Fluids and Barriers of the CNS

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The impact of chronic and acute sleep deprivation on key Alzheimer's disease biomarkers: a systematic review and meta-analysis

Giovanni Gosch Berton[1], Amanda Cyntia Lima Fonseca Rodrigues[2], Nicole Mombelli Mattei[1], Flavia Dreon Calza[1], Raul Hanel Dias[1], Érica Lúcia Menegat[1], Isabella de Abreu Brkanitch[1], Jeremias Antônio Lago[1] and Gina Hadley[3*]

Abstract

Background Sleep disruption is recognized as a risk factor for Alzheimer's disease (AD). Both chronic and acute sleep deprivation (SD) may increase cerebrospinal fluid (CSF) levels of amyloid-beta (Aβ) and tau, potentially complicating early AD diagnoses. Some studies also suggest an inverse relationship in plasma biomarker levels, although these effects remain poorly characterized.

Methods We conducted a systematic review and meta-analysis to examine whether SD elevates CSF concentrations of key AD biomarkers (Aβ40, Aβ42, total tau [t-tau], phosphorylated tau [p-tau]) in individuals without established AD.

Results Six studies ($n = 169$ participants) were included. Pooled results showed that SD significantly raised CSF Aβ40 (mean difference [MD]: 31.88, 95% CI: 25.61–38.15) and Aβ42 (MD: 37.32, 95% CI: 32.67–41.97 after sensitivity analysis). While initial analyses suggested inconsistent findings for t-tau and p-tau, excluding outlier data consistently revealed elevated levels in both (t-tau MD: 37.81, 95% CI: 23.27–52.35; p-tau MD: 1.01, 95% CI: 0.26–1.77). Possible publication bias was noted, but overall findings indicate that SD may cause meaningful biomarker fluctuations.

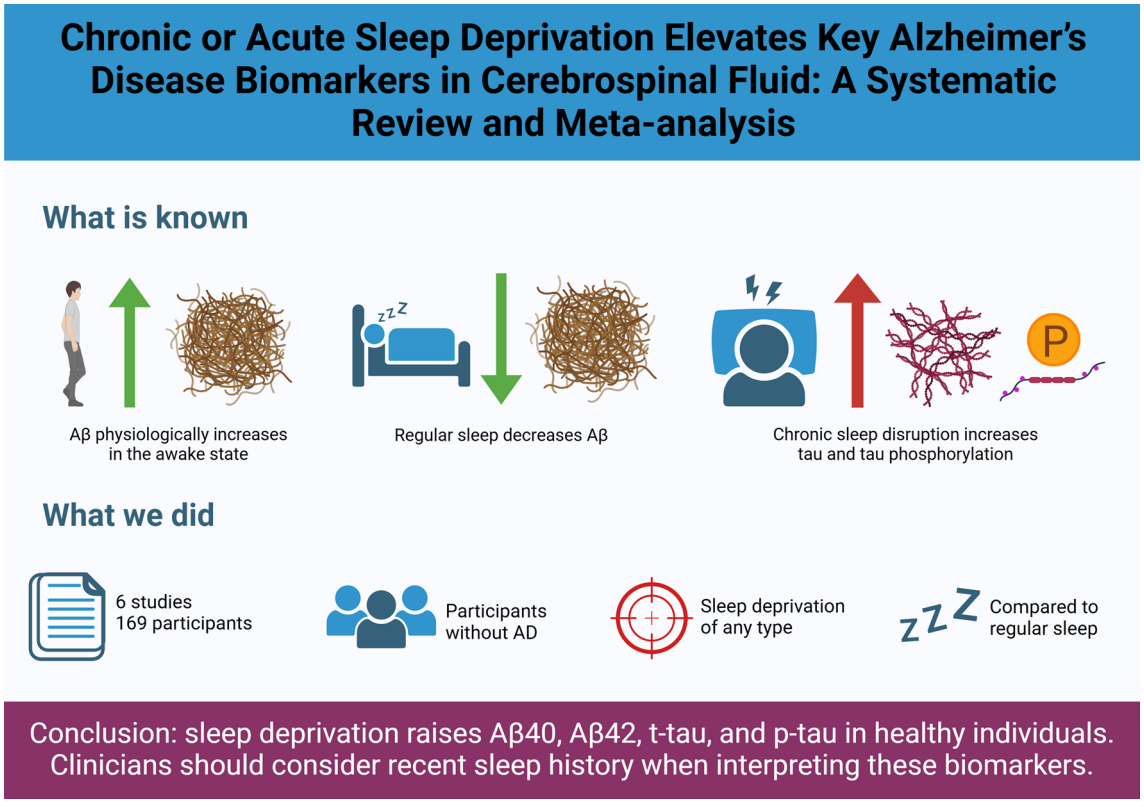
Conclusion Short- or long-term SD may transiently elevate CSF Aβ and tau, underscoring the importance of assessing recent sleep history when interpreting AD biomarkers. Although not directly evaluated here, preliminary data suggest plasma biomarkers might move in the opposite direction, warranting further investigation. Clinically, these results highlight the potential impact of sleep patterns on biomarker-driven AD risk assessments. Addressing SD could thus be a valuable target for both optimizing diagnostic accuracy and potentially slowing early neurodegenerative processes.

Keywords Alzheimer disease, Sleep deprivation, Cerebrospinal fluid, Amyloid beta-peptides, Tau proteins

*Correspondence:
Gina Hadley
gina.hadley@hmc.ox.ac.uk

Full list of author information is available at the end of the article

Graphical Abstract



Introduction

Sleep disruption is recognized as a risk factor for Alzheimer's disease (AD), and changes in sleep patterns occur even in its preclinical stages - before the onset of cognitive symptoms [1]. Sleep decreases amyloid-beta (Aβ), while it increases in the awake state, and chronic sleep disruption increases tau and tau phosphorylation [1]. Extracellular aggregation of Aβ as insoluble plaques begins up to 20 years before the onset of AD symptoms [2]. Furthermore, cognitive decline is preceded by hyperphosphorylated tau (p-tau) tangles and neuronal death; therefore, it is crucial to identify potential patients in the earliest possible stage [3]. Moreover, cerebrospinal fluid (CSF) levels of Aβ42, total tau (t-tau), and p-tau are strongly correlated with brain levels [3]. Those assessments are crucial for the early diagnosis of AD [3].

The brain clears substances through multiple pathways, including glymphatic flow, perivascular efflux, lymphatic drainage, and transport across the blood-brain barrier. Many of these mechanisms are related to sleep and the removal of Aβ peptides. Additionally, Aβ can exit the brain via the blood-CSF barrier using p-glycoprotein and lipoprotein receptor-related protein-1 (LRP1) transporters. Although the activity of p-glycoproteins varies diurnally, it has not been associated with sleep. Mechanisms of tau clearance may involve exosomes, lymphatic vessels, and glymphatic pathways, on which the brain depends for the clearance of proteins and metabolites from the brain interstitial fluid to the blood and the CSF [2, 4].

Sleep disturbance is a recognized risk factor for AD; however, the molecular mechanisms through which it exerts its effects remain uncertain [5]. Several studies have evaluated the interaction between sleep disturbance and CSF biomarkers, although the results are still unclear. Sleep loss has been suggested to disrupt the brain-CSF barrier, thus decreasing AD biomarkers in the plasma but increasing them in the CSF, potentially due to altered blood-CSF barrier function or altered CSF flow or turnover [2]. Although the disruption of the blood-brain barrier is thought to contribute to AD pathogenesis, plasma biomarkers are also gaining importance in AD diagnosis. It remains unclear which CSF biomarkers might be most affected by sleep deprivation (SD) and whether these changes would affect plasma measures [2].

Typically, wakefulness promotes the production and secretion of Aβ, while sleep increases its clearance and decreases its production [2]. Therefore, circadian rhythms in Aβ homeostasis could be impacted by SD, which may be accompanied by oxidative stress impairing Aβ metabolism [5]. Since the increasing deposition of

Aβ can lower its CSF levels, it is important to analyze the effects of SD in healthy individuals compared to normal sleep controls. Investigating the alterations in these CSF biomarkers due to SD could elucidate early pathological mechanisms and identify potential intervention points.

We aimed to determine which biomarkers are or are not altered by SD, to help clinicians make better-informed decisions when interpreting the results of sleep-deprived patients. Consequently, our objective was to gather the largest set of patients, without age or follow-up restrictions, to observe how CSF biomarkers change in the presence of SD.

Methods

Study design

This is a systematic review and meta-analysis performed and reported according to the Cochrane Collaboration [6] recommendations and the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement guidelines [7]. The study protocol was prospectively registered with the National Institute for Health Research International Registry of Systematic Reviews (PROSPERO, CRD42023453244) [8].

Eligibility criteria

We included studies that met all the following criteria: (1) Randomized Controlled Trial (RCT) or observational studies; (2) comparing the level of AD biomarkers in (3) healthy individuals or patients with AD who underwent SD of any type, compared to normal sleep controls; (4) published in English. No restrictions were applied to the exposure or duration of follow-up. We excluded studies that (1) were not RCTs or observational studies; (2) did not have a control group; or (3) did not assess the outcomes of interest. Studies with overlapping patient samples were also excluded, retaining only the study with the largest sample size in such instances.

Search strategy and data extraction

We systematically searched PubMed, Embase, and the Cochrane Central Register of Controlled Trials for studies published until December 2024 using the following strategy composed of MeSH terms adapted to each database: (sleep deprivation) AND (Alzheimer) AND (cerebrospinal fluid) AND (biomarkers). Two authors (G.G.B. and N.M.M.) independently screened the studies and extracted the data following predefined criteria; titles, abstracts, and full texts were assessed when necessary. Where indicated, a third author (A.C.L.F.R.) resolved disagreements.

Outcomes

We included all CSF biomarker endpoints present in at least three studies; therefore, the included outcomes were Aβ42, Aβ40, t-tau, and p-tau.

Quality assessment

The Risk Of Bias In Non-randomized Studies – of Exposure (ROBINS-E) tool, from the Cochrane Collaboration [9], was employed by two independent authors (G.G.B. and N.M.M.), who evaluated the risk of bias across the domains presented in the next section. Disagreements were resolved by consensus. Two independent authors (G.G.B. and J.A.L.) followed the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) handbook guidelines [10] to assess the level of certainty of the evidence in this meta-analysis. They analyzed study limitations, inconsistency, indirectness, imprecision, and publication bias. Ultimately, the level of evidence was classified as high, moderate, low, and very low [7]. Disagreements were resolved by consensus.

Statistical analyses

All outcomes were analyzed as continuous variables, using mean differences (MD) with 95% confidence intervals (CI). Heterogeneity was quantified using the I^2 statistic and Cochran's Q test, with $I^2 < 25\%$ indicating low, 25–75% moderate, and $> 75\%$ high heterogeneity [11]. A random-effects model incorporating the DerSimonian-Laird estimator for variance between studies was used. Hartung–Knapp adjustments were applied to improve robustness and provide potentially more conservative confidence intervals, enhancing the reliability of the pooled estimates. For each primary random-effects meta-analysis, we also calculated 95% prediction intervals to describe the expected range of true effects in future studies conducted in similar populations, and reported these alongside the pooled estimates in the forest plots. Statistical significance was established $p \leq 0.05$ [6, 7]. Sensitivity analyses were carried out by excluding one study at a time.

We derived the standard deviation for a study that did not report variances directly [1]. Using the reported mean difference, sample sizes, and p-value, we back-calculated the standard deviation by first determining the t-statistic from the p-value and degrees of freedom. The standard error of the mean difference was then calculated as the mean difference divided by the t-statistic. Assuming equal variances, the pooled standard deviation was determined using the relationship between the standard error and the pooled standard deviation. This approach ensured consistency and inclusion of the study in the meta-analysis, adhering to the recommendations for handling missing data [6, 7].

First, we plotted the means and standard deviations (SD) of both groups from each study to obtain their mean differences (Supplementary Figure 1-4), so that we could re-run the meta-analysis including a trial that reported only mean differences [2, 12].

To evaluate the presence of publication bias in this meta-analysis, we used funnel plots that displayed the distribution of effect estimates against their corresponding standard errors. Because fewer than ten studies were included ($n < 10$), formal statistical tests for funnel plot asymmetry, such as Egger's regression test, were not performed according to Cochrane recommendations and due to limited statistical power in small samples. Instead, we relied on a qualitative assessment of funnel plot symmetry to infer potential publication bias [11]. All analyses were performed in R (version 4.4.2) within RStudio (version 2024.09.1 + 394), using the packages 'meta' and 'metafor' [12–14]. After a comprehensive literature search, we included 6 studies comprising a total sample of 169 participants, in a process described in Fig. 1. We evaluated only outcomes available in at least three studies; thus, it was not possible to include a subgroup of patients with AD. The characteristics of individual studies are summarized in Table 1.

Across included studies, populations and sleep-exposure paradigms differed (e.g., experimental acute deprivation vs. clinical sleep disorders), so our results should be interpreted as the average effect of sleep deprivation across heterogeneous, but clinically relevant, settings.

Quantitative synthesis

We conducted each meta-analysis to address the question: "After sleep deprivation, do CSF concentrations of the target biomarker tend to be higher, lower, or unchanged in healthy individuals compared with regular sleep, and is that pattern consistent across studies?"

To answer this, we focused on four complementary outputs: (1) the pooled mean difference (MD), which quantifies the average change in biomarker concentration after sleep deprivation versus control sleep; (2) the 95% confidence interval (CI), which reflects the precision of that average estimate; (3) heterogeneity (I^2 and Cochran's Q), which indicates whether study results are broadly consistent or vary substantially; and (4) the 95% prediction interval, which translates the meta-analysis into a practical expectation - i.e., the range of effects a future similar study might observe, acknowledging between-study variability.

Because the included studies differed in design and population, the random-effects model is conceptually aligned with our question as it estimates an average effect while allowing the "true" effect to vary across study contexts.

Aβ40

Three studies contributed data on CSF Aβ40. Sleep deprivation was consistently associated with higher Aβ40 concentrations compared with regular sleep. In the primary random-effects model, the pooled MD was 31.88 pg/mL (95% CI: 25.61–38.15; $p = 0.0021$; Fig. 2A), indicating a robust increase in Aβ40 after sleep deprivation. In practical terms, this pooled MD means that, on average, CSF Aβ40 measured after sleep deprivation was ~32 pg/mL higher than after regular sleep. Heterogeneity was very low ($I^2 = 0.0\%$; $Q = 0.37$; $p = 0.83$), which indicates that the size and direction of the Aβ40 increase were highly consistent across the included studies rather than being driven by conflicting results. The 95% prediction interval ranged from 17.26 to 46.50 pg/mL, suggesting that a future study in a similar population would still be expected to observe an increase in Aβ40, with the most plausible effects falling within this range.

Leave-one-out sensitivity analyses yielded similar effect estimates and confirmed the stability of this finding (Fig. 2B). We performed this analysis to test whether the pooled result was disproportionately influenced by any single study (e.g., due to design differences, sample size, or outlying results). When each study was omitted in turn, the pooled MD ranged from 29.90 to 33.68 pg/mL, with all confidence intervals remaining clearly above zero (for example, omitting Chen 2018: MD 33.68, 95% CI: 19.44–47.92; omitting Liu 2023: MD 29.90, 95% CI: 14.57–45.22; omitting Olsson 2018: MD 31.88, 95% CI: 7.86–55.89). In all of these models, heterogeneity remained at $I^2 = 0\%$, indicating that the increased Aβ40 levels were statistically robust and not driven by any single influential study. Taken together, these outputs support that sleep deprivation is associated with a reproducible, directionally consistent elevation in CSF Aβ40.

Aβ42

Seven studies were included in the Aβ42 analysis. In the primary random-effects model, sleep deprivation was associated with higher CSF Aβ42 levels, with a pooled MD of 34.85 pg/mL (95% CI: 7.30–62.40; $p = 0.0212$; Fig. 2C). In practical terms, the pooled estimate suggests an average increase of ~ 35 pg/mL in CSF Aβ42 after sleep deprivation compared with regular sleep. Heterogeneity was moderate ($I^2 = 52.8\%$; $Q = 12.72$; $p = 0.0476$), meaning that the magnitude (and in some cases the direction) of the effect differed across studies, which was an expected possibility given differences in populations and sleep-disruption phenotypes. The prediction interval ranged from 2.72 to 66.99 pg/mL, therefore most future comparable

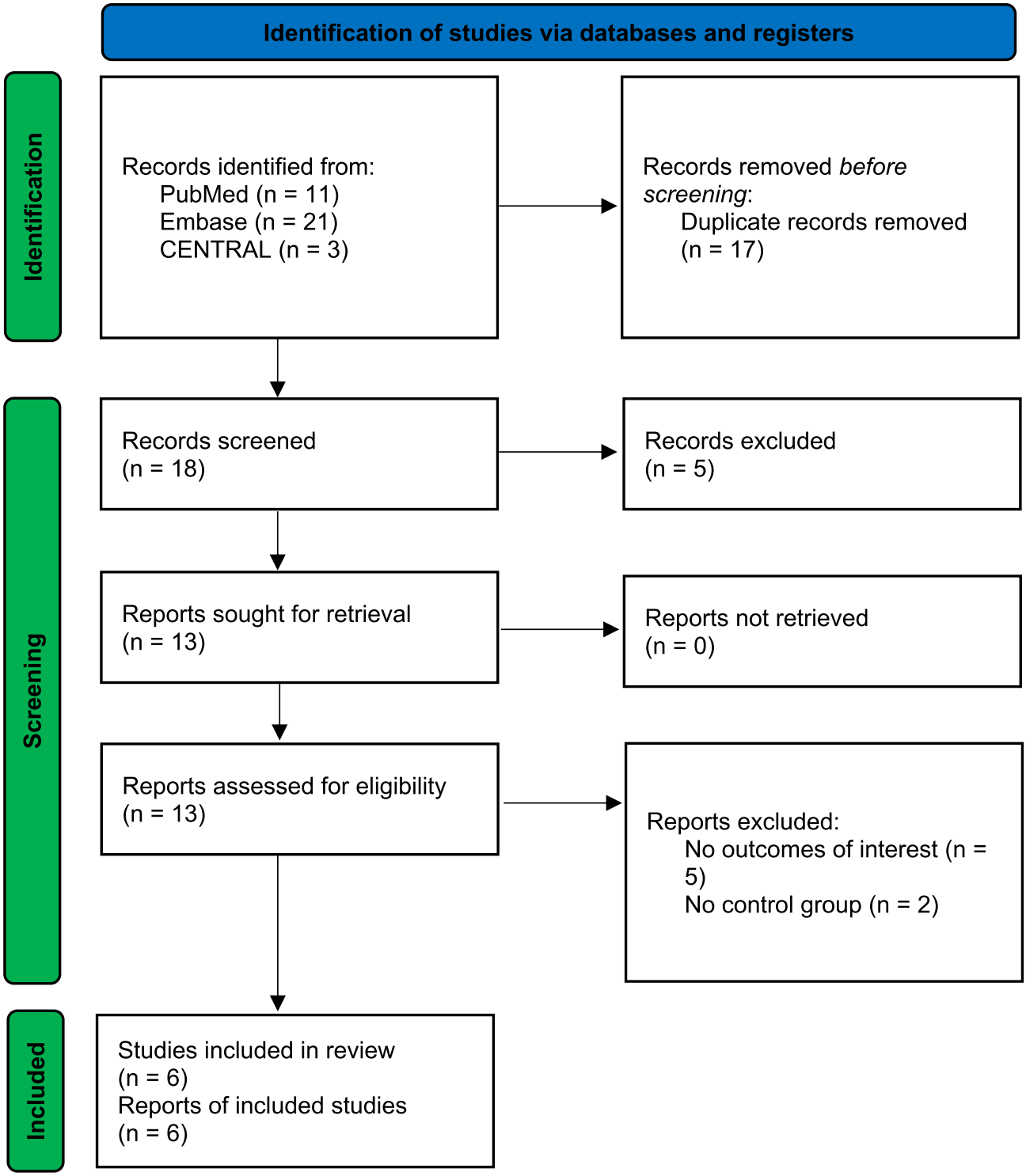


Fig. 1 PRISMA (2020) flow diagram of study screening and selection

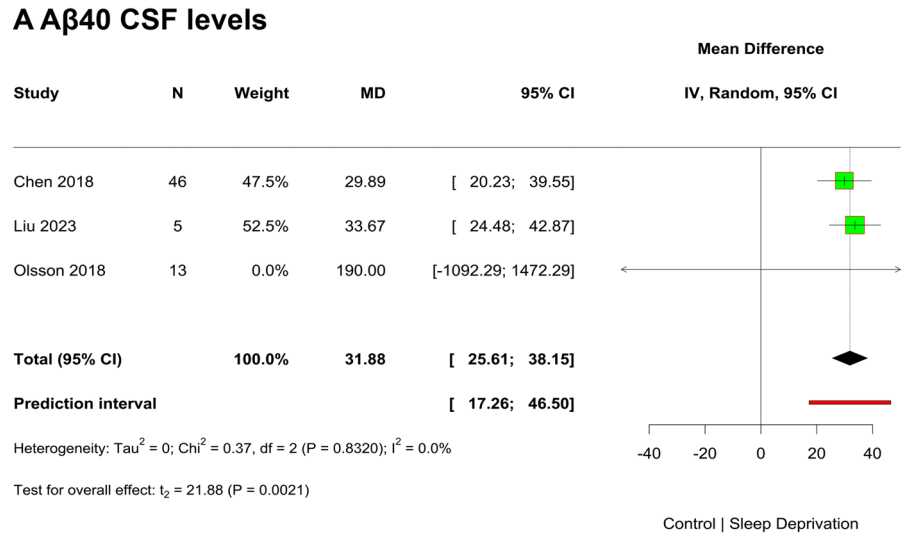
studies would still be expected to show higher Aβ42 after sleep deprivation, but the size of that increase may vary.

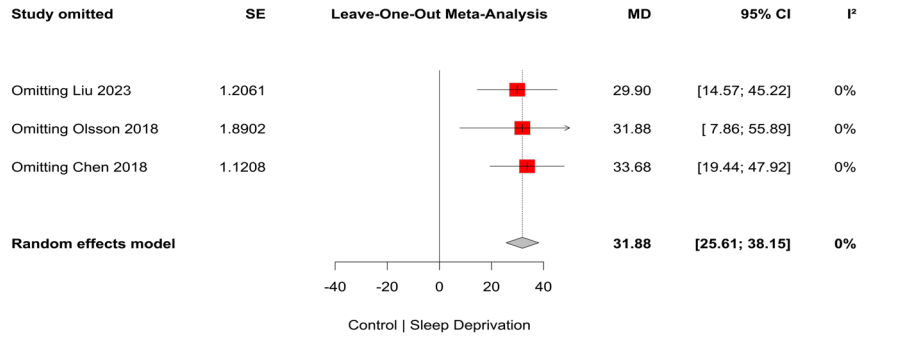
Sensitivity analysis showed that this heterogeneity was largely driven by the Fernandes 2022 OSAS study. We examined this because moderate heterogeneity raises the question of whether one study context is meaningfully different from the others and therefore dilutes the interpretability of the "average" effect. When this study was excluded, the pooled effect became more precise and homogeneous, with a MD of 37.32 pg/mL (95% CI:

Table 1 Baseline characteristics of included studies

Authors	Year	Study type	Patients (n)	Population	Exposure [Duration]	CSF Collection Protocol [Bioanalytical Method]	Female (%)	Comorbidities	Age (Mean ± SD) [Range]	APoE4%)	MMSE (Mean ± SD)	PSQI (Mean ± SD)	ESS (Mean ± SD)	Available outcomes
Chen et al.	2018	Case-control study	46	Patients with chronic insomnia based on DSM-IV-R criteria	Chronic insomnia [> 6 months – DSM-IV-R]	Single lumbar puncture; in the early morning [ELISA]	65.22	Hypertension (30.43%) Diabetes mellitus (13.04%)	53.29 ± 5.62 [43–67]	NA	29.61 ± 0.85	12.22 ± 3.12	NA	Aβ42, Aβ40, t-tau, p-tau.
Fernandes et al.	2022	Observational comparative study	47	Patients with obstructive sleep apnea syndrome and patients with periodic limb movement disorder	Chronic obstructive sleep apnea syndrome and periodic limb movement disorder [NA]	Single lumbar puncture; in the morning [ELISA]	35.83	NA	64.93 ± 5.76 [NA]	38,3	NA	NA	NA	Aβ42, t-tau, p-tau.
Ju et al.	2017	Randomised cross-over controlled trial	17	Healthy adults	Slow wave activity disruption [One night]	Single lumbar puncture; in the morning [ELISA]	65	NA	54.1 ± 6.7 [35–65]	29	29.6 ± 0.5	4.2 ± 1.6	5.6 ± 3.6	Aβ40, t-tau, p-tau.
Liguori et al.	2016	Case-control study	46	Patients with mild cognitive impairment due to AD and healthy controls*	Sleep complaints based on PSQI score [Long-term]	Single lumbar puncture; in the morning [ELISA]	66.66	NA	69.2 ± 3.03 [NA]	NA	29.13 ± 0.99	NA	NA	Orexin, t-tau, p-tau, Aβ42.
Liu et al.	2023	Cross-over experimental study	5	Healthy adults	Controlled sleep deprivation [One night]	Lumbar catheter with CSF sampling every 2 h over 36 h; effects estimated from mean baseline (07:00–19:00) vs overnight (01:00–11:00) [IP–LC/MS]	66.66	NA	48.07 ± 10.24 [30–60]	NA	28.8 ± 0.50	NA	NA	Aβ42, Aβ40, t-tau, p-tau.
Olsson et al.	2018	Randomised cross-over controlled trial	13	Healthy adults	Maximum 4 hours of sleep per night [5–8 nights]	Single lumbar puncture; in the morning [ELISA]	30.08	NA	25 ± 4.0 [20–40]	NA	NA	NA	6 ± **3**	Aβ42, Aβ40, t-tau, p-tau.

Abbreviations: AD, Alzheimer's disease; DSM-IV-R, Diagnostic and Statistical Manual of Mental Disorders IV revised; ELISA, Enzyme-Linked Immunosorbent Assay; ESS, Epworth Sleepiness Scale; IP–LC/MS, immunoprecipitation followed by liquid chromatography–mass spectrometry; MMSE, Mini-Mental State Examination; NA, not available; PSQI, Pittsburgh Sleep Quality Index. *To maintain comparability, we used only the control group results





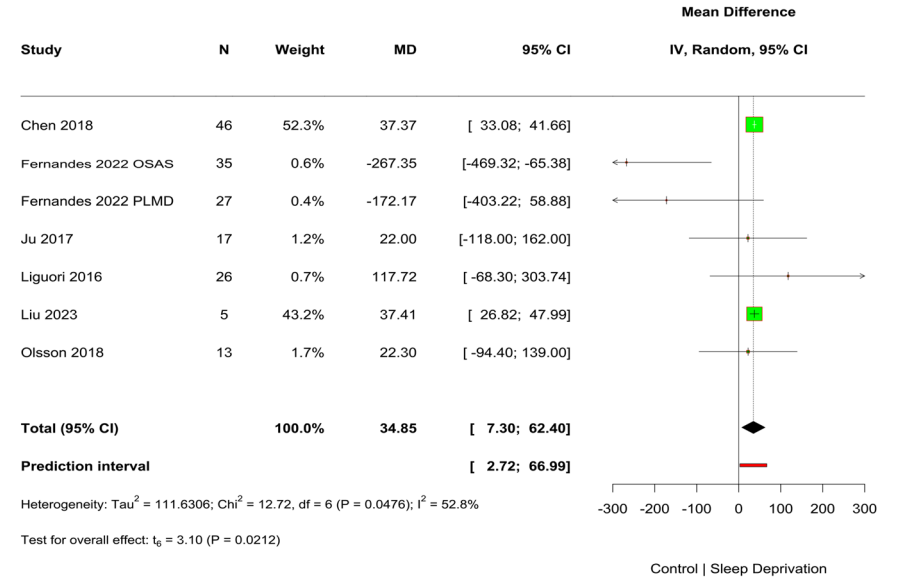


Fig. 2 (continued)

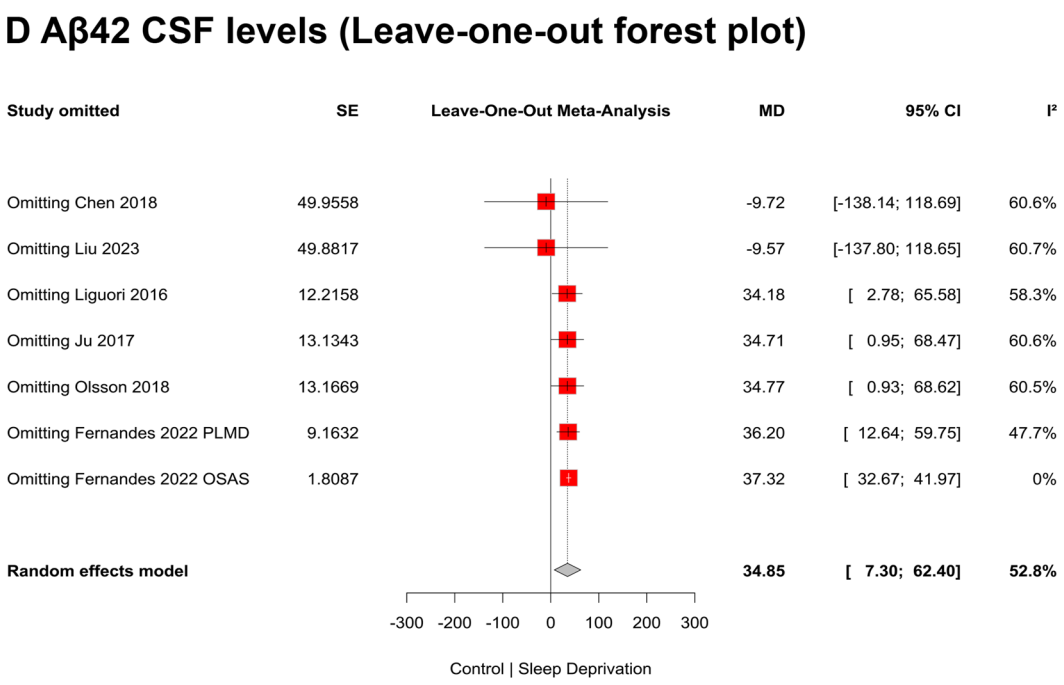


Fig. 2 Cerebrospinal fluid amyloid-β biomarkers (Aβ40 and Aβ42): random-effects meta-analyses and leave-one-out sensitivity analyses. Panel A (Aβ40 CSF levels) and Panel C (Aβ42 CSF levels) show random-effects forest plots of the mean difference (MD, pg/mL) in CSF biomarker concentration after sleep deprivation versus control sleep. For each study, the square represents the study-specific MD and the horizontal line its 95% confidence interval (CI); square size/"Weight" reflects the study's inverse-variance contribution under the random-effects model. The solid vertical line at 0 denotes no difference between conditions, and the dotted vertical line marks the pooled estimate. The diamond represents the pooled MD with its 95% CI. The horizontal bar labelled "Prediction interval" indicates the 95% prediction interval, i.e., the expected range of true effects in a future study conducted in a similar population and setting. Heterogeneity is summarized by τ^2. (between-study variance), Cochran's Q (χ^2) with its p value, and I^2 (percentage of total variability attributable to between-study heterogeneity). Positive MD values (right side of the axis) indicate higher CSF biomarker concentrations after sleep deprivation than after control sleep. Where CIs extend beyond the plotted axis limits, arrows indicate truncation. Panel B (Aβ40 leave-one-out forest plot) and Panel D (Aβ42 leave-one-out forest plot) present leave-one-out sensitivity analyses, in which the pooled random-effects MD is recalculated after omitting one study (or subgroup) at a time (listed under "Study omitted"). Each row shows the re-estimated pooled MD (square) and 95% CI (horizontal line), with the corresponding I^2 reported on the right; the bottom diamond shows the overall pooled estimate including all studies

32.67–41.97; $I^2 = 0\%$; Fig. 2D). The disappearance of heterogeneity and the narrowing of the confidence interval indicate a consistent direction of effect across the remaining studies, reinforcing the reliability of the association between sleep deprivation and increased Aβ42.

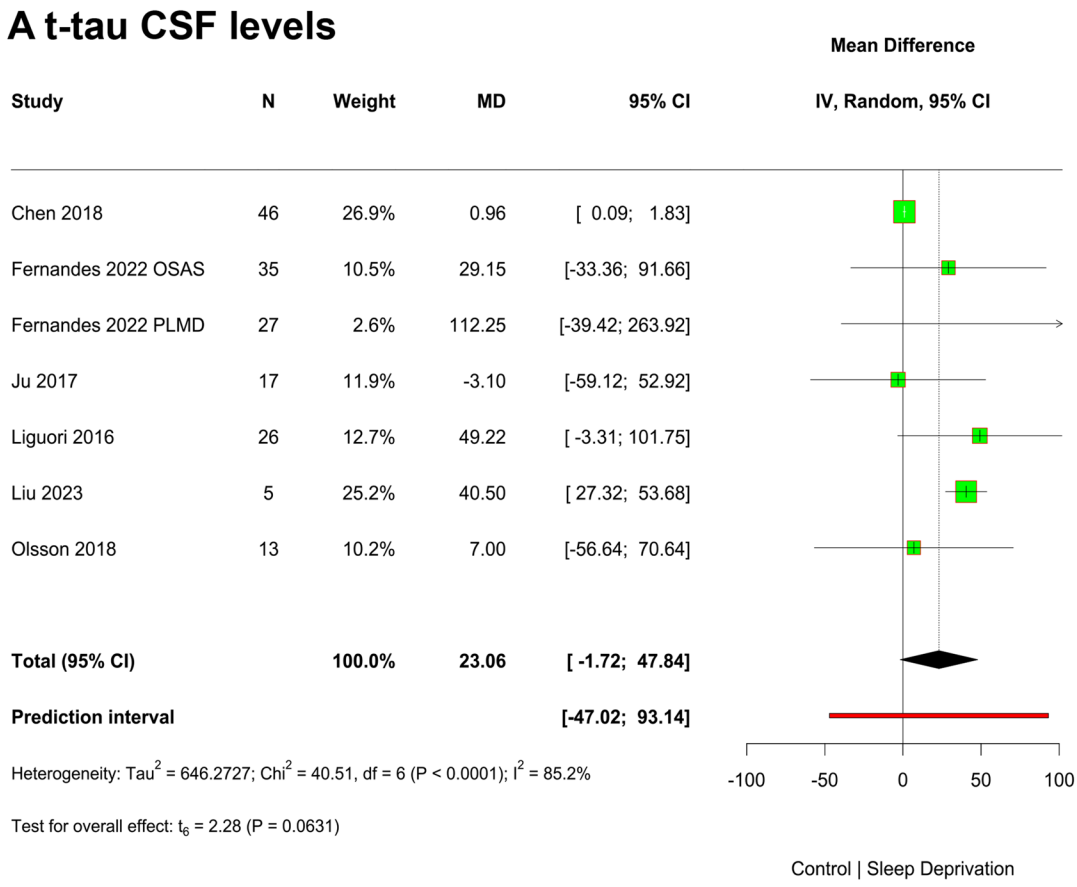
Total tau (t-tau)

Seven studies contributed to the t-tau meta-analysis. In the initial pooling, sleep deprivation was associated with a non-significant increase in t-tau (MD: 23.06 pg/mL; 95% CI: −1.72 to 47.84; $p = 0.0631$; Fig. 3A). Here, the CI crosses zero, which means that, based on the full set of included studies, we cannot rule out the possibility of no average change in t-tau. Substantial between-study heterogeneity was present ($I^2 = 85.2\%$; $Q = 40.51$; $p < 0.0001$), indicating that study results differed markedly and that interpreting a single pooled average without exploring inconsistency would be potentially misleading. The 95% prediction interval (−47.2 to 93.14 pg/mL) reinforces that under the initial heterogeneous model, a future study could plausibly observe anything from a decrease to a large increase, depending on context.

Leave-one-out analysis identified Chen 2018 as the main contributor to heterogeneity. When this study was removed, the association between sleep deprivation and t-tau became statistically significant and homogeneous (Fig. 3B). The resulting pooled MD was 37.81 pg/mL (95% CI: 23.27–52.35; $p = 0.0011$), with $I^2 = 0\%$. In practical terms, once the outlying influence is removed, the remaining studies support an average increase of ~ 38 pg/mL in CSF t-tau after sleep deprivation, with results that are mutually consistent. The shift from highly heterogeneous, non-significant results to a precise, homogeneous, and statistically significant effect highlights the disproportionate impact of a single outlier and clarifies the underlying signal of increased t-tau following sleep deprivation.

Phosphorylated tau (p-tau)

Six studies were included in the p-tau meta-analysis. In the primary random-effects model, sleep deprivation was



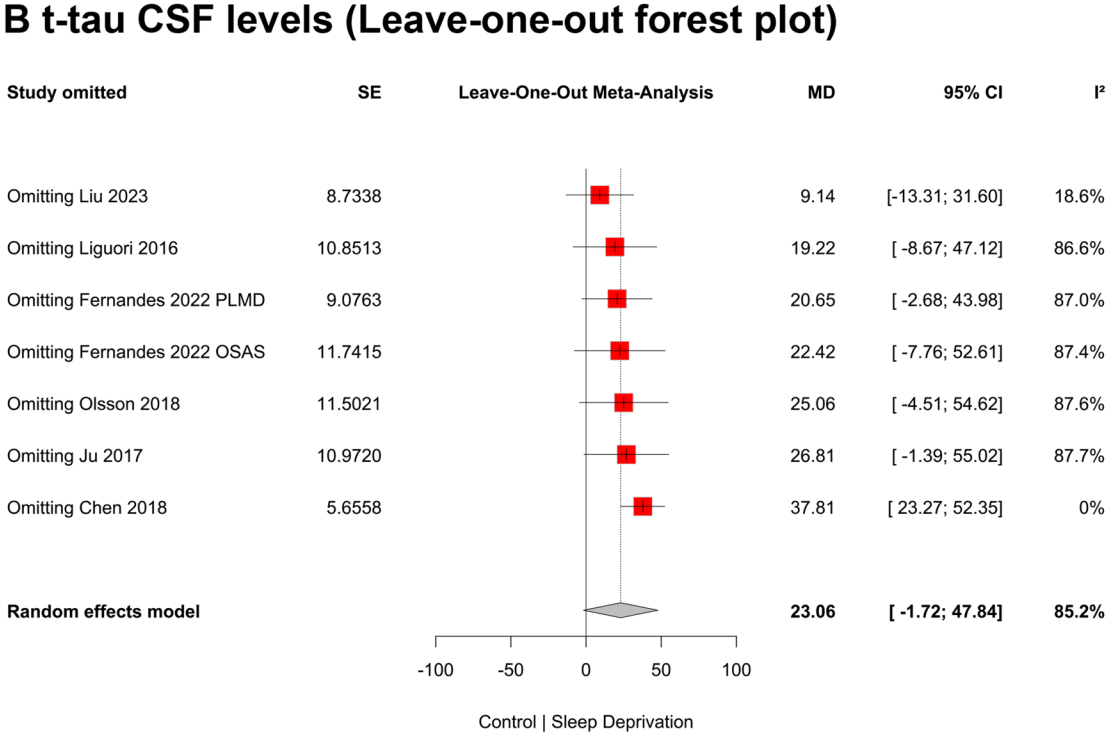
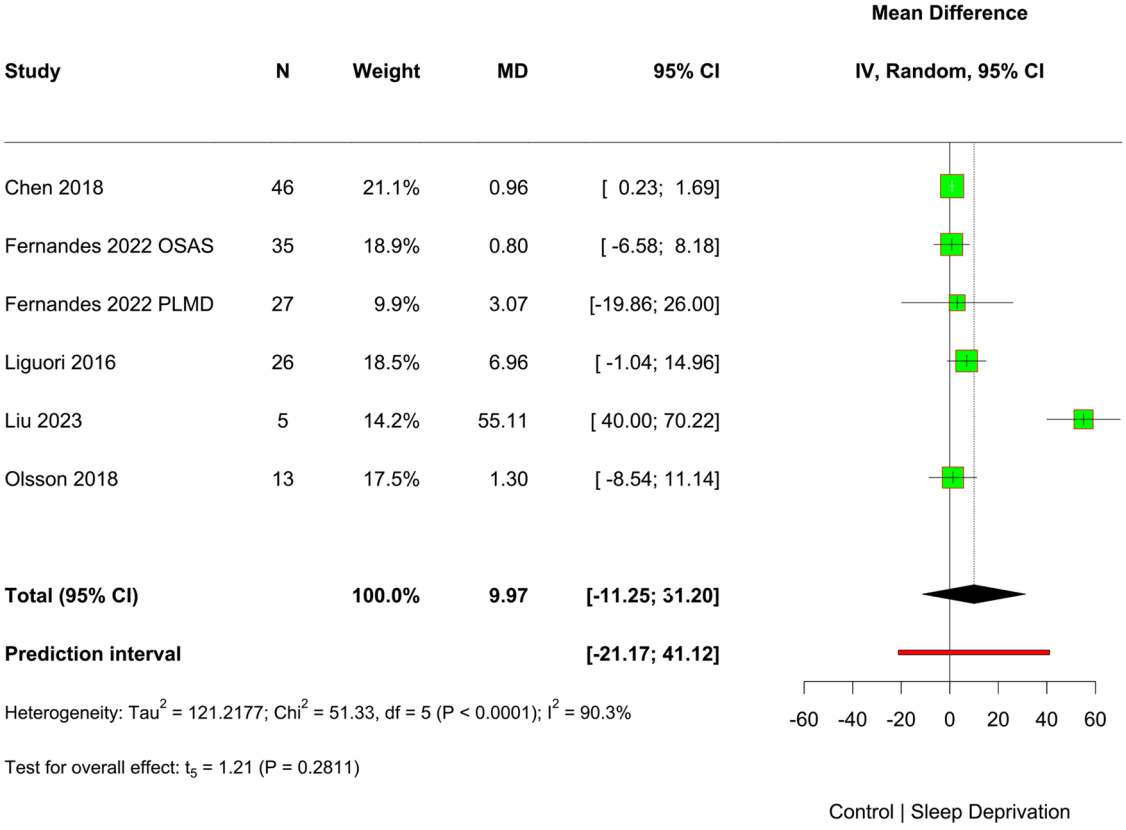


Fig. 3 (continued)

C p-tau CSF levels



D p-tau CSF levels (Leave-one-out forest plot)

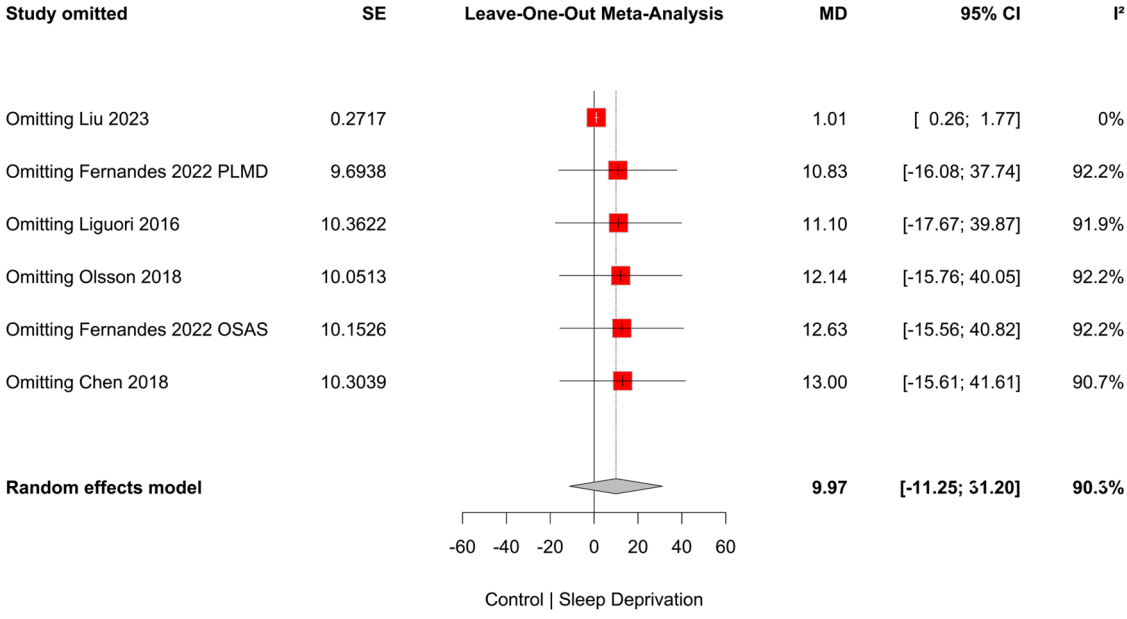


Fig. 3 (See legend on next page.)

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Fig. 3 Cerebrospinal fluid tau biomarkers (t-tau and p-tau): random-effects meta-analyses and leave-one-out sensitivity analyses. Panel A (t-tau CSF levels) and Panel C (p-tau CSF levels) show random-effects forest plots of the mean difference (MD) in CSF total tau (t-tau) and phosphorylated tau (p-tau) after sleep deprivation versus control sleep. Squares represent study-specific MDs and horizontal lines their 95% CIs; square size/"Weight" reflects inverse-variance contribution under the random-effects model. The solid vertical line at 0 denotes no difference; the dotted vertical line marks the pooled estimate; and the diamond shows the pooled MD with its 95% CI. The "Prediction interval" bar represents the 95% prediction interval (expected range of true effects for a future similar study). Heterogeneity is summarized by τ^2, Cochran's Q (χ^2) with p value, and I^2. Positive MD values (right side of the axis) indicate higher CSF tau concentrations after sleep deprivation than after control sleep. Arrows denote confidence intervals extending beyond the plotted axis limits. Panel B (t-tau leave-one-out forest plot) and Panel D (p-tau leave-one-out forest plot) present leave-one-out sensitivity analyses, recalculating the pooled random-effects MD after omitting each study in turn. Each row displays the re-estimated pooled MD (square) with its 95% CI (horizontal line) and the corresponding I^2; the bottom diamond shows the overall pooled estimate including all studies

associated with a non-significant increase (MD: 9.97 pg/mL; 95% CI: −11.25 to 31.20; $p = 0.2811$; Fig. 3C), accompanied by very high heterogeneity ($I^2 = 90.3\%$; $Q = 51.33$; $p < 0.0001$). As with t-tau, the combination of a CI crossing zero and very high heterogeneity indicates that the available studies do not converge on a single, stable estimate in the primary model. A 95% prediction interval (−21.7 to 41.12 pg/mL) reflected the wide uncertainty in both magnitude and direction of effects under such heterogeneity.

Sensitivity analyses showed that the Liu 2023 [2] study was the main driver of heterogeneity. When this study was omitted, the pooled effect became significant, with sleep deprivation associated with a modest but consistent increase in p-tau (MD: 1.01 pg/mL; 95% CI: 0.26–1.77; $p = 0.0204$; $I^2 = 0\%$; Fig. 3D). This sensitivity model supports a clear, but small, average increase in p-tau after sleep deprivation, with high cross-study consistency once the influential study is removed. In this model, the confidence interval was narrow and entirely above zero, demonstrating a stable direction of effect across the remaining studies despite the small absolute magnitude of change. Therefore, the practical interpretation for p-tau is twofold: (1) the evidence for an "average increase" becomes convincing only after addressing influential heterogeneity; and (2) when present, the estimated mean increase is quantitatively modest.

Quality assessment

Risk of bias

In our assessment, no study had a low overall risk of bias, but only one was considered to have a high risk of bias. The ROBINS-E–based evaluation across individual domains and the overall judgments are summarized in Fig. 4. This matters for interpretation because observed biomarker differences could be partly attributable to design-related limitations (e.g., confounding in observational comparisons), which reduces confidence that the pooled estimates reflect the true causal effect of sleep deprivation alone. In a visual analysis, the funnel plot for t-tau appears to form a more symmetrical distribution of data points around the central estimate line (Supplementary Figure 5), with the studies spreading outwards as the standard error increases, suggesting a relatively balanced pattern. By contrast, the plots for Aβ40, Aβ42, and p-tau appear more irregular and less funnel-shaped (Supplementary Figures 6–8). This irregularity may be due to the limited number of included studies, especially for Aβ40, which makes it difficult to discern whether any observed asymmetry is beyond random variation. In summary, these funnel plots do not "prove" publication bias; rather, they indicate that the small evidence base limits our ability to exclude it, particularly for outcomes supported by few studies. Nonetheless, we minimized potential publication bias from outlier studies through sensitivity analyses in which we excluded one study at a time.

GRADE

In qualitative analysis, we deemed the certainty of evidence for Aβ40 and Aβ42 as low, due to the high risk of bias of one of the pooled studies and the possibility of publication bias. In addition, p-tau had a small magnitude of effect and substantial initial heterogeneity, so we considered its certainty of evidence to be very low. On the other hand, t-tau was not influenced by the study with a high risk of bias in our sensitivity analyses, and the funnel plot did not suggest publication bias; thus, we considered it to have a high certainty of evidence.

Discussion

This meta-analysis demonstrated that Aβ40, Aβ42, p-tau, and t-tau are affected by chronic or acute SD in healthy individuals. Aβ40 is the most abundant amyloid-β species and is less prone to fluctuations caused by amyloid plaques [1]. Since existing plaques can abolish the diurnal variation of Aβ related to sleep, leading to abnormally low Aβ42 [1], it was critical to focus on individuals without AD; observing a concordant rise in Aβ40 and Aβ42 lends strength to our findings. Half of the studies included in this review evaluated the chronic effects of SD on AD biomarkers, while the other half investigated the acute impact of SD, even if it was only for one night [2, 4, 15]. The data suggest that SD elevates the levels of Aβ and tau in the CSF while reducing them in the plasma [2], indicating that clinicians should consider not only long-term sleep quality but also the possibility that missing one night of sleep could influence biomarker results before blood or CSF collection.

Fig. 4 Risk-of-bias assessment for the included studies using the ROBINS-E tool. Panel a shows the traffic-light plot with risk-of-bias judgements for each study across the seven ROBINS-E domains: D1, bias due to confounding; D2, bias arising from measurement of the exposure; D3, bias in selection of participants into the study (or into the analysis); D4, bias due to post-exposure interventions; D5, bias due to missing data; D6, bias arising from measurement of the outcome; and D7, bias in selection of the reported result. Panel B shows the summary bar plot indicating, for each domain and for the overall risk-of-bias judgement, the proportion of studies rated as low risk (green), some concerns (yellow), or high risk (red)

Longer sleep latency, shorter sleep duration, and greater sleep efficiency have been associated with a higher p-tau/Aβ42 ratio, although this appears to vary by age [16]. Sleep insufficiency (fewer than six hours) is correlated with a higher risk of cognitive decline and AD, but the age dependence of these relationships implies that relying on self-reported sleep measures to measure AD risk may be inadequate [16, 17]. Additional findings indicate that one night of SD lowers the clearance of Aβ, t-tau, and p-tau from the central nervous system [2], suggesting that even brief disruptions can have appreciable effects. The cycle by which accumulating Aβ diminishes both the duration and quality of sleep is of concern, as wakefulness further increases Aβ deposition [17]. Alterations in orexin signaling may contribute to prolonged wakefulness [17]. While the orexin system is believed to be involved in early AD and to be linked to sleep disturbance in mild cognitive impairment, particularly in REM sleep [15], disturbances in non-REM sleep have been reported to increase levels of Aβ and tau, possibly by impacting synaptic activity rather than a broad protein clearance mechanism [1].

We hypothesize that the inverse CSF–plasma biomarker relationship reported previously also applies here and would manifest as reduced AD plasma biomarker levels post-SD. Further studies focusing on plasma-based measures could clarify whether these fluctuations have clinical implications for early detection or prognosis.

More research involving patients with established AD is also warranted to determine whether repeated or chronic SD could alter the clinical trajectory of the disease, as well as to elucidate the still controversial effects of SD on the orexin system and its significance in the development of AD. Furthermore, sleep disturbances have also been associated with both vascular dementia and all-cause dementia [18], highlighting the need for additional studies to determine the generalizability of our findings to other etiologies of dementia.

The limitations of this work include substantial between-study variability in baseline biomarker levels, the presence of observational designs, and heterogeneity of enrolled populations. While these features enhance external validity, they reduce the certainty of inferences for specific subgroups. Notably, Ju et al. (2017) reported in the crossover cohort that the order of conditions (sleep disruption first vs. sham first) did not affect the results, and no differences were observed between APOE-ε4 carriers and non-carriers [1]. A methodological strength is that none of the included studies used repeated lumbar punctures in close succession - a known confounder that can artificially elevate CSF Aβ concentrations - thereby reducing procedure-related bias [16]. Sensitivity analyses yielded consistent estimates, strengthening confidence in the findings. Nonetheless, prospective studies with randomized protocols and rigorous monitoring of sleep parameters are needed to determine the extent to which sleep-disruption–related fluctuations in AD biomarkers correspond to clinically meaningful outcomes. Accordingly, we report associations rather than causation at this stage.

Conclusion

This systematic review and meta-analysis indicates that both acute and chronic SD could raise CSF levels of Aβ40, Aβ42, t-tau, and p-tau among healthy individuals. Although further high-quality studies are needed, including those involving individuals with AD, clinicians should consider recent sleep history when interpreting these biomarkers. SD could confound diagnostic evaluations by artificially elevating AD-related biomarkers in the CSF, while at the same time reducing them in the plasma. Recognizing and targeting sleep disturbances may thus not only improve overall well-being but also mitigate processes that initiate or accelerate AD-related neurodegeneration. Future research should explore whether tackling chronic SD can alter clinical outcomes or slow disease progression .

Abbreviations

AD	Alzheimer's disease
APOE4	Apolipoprotein E epsilon 4 allele
DSM-IV-R	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Revised
REM	Rapid Eye Movement
NA	Not Applicable
Aβ	Amyloid-beta
Aβ40	Amyloid-beta peptide 40
Aβ42	Amyloid-beta peptide 42
t-tau	Total tau
p-tau	Phosphorylated tau
CSF	Cerebrospinal fluid
LRP1	Low-density lipoprotein receptor-related protein 1
RCT	Randomized Controlled Trial
ROBINS-E	Risk Of Bias In Non-randomized Studies – of Exposure
GRADE	Grading of Recommendations, Assessment, Development, and Evaluation
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO	International Prospective Register of Systematic Reviews
MD	Mean Difference
CI	Confidence Interval
SD	Standard Deviation
MMSE	Mini-Mental State Examination
PSQI	Pittsburgh Sleep Quality Index
ESS	Epworth Sleepiness Scale

Supplementary Information

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Supplementary material 1

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Author contributions

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Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

During the preparation of this work the authors used ChatGPT and Writefull in order to improve language and readability. After using this tool/service, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

Ethics approval and consent to participate

Not applicable.

Consent for publication
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Competing interests
The authors declare no competing interests.

Author details
[1]School of Medicine, University of Passo Fundo (UPF), Passo Fundo, RS, Brazil
[2]Department of Neurology, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA
[3]Nuffield Department of Clinical Neurosciences, University of Oxford, Oxford, UK

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