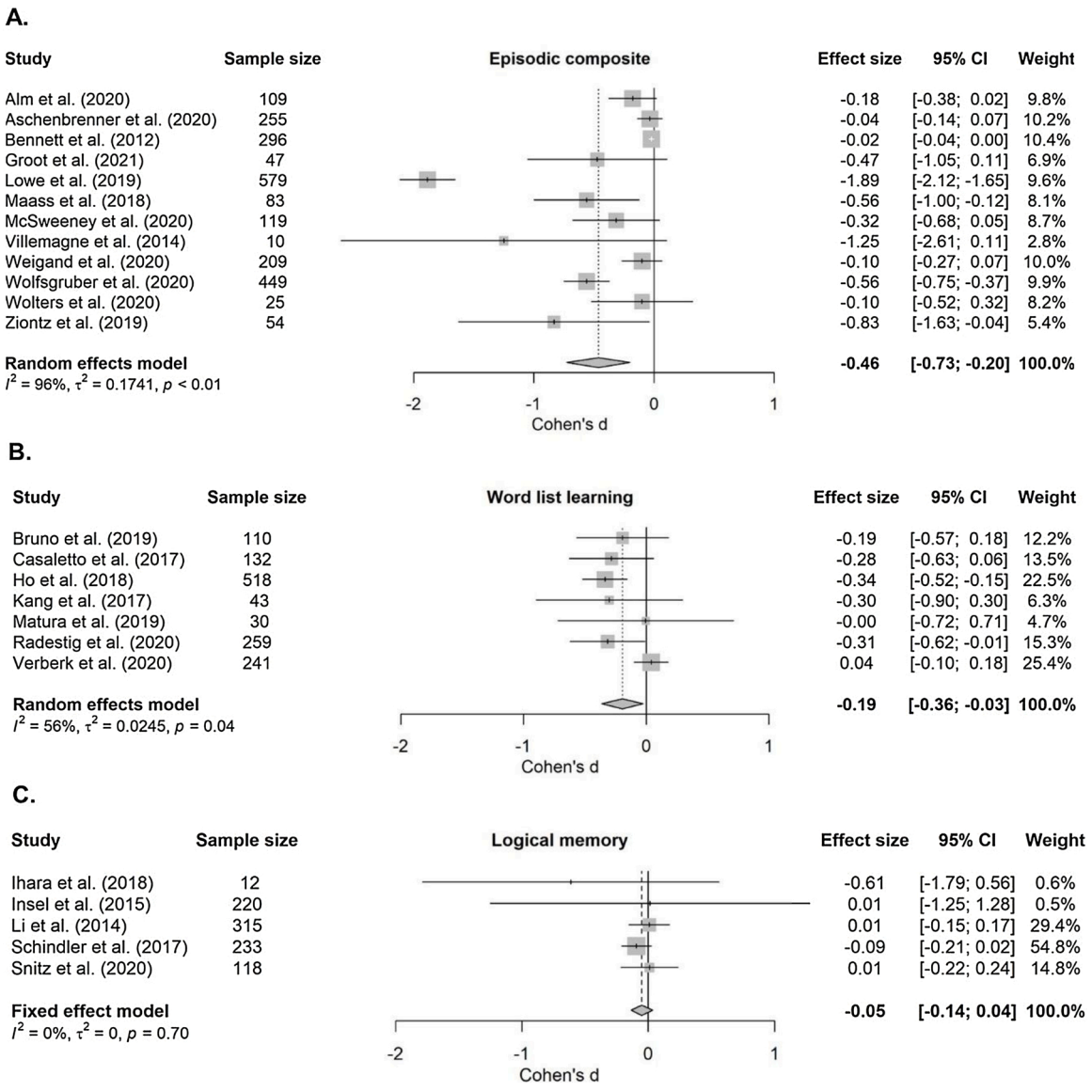

Fig. 5. Forest plots of association between tau burden and episodic memory tasks, (**A.**) episodic composite scores, (**B.**) delayed recall on word lists, and (**C.**) delayed recall on Logical Memory tasks. Greater tau burden associated with lower task performance is represented by negative effect sizes. Study weight is represented by size of the squares.

Table 4
Subgroup analyses.

			Q, df, *P* value		
Moderators	Mean sample age <70 vs. > 70 years	CSF vs. PET vs. histopathology	No covariates vs. adjusted for covariates	Categorical vs. continuous	Non SCD vs. only SCD
All episodic tasks, *n*	14 vs. 10 3.05, 1, 0.0807	13 vs. 10 vs. 1 9.43, 2, 0.0089	5 vs. 19 0.04, 1, 0.8478	5 vs. 19 1.66, 1, 0.1979	21 vs. 3 0.08, 1, 0.7741
Episodic composite, *n*	6 vs. 6 1.59, 1, 0.2079	3 vs. 8 vs. 1 6.09, 2, 0.0477	2 vs. 10 0.45, 1, 0.5008	1 vs. 11 145.93, 1, < 0.0001	10 vs. 2 0.19, 1, 0.6618
Word-list learning, *n*	5 vs. 2 5.76, 1, 0.0164	6 vs. 1. vs. 0 0.12, 1, 0.7275	2 vs. 5 0.71, 1, 0.4008	2 vs. 5 5.76, 1, 0.0164	6 vs. 1 12.37, 1, 0.0004
All semantic tasks, n	9 vs. 8 0.41, 1, 0.5207	8 vs. 8 vs. 1 5.94, 2, 0.0512	4 vs. 13 1.89 1 0.1688	4 vs. 13 0.79, 1, 0.3738	13 vs. 4 1.73, 1, 0.1885
Semantic composite, *n*	3 vs. 4 0.06, 1, 0.8078	1 vs. 5 vs. 1 12.47, 2, 0.0020	1 vs. 6 0.00, 1, 0.9860	1 vs. 6 18.19, 1, <0.0001	5 vs. 2 0.67, 1, 0.4114
Semantic fluency, *n*	3 vs. 3 1.20, 1, 0.2736	5 vs. 1 vs. 0 0.02, 1, 0.8936	1 vs. 5 0.89, 1, 0.3446	2 vs. 4 1.56, 1, 0.2112	5 vs. 1 10.84, 1, 0.0010

Note. Bold indicates statistically significant findings ($p < 0.10$).

simultaneously assessed, it is challenging to determine their temporal relationship. Longitudinal studies could offer more insight into cognitive deterioration over time and may elaborate on disease outcome. The low number of studies that evaluated individual tasks in the association between tau and episodic (logical memory, n = 5) and semantic cognition (semantic composite scores, n = 7; semantic fluency, n = 6; and picture naming, n = 3) limited our ability to assess the sensitivity of these tasks with more conclusive observations. A third limitation arose from excluding 24 studies that did not provide sufficient information to compute effect sizes, leading to poorer statistical power and possible overestimation of the results. Lastly, we found that the risk of bias within studies mostly stemmed from non-representative samples used in cohort studies, as they were often not truly representative of the average older adult in the community, but a selected group of individuals (often volunteers). Additionally, study samples may not be racially and ethnically diverse, as the majority of participants are often well-educated white individuals.

Various directions for future research can be identified. When measuring subtle cognitive impairment, the focal aspect of tau accumulation should be taken into account by measuring tau burden through the retention of tau tracers using PET. Future work should also investigate the effect of race/ethnicity in the association between tau and cognition, as Black individuals depict lower levels of CSF-tau but higher levels of postmortem neurofibrillary tangles (Ziontz et al., 2019). The role of Aβ on the mechanism through which tau mediates its effects on cognition should be further investigated (Weigand et al., 2020), by assessing the association of tau and cognition in Aβ-positive and Aβ-negative cognitively unimpaired individuals. We found no eligible studies that investigated tau burden using blood plasma, probably due to the relative novelty of assays that are sensitive enough for plasma tau detection (Ding et al., 2021). To address this gap in literature, future research should investigate the association of plasma tau to episodic and semantic memory performance. Plasma tau combined with other biomarkers has shown to accurately predict the conversion to Alzheimer's disease and the use of plasma tau also offers a less invasive alternative to detect tau burden (Palmqvist et al., 2021). Finally, future research should investigate and increase sensitivity of existing and new neuropsychological tasks to detect subtle cognitive effects in older populations without dementia.

Our findings demonstrated that tau burden relates to both episodic and semantic memory impairment in older individuals without a diagnosis of MCI or manifest dementia. Sensitive metrics of neuropsychological tasks are needed to better detect these subtle cognitive effects to investigate episodic and semantic memory as cognitive markers in the preclinical stage. Future studies should investigate tau burden with methods that take the focal aspect of tau accumulation into account (i.e., using PET imaging opposed to CSF). Investigating the relationship of tau in older individuals without dementia with episodic and semantic impairment at baseline, decline over time, and development of incident dementia is important as these factors may predict the conversion towards Alzheimer's disease. Aggregating a robust body of evidence consistent with the current results would propose a role for tau in combination with cognitive markers as a biomarker for early *clinical* diagnosis and possible clinical target for timely intervention.

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CRediT authorship contribution statement

Teuntje A.D. Pelgrim: Data curation, Formal analysis, Investigation, Writing - original draft, Visualization, Writing - review & editing. **Magdalena Beran:** Data curation, Writing - review & editing. **Emma L. Twait:** Methodology, Writing - review & editing. **Mirjam I. Geerlings:** Writing - review & editing. **Jet M.J. Vonk:** Conceptualization, Methodology, Writing - review & editing, Supervision.

Declaration of Competing Interest

None declared.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.arr.2021.101449.

References

Alm, K.H., Faria, A.V., Moghekar, A., Pettigrew, C., Soldan, A., Mori, S., Albert, M., Bakker, A., 2020. Medial temporal lobe white matter pathway variability is associated with individual differences in episodic memory in cognitively normal older adults. Neurobiol. Aging 87, 78–88. https://doi.org/10.1016/j.neurobiolaging.2019.11.011.

Arriagada, P.V., Growdon, J.H., Hedley-Whyte, E.T., Hyman, B.T., 1992. Neurofibrillary tangles but not senile plaques parallel duration and severity of Alzheimer's disease. Neurology 42, 631–639. https://doi.org/10.1212/wnl.42.3.631.

Aschenbrenner, A.J., Gordon, B.A., Benzinger, T.L.S., Morris, J.C., Hassenstab, J.J., 2018. Influence of tau PET, amyloid PET, and hippocampal volume on cognition in Alzheimer disease. Neurology 91. https://doi.org/10.1212/WNL.0000000000006075.

Aschenbrenner, A.J., Gordon, B.A., Fagan, A.M., Schindler, S.E., Balota, D.A., Morris, J.C., Hassenstab, J.J., Tales, A., 2020. Neurofilament light predicts decline in attention but not episodic memory in preclinical alzheimer's disease. J. Alzheimers Dis. 74, 1119–1129. https://doi.org/10.3233/JAD-200018.

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 Dement. Diagnosis, Assess. Dis. Monit. https://doi.org/10.1016/j.dadm.2016.09.002.

Balduzzi, S., Rücker, G., Schwarzer, G., 2019. How to perform a meta-analysis with R: a practical tutorial. Evid. Based. Ment. Health 22, 153–160. https://doi.org/10.1136/EBMENTAL-2019-300117.

Bateman, R., Xiong, C., Benzinger, T., Fagan, A., Goate, A., Fox, N., Marcus, D., Cairns, N., Xie, X., Blazey, T., Holtzman, D., Santacruz, A., Buckles, V., Oliver, A., Moulder, K., Aisen, P., Ghetti, B., Klunk, W., McDade, E., Martins, R., Masters, C., Mayeux, R., Ringman, J., Rossor, M., Schofield, P., Sperling, R., Salloway, S., Morris, J.C., 2012. Clinical and biomarker changes in dominantly inherited Alzheimer's disease. N. Engl. J. Med. 367, 795–804. https://doi.org/10.1056/NEJMOA1202753.

Bennett, D.A., Wilson, R.S., Boyle, P.A., Buchman, A.S., Schneider, J.A., 2012. Relation of neuropathology to cognition in persons without cognitive impairment. Ann. Neurol. 72, 599–609. https://doi.org/10.1002/ana.23654.

Binder, J.R., Desai, R.H., Graves, W.W., Conant, L.L., 2009. Where is the semantic system? A critical review and meta-analysis of 120 functional neuroimaging studies. Cereb. Cortex 19, 2767–2796. https://doi.org/10.1093/CERCOR/BHP055.

Braak, H., Braak, E., 1997. Frequency of stages of Alzheimer-related lesions in different age categories. Neurobiol. Aging 18, 351–357. https://doi.org/10.1016/S0197-4580(97)00056-0.

Braak, H., Thal, D.R., Ghebremedhin, E., Del Tredici, K., 2011. Stages of the pathologic process in alzheimer disease: age categories from 1 to 100 years. J. Neuropathol. Exp. Neurol. 70, 960–969. https://doi.org/10.1097/NEN.0b013e318232a379.

Bruno, D., Gleason, C.E., Koscik, R.L., Pomara, N., Zetterberg, H., Blennow, K., Johnson, S.C., 2019. The recency ratio is related to CSF amyloid beta 1-42 levels in MCI-AD. Int. J. Geriatr. Psychiatry 34, 415–419. https://doi.org/10.1002/gps.5029.

Casaletto, K.B., Elahi, F.M., Bettcher, B.M., Neuhaus, J., Bendlin, B.B., Asthana, S., Johnson, S.C., Yaffe, K., Carlsson, C., Blennow, K., Zetterberg, H., Kramer, J.H., 2017. Neurogranin, a synaptic protein, is associated with memory independent of Alzheimer biomarkers. Neurology 89, 1782–1788. https://doi.org/10.1212/WNL.0000000000004569.

Chen, X., Cassady, K., Adams, J.N., Harrison, T.M., Baker, S.L., Jagust, W.J., 2020. Regional tau effects on prospective cognitive change in cognitively normal older adults. J. Neurosci. JN-RM-2111-20. https://doi.org/10.1523/jneurosci.2111-20.2020.

Cohen, J., 1988. The Effect Size Index: D, in: Statistical Power Analysis for the Behavioral Sciences.

Crary, J.F., Trojanowski, J.Q., Schneider, J.A., Abisambra, J.F., Abner, E.L., Alafuzoff, I., Arnold, S.E., Attems, J., Beach, T.G., Bigio, E.H., Cairns, N.J., Dickson, D.W., Gearing, M., Grinberg, L.T., Hof, P.R., Hyman, B.T., Jellinger, K., Jicha, G.A., Kovacs, G.G., Knopman, D.S., Kofler, J., Kukull, W.A., Mackenzie, I.R., Masliah, E., McKee, A., Montine, T.J., Murray, M.E., Neltner, J.H., Santa-Maria, I., Seeley, W.W., Serrano-Pozo, A., Shelanski, M.L., Stein, T., Takao, M., Thal, D.R., Toledo, J.B., Troncoso, J.C., Vonsattel, J.P., White, C.L., Wisniewski, T., Woltjer, R.L., Yamada, M., Nelson, P.T., 2014. Primary age-related tauopathy (PART): a common pathology associated with human aging. Acta Neuropathol. 128, 755–766. https://doi.org/10.1007/s00401-014-1349-0.

Ding, X., Tuo, Q., Lei, P., 2021. An introduction to ultrasensitive assays for plasma tau detection. J. Alzheimers Dis. 80, 1353–1362. https://doi.org/10.3233/JAD-201499.

Drago, V., Babiloni, C., Bartrés-Faz, D., Caroli, A., Bosch, B., Hensch, T., Didic, M., Klafki, H.W., Pievani, M., Jovicich, J., Venturi, L., Spitzer, P., Vecchio, F., Schoenknecht, P., Wiltfang, J., Redolfi, A., Forloni, G., Blin, O., Irving, E., Davis, C., Hrdemark, H.G., Frisoni, G.B., 2011. Disease tracking markers for Alzheimers Disease at the prodromal (MCI) stage. J. Alzheimers Dis. 26, 159–199. https://doi.org/10.3233/JAD-2011-0043.

Ferri, C.P., Prince, M., Brayne, C., Brodaty, H., Fratiglioni, L., Ganguli, M., Hall, K., Hasegawa, K., Hendrie, H., Huang, Y., Jorm, A., Mathers, C., Menezes, P.R., Rimmer, E., Scazufca, M., 2005. Global prevalence of dementia: a Delphi consensus study. Lancet 366, 2112–2117. https://doi.org/10.1016/S0140-6736(05)67889-0.

Gallagher, M., Koh, M.T., 2011. Episodic memory on the path to Alzheimer's disease. Curr. Opin. Neurobiol. https://doi.org/10.1016/j.conb.2011.10.021.

Gordon, B.A., Friedrichsen, K., Brier, M., Blazey, T., Su, Y., Christensen, J., Aldea, P., McConathy, J., Holtzman, D.M., Cairns, N.J., Morris, J.C., Fagan, A.M., Ances, B.M., Benzinger, T.L.S., 2016. The relationship between cerebrospinal fluid markers of Alzheimer pathology and positron emission tomography tau imaging. Brain 139, 2249–2260. https://doi.org/10.1093/brain/aww139.

Greene, J.D.W., Baddeley, A.D., Hodges, J.R., 1996. Analysis of the episodic memory deficit in early Alzheimer's disease: evidence from the doors and people test. Neuropsychologia 34, 537–551. https://doi.org/10.1016/0028-3932(95)00151-4.

Groot, C., Doré, V., Robertson, J., Burnham, S.C., Savage, G., Ossenkoppele, R., Rowe, C. C., Villemagne, V.L., 2020. Mesial temporal tau is related to worse cognitive performance and greater neocortical tau load in amyloid-β–negative cognitively normal individuals. Neurobiol. Aging 97, 41–48. https://doi.org/10.1016/j.neurobiolaging.2020.09.017.

Hänninen, T., Koivisto, K., Reinikainen, K.J., Helkala, E.-L., Soininen, H., Mykkänen, L., Laakso, M., Riekkinen, P.J., 1996. Prevalence of ageing-associated cognitive decline in an elderly population. Age Ageing 25, 201–205. https://doi.org/10.1093/ageing/25.3.201.

Hedden, T., Oh, H., Younger, A.P., Patel, T.A., 2013. Meta-analysis of amyloid-cognition relations in cognitively normal older adults. Neurology 80, 1341–1348. https://doi.org/10.1212/WNL.0b013e31828ab35d.

Ho, J.K., Nation, D.A., 2018. Neuropsychological profiles and trajectories in preclinical alzheimer's disease. J. Int. Neuropsychol. Soc. 24, 693–702. https://doi.org/10.1017/S135561771800022X.

Hodges, J.R., 2000. In: Tulving, E., Craik, F.I.M. (Eds.), Memory in the Dementias- The Oxford Handbook of Memory - Google Boeken. Oxford University Press, NY, USA.

Holtzman, D.M., Morris, J.C., Goate, A.M., 2011. Alzheimer's disease: the challenge of the second century. Sci. Transl. Med. https://doi.org/10.1126/scitranslmed.3002369.

Ihara, R., Iwata, A., Suzuki, K., Ikeuchi, T., Kuwano, R., Iwatsubo, T., 2018. Clinical and cognitive characteristics of preclinical Alzheimer's disease in the Japanese Alzheimer's Disease Neuroimaging Initiative cohort. Alzheimer's Dement. Transl. Res. Clin. Interv. 4, 645–651. https://doi.org/10.1016/j.trci.2018.10.004.

Ingelsson, M., Fukumoto, H., Newell, K.L., Growdon, J.H., Hedley-Whyte, E.T., Frosch, M.P., Albert, M.S., Hyman, B.T., Irizarry, M.C., 2004. Early Aβ accumulation and progressive synaptic loss, gliosis, and tangle formation in AD brain. Neurology 62, 925–931. https://doi.org/10.1212/01.WNL.0000115115.98960.37.

Insel, P.S., Mattsson, N., Mackin, R.S., Kornak, J., Nosheny, R., Tosun-Turgut, D., Donohue, M.C., Aisen, P.S., Weiner, M.W., 2015. Biomarkers and cognitive endpoints to optimize trials in Alzheimer's disease. Ann. Clin. Transl. Neurol. 2, 534–547. https://doi.org/10.1002/acn3.192.

Jack, C.R., Knopman, D.S., Jagust, W.J., Petersen, R.C., Weiner, M.W., Aisen, P.S., Shaw, L.M., Vemuri, P., Wiste, H.J., Weigand, S.D., Lesnick, T.G., Pankratz, V.S., Donohue, M.C., Trojanowski, J.Q., 2013. Tracking pathophysiological processes in Alzheimer's disease: an updated hypothetical model of dynamic biomarkers. Lancet Neurol. https://doi.org/10.1016/S1474-4422(12)70291-0.

Kang, J.M., Lee, S.Y., Seo, S., Jeong, H.J., Woo, S.H., Lee, H., Lee, Y.B., Yeon, B.K., Shin, D.H., Park, K.H., Kang, H., Okamura, N., Furumoto, S., Yanai, K., Villemagne, V.L., Seong, J.K., Na, D.L., Ido, T., Cho, J., Lee, K.M., Noh, Y., 2017. Tau positron emission tomography using [18F]THK5351 and cerebral glucose hypometabolism in Alzheimer's disease. Neurobiol. Aging 59, 210–219. https://doi.org/10.1016/j.neurobiolaging.2017.08.008.

Li, G., Millard, S.P., Peskind, E.R., Zhang, J., Yu, C.E., Leverenz, J.B., Mayer, C., Shofer, J. S., Raskind, M.A., Quinn, J.F., Galasko, D.R., Montine, T.J., 2014. Cross-sectional and longitudinal relationships between cerebrospinal fluid biomarkers and cognitive function in people without cognitive impairment from across the adult life span. JAMA Neurol. 71, 742–751. https://doi.org/10.1001/jamaneurol.2014.445.

Lovden, M., Ronnlund, M., Wahlin, A., Backman, L., Nyberg, L., Nilsson, L.-G., 2004. The extent of stability and change in episodic and semantic memory in old age: demographic predictors of level and change. J. Gerontol. Ser. B Psychol. Sci. Soc. Sci. 59, P130–P134. https://doi.org/10.1093/geronb/59.3.P130.

Lowe, V.J., Bruinsma, T.J., Wiste, H.J., Min, H.K., Weigand, S.D., Fang, P., Senjem, M.L., Therneau, T.M., Boeve, B.F., Josephs, K.A., Pandey, M.K., Murray, M.E., Kantarci, K., Jones, D.T., Vemuri, P., Graff-Radford, J., Schwarz, C.G., Machulda, M.M., Mielke, M.M., Roberts, R.O., Knopman, D.S., Petersen, R.C., Jack, C.R., 2019. Cross-sectional associations of tau-PET signal with cognition in cognitively unimpaired adults. Neurology 93, E29–E39. https://doi.org/10.1212/WNL.0000000000007728.

Maass, A., Lockhart, S.N., Harrison, T.M., Bell, R.K., Mellinger, T., Swinnerton, K., Baker, S.L., Rabinovici, G.D., Jagust, W.J., 2018. Entorhinal tau pathology, episodic memory decline, and neurodegeneration in aging. J. Neurosci. 38, 530–543. https://doi.org/10.1523/JNEUROSCI.2028-17.2017.

Mandelkow, E.M., Mandelkow, E., 1998. Tau in Alzheimer's disease. Trends Cell Biol. 8, 425–427. https://doi.org/10.1016/S0962-8924(98)01368-3.

Marks, S.M., Lockhart, S.N., Baker, S.L., Jagust, W.J., 2017. Tau and β-amyloid are associated with medial temporal lobe structure, function, and memory encoding in normal aging. J. Neurosci. 37, 3192–3201. https://doi.org/10.1523/JNEUROSCI.3769-16.2017.

Matura, S., Köhler, J., Reif, A., Fusser, F., Karakaya, T., Scheibe, M., Ehret, F., Hartmann, D., Kang, J.S., Mayer, C., Prvulovic, D., Pantel, J., 2019. Intrinsic functional connectivity, CSF biomarker profiles and their relation to cognitive function in mild cognitive impairment. Acta Neuropsychiatr. 32 https://doi.org/10.1017/neu.2019.49.

McSweeney, M., Pichet Binette, A., Meyer, P.F., Gonneaud, J., Bedetti, C., Ozlen, H., Labonté, A., Rosa-Neto, P., Breitner, J., Poirier, J., Villeneuve, S., 2020. Intermediate flortaucipir uptake is associated with Aß-PET and CSF tau in asymptomatic adults. Neurology 94, e1190–e1200. https://doi.org/10.1212/WNL.0000000000008905.

Mitchell, T.W., Mufson, E.J., Schneider, J.A., Cochran, E.J., Nissanov, J., Han, L.-Y., Bienias, J.L., Lee, V.M.-Y., Trojanowski, J.Q., Bennett, D.A., Arnold, S.E., 2002. Parahippocampal tau pathology in healthy aging, mild cognitive impairment, and early Alzheimer's disease. Ann. Neurol. 51, 182–189. https://doi.org/10.1002/ana.10086.

Moher, D., Liberati, A., Tetzlaff, J., Altman, D.G., 2009. Reprint—preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Phys. Ther. 89, 873–880. https://doi.org/10.1093/ptj/89.9.873.

Nelson, P.T., Alafuzoff, I., Bigio, E.H., Bouras, C., Braak, H., Cairns, N.J., Castellani, R.J., Crain, B.J., Davies, P., Tredici, K.Del, Duyckaerts, C., Frosch, M.P., Haroutunian, V., Hof, P.R., Hulette, C.M., Hyman, B.T., Iwatsubo, T., Jellinger, K.A., Jicha, G.A., Kövari, E., Kukull, W.A., Leverenz, J.B., Love, S., MacKenzie, I.R., Mann, D.M., Masliah, E., McKee, A.C., Montine, T.J., Morris, J.C., Schneider, J.A., Sonnen, J.A., Thal, D.R., Trojanowski, J.Q., Troncoso, J.C., Wisniewski, T., Woltjer, R.L., Beach, T. G., 2012. Correlation of alzheimer disease neuropathologic changes with cognitive status: a review of the literature. J. Neuropathol. Exp. Neurol. https://doi.org/10.1097/NEN.0b013e31825018f7.

Nordberg, A., 2004. PET imaging of amyloid in Alzheimer's disease. Lancet Neurol. https://doi.org/10.1016/S1474-4422(04)00853-1.

Olsson, B., Lautner, R., Andreasson, U., Öhrfelt, A., Portelius, E., Bjerke, M., Hölttä, M., Rosén, C., Olsson, C., Strobel, G., Wu, E., Dakin, K., Petzold, M., Blennow, K., Zetterberg, H., 2016. CSF and blood biomarkers for the diagnosis of Alzheimer's disease: a systematic review and meta-analysis. Lancet Neurol. 15, 673–684. https://doi.org/10.1016/S1474-4422(16)00070-3.

Ossenkoppele, R., Jansen, W.J., Rabinovici, G.D., Knol, D.L., Flier, W.M., van der Berckel, B.N.M., et al., 2015. Prevalence of amyloid PET positivity in dementia syndromes: a meta-analysis. JAMA 313, 1939–1950. https://doi.org/10.1001/JAMA.2015.4669.

Ouzzani, M., Hammady, H., Fedorowicz, Z., Elmagarmid, A., 2016. Rayyan-a web and mobile app for systematic reviews. Syst. Rev. 5, 1–10. https://doi.org/10.1186/s13643-016-0384-4.

Palmqvist, S., Tideman, P., Cullen, N., Zetterberg, H., Blennow, K., Dage, J.L., Stomrud, E., Janelidze, S., Mattsson-Carlgren, N., Hansson, O., 2021. Prediction of future Alzheimer's disease dementia using plasma phospho-tau combined with other accessible measures. Nat. Med. 2021 (276), 1034–1042. https://doi.org/10.1038/s41591-021-01348-z, 27.

Papp, K.V., Mormino, E.C., Amariglio, R.E., Munro, C., Dagley, A., Schultz, A.P., Johnson, K.A., Sperling, R.A., Rentz, D.M., 2016. Biomarker validation of a decline in semantic processing in preclinical alzheimer's disease. Neuropsychology 30, 624–630. https://doi.org/10.1037/neu0000246.

Pereira, T.V., Patsopoulos, N.A., Salanti, G., Ioannidis, J.P.A., 2010. Critical interpretation of Cochran's Q test depends on power and prior assumptions about heterogeneity. Res. Synth. Methods 1, 149–161. https://doi.org/10.1002/jrsm.13.

Pooler, A.M., Polydoro, M., Maury, E.A., Nicholls, S.B., Reddy, S.M., Wegmann, S., William, C., Saqran, L., Cagsal-Getkin, O., Pitstick, R., Beier, D.R., Carlson, G.A., Spires-Jones, T.L., Hyman, B.T., 2015. Amyloid accelerates tau propagation and toxicity in a model of early Alzheimer's disease. Acta Neuropathol. Commun. 3, 14. https://doi.org/10.1186/s40478-015-0199-x.

Radestig, M.A., Skoog, J., Zetterberg, H., Kern, J., Zettergren, A., Sacuiu, S., Waern, M., Wetterberg, H., Blennow, K., Skoog, I., Kern, S., 2021. Cognitive performance and cerebrospinal fluid markers in preclinical alzheimer's disease: results from the Gothenburg H70 birth cohort studies. J. Alzheimers Dis. 79, 225–235. https://doi.org/10.3233/JAD-200751.

Reijs, B.L.R., Ramakers, I.H.G.B., Köhler, S., Teunissen, C.E., Koel-Simmelink, M., Nathan, P.J., Tsolaki, M., Wahlund, L.O., Waldemar, G., Hausner, L., Vandenberghe, R., Johannsen, P., Blackwell, A., Vanderstichele, H., Verhey, F., Visser, P.J., 2017. Memory correlates of alzheimer's disease cerebrospinal fluid markers: a longitudinal cohort study. J. Alzheimers Dis. 60, 1119–1128. https://doi.org/10.3233/JAD-160766.

Rstudio, T., 2020. RStudio: Integrated Development for R. Rstudio Team, PBC, Boston. MA URL http//www.rstudio.com/.. https://doi.org/10.1145/3132847.3132886.

Schindler, S.E., Jasielec, M.S., Weng, H., Hassenstab, J.J., Grober, E., McCue, L.M., Morris, J.C., Holtzman, D.M., Xiong, C., Fagan, A.M., 2017. Neuropsychological

measures that detect early impairment and decline in preclinical Alzheimer disease. Neurobiol. Aging 56, 25–32. https://doi.org/10.1016/j.neurobiolaging.2017.04.004.

Schmand, B., Huizenga, H.M., Van Gool, W.A., 2010. Meta-analysis of CSF and MRI biomarkers for detecting preclinical Alzheimer's disease. Psychol. Med. (Paris) 40, 135–145. https://doi.org/10.1017/S0033291709991516.

Snitz, B.E., Tudorascu, D.L., Yu, Z., Campbell, E., Lopresti, B.J., Laymon, C.M., Minhas, D.S., Nadkarni, N.K., Aizenstein, H.J., Klunk, W.E., Weintraub, S., Gershon, R.C., Cohen, A.D., 2020. Associations between NIH Toolbox Cognition Battery and in vivo brain amyloid and tau pathology in non-demented older adults. Alzheimer's Dement. Diagnosis, Assess. Dis. Monit. 12 https://doi.org/10.1002/dad2.12018.

Tchakoute, C.T., Sainani, K.L., Henderson, V.W., 2017. Semantic memory in the clinical progression of alzheimer disease. Cogn. Behav. Neurol. 30, 81–89. https://doi.org/10.1097/WNN.0000000000000131.

Thijssen, E.H., La Joie, R., Wolf, A., Strom, A., Wang, P., Iaccarino, L., Bourakova, V., Cobigo, Y., Heuer, H., Spina, S., VandeVrede, L., Chai, X., Proctor, N.K., Airey, D.C., Shcherbinin, S., Duggan Evans, C., Sims, J.R., Zetterberg, H., Blennow, K., Karydas, A.M., Teunissen, C.E., Kramer, J.H., Grinberg, L.T., Seeley, W.W., Rosen, H., Boeve, B.F., Miller, B.L., Rabinovici, G.D., Dage, J.L., Rojas, J.C., Boxer, A. L., Forsberg, L., Knopman, D.S., Graff-Radford, N., Grossman, M., Huey, E.H., Onyike, C., Kaufer, D., Roberson, E., Ghoshal, N., Weintraub, S., Appleby, B., Litvan, I., Kerwin, D., Mendez, M., Bordelon, Y., Coppola, G., Ramos, E.M., Tartaglia, M.C., Hsiung, G.Y., MacKenzie, I., Domoto-Reilly, K., Foroud, T., Dickerson, B.C., 2020. Diagnostic value of plasma phosphorylated tau181 in Alzheimer's disease and frontotemporal lobar degeneration. Nat. Med. 26 https://doi.org/10.1038/s41591-020-0762-2.

Van Aert, R.C.M., Wicherts, J.M., Van Assen, M.A.L.M., 2019. Publication bias examined in meta-analyses from psychology and medicine: a meta-meta-analysis. PLoS One 14, e0215052. https://doi.org/10.1371/journal.pone.0215052.

Venneri, A., Jahn-Carta, C., De Marco, M., Quaranta, D., Marra, C., 2018. Diagnostic and prognostic role of semantic processing in preclinical Alzheimer's disease. Biomark. Med. https://doi.org/10.2217/bmm-2017-0324.

Verberk, I.M.W., Hendriksen, H.M.A., van Harten, A.C., Wesselman, L.M.P., Verfaillie, S. C.J., van den Bosch, K.A., Slot, R.E.R., Prins, N.D., Scheltens, P., Teunissen, C.E., Van der Flier, W.M., 2020. Plasma amyloid is associated with the rate of cognitive decline in cognitively normal elderly: the SCIENCe project. Neurobiol. Aging 89, 99–107. https://doi.org/10.1016/j.neurobiolaging.2020.01.007.

Verma, M., Howard, R.J., 2012. Semantic memory and language dysfunction in early Alzheimer's disease: a review. Int. J. Geriatr. Psychiatry. https://doi.org/10.1002/gps.3766.

Viechtbauer, W., 2010. Conducting meta-analyses in r with the metafor package. J. Stat. Softw. 36, 1–48. https://doi.org/10.18637/JSS.V036.I03.

Villemagne, V.L., Furumoto, S., Fodero-Tavoletti, M.T., Mulligan, R.S., Hodges, J., Harada, R., Yates, P., Piguet, O., Pejoska, S., Doré, V., Yanai, K., Masters, C.L., Kudo, Y., Rowe, C.C., Okamura, N., 2014. In vivo evaluation of a novel tau imaging tracer for Alzheimer's disease. Eur. J. Nucl. Med. Mol. Imaging 41, 816–826. https://doi.org/10.1007/s00259-013-2681-7.

Villemagne, V.L., Fodero-Tavoletti, M.T., Masters, C.L., Rowe, C.C., 2015. Tau imaging: early progress and future directions. Lancet Neurol. https://doi.org/10.1016/S1474-4422(14)70252-2.

Vonk, J., Borghesani, V., Battistella, G., Younes, K., DeLeon, J., Welch, A., Hubbard, H.I., Miller, Z.A., Miller, B.L., Gorno-Tempini, M.L., 2019a. Verbal Semantics and the Left Dorsolateral Anterior Temporal Lobe: a Longitudinal Case of Bilateral Temporal Degeneration, pp. 865–885. https://doi.org/10.1080/02687038.2019.165993534.

Vonk, J., Flores, R.J., Rosado, D., Qian, C., Cabo, R., Habegger, J., Louie, K., Allocco, E., Brickman, A.M., Manly, J.J., 2019b. Semantic network function captured by word frequency in nondemented APOE ε4 carriers. Neuropsychology 33, 256–262. https://doi.org/10.1037/neu0000508.

Vonk, J., Higby, E., Nikolaev, A., Cahana-Amitay, D., Spiro, A., Albert, M.L., Obler, L.K., 2020a. Demographic effects on longitudinal semantic processing, working memory, and cognitive speed. Journals Gerontol. Ser. B 75, 1850–1862. https://doi.org/10.1093/geronb/gbaa080.

Vonk, J., Twait, E., Scholten, R., Geerlings, M., 2020b. Cross-sectional associations of amyloid burden with semantic cognition in older adults without dementia: a systematic review and meta-analysis. Mech. Ageing Dev. https://doi.org/10.1016/j.mad.2020.111386.

Weigand, A.J., Bangen, K.J., Thomas, K.R., Delano-Wood, L., Gilbert, P.E., Brickman, A. M., Bondi, M.W., 2020. Is tau in the absence of amyloid on the Alzheimer's continuum?: a study of discordant PET positivity. Brain Commun. 2 https://doi.org/10.1093/braincomms/fcz046.

Wells, G., Shea, B., O'Connell, D., Peterson, J., Welch, V., Losos, M., Tugwell, P., 2014. Newcastle-Ottawa Quality Assessment Scale Cohort Studies. [WWW Document]. Vis. Commun. Q.

Wickham, H., François, R., Henry, L., Müller, K., 2021. A Grammar of Data Manipulation [R Package Dplyr Version 1.0.7] [WWW Document]. URL https://cran.r-project.org/package=dplyr (accessed 7.28.21).

Wilson, R.S., Leurgans, S.E., Boyle, P.A., Bennett, D.A., 2011. Cognitive decline in prodromal alzheimer disease and mild cognitive impairment. Arch. Neurol. 68, 351–356. https://doi.org/10.1001/archneurol.2011.31.

Wolfsgruber, S., Kleineidam, L., Guski, J., Polcher, A., Frommann, I., Roeske, S., Spruth, E.J., Franke, C., Priller, J., Kilimann, I., Teipel, S., Buerger, K., Janowitz, D., Laske, C., Buchmann, M., Peters, O., Menne, F., Fuentes Casan, M., Wiltfang, J., Bartels, C., Düzel, E., Metzger, C., Glanz, W., Thelen, M., Spottke, A., Ramirez, A., Kofler, B., Fließbach, K., Schneider, A., Heneka, M.T., Brosseron, F., Meiberth, D., Jessen, F., Wagner, M., 2020. Minor neuropsychological deficits in patients with subjective cognitive decline. Neurology 95, e1134–e1143. https://doi.org/10.1212/WNL.0000000000010142.

Wolters, E.E., Ossenkoppele, R., Verfaillie, S.C.J., Coomans, E.M., Timmers, T., Visser, D., Tuncel, H., Golla, S.S.V., Windhorst, A.D., Boellaard, R., van der Flier, W.M., Teunissen, C.E., Scheltens, P., van Berckel, B.N.M., 2020. Regional [18F]flortaucipir PET is more closely associated with disease severity than CSF p-tau in Alzheimer's disease. Eur. J. Nucl. Med. Mol. Imaging 47, 2866–2878. https://doi.org/10.1007/s00259-020-04758-2.

Zakzanis, K.K., 1998. Quantitative evidence for neuroanatomic and neuropsychological markers in dementia of the alzheimer's type. J. Clin. Exp. Neuropsychol. 20, 259–269. https://doi.org/10.1076/jcen.20.2.259.1174.

Zempel, H., Mandelkow, E.-M., 2012. Linking Amyloid-ß and tau: Amyloid-ß induced synaptic dysfunction via local wreckage of the neuronal cytoskeleton. Neurodegener. Dis. 10, 64–72. https://doi.org/10.1159/000332816.

Ziontz, J., Bilgel, M., Shafer, A.T., Moghekar, A., Elkins, W., Helphrey, J., Gomez, G., June, D., McDonald, M.A., Dannals, R.F., Azad, B.B., Ferrucci, L., Wong, D.F., Resnick, S.M., 2019. Tau pathology in cognitively normal older adults. Alzheimer's Dement. Diagnosis, Assess. Dis. Monit. 11, 637–645. https://doi.org/10.1016/j.dadm.2019.07.007.