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Review article

Association between anxiety symptoms and Alzheimer's disease biomarkers in cognitively healthy adults: A systematic review and meta-analysis

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ABSTRACT

Objective: Anxiety has been identified as both a risk factor and prodromal symptom for Alzheimer's disease (AD) and related dementias, however, the underlying neurobiological correlates remain unknown. The aim of this systematic review and meta-analysis was to examine the association between anxiety symptoms and two defining markers of AD neuropathology: amyloid-beta (Aβ) and tau.

Methods: Systematic literature searches were conducted across 5 databases. Studies investigating the relationship between anxiety and AD neuropathology (i.e., Aβ and/or tau) in cognitively healthy adults were eligible. Where possible, effect sizes were combined across studies, for Aβ and tau separately, using random-effects meta-analyses. Sensitivity analyses were performed to assess whether results differed according to anxiety type (i.e., state and trait) and biomarker assessment modality (i.e., positron emission tomography and cerebrospinal fluid).

Results: Twenty-seven studies reporting data from 14 unique cohorts met eligibility criteria. Random-effects meta-analyses revealed no associations between self-reported anxiety symptoms and either Aβ (13 studies, Fisher's z = 0.02, 95% confidence interval [CI] -0.01–0.05, $p = 0.194$) or tau (4 studies, Fisher's z = 0.04, 95% CI -0.02–0.09, $p = 0.235$). Results remained unchanged across sensitivity analyses.

Conclusions: In cognitively healthy adults, meta-analytic syntheses revealed no associations between anxiety symptoms and either Aβ or tau. There is a critical need, however, for larger studies with follow-up periods to examine the effect of anxiety symptom onset, severity, and chronicity on AD neuropathology. Additionally, further research investigating other potential neurobiological correlates is crucial to advance scientific understanding of the relationship between anxiety and dementia.

1. Introduction

Dementia, of which Alzheimer's disease (AD) is the most common late-life form, is expected to triple in global prevalence by 2050 [1]. With no effective treatment strategies, identifying modifiable risk factors of dementia and elucidating underlying neurobiological correlates is paramount in addressing the predicted increase in dementia cases [2].

Anxiety disorders have been identified as the most prevalent of all mental health conditions [3]. Epidemiological research suggests that up to 33.7% of the Western population are affected by an anxiety disorder during their lifetime [3], with the prevalence of subclinical anxiety symptoms estimated to be twice that of the full syndrome [4]. Across all dementia stages anxiety is pervasive [5], however, emerging evidence indicates that anxiety may not only be a comorbid disorder or sequela of dementia, but also a risk factor [6].

The temporal relationship between anxiety and dementia has been investigated in numerous meta-analyses [7–14], with the majority finding prior anxiety (both clinical diagnoses and self-reported symptoms) to be associated with an increased risk of subsequent all-cause dementia [7–11] and AD dementia [12,13]. In most studies, however,

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the time between initial anxiety assessment and dementia diagnosis is relatively short (i.e., <10 years). Given the insidious nature of dementia, anxiety could thus still be a result of neurobiological changes, which in the case of AD dementia, are known to precede the onset of cognitive symptoms by 10 to 20 years [15].

Whether anxiety is a prodromal symptom, or a risk factor of dementia remains unclear. Nonetheless, elucidating underlying neurobiological correlates is crucial to advance scientific understanding of the relationship between anxiety and dementia. This is a nascent filed of research, however inconsistent findings have been reported (e.g., positive, negative, and no associations between anxiety symptoms and AD neuropathology). A meta-analytic approach in this context is vital to address the uncertainty and elucidate the relationship between anxiety and AD neuropathology. The aim of the current study was therefore to conduct a systematic review and meta-analysis to examine the association between anxiety and two defining markers of AD neuropathology: amyloid-beta (Aβ) and tau.

2. Methods

This study was conducted in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations [16] and registered with PROSPERO (CRD42020189425).

2.1. Search strategy

Five databases (CINAHL, Embase, Medline, PsycINFO, and Web of Science) were systematically searched through to May 2021. Further, Google Scholar was searched to identify additional studies through forward searches until February 2022 [17]; and the reference lists of relevant articles examined for eligible primary studies.

For the database searches, terms related to anxiety were combined with those related to Aβ and tau (Supplementary Table 1). Search terms were marginally edited for each database to account for the requirements of different search engines, and in databases which allowed, appropriate MeSH terms were included to supplement the existing search strategy. No limits were placed on date of publication, and animal studies were removed following Cochrane guidelines [18].

2.2. Study selection

Covidence was used to facilitate screening [19]. Two reviewers independently screened titles and abstracts, followed by full texts against eligibility criteria to identify relevant articles. Cases of disagreement were resolved through discussions with a third reviewer.

Studies were selected if they were: (i) cross-sectional (or included baseline analyses if longitudinal), (ii) reported data on cognitively healthy adults with a mean age over 18 years, (iii) assessed anxiety via a self-report symptom questionnaire or via established clinical criteria (e.g., International Classification of Diseases) for generalised anxiety disorder, (iv) included an in vivo (e.g., positron emission tomography [PET], cerebrospinal fluid [CSF], blood plasma) or post-mortem measurement of Aβ or tau, and (v) were published in an English language, peer-reviewed journal. Studies that primarily focussed on participants with a significant medical or psychiatric disorder that was not generalised anxiety disorder (e.g., major depressive disorder, stroke) or only included an informant-based assessment of anxiety (e.g., the Neuropsychiatric Inventory Questionnaire) were excluded. Authors of eligible studies were contacted if articles were unobtainable or additional information was required.

2.3. Data extraction

A standardised form was developed to extract the following data from eligible studies: (i) authors and year of publication; (ii) study sample characteristics; (iii) anxiety measurement; (iv) AD biomarker type and measurement; and (v) data required for meta-analysis (e.g., correlation coefficients and sample sizes). Two reviewers independently extracted data, with a third reviewer comparing data extraction forms and resolving any discrepancies.

2.4. Quality appraisal

The National Heart, Lung, and Blood Institute Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies was utilised to assess study quality (www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools). It comprises 14 criteria designed to aid appraisal of internal validity (i.e., risk of selection-, information-, or measurement bias, or confounding). Inherent to the cross-sectional design of all included studies, four criteria related to the (i) temporality of exposure and outcome assessments, (ii) time between exposure and outcome assessments, (iii) number of exposure assessments, and (iv) follow-up rate were automatically marked as "not applicable" [20]. Each study was independently assessed against the remaining 10 criteria by two reviewers and classified according to their quality: poor quality (0–3), fair quality (4–6), and good quality (7–10). Any disagreements were resolved by a third reviewer.

2.5. Data synthesis and analysis

Effect sizes were calculated based on correlation coefficients and sample sizes, and when unavailable, were calculated using other available data (e.g., beta and standard error). Effect sizes were combined across studies, for Aβ and tau separately, using random-effects meta-analyses that accounted for between-study heterogeneity [21]. To reduce variability across studies, effect sizes from unadjusted models were preferentially pooled. Where multiple similar outcomes were reported from the same cohort, effect sizes were selected according to an a priori determined hierarchy. Specifically, we prioritised: (i) estimates from the largest sample; (ii) trait over state anxiety; (iii) PET over CSF; and (iv) continuous over categorical measures of anxiety, Aβ, and tau. Further, for PET studies, we focused on global measures of Aβ deposition, and tau aggregation in the entorhinal cortex, as it is one of the earliest regions to manifest detectable elevated tau PET signals [22]. For CSF studies, p-tau was prioritised over t-tau, as it is more closely associated with AD pathology and becomes abnormal earlier in the AD cascade [23]. Finally, where studies categorised anxiety, Aβ, or tau, data from highest cut-offs were selected.

Where enough data was available (i.e., at least two studies), sensitivity analyses were performed to assess whether results differed according to anxiety type (i.e., trait [a stable, personality-like characteristic] versus state [a transient psychological reaction]) and biomarker assessment modality (i.e., PET versus CSF).

For each meta-analysis, heterogeneity was assessed using the I^2 (i.e., proportion of observed dispersion due to real variation in effect sizes, rather than random error, with values ≥75% indicating considerable heterogeneity) and Tau^2 (i.e., between-study variance) statistics. Publication bias was evaluated by examining funnel plots, the Egger intercept, Kendall tau, and trim-and-fill method, when >10 studies were included in a meta-analysis [24]. All analyses were conducted using the '*metafor*' package in R (version 4.1.1).

3. Results

The literature search yielded a total of 16,795 articles, with 10,973 remaining after deduplication. Following title and abstract screening, 88 articles were included for full-text review. During full-text review another 62 articles were excluded, resulting in 26 articles, comprising 27 studies, meeting eligibility criteria (Fig. 1). Twenty-six studies, including 13 independent (i.e., unique) cohorts, assessed Aβ pathology; and five of these studies, including four independent cohorts, also assessed tau pathology. One study used a PET tracer (i.e., the FDDNP

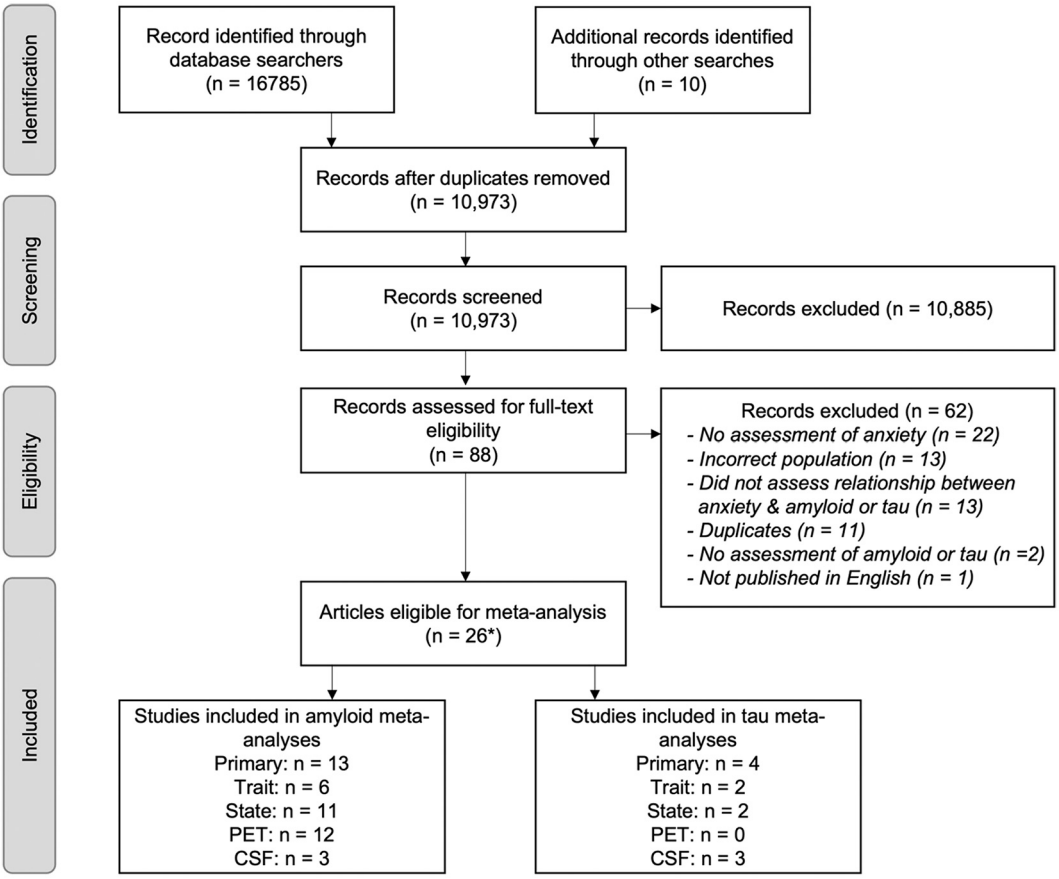

Fig. 1. PRISMA flow diagram outlining the systematic review process. *Whilst 26 studies were eligible for meta-analysis studies frequently reported data on overlapping samples (i.e., utilised the same cohorts). To ensure only one effect size per cohort was included in each meta-analysis, studies were selected based on the previously described hierarchy (see Supplementary Table 4 and Supplementary Table 5).

compound) which binds to both cerebral Aβ plaques and neurofibrillary tangles.

3.1. Study and participant characteristics

Characteristics of all 27 eligible studies are presented in Table 1 and summarised in Supplementary Table 2. Across the 27 studies sample sizes varied considerably, ranging from 11 to 1705 participants (median: 118). The majority of studies were conducted in North America ($k = 16$; 59.3%); the remainder took place in Europe ($k = 4$; 14.8%), Australia ($k = 3$; 11.1%), Asia ($k = 3$; 11.1%) and/or intercontinentally ([North America, Australia, and Asia] $k = 1$; 3.7%).

The mean age of participants ranged from 48.4 to 78.3 years (median: 70.3 years), and the proportion of female participants ranged from 30.4% to 81.8% (median: 52.4%). Participants were generally well educated, with mean education ranging from 12.9 to 17.8 years (median: 15.6 years).

All studies assessed anxiety via standardised self-report symptom scales. Eight different scales were utilised across studies, with the State and Trait Anxiety Inventory being the most common ($k = 8$; 29.6%). Five studies (18.5%) assessed both trait and state anxiety, whilst the remainder measured just one anxiety type (trait: $k = 6$; 22.2%; state: $k = 16$; 59.3%). Levels of self-reported anxiety were generally low across studies (Supplementary Table 3). No studies reported including participants with clinically diagnosed anxiety, and this diagnosis was a specific exclusion criterion in 14 studies (51.9%). However, nine studies (33.3%) utilised established cut-off scores to estimate the proportion of participants with anxiety symptoms reaching a clinical threshold (median: 6.0%; range: 0.0% to 13.7%).

Aβ was measured in 26 studies (96.3%), via PET ($k = 25$, 96.2%) and/or CSF ($k = 3$, 11.5%). The proportion of Aβ positive participants was reported in 19 studies and ranged from 15.9% to 68.4% (median: 27.3%). Tau was measured in five studies (18.5%). Across these studies, two used PET (40.0%) and three CSF (60.0%). A single PET study used the FDDNP compound which binds to both cerebral Aβ plaques and neurofibrillary tangles. No eligible studies included blood or post-mortem measures of Aβ or tau pathology.

Quality assessment scores ranged between six and nine (Supplementary Table 4), with just over half of the studies receiving a 'Good' quality rating ($k = 15$; 55.6%) and the remainder a 'Fair' quality rating.

3.2. Qualitative synthesis of results

3.2.1. Amyloid-beta

Four studies investigated the association between anxiety symptoms and global Aβ burden in the Harvard Aging Brain Study [25–28]. In two studies where anxiety symptoms were assessed via the Hospital and Anxiety Depression Scale (HADS), higher symptoms were associated with greater Aβ burden [26,28]. However, in two studies which utilised the anxiety-concentration cluster of the Geriatric Depression Scale, no associations were observed [25,27].

Similarly, four studies investigated the association between anxiety symptoms and Aβ burden in the Mayo cohort [29–32]. Across three studies, no associations were observed between anxiety symptoms and regional Aβ deposition (i.e., cortical, amygdala, striatum or thalamus) [32], CSF Aβ42 levels [29], or Aβ positivity [31]. However, in one study, a positive association between anxiety symptoms and global Aβ deposition and Aβ positivity was reported [30]. Additional analyses,

Table 1
Characteristics of samples included in the systematic review and/or meta-analysis.

Study reference (Cohort or Institution, Country)	N[a]	Age, Mean y. (SD)	Sex, Female %	Education, Mean y. (SD)	Ethnicity, White %	APOE, ε4+ %	Anxiety measure (type)	Clinical anxiety, %	Biomarker measure (tracer/ type)	Biomarker positive, %	Covariates
Babulal et al., 2016 [39] (Washington U., USA)	118	72.5 (4.7)	51.7	16.1 (2.6)	90.7	NR	POMS-SF tension-anxiety subscale (state)	NR	PET (^{11}C-PiB) and CSF (Aβ42, t-tau, p-tau$_{181}$, t-tau/Aβ42, p-tau$_{181}$/Aβ42)	NR	Age, sex, education
Burns et al., 2017 [40] (U. of Kansas Alzheimer's Prevention through Exercise Trial, USA)	97	71.7 (5.5)	60.8	16.6 (2.6)	96.9	NR	BAI (state)	0	PET (^{18}F-florbetapir)	Aβ+: 27.8	None
Chen et al., 2019 [45] (Dallas Lifespan Brain Study, USA)	85	67.0 (15.1)	65.9	16.0 (2.3)	NR	20.0	NIHTB fear survey (state)	NR	PET (AV45-florbetapir)	Aβ + (lib.): 37.6 Aβ + (con.): 28.2	None
Donovan et al., 2015 [25] (HABS, USA)	220	74.0 (6.1)	60.0	NR	NR	NR	GDS anxiety-concentration cluster (trait)	NR	PET (^{11}C-PiB)	Aβ+: 27.3	None
Donovan et al., 2016 [26] (HABS, USA)	79	76.4 (6.2)	54.4	NR	NR	28.0	HADS-A (state)	6.0 [d]	PET (^{11}C-PiB)	Aβ+: 32.0	None
Donovan et al., 2018 [27] (HABS, USA)	270	73.6 (6.1)	58.5	NR	NR	29.3	GDS anxiety-concentration cluster (trait)	NR	PET (^{11}C-PiB)	NR	None
Funaki et al., 2019 [33] (Keio U. Hospital, Japan)	42	74.4 (4.7)	52.4	15.1 (2.1)	NR	40.0	STAI (trait and state)	NR	PET (^{18}F-florbetapir)	Aβ+: 23.8	None
Grill et al., 2020 [41] (A4 Study, USA, Canada, Australia & Japan)	1705	71.5 (4.7)	60.1	16.7 (2.7)	94.5	47.0	STAI 6-item (state)	NR	PET (^{18}F-florbetapir)	Aβ+: 68.4	Age, sex, family history of dementia, CFI
Hanseeuw et al., 2020 [28] (HABS, USA)	118	75.9 (5.7)	61.9	16.1 (2.7)	NR	33.0	HADS-A (state)	9.3 [e]	PET (^{11}C-PiB)	Aβ+: 36.4	Age, sex, education, MMSE, GDS
Hollands et al., 2015 [36] (AIBL, Australia)	275	69.5 (6.6)	53.6	> 12y, 60.1% [c]	NR	30.4	HADS-A (state)	NR	PET (^{11}C-PiB)	Aβ+: 21.1	None
Krell-Roesch et al., 2018 [30] (Mayo Clinic Study of Aging, USA)	1038	73 (67, 79) [b]	46.9	> 12y, 71.8% [c]	NR	26.9	BAI (state)	4.9 [f]	PET (^{11}C-PiB)	Aβ+: 36.5	Age, sex
Krell-Roesch et al., 2019 [31] (Mayo Clinic Study of Aging, USA)	1440	50 – 69y, 43.9% [d] 70 – 95y, 56.1% [d]	46.6	> 12y, 74.4% [c]	NR	27.3	BAI (state)	5.7 [f]	PET (^{11}C-PiB)	Aβ+: 30.9	Age, sex, education, APOE ε4 genotype
Krell-Roesch et al., 2021 [32] (Mayo Clinic Study of Aging, USA)	838	78.3 (5.4)	46.2	14.6 (2.8)	NR	26.0	BAI (state)	4.8 [f]	PET (^{11}C-PiB)	NR	Age, sex, education, APOE ε4 genotype
Krell-Roesch et al., 2022 [29] (Mayo Clinic Study of Aging, USA)	698	72.3 (50.7, 95.3) [b]	43.3	14.0 (8.0, 20.0) [b]	NR	26.0	BAI (state)	6.4 [f]	CSF (Aβ42, t-tau, p-tau$_{181}$, t-tau/Aβ42, p-tau$_{181}$/Aβ42)	NR	Age, sex, education, APOE ε4 genotype
Lavretsky et al., 2009 [50] (U. of California, USA)	20	63.7 (12.5)	40.0	17.7 (2.7)	NR	NR	STAI (state & trait)	NR	PET (FDDNP)	NR	Age
Lim et al., 2015 [42] (U. of	63	62.8 (5.4)	61.9	17.2 (2.8)	NR	46.8	DASS-A (state)	NR	PET (^{18}F-florbetapir)	Aβ+: 23.8	None

(*continued on next page*)

Table 1 (*continued*)

Study reference (Cohort or Institution, Country)	N[a]	Age, Mean y. (SD)	Sex, Female %	Education, Mean y. (SD)	Ethnicity, White %	APOE, ε4+ %	Anxiety measure (type)	Clinical anxiety, %	Biomarker measure (tracer/ type)	Biomarker positive, %	Covariates
Rhode Island, USA)											
Lim et al., 2016 [43] (U. of Rhode Island, USA)	11	61.6 (4.2)	81.8	17.8 (3.1)	NR	54.5	DASS-A (state)	NR	PET (^{18}F-florbetapir)	Aβ+: 27.3	None
Marchant et al., 2020a [46] (PREVENT-AD, Canada)	113	67.5 (5.0)	75	15.1 (3.2)	NR	40.0	GAI (trait)	NR	PET (^{18}F-NAV4694 & ^{18}F-AV1451)	Aβ+: 15.9	None
Marchant et al., 2020b [46] (IMAP+, France)	68	67.6 (9.4)	49.0	12.9 (3.7)	NR	24.0	STAI (trait)	NR	PET (^{18}F-florbetapir)	Aβ+: 17.6	None
Moulinet et al., 2022 [47] (IMAP+, France)	138	48.4 (19.0)	51.9	13.2 (3.2)	NR	NR	STAI (state)	NR	PET (^{18}F-florbetapir)	NR	Education, depression
Pavisic et al., 2021 [44] (Insight 46, UK)	420	70.6 (0.7)	49.8	> O-levels or equivalent, 53.8% [c]	100	30.0	STAI (state & trait)	NR	PET (^{18}F-florbetapir)	Aβ+: 18.3	None
Pichet Binette et al., 2021 [48] (PREVENT-AD, Canada)	115	67.6 (5.0)	75.0	15.0 (3.2)	NR	38.0	GAI (trait)	NR	PET (^{18}F-NAV4694 & ^{18}F-AV1451)	NR	None
Pietrzak et al., 2015 [37] (AIBL, Australia)	524	70.0 (6.8)	52.0	> 12y, 56.8% [c]	NR	32.7	HADS-A (state)	13.5 [e]	PET (^{11}C-PiB, ^{18}F-florbetapir, or ^{18}F-flutemetamol)	Aβ+: 34.2	None
Pietrzak et al., 2017 [38] (AIBL, Australia)	416	69.3 (6.6)	55.3	> 14y, 36.5% [c]	NR	27.6	HADS-A (state)	13.7 [e]	PET (^{11}C-PiB, ^{18}F-florbetapir, or ^{18}F-flutemetamol)	Aβ+: 23.1	Age, APOE ε4 genotype
Sannemann et al., 2020 [49] (DELCODE, Germany)	194	69.6 (5.7)	53.7	14.7 (2.9)	NR	NR	GAI-SF (trait)	NR	CSF (Aβ42, t-tau, p-tau$_{181}$)	Aβ+: 19.6 t-tau+: 26.0 p-tau$_{181}$+: 28.9	Age, sex, education, memory factor score
Wake et al., 2018 [34] (Keio U. School of Medicine, Japan)	42	74.4 (4.8)	52.4	15.0 (2.1)	NR	NR	STAI (trait and state)	NR	PET (^{18}F-florbetapen)	Aβ+: 23.8	None
Wake et al., 2020 [35] (Keio U. Hospital, Japan)	42	74.4 (4.8)	52.4	15.0 (2.1)	NR	NR	STAI (state & trait)	NR	PET (^{18}F-florbetapen)	Aβ+: 23.8	None

Abbreviations: Aβ, Amyloid beta; AIBL, Australian Imaging, Biomarker & Lifestyle Flagship Study of Aging; APOE, Apolipoprotein E; BAI, Beck Anxiety Inventory; CSF, Cerebrospinal fluid; con., Conservative; DASS-A, Depression Anxiety Stress Scales – Anxiety; DELCODE, DZNE-Longitudinal Cognitive Impairment and Dementia Study; GAI, Geriatric Anxiety Inventory; GAI-SF, Geriatric Anxiety Inventory – Short Form; GDS, Geriatric Depression Scale; HABS, Harvard Aging Brain Study; HADS-A, Hospital Anxiety and Depression Scale – Anxiety; IMAP+, Imagerie Multimodale de la Maladie d'Alzheimer à un stade Précoce; lib., Liberal; NIHTB, National Institutes of Health Toolbox; NR, Not reported; PET, positron emission tomography; PiB, Pittsburgh compound B; POMS-SF, Profile of Mood States – Short Form; PREVENT-AD, Pre-symptomatic Evaluation of Experimental or Novel Treatments for Alzheimer's disease; SD, Standard deviation; STAI, State-Trait Anxiety Inventory; U., University; UK, United Kingdom; US, United States; y. Years.

[a] N presented for the number of participants included in analyses. In some instances, the number of participants included in analyses differs from the number of participants demographic data is provided for: Donovan et al., 2015 ($N = 220$, but demographic data from $N = 248$ [28 participants with missing Aβ data]); Hollands et al., 2015 ($N = 275$, but demographic data from $N = 289$ [14 participants missing anxiety data]); Pietrazak et al., 2015 ($N = 524$, but demographic data from $N = 333$ [additional data provided by authors]); Krell-Roesch et al., 2019 ($N = 1440$, but demographic data from $N = 1443$ [3 participants missing anxiety data]); Krell-Roesh et al., 2021 ($N = 838$, but demographic data from $N = 842$ [N = 1 missing anxiety data and N = 3 missing covariate [APOE genotype] data]); Krell-Roesch et al., 2022 ($N = 698$, but demographic data from $N = 699$ [1 participant missing anxiety data]); Moulinet et al., 2022 ($N = 138$, but demographic data from $N = 210$ [72 participants missing Aβ data]); Sannemann et al., 2020 ($N = 194$, but demographic data from 495 [301 participants missing Aβ /tau data]).

[b] Data presented as median (interquartile range).

[c] Data presented as % above specified cut-off.

[d] HADS-A score ≥ 9.

[e] HADS-A score ≥ 8.

[f] BAI ≥10.

conducted in latter three studies, revealed no associations between clinically relevant anxiety symptoms (i.e., Beck Anxiety Inventory [BAI]) ≥ 10) and Aβ [29–31].

The Australian Imaging, Biomarkers, and Lifestyle (AIBL) Study and Keio University Hospital memory clinic cohort were utilised in three studies each [33–38]. Across all six studies, no associations were observed between anxiety symptoms [33–38], or clinically relevant anxiety symptoms (i.e., HADS ≥8) [38], and Aβ status. A further seven studies, utilising five independent cohorts, also investigated the association between anxiety symptoms and Aβ status [39–45]. Six studies reported no associations between anxiety symptoms and Aβ status [39–44], and one found anxiety symptoms to be higher in the Aβ negative group, but only when a liberal threshold was used to determine Aβ status [45]. Consonant with these primarily null findings, anxiety symptoms were not associated with global Aβ deposition in studies which utilised the Imagerie Multimodale de la Maladie d'Alzheimer à un stade Précoce [46,47] and Pre-symptomatic Evaluation of Experimental or Novel Treatments for Alzheimer's disease [46,48] cohorts. Further, in another independent cohort, no associations were observed between anxiety symptoms or clinically relevant anxiety symptoms (i.e., Geriatric Anxiety Inventory [GAI]-short form ≥2) and CSF Aβ42 levels [49].

Finally, one study used the FDDNP tracer which binds to both Aβ and tau, and found positive associations between anxiety symptoms and FDDNP binding in the medial temporal and frontal regions, but not the lateral temporal, parietal, or posterior cingulate regions [50].

3.2.2. Tau

Across three independent cohorts, no associations were observed between anxiety symptoms and levels of CSF t-tau or p-tau$_{181}$ [29,39,49]. Results remained unchanged in analyses only including participants who reported anxiety symptoms above a threshold suggestive of a clinical level of anxiety (i.e., GAI ≥ 10 or GAI-short form ≥2) [29,49]. Further, in two studies which utilised the same cohort, no associations were observed between anxiety symptoms and regional tau-PET standardised uptake value ratios (i.e., Braak stages I, III, and IV [48] and the entorhinal cortex and inferior temporal cortex [46]).

3.3. Quantitative synthesis of results

All studies reported data amenable to meta-analysis (or authors provided these on request [k = 4]). One study [50], however, was excluded from all meta-analyses as it used a PET tracer which binds to both Aβ and tau. Further, to ensure only one effect size per cohort was included in each meta-analysis, studies were selected based on the previously described hierarchy (see Methods and Supplementary Table 5 and Supplementary Table 6). This resulted in 13 studies being included in the primary Aβ meta-analysis and four studies in the primary tau meta-analysis.

3.3.1. Amyloid-beta

The primary meta-analysis of 13 studies (N = 5141) revealed no association between anxiety symptoms and Aβ levels (Fisher's z = 0.02, [−0.01 to 0.05], p = 0.194; Fig. 2 and Supplementary Table 7). Heterogeneity between studies was low (I^2 = 0.0%) and there was no evidence of publication bias (Supplementary Table 8 and Supplementary Fig. 1). Results were substantively unchanged in sensitivity analyses (Supplementary Table 6 and Supplementary Fig. 2) which stratified studies according to anxiety type (trait: k = 6, Fisher's z = 0.02, p = 0.580; state: k = 11, Fisher's z = 0.02, p = 0.262) and biomarker modality (PET: k = 12, Fisher's z = 0.02, p = 0.185; CSF: k = 3, Fisher's z = 0.07, p = 0.128). There was moderate heterogeneity (I^2 = 40.7%) in the CSF sensitivity meta-analysis and low heterogeneity ($I^2 \leq$ 4.5%) across trait, state, and PET sensitivity meta-analyses. For sensitivity analyses containing at least 10 studies (i.e., state and PET) there was no evidence of publication bias (Supplementary Table 8 and Supplementary Fig. 1).

3.3.2. Tau

The primary meta-analysis of four studies (N = 1126) revealed no association between anxiety symptoms and tau pathology (Fisher's z = 0.04, [−0.02 to 0.09], p = 0.235; Fig. 3 and Supplementary Table 7) and there was no evidence of between study heterogeneity (I^2 = 0.0%). The results were substantively unchanged in CSF (k = 3, Fisher's z = 0.03, p = 0.410), trait anxiety (k = 2, Fisher's z = 0.05, p = 0.439), and state anxiety (k = 2, Fisher's z = 0.03, p = 0.360) sensitivity analyses (Supplementary Table 7 and Supplementary Fig. 3). Across all sensitivity meta-analyses heterogeneity was low ($I^2 \leq$ 2.2%).

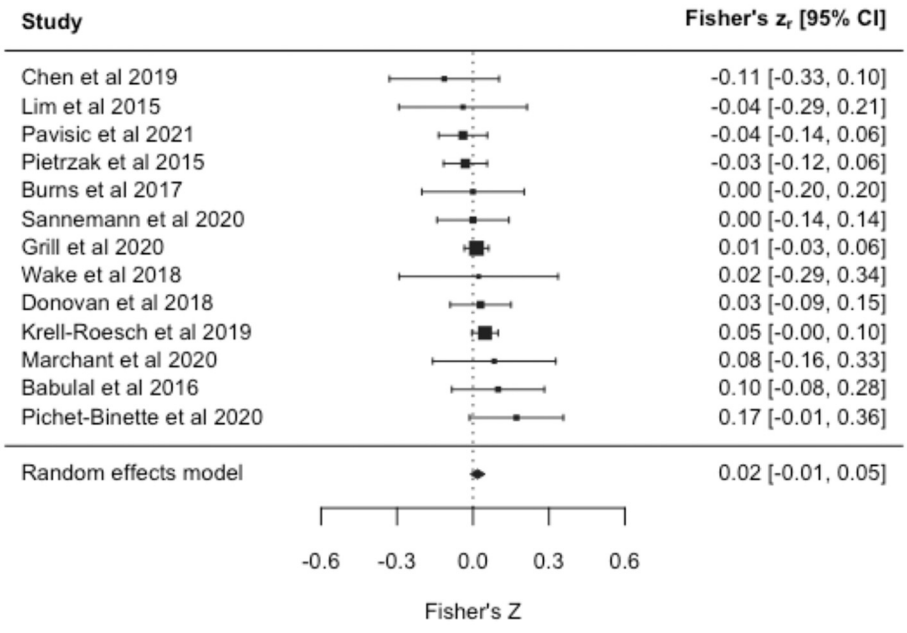

Fig. 2. Forest plot of the associations between anxiety symptoms and Aβ pathology in cognitively healthy adults. Effect sizes are Fisher's Z with corresponding 95% confidence intervals (CI). Results were similar across sensitivity analyses (Supplementary Fig. 2).

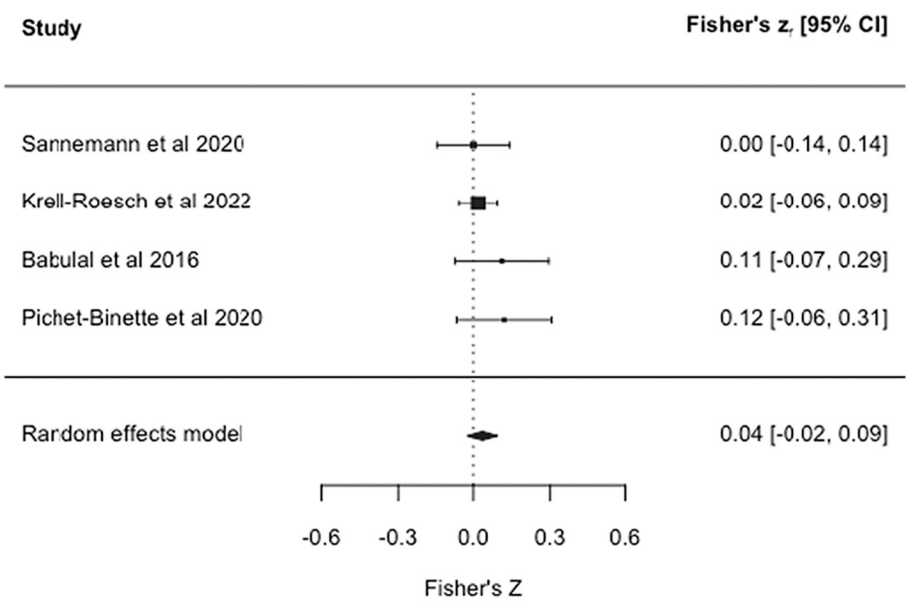

Fig. 3. Forest plot of the associations between anxiety symptoms and tau pathology in cognitively healthy adults. Effect sizes are Fisher's Z with corresponding 95% confidence intervals (CI). Results were similar across sensitivity analyses (Supplementary Fig. 3).

4. Discussion

The purpose of this study was to advance our scientific understanding of the relationship between anxiety and dementia. To do so, we conducted a series of meta-analyses to examine the association between anxiety symptoms and neuropathological hallmarks of AD (i.e., Aβ and tau) in cognitively healthy adults. Our primary meta-analyses revealed no associations between anxiety symptoms and either Aβ or tau pathology. Further, results were substantively unchanged across sensitivity analyses assessing the effects of anxiety type (i.e., trait and state) and biomarker assessment modality (i.e., PET and CSF).

Converging meta-analytic evidence attests to anxiety (both clinically diagnosed anxiety and anxiety symptoms) being associated with an increased incidence of all-cause dementia [7–11] and AD dementia [12,13]. Whether anxiety represents a risk factor or a prodromal symptom, however, remains unclear. In relation to this latter hypothesis, late-life elevations in anxiety levels corresponding with accumulating Aβ and tau pathology would support the notion of anxiety as an AD dementia prodrome. If anxiety is a prodromal AD symptom a positive cross-sectional relationship between anxiety and neuropathological hallmarks of AD would therefore be expected. By aggregating results across existing cross-sectional studies, our meta-analytic findings do not support the notion that anxiety is a prodrome of incipient AD dementia. However, a recent longitudinal study reported that higher levels of CSF AD biomarkers predicted greater increases in anxiety symptoms [51], thus indicating that relationships may become evident over time.

In relation to the former proposition, whether anxiety represents a risk factor for AD dementia, this remains unclear. For example, it is possible that participants (i.e., cognitively healthy older adults aged ≥18) were too early in the disease course for any association to be present (i.e., not enough Aβ and/or tau has aggregated to detect a relationship). However, participants included in meta-analyses were primarily older adults (Aβ: median age = 70.3 years; tau: median age = 69.6 years) and a large proportion had significant Aβ pathology (Aβ positive: median = 27.3%), thus rendering this an unlikely explanation. The question, however, remains open for tau. Although cut-points for determining presence of tau pathology have been proposed, no agreed upon threshold has been established due to high methodological heterogeneity across studies [52].

Whilst anxiety has been associated with an increased risk of AD dementia, stronger and more consistent associations have been reported in relation to risk of all-cause dementia [11,12] and vascular dementia [13]. Further, AD dementia often involves a complex constellation of pathologies, expanding beyond Aβ and tau [53]. Considering our findings within the wider context, the association between anxiety symptoms and increased dementia risk (and by proxy, AD dementia) is therefore likely through mechanisms outside of an Aβ or tau pathway.

Numerous alternative etiologies have been postulated to explain the association between anxiety and AD dementia. In particular, the hypothalamic-pituitary-adrenal (HPA) axis has been identified as a potential underlying biological mechanism. Anxiety disorders have been associated with HPA axis dysregulation [54], with oversecretion of glucocorticoids a direct consequence of such perturbation. Raised glucocorticoids levels may in turn increase vulnerability to dementia by promoting pathological processes, such as hippocampal atrophy [55]. Further, high levels of glucocorticoids are known to increase the risk of cardio- and cerebro-vascular diseases [56,57], which are themselves risk factors for AD dementia [58] and vascular dementia [59]. Inflammation has been identified as another candidate biological mechanism. Systemic and intestinal inflammation have been implicated in the pathophysiology of anxiety [60,61], and there is growing evidence for a role of inflammation in the development of AD pathology, including early in the AD continuum, before the accumulation of Aβ plaques [62]. Another hypothesis is that anxiety confers increased dementia risk through lowering levels of cognitive reserve (i.e., adaptability that helps to explain differential susceptibility of cognitive abilities or day-to-day function to brain aging, pathology, or insult [63]). Indeed, lower levels of cognitive reserve have been reported in older adults with clinically relevant anxiety symptoms, compared to those without [64]. Additionally, anxiety disorders are often enduring and frequently accompanied by avoidance behaviours. Engagement with avoidance behaviours across the life course may lower cognitive reserve levels by increasing social isolation [64] and reducing physical activity [65], both of which have independently been implicated as dementia risk factors [66,67].

The relationship (or lack of) between anxiety symptoms and AD neuropathology may be contingent on a variety of factors, including the severity, chronicity, and timing of anxiety symptoms. For instance, as is observed for depression [68], a threshold effect may exist, whereby associations between anxiety and AD pathology emerge only at clinical

levels. No eligible studies, however, reported including participants with clinically diagnosed anxiety disorders. Further, only a minority of studies specified the number of participants with self-reported anxiety symptoms above a threshold suggestive of clinical anxiety, thus it was not feasible to statistically examine the possibility of a threshold effect. Five studies (reporting data from three independent cohorts), however, did examine the association between clinically significant anxiety symptoms and Aβ burden [29–31,38,49]. No associations were observed; however, studies were likely very underpowered as the number of participants reporting anxiety symptoms of clinical significance was extremely low. Studies including participants with clinical levels of anxiety (e.g., adults with generalised anxiety disorder) are required to help elucidate whether anxiety levels need to exceed a critical threshold beyond which normal neuropathology is not sustained. The timing (i.e., age of onset) of anxiety symptoms may also be an important determining factor in the relationship between anxiety and AD neuropathology. For example, stressful life events occurring earlier in the life course, compared to later life stressors, have been associated with a higher risk of dementia [69]. Indeed, it has been proposed that adverse early life events may exert lifelong effects on health (including increasing vulnerability to dementia), by impacting brain development, resulting in poorer health behaviours and lower levels of cognitive reserve [69,70]. However, whilst early life may represent a critical period of vulnerability, evidence from the depression literature suggests that chronicity of symptoms may be of greater importance [71]. The effect of symptom chronicity on dementia risk has also been observed in relation to stress, with chronic psychological stress, compared to individual midlife stress exposures, more consistently associated with increased dementia risk [69]. The primarily cross-sectional design of eligible studies precludes investigations into the effects of early life anxiety and the chronicity of anxiety symptoms on the relationship between anxiety and AD neuropathology. In one study that did investigate the association between anxiety symptoms and change in Aβ burden, no association was observed [47]. Anxiety levels, however, were very low, reducing power to detect effects, and the follow-up period (i.e., mean duration = 2.4 years) likely too short to capture protracted pre-clinical AD-related processes. Longitudinal studies, adopting life course developmental perspectives, are required to assess the effects of anxiety severity, chronicity, and timing on AD neuropathology.

4.1. Limitations and future directions

The study has several limitations. First, although eligible studies included samples from four continents, participants were generally highly educated, predominantly white (when ethnicity was reported), from high-income countries, and had low levels of anxiety; this homogeneity limits the generalizability of findings. Future studies specifically recruiting participants with lower socioeconomic status and educational attainment, from more ethnically diverse communities, and with clinical diagnoses of anxiety, are warranted. In particular, studies investigating the impact of ethnicity/race on the relationship between anxiety and AD neuropathology are needed, as racial differences in the presentation of anxiety symptoms [72] and longitudinal trajectories of AD biomarkers [73] have been reported. Second, eligible studies frequently utilised data from the same cohorts. As the resulting dependencies (i.e., overlap between individuals across multiple studies) can produce spurious associations if data from overlapping participants are not removed, only one effect size per cohort was included in each random-effects meta-analysis. Therefore, despite conducting a thorough literature search resulting in the identification of 27 eligible studies, less than half of the studies could be included in the primary meta-analyses (Aβ: $k = 13$; tau: $k = 4$). The removal of studies with overlapping samples reduced power to detect effects, particularly in relation to tau. Further research investigating the association between anxiety and tau is required, especially as stress appears to be a critical factor influencing tau-mediated pathogenesis in AD dementia, more so than Aβ [74]. Third, despite no statistical evidence of heterogeneity, variability in sample characteristics (e.g., proportion of Aβ-positive individuals, number of APOE ε4 carriers, average anxiety levels) and methodological differences (e.g., in anxiety assessments, time between anxiety and AD biomarker assessments, Aβ processing, analytic approaches, reporting of findings) were evident across studies. These differences may potentially account for conflicting findings reported across existing studies. In particular, greater methodological homogeneity (e.g., utilisation of the Centiloid scale to standardise measurements of Aβ PET imaging) would help facilitate between-study comparisons and aid future meta-analytic efforts. Fourth, despite evidence that anxiety and depressive symptoms often co-occur, only one study adjusted analyses for depressive symptoms. Studies investigating the association between anxiety and AD neuropathology independent of possible comorbid depressive symptomatology are needed. Finally, the relationship between anxiety and AD neuropathology may be mediated or moderated by: genetic (e.g., APOE genotype) [75], health and lifestyle (e.g., sleep quality) [76], and pharmacological (e.g., selective serotonin reuptake inhibitors) [77] factors. Given the limited number of studies, we were unable to assess the influence of any potential mediating factors on the relationship between anxiety and AD neuropathology. Longitudinal research, including large sample sizes and comprehensive assessments are crucial for elucidating factors which may influence the association between anxiety and AD neuropathology.

In conclusion, our meta-analytic syntheses of extant studies revealed no associations between anxiety and AD neuropathology (i.e., Aβ and tau) in cognitively healthy adults. An association between anxiety and dementia-related neurobiological correlates, however, is likely complex, underpinned by multiple factors, and not restricted to AD neuropathology. Large, life-course studies with comprehensive assessments are required to investigate the effect of different factors (e.g., severity, chronicity, and timing of anxiety symptoms) which might mediate the relationship between anxiety and AD neuropathology. Improving our understanding of the neuropathological correlates linking anxiety with dementia is of substantial public health importance and may help provide novel approaches to enhancing cognitive health in late life.

Declaration of Competing Interest

The authors have no competing interests to report.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychores.2023.111159.

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