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SYSTEMATIC REVIEW/META-ANALYSIS

Diffusion Tensor Imaging Along the Perivascular Space for Characterizing Cerebral Interstitial Fluid Dynamics in Alzheimer's Disease: A Systematic Review and Meta-Analysis

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ABSTRACT

BACKGROUND: Diffusion Tensor Imaging along the Perivascular Space (DTI-ALPS) has emerged as a measure of cerebral interstitial fluid dynamics, a proposed component of the glymphatic system, which may provide insight into central nervous system fluid transport and waste clearance.

PURPOSE: Our study aimed to evaluate whether DTI-ALPS can serve as a reliable, noninvasive imaging biomarker of altered interstitial fluid dynamics across the Alzheimer's Disease (AD) continuum.

DATA SOURCES: We searched Scopus, Web of Science, and PubMed for articles published through October 2024.

STUDY SELECTION: Studies were included if they reported the ALPS-index in AD, mild cognitive impairment (MCI), and healthy control groups. Studies were excluded if they lacked sufficient data or involved overlapping cohorts.

DATA ANALYSIS: Using standardized mean difference (SMD), we compared the ALPS-index in AD and MCI groups to healthy controls. We assessed the association between the ALPS index and cognitive function using a random-effects model. A qualitative risk bias assessment was conducted using the Newcastle-Ottawa Scale (NOS).

DATA SYNTHESIS: Nineteen studies met the inclusion criteria. The overall ALPS index was significantly lower in AD subjects than in healthy controls (SMD = -1.07, 95% CI: -1.57 to -0.56). Statistically significant differences were also observed between AD and MCI subjects (SMD = -0.25, 95% CI: -0.40 to -0.10), as well as between MCI and healthy control subjects (SMD = -0.81, 95% CI: -1.57 to -0.06). Additionally, the ALPS index showed a statistically significant association with Mini-Mental State Examination scores (pooled correlation effect size = 0.43, 95% CI: 0.28 to 0.57). A negative correlation was also observed between the ALPS index and amyloid deposition on PET, with a pooled correlation effect size of -0.42 (95% CI: -0.66 to -0.19, $p < 0.001$).

LIMITATIONS: Potential limitations include heterogeneity across imaging protocols, variability in cognitive assessments, and possible publication bias.

CONCLUSIONS: The DTI-ALPS technique showed significant differences among cognitive groups across the AD continuum and was associated with cognitive scores and brain amyloidosis. This provides further evidence that DTI-ALPS could be useful in detecting altered cerebral interstitial fluid dynamics in MCI and AD.

ABBREVIATIONS: AD = Alzheimer's disease; Aß = beta-amyloid; PET = positron emission tomography; PiB = Pittsburgh Compound B; FBB = Florbetaben; CL = Centiloid.

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INTRODUCTION

The discovery of the glial-lymphatic, or glymphatic, clearance system in 2012 sparked enormous interest in better understanding how we clear toxins and metabolic waste from the brain and in developing noninvasive approaches to imaging this system. A key component of the glymphatic system is aquaporin-4 (AQP-4), a water channel on the astrocytic endfeet in the perivascular space that facilitates glymphatic-interstitial fluid exchange.

Currently, the most direct method to measure glymphatic function requires injection of intrathecal gadolinium contrast into the spinal canal and serial MR imaging of the brain, as the contrast tracks through cerebrospinal fluid (CSF) spaces [1, 2]. While this approach provides clear imaging of CSF-filled structures, including T2-hyperintense perivascular spaces, and periarterial spaces, it is more difficult to visualize perivenous and interstitial fluid compartments in the deep white matter [3-5].

In 2017, Taoka et al. introduced "diffusion tensor image analysis along the perivascular space" (DTI-ALPS) as a noninvasive MR method that uses diffusion MRI to quantify water diffusivity along the deep medullary veins at the level of the lateral ventricles **(Figure 1)** [6, 7]. Studies that have applied the ALPS index have shown a lower ALPS index in AD and an association with Aβ deposition [8-10]. Although this method has met with criticism [7, 11], there have been steps toward validating this technique by correlating with a DTI-based MRI measure of free water and intrathecal gadolinium clearance [12, 13]. The ALPS index also shows high interrater reliability and test-retest repeatability [8].

In this meta-analysis, we systematically reviewed the existing literature to better synthesize available evidence on the reliability of the ALPS index in distinguishing AD from healthy controls. We also explored its association with cognitive decline and brain amyloidosis to assess whether the ALPS index has potential as a reliable diagnostic imaging tool for altered cerebral interstitial fluid dynamics across the AD continuum.

MATERIALS AND METHODS

Population and Eligibility Criteria

This study was structured in alignment with the PRISMA 2020 guidelines to ensure comprehensive and transparent reporting of systematic reviews and meta-analyses [14]. This study was registered on the international Prospective Register of Systematic Reviews (PROSPERO)—*CRD42024560698*. We included all peer-reviewed research articles that assessed the ALPS index (overall, right hemispheric, and left hemispheric) in individuals with AD; our search covered cohort, cross-sectional, and case-control studies, including those that examined this index's diagnostic, prognostic, and longitudinal value. We excluded studies that lacked a full paper, had incomplete data, relied solely on in-silico methods, focused on animal subjects, or were reviews or editorials. Additional details are in the **Online Supplemental File**.

Study risk of bias assessment

We evaluated the risk of bias in individual studies using the Newcastle-Ottawa Scale (NOS)—a widely recognized tool for assessing the quality of cohort and case-control studies. The NOS checklist assesses three key domains (**Online Supplemental File**) [15]: Selection (participant selection and recruitment); Comparability (control for confounding variables); and Outcome (cohort studies) or Exposure (case-control studies). Studies were then rated based on their total score: greater than 7 indicated high quality; 5-6 indicated medium quality; and less than 5 indicated low quality. This assessment helped us identify potential biases and evaluate the overall quality of studies.

Synthesis methods

We performed our analyses using Stata MP (V.17.0) with the "metan" package (StataCorp, College Station, Texas, USA), applying a significance level of $P < 0.05$. A meta-analysis was performed to evaluate the ALPS index, comparing AD, HC, and MCI groups using mean difference (MD) and standardized mean difference (SMD) with 95% confidence intervals (CI) [16]. Hedges's g was selected to measure SMD effect size, since the sample size was below 20 participants in at least one group [17], which allowed for the classification of effect sizes as no effect (< 0.2), small (0.2 to 0.5), medium (0.5 to 0.8), and large (> 0.8). A positive SMD typically indicates that the intervention group performed better than the control group, while a negative SMD suggests the opposite [18].

We also converted Pearson correlation coefficients to Fisher's Z and standard error (SE) to assess the correlations between the ALPS index and cognitive function. Due to methodological heterogeneity, a random-effects model (REM) with restricted maximum likelihood (REML) was used [19]. For comparisons involving fewer than 10 studies, the Hartung-Knapp modification with a prediction interval (95% CI) was applied [20].

Heterogeneity was assessed using the Q test (χ^2) and the I^2 statistic, which is categorized as follows [21]: 0% to 25% (possibly unimportant), 25% to 50% (moderate), 50% to 75% (substantial), and 75% to 100% (considerable). To detect publication bias by examining the relationship between study effect sizes and their precision, we applied the Egger's test ($P \leq 0.10$) and trim-and-fill plots for studies of fewer than 10. Contour lines representing statistical significance levels were added to funnel plots to enhance the analysis. This helps distinguish publication bias from other causes of asymmetry. For a better visual representation of bias, Doi plots were used for analyses with at least 10 studies [22-25]. The Doi plot, proposed as an alternative to Egger's regression for assessing publication bias, was evaluated using the LFK index. The LFK index classifies asymmetry as follows: no asymmetry (-1 < LFK < 1), minor asymmetry (-2 to -1 or 1 to 2), and major asymmetry (< -2 or > 2). These metrics provide a quantitative measure to detect and assess bias [26].

Subgroup analyses were conducted for results with $I^2 > 50\%$ [27], while sensitivity analyses employed two strategies: leave-one-out

removal and subgrouping by NOS quality assessment score (high, medium, low) to assess the impact of individual studies on the overall findings.

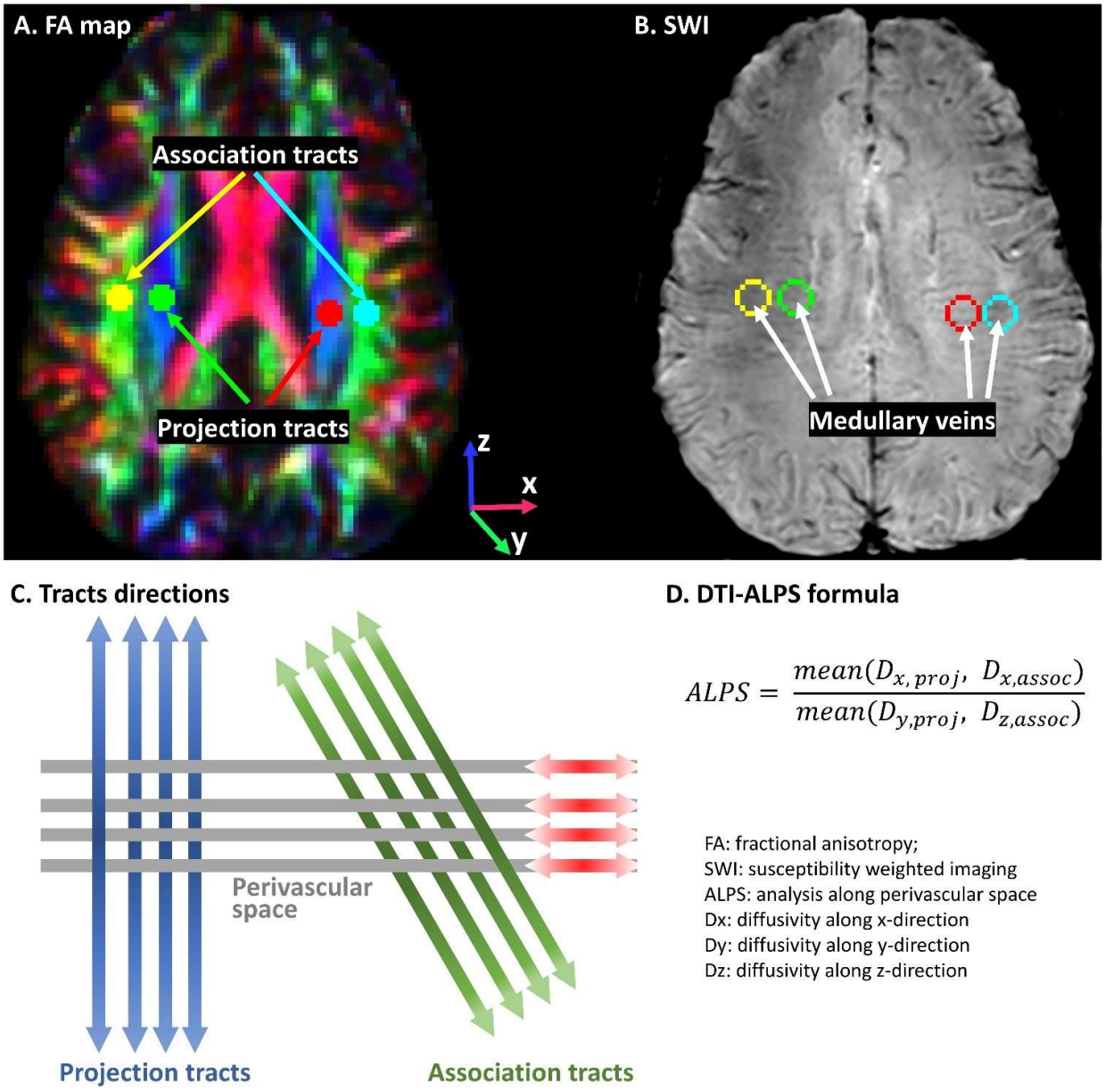

FIG 1. The DTI-ALPS analytical method applied to Alzheimer's Disease (AD). A) Fractional anisotropy (FA) map of the major cerebral white matter tracts. B) Susceptibility weighted imaging (SWI) demonstrating the deep medullary veins (linear hypointense structures coursing through the white matter, some of which course through the yellow, green, red, and blue circles, which represent the association (yellow and blue) and projection (green and red) tracts. Interstitial/glymphatic fluid is believed to course along these deep medullary veins. C) Schematic representation of the projection (blue arrows) and association (green arrows) tracts relative to the perivascular space (gray lines). D) The formula for the Analysis Along Perivascular Space (ALPS) index, is used to estimate the diffusivity along different tracts.

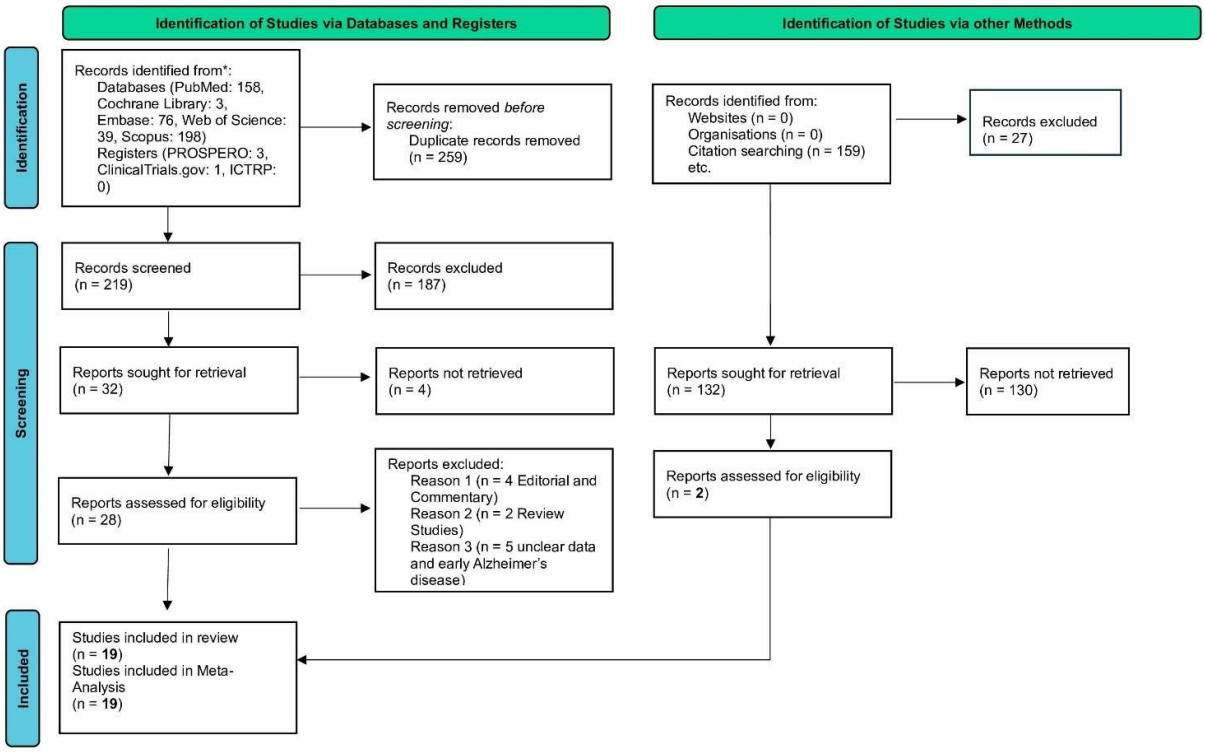

FIG 2. PRISMA 2020 flow diagram illustrating the systematic review process, including the identification, screening, eligibility, and inclusion stages. Details include records from databases, registers, and other sources, besides the reasons for exclusions at each step.

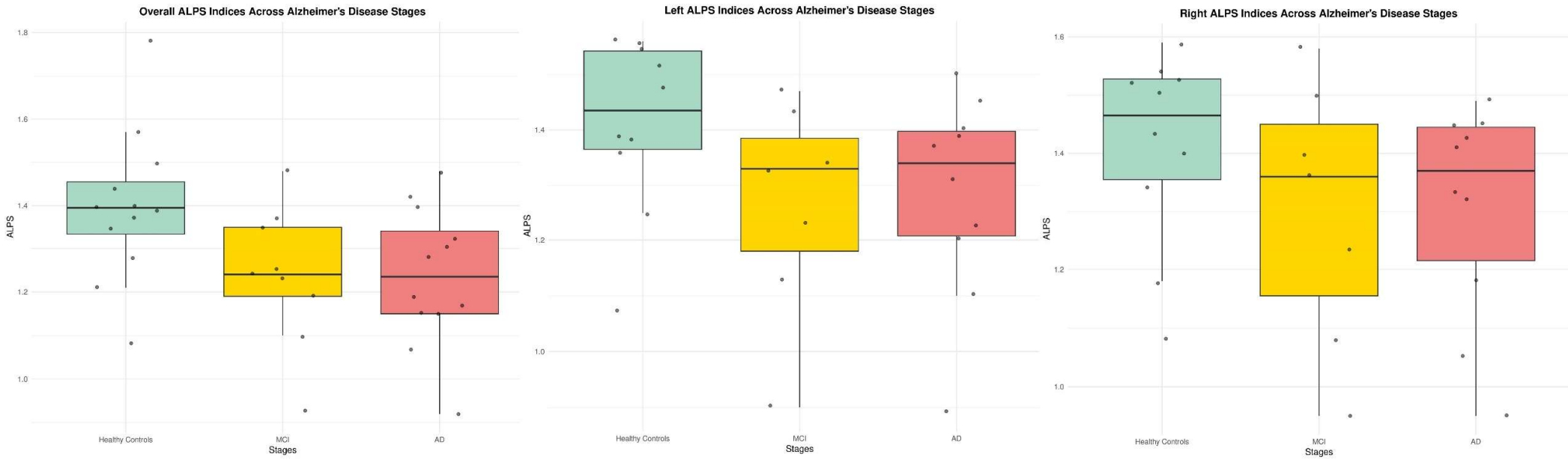

FIG 3. ALPS Indices across Alzheimer's disease stages. (A) Boxplots showing the overall ALPS index across three groups: healthy controls, mild cognitive impairment (MCI), and Alzheimer's disease (AD). (B) This panel illustrates the ALPS index specifically for the left hemisphere across the same three diagnostic groups. Comparisons across groups may reveal lateralized fluid clearance alterations in AD progression. (C) This panel depicts the ALPS index for the right hemisphere.

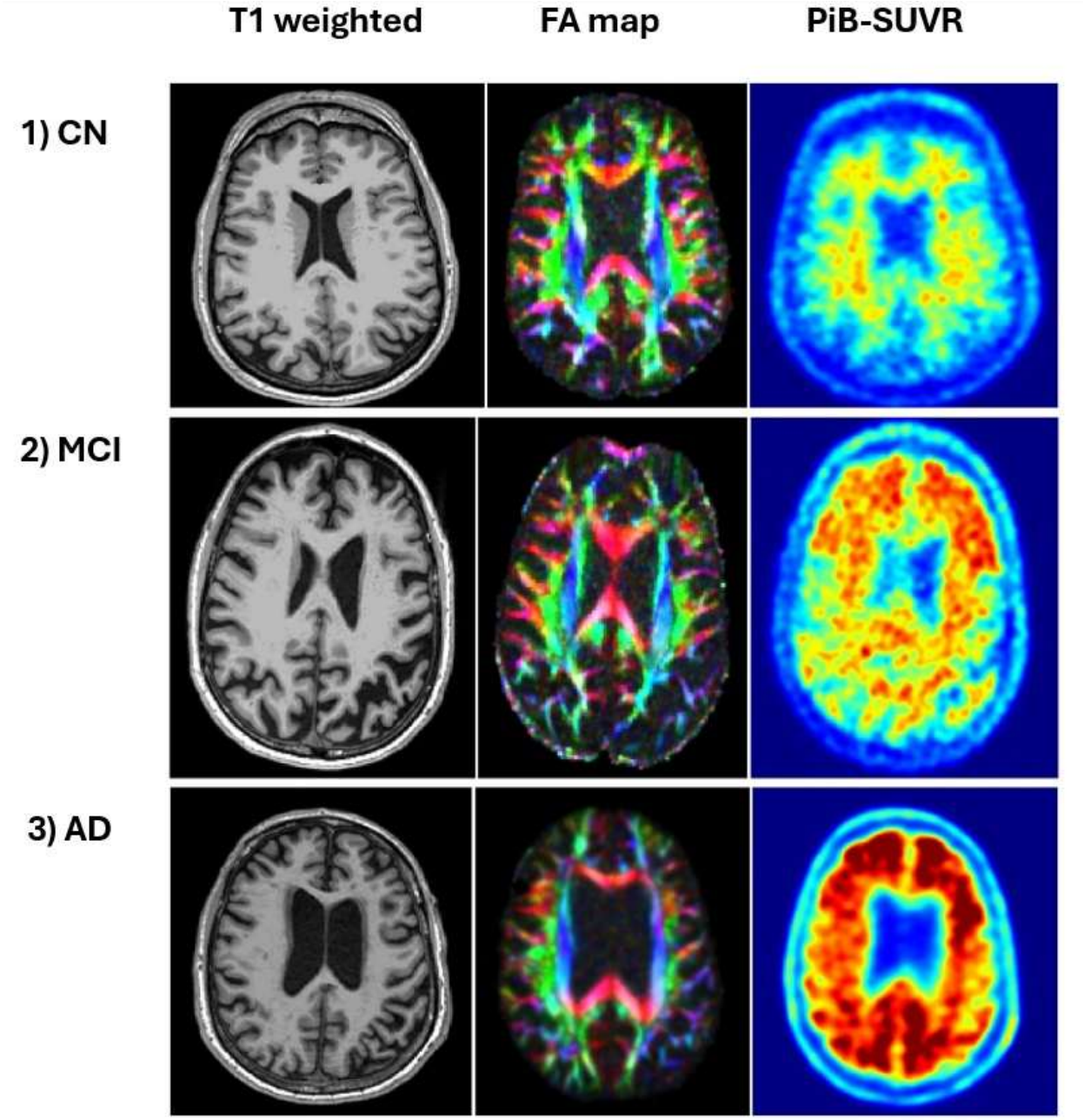

FIG 4. Three case examples from our data [9], representing different stages along the AD continuum: cognitively normal (CN), mild cognitive impairment (MCI), and Alzheimer's disease (AD). A T1-weighted (T1w) MR image, fractional anisotropy (FA) map from diffusion tensor imaging (DTI), and [11C] Pittsburgh compound B (PiB) standardized uptake value ratio (SUVR) image are shown for each participant. **1)** CN (69-year-old male): T1w MR shows no significant atrophy with a mean ALPS index of 1.26. PiB SUVR image shows off-target binding of the amyloid tracer to white matter, indicating amyloid negativity. **2)** MCI (70-year-old male): T1w MR shows mild cortical atrophy, particularly in the left parietal lobe, with a mean ALPS index of 1.21; PiB SUVR shows amyloid deposition, particularly in the frontal lobes. **3)** AD (71-year-old male): T1w MR shows cortical atrophy primarily in the right frontal and bilateral parietal lobes, with a mean ALPS index of 1.13; PiB SUVR shows marked cortical deposition of amyloid.

RESULTS

Study selection

Two researchers independently screened 478 studies per PRISMA guidelines **(Figure 2)**, leaving 19 studies for inclusion in this meta-analysis [6, 9, 14, 15, 28-42]. Eleven single-center and eight multi-center studies published between 2017 and 2024 were included, totaling 2,219 participants: 598 (27%) with late-onset AD, 1,039 (47%) healthy controls, and 582 (26%) with MCI (**Online Supplemental File**).

The Overall DTI-ALPS index

Twelve studies reported an overall ALPS index in both AD and HC cohorts **(Figure 3A)** [9, 14, 28, 29, 31-36, 40]. Pooled estimates showed an MD of -0.16 (95% CI: -0.20 to -0.12) and an SMD of -1.07 (95% CI: -1.57 to -0.56, $p < 0.001$, I^2: 93.4%), providing evidence for a lower ALPS index in AD compared to HC (**Online Supplemental File**). Eight studies reported an overall ALPS index in both AD and MCI cohorts [9, 28, 29, 32, 33, 36, 40]. Pooled estimates showed an MD of -0.04 (95% CI: -0.06 to -0.02) and an SMD of -0.25 (95% CI: -0.40 to -0.10, $p = 0.01$, I^2: 2.4%), providing evidence for a lower ALPS index in AD compared to MCI. Nine studies reported an overall ALPS index in both MCI and HC cohorts [9, 28, 29, 32, 33, 36, 39, 40]. Pooled estimates showed an MD of -0.11 (95% CI: -0.16 to -0.06) and an SMD of -0.81 (95% CI: -1.57 to -0.06, $p = 0.04$, I^2: 95.9%), providing evidence for a lower ALPS index in MCI compared to HC.

The Left ALPS index

Ten studies reported a left ALPS index in both AD and HC cohorts (**Figure 3B**) [9, 15, 32, 35-38, 40]. Pooled estimates showed an MD of -0.14 (95% CI: -0.17 to -0.10) and an SMD of -0.71 (95% CI: -0.93 to -0.50, $p < 0.001$, I^2: 46.0%) (**Online Supplemental File**). Six studies reported a left ALPS index in both AD and MCI cohorts [9, 15, 32, 36, 40]. Pooled estimates showed an MD of -0.03 (95% CI: -0.05 to 0.00) and an SMD of -0.15 (95% CI: -0.33 to 0.03, $p = 0.09$, I^2: 0.0%), showing a nonsignificant trend for a lower left ALPS index in AD compared to MCI. Seven studies reported a left ALPS index in comparing MCI and HC cohorts [9, 15, 32, 36, 39, 40]. Pooled estimates showed an MD of -0.12 (95% CI: -0.16 to -0.08) and an SMD of -0.78 (95% CI: -1.64 to 0.08, $p = 0.07$, I^2: 94.0%), showing a nonsignificant trend for a lower left ALPS index in MCI compared to HC.

The Right ALPS index

Ten studies reported a right ALPS index in both AD and HC cohorts (**Figure 3C**) [9, 15, 32, 35-38, 40]. Pooled estimates showed an MD of -0.12 (95% CI: -0.15 to -0.08) and an SMD of -0.61 (95% CI: -0.84 to -0.38, $p < 0.001$, I^2: 51.9%), providing evidence for a lower right ALPS index in AD compared to HC (**Online Supplemental File**). Seven studies reported a right ALPS index in comparing AD and MCI cohorts [9, 14, 15, 32, 36, 40]. Pooled estimates showed an MD of -0.02 (95% CI: -0.05 to 0.00) and an SMD = -0.13 95% CI -0.27 to 0.01, $p = 0.06$, I^2: 00.0%), showing a nonsignificant trend for a lower right ALPS index in AD compared to MCI. Seven studies reported a right ALPS index in both MCI and HC cohorts [9, 15, 32, 39, 40]. Pooled estimates from the meta-analysis showed an MD of -0.10 (95% CI: -0.12 to -0.08) and an SMD of -0.60 (95% CI: -1.35 to 0.16, $p = 0.1$, I^2: 90.6%).

Association between the ALPS index and cognitive status

Eight studies reported correlations between the overall ALPS index and MMSE scores (**Online Supplemental File**) [14, 28, 29, 31, 33-35]. Pooled estimates showed a significant meta correlation between the ALPS index and MMSE scores with an effect size of 0.43 (95% CI: 0.28 to 0.57, $p < 0.001$, I^2: 66.0%). Five studies reported correlations between the overall ALPS index and MoCA scores [14, 28, 29, 31, 33-35]. Pooled estimates showed a non-significant increase in ALPS index with higher MoCA scores (effect size = 0.35, 95% CI: 0.07 to 0.63, $p < 0.001$, I^2: 89.4%).

Given substantial heterogeneity ($I^2 > 50\%$), results were also divided into two groups based on whether they were single or multicenter studies to identify the source of the heterogeneity (**Online Supplemental File**). For example, the I^2 in studies reporting the overall ALPS index comparing AD versus HC (93.4%) and MCI versus HC (95.9%), the left ALPS index comparing MCI versus HC (94.0%) , and the right ALPS index comparing AD versus HC (51.9%) and comparing the MCI versus HC (89.6%) showed substantial heterogeneities. The I^2 decreased significantly when only considering multicenter studies for the overall ALPS index comparing AD and HC (I^2 of 48.2%) and the right ALPS index comparing AD and HC (I^2 of 86.4%), suggesting less heterogeneity in multicenter studies. However, the I^2 decreased less significantly for the other study comparisons.

Association between the ALPS index and amyloid deposition

Four studies have examined the correlation between the overall ALPS index and amyloid deposition using various PET tracers, including [11C] Pittsburgh Compound B (PIB), [18F] Florbetaben (FBB), and [18F] Florbetapir [9, 31, 35]. The pooled analysis revealed a negative correlation between the ALPS index and amyloid deposition, with an effect size of -0.42 (95% CI: -0.66 to -0.19, $p < 0.001$), though substantial heterogeneity was observed ($I^2 = 63.5\%$) (**Online Supplemental File**). Among these studies, three reported a negative correlation between the ALPS index and the presence of amyloid PET positivity, whereas one study found no statistically significant association [31]. Similarly, two studies investigated the relationship between the ALPS index and amyloid PET standardized uptake value ratio (SUVR) [9, 14], employing multiple PET tracers, including PIB and FBP. The pooled effect size was -0.21 (95% CI: -0.51 to 0.10, $p = 0.19$), indicating a modest negative correlation between the ALPS index and SUVR, though heterogeneity was moderate ($I^2 = 57.8\%$). Additional sensitivity analyses are detailed in the (**Online Supplemental File**).

DISCUSSION

Despite decades of AD research based on the amyloid cascade hypothesis, how and why Aβ deposition occurs in the brain in the first

place remains a critical area of research [43]. Glymphatic system dysfunction has been proposed as a pathway by which reduced fluid clearance of toxins and waste products can lead to the buildup of Aβ. Direct measurements of glymphatic/CSF fluid clearance are invasive, requiring lumbar puncture, and cumbersome. However, in recent years, DTI-ALPS has emerged as a noninvasive tool for assessing interstitial fluid dynamics along para-venous spaces, or interstitial fluidopathy, believed to be a component of the glymphatic system [6, 9].

A recent study used a Bayesian framework to perform a meta-analysis of 11 AD studies that used DTI-ALPS [44]. We extended this work by conducting a classical effect size meta-analysis with 19 studies. The main difference between the Bayesian Log10 model meta-analysis and the classical effect size model meta-analysis lies in their statistical frameworks and how they handle uncertainty. Bayesian meta-analysis incorporates prior distributions and updates beliefs based on observed data [45-48]. In contrast, classical meta-analysis typically relies on fixed or random effects models, focusing on point estimates like MD or SMDs without incorporating prior information [47, 49, 50]. The advantage of the classical model is its straightforward interpretation and established methodologies, which can make it easier to communicate to audiences familiar with traditional statistics.

The ALPS index has been proposed as a quantitative measure that reflects the clearance of interstitial fluid (ISF) and metabolic waste, including misfolded proteins [9, 13, 51]. In recent years, several studies using DTI-ALPS have shown changes in the ALPS index as the disease progresses from subjective cognitive decline (SCD) to MCI and AD [6, 28, 29, 31, 33]; for example, studies have shown subtle reductions in ALPS index values in SCD, more pronounced impairment in MCI, and marked reductions in AD patients.

Findings also suggest a lower ALPS index and increased amyloid burden [9, 31, 35]. While pooled estimates indicated a modest negative correlation between the ALPS index and amyloid deposition, substantial heterogeneity across studies suggests methodological differences, including variations in PET tracers and imaging protocols. Studies assessing the correlation between the ALPS index and amyloid PET SUVR have reported a generally negative association, although the strength and direction of this relationship vary across studies [9, 14, 31]. This may be attributed to fundamental differences between amyloid tracers such as PIB and FBP [52, 53], as these amyloid-specific tracers primarily capture pathological accumulation, which is thought to be linked to impaired clearance mechanisms. The observed variability suggests that tracer-specific properties, metabolic versus amyloid-related imaging targets, and methodological differences may influence the association between glymphatic function and amyloid accumulation.

The impaired ISF dynamics reflected by a reduced ALPS index suggest that the brain's waste clearance pathways are disrupted in the white matter free water—exacerbating oxidative stress—and accelerating neurodegenerative processes [13]. This connection highlights the potential of the ALPS in studying the glymphatic system, linking it directly to the pathological burden of Aβ and tau, and underscores its relevance in understanding the progression and underlying mechanisms of AD (**Figure 4).**

A key strength of DTI-ALPS is its association with cognitive measures. Studies have shown that lower ALPS index values are associated with poorer performance on various cognitive tests, including memory, executive function, and processing speed assessments [6, 42]. This relationship is observed across the AD continuum, from SCD to MCI and AD. Importantly, the DTI-ALPS index is believed to reflect microstructural and neurofluid changes distinct from brain atrophy or amyloid burden, offering complementary insight into early neurodegenerative processes and glymphatic dysfunction [54]. On the other hand, Aβ deposition is a hallmark of AD, and its relationship with DTI-ALPS findings has been the subject of considerable investigation—reduced ALPS index values are closely linked to increased Aβ accumulation, as measured by amyloid PET imaging. This relationship further supports the role of the glymphatic system in Aβ clearance [14, 29].

Interestingly, some studies suggest that glymphatic dysfunction, as indicated by reduced ALPS indices, may precede significant Aβ deposition, suggesting that ALPS indices could serve as an early marker for individuals at risk of developing AD [14, 29, 32]; however, Zhou et al. have reported that compared with vCSF, ALPS is more associated with later-stage deposition of amyloid [9]. This discrepancy underscores the need for further investigation to determine whether ALPS indices—may stem from variations in study design, population characteristics, or differences in the sensitivity of imaging techniques, highlighting the complexity of glymphatic dysfunction's role in AD progression. Importantly, amyloid accumulation may itself impair glymphatic clearance by disrupting perivascular astrocytic aquaporin-4 (AQP4) polarization and perivascular architecture—suggesting that reduced glymphatic flow might not only cause but also result from early Aβ pathology [55].

Matsushita et al. suggested an association between DTI-ALPS metrics, brain temperature, and fluid biomarkers such as CSF Aβ and tau [34]. Elevated brain temperature, which can reflect increased metabolic activity, may impact the diffusivity patterns observed in DTI-ALPS, potentially indicating disrupted glymphatic function. Similarly, fluid biomarkers associated with AD, particularly amyloid and tau, show an association with altered DTI-ALPS metrics, suggesting that these molecular markers of neurodegeneration may affect or be affected by glymphatic clearance processes, underscoring the complementary utility of DTI-ALPS in assessing early pathological changes in early stages cognitive decline according to our meta-analysis which support more changes in the memory declining to MCI than progression from MCI to AD [29, 30, 56].

DTI-ALPS has notable limitations; one main challenge is its anatomical focus. While the glymphatic system encompasses gray and white matter regions, including periarterial and para-venous spaces, as well as interstitium and astrocytic endfeet, the ALPS index mainly measures water diffusivity along medullary veins in white matter regions. This raises questions about its ability to capture glymphatic activity and its regional variations fully [57]. The resolution and specificity of DTI-ALPS in distinguishing glymphatic from other interstitial or fluid clearance mechanisms remain debated. Other limitations include sensitivity to motion artifacts and potential confounding by age-related microstructural changes in white matter, complicating interpretation [51]. Furthermore, leukoaraiosis—common in older adults—can independently alter DTI measures [58]. However, because of limited data, this potential confounder could not be systematically adjusted for in our analysis. While DTI-ALPS provides a proxy for glymphatic function, it may not directly reflect

the full complexity of brain fluid dynamics [7]. However, its non-invasive nature and sensitivity to early changes in glymphatic function make it an attractive candidate for inclusion in AD diagnostic protocols. DTI-ALPS can complement other imaging techniques, such as amyloid PET and tau PET, providing a more comprehensive view of brain function as impacted by AD pathology [9]. Another limitation, which may contribute to the heterogeneity of these analyses, is the lack of technical standardization across studies. A prior study that focused on test-retest variability found that the ALPS index can be influenced by the imaging plane, head position, number of motion-probing gradient axes, and echo time, whereas different scanner and ROI placement strategies did not significantly affect reproducibility [59]. In response to this technical variability, there are now publicly shared DTI-ALPS processing pipelines on platforms such as GitHub, which may enhance methodological transparency and reproducibility of future studies. Taken together, it is advisable to consider DTI-ALPS results with caution and to employ a multimodal approach for a more comprehensive assessment of the glymphatic system, as the ALPS index mainly reflects changes in the deep white matter rather than neurofluid dynamics in the gray matter or subpial/perivascular spaces [7, 57]. ALPS has been shown to correlate with markers of amyloid burden, neuroinflammation, and small-vessel disease, reinforcing its role in the broader pathophysiological landscape of neurodegeneration [9]. By synthesizing data across studies, meta-analysis can clarify these relationships, identify potential moderating factors, and contribute to standardizing ALPS measurements for future research.

CONCLUSIONS

In conclusion, DTI-ALPS holds promise as a complementary early biomarker for AD progression due to its ability to study glymphatic system functionality across the AD continuum and its association with cognitive measures and Aβ deposition. However, further research is needed to standardize the technique and assess its utility in longitudinal and interventional studies. As our understanding of the glymphatic system and its dysfunction in AD deepens, DTI-ALPS may become an integral part of the diagnostic landscape for AD.

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SUPPLEMENTAL FILES

APPENDIX I: Search terms and strategies

Search strategy for **PubMed/Medline (NLM)**

Last searched October 13, 2024

((((((((((((((((("Nervous System Diseases"[Mesh]) OR "Central Nervous System Diseases"[Mesh]) OR "Brain Diseases"[Mesh]) OR "Dementia"[Mesh]) OR "Alzheimer Disease"[TIAB]) OR "Lewy Body Disease"[Mesh]) OR "Dementia, Vascular"[Mesh]) OR "Frontotemporal Lobar Degeneration"[Mesh]) OR "Cognitive Dysfunction"[Mesh]) AND "Diagnostic Techniques and Procedures"[Mesh]) OR "Diagnostic Imaging"[Mesh]) OR "Magnetic Resonance Imaging" [TIAB]) OR "Neuroimaging"[Mesh]) OR "Diffusion Magnetic Resonance Imaging" [TIAB]) OR "Diffusion Tensor Imaging" [TIAB]) AND "Cardiovascular System"[Mesh]) OR "Central Nervous System"[Mesh]) OR "Brain"[Mesh]) OR "Glymphatic System"[Mesh]

Document Types: Article

Search strategy for **WEB OF SCIENCE (WoS)**

Last searched October 13, 2024

Ts=((((((((((((((((("Nervous System Diseases") OR "Central Nervous System Diseases") OR "Brain Diseases") OR "Dementia") OR "Alzheimer Disease") OR "Lewy Body Disease") OR "Dementia, Vascular") OR "Frontotemporal Lobar Degeneration") OR "Cognitive Dysfunction") AND "Diagnostic Techniques and Procedures") OR "Diagnostic Imaging") OR "Magnetic Resonance Imaging") OR "Neuroimaging") OR "Diffusion Magnetic Resonance Imaging") OR "Diffusion Tensor Imaging") AND "Cardiovascular System") OR "Central Nervous System") OR "Brain") OR "Glymphatic System"

Document Types: Article

Search strategy for **Scopus**

Last searched October 13, 2024

TITLE-ABS-KEY ((((((((((((((((("Nervous System Diseases") OR "Central Nervous System Diseases") OR "Brain Diseases") OR "Dementia") OR "Alzheimer Disease") OR "Lewy Body Disease") OR "Dementia, Vascular") OR "Frontotemporal Lobar Degeneration") OR "Cognitive Dysfunction") AND "Diagnostic Techniques and Procedures") OR "Diagnostic Imaging") OR "Magnetic Resonance Imaging") OR "Neuroimaging") OR "Diffusion Magnetic Resonance Imaging") OR "Diffusion Tensor Imaging") AND "Cardiovascular System") OR "Central Nervous System") OR "Brain") OR "Glymphatic System"

Document Types: Article

Search strategy for **Embase®**

Last searched October 13, 2024

TITLE-ABS-KEY (("Nervous System Diseases" OR "Central Nervous System Diseases" OR "Brain Diseases" OR "Dementia" OR "Alzheimer Disease" OR "Lewy Body Disease" OR "Dementia, Vascular" OR "Frontotemporal Lobar Degeneration" OR "Cognitive Dysfunction") AND "Diagnostic Techniques and Procedures") OR "Diagnostic Imaging") OR "Magnetic Resonance Imaging") OR "Neuroimaging") OR "Diffusion Magnetic Resonance Imaging") OR "Diffusion Tensor Imaging") AND "Cardiovascular System") OR "Central Nervous System") OR "Brain") OR "Glymphatic System"

Document Types: Article

Search strategy for **EBSCO** (SPORTDiscus, CINAHL)

Last searched October 13, 2024

(("Nervous System Diseases" OR "Central Nervous System Diseases" OR "Brain Diseases" OR "Dementia" OR "Alzheimer Disease" OR "Lewy Body Disease" OR "Dementia, Vascular" OR "Frontotemporal Lobar Degeneration" OR "Cognitive Dysfunction") AND "Diagnostic Techniques and Procedures") OR "Diagnostic Imaging") OR "Magnetic Resonance Imaging") OR "Neuroimaging") OR "Diffusion Magnetic Resonance Imaging") OR "Diffusion Tensor Imaging") AND "Cardiovascular System") OR "Central Nervous System") OR "Brain") OR "Glymphatic System"

Search strategy for **Cochrane**

Last searched October 13, 2024

("Nervous System Diseases" OR "Central Nervous System Diseases" OR "Brain Diseases" OR "Dementia" OR "Alzheimer Disease" OR "Lewy Body Disease" OR "Dementia, Vascular" OR "Frontotemporal Lobar Degeneration" OR "Cognitive Dysfunction") AND "Diagnostic Techniques and Procedures") OR "Diagnostic Imaging") OR "Magnetic Resonance Imaging") OR "Neuroimaging") OR "Diffusion Magnetic Resonance Imaging") OR "Diffusion Tensor Imaging") AND "Cardiovascular System") OR "Central Nervous System") OR "Brain") OR "Glymphatic System"

Additional detailed methods for the search strategy:

We conducted our search across multiple databases, including Scopus, Medline, Web of Science (WoS), Cochrane, Embase, PROSPERO, clinical trial registries (ClinicalTrials.gov), and ICTRP, to identify articles published up to October 2024. Additionally, gray literature, articles without available full text, irrelevant studies, and studies that did not report diagnostic performance indices were excluded. We reviewed citations and article references to ensure thoroughness, using both backward and forward citation tracking to uncover relevant studies. We utilized Medical Subject Headings (MeSH) terms and non-MeSH terms to identify and retrieve relevant studies

Selection process and data collection

We initially screened the titles and abstracts of the retrieved studies to identify suitable ones. We then independently evaluated the full texts to confirm their eligibility based on our predefined criteria. We used the Rayyan tool—https://www.rayyan.ai/*;* a free web-based tool that uses artificial intelligence to streamline the process of systematic reviews and literature screening—for the initial screening [1]. Data extraction was done independently by two authors (MK, KS) using a standardized checklist. Any discrepancies were resolved through discussion. We obtained mean ± standard deviation (SD) ALPS indices from the articles when available. For data extraction from figures without reported data, we used GetData Graph Digitizer (Version 2.26). Before resorting to indirect data extraction, we attempted to contact the authors via email up to three times to request the necessary data. Of note, the eligibility for inclusion and exclusion was defined using the Population, Intervention, Comparison, Outcomes, and Study (PICOS) framework [2].

Effect measures and Certainty of evidence

We used a standardized form to extract data from the included studies. The extracted data covered various aspects, including study characteristics—such as author, location, year, design, and the stage of cognitive impairment—along with population features and group sizes for both cases and controls. We also captured key outcomes, limitations, and results, focusing on specific data points like ALPS index values. For the meta-analysis, we extracted mean ± SD for ALPS index values: overall, right hemispheric, and left hemispheric. This approach ensured a comprehensive analysis of the included studies. Note that the certainty of evidence was assessed for primary outcomes using the Grading of Recommendations Assessment, Development, and Evaluation (**GRADE**) approach [3].

APPENDIX II:

The Newcastle-Ottawa Scale quality risk-of-bias assessment tool for observational studies

Supplementary Table 1. The Newcastle-Ottawa Scale (NOS) quality assessment of the included studies in this meta-analysis (details).

Study	Selection of case and controls				Comparability of cases and controls	Exposure			Total
	Is the case definition adequate	Representativeness of the cases	Selection of Controls	Definition of Controls	Comparability of cases and controls on the basis of the design or analysis	Ascertainment of exposure	Same method of ascertainment for cases and controls	Non-Response Rate	
Sacchi, Luca et al., et al. 2024, Italy [4]	☆	☆	☆	☆	☆☆	☆	☆	-	☆☆☆☆☆☆☆☆ (8)
Li, Y., et al. 2024, China [5]	☆	☆	☆	☆	☆	-	-	-	☆☆☆☆☆ (5)
Sun, Y. W et al. 2024, China [6]	☆	☆	☆	☆	☆		-	-	☆☆☆☆☆ (5)
Zhou, Liangdong et al. 2024, USA [7]	☆	☆	☆	☆	☆☆	☆	☆	-	☆☆☆☆☆☆☆☆ (8)
Kim, Minjae et al. 2024, Republic of Korea [8]	☆	☆	☆	☆	☆☆	-	☆	-	☆☆☆☆☆☆☆☆ (8)
Zhang, Xue et al. 2024, China [9]	☆	☆	☆	☆	☆☆	☆	☆	-	☆☆☆☆☆☆☆☆ (8)
Hong, Hui et al. 2024, China [10]	☆	☆	☆	☆	☆☆	☆	☆	-	☆☆☆☆☆☆☆☆ (8)
Huang, Shu-Yi et al. 2024, China [11]	☆	☆	☆	☆	☆	-	-	-	☆☆☆☆☆ (5)
Matsushita, Shu et al. 2024, Japan [12]	☆	☆	☆	☆	☆☆	☆	☆	-	☆☆☆☆☆☆☆☆ (8)
Zhong, Jiayi et al. 2023, China [13]	☆	-	☆	☆	☆	-	☆	-	☆☆☆☆☆ (5)
Zhong, Jiayi et al. 2023, China (Conference Abstract) [14]	☆	-	☆	☆	☆	-	☆	-	☆☆☆☆☆ (5)
Saito, Yuya et al. 2023, Japan [15]	☆	-	☆	☆	☆	-	☆	-	☆☆☆☆☆ (5)
Saito, Yuya et al. 2023, Japan [16]	☆	☆	☆	☆	-	-	☆	-	☆☆☆☆☆ (5)
Liang, Tian et al. 2023, China [17]	-	☆	☆	☆	☆	-	☆	-	☆☆☆☆☆ (5)
Hsu, Jung-Lung et al. 2023, Taiwan [18]	☆	☆	☆	☆	☆☆	☆	☆	-	☆☆☆☆☆☆☆☆ (8)
Kamagata, Koji et al. 2022, Japan [2]	☆	☆	☆	☆	-	-	☆	-	☆☆☆☆☆ (5)
Ota, Miho et al. 2022, Japan [19]	☆	☆	☆	☆	☆☆	☆	☆	-	☆☆☆☆☆☆☆☆ (8)
Steward, Christopher E et al. 2021, Australia [20]	-	☆	☆	☆	☆	-	☆	-	☆☆☆☆☆ (5)
Taoka, Toshiaki et al. 2017, Japan [21]	☆	-	-	☆	☆☆	-	☆	-	☆☆☆☆☆ (5)

Supplementary Table 2: The summary of findings based on the GRADE assessment for mean difference and standardized mean difference with 95% confidence intervals (CI) with other important factors. The ALPS index studies for the AD versus MCI and MCI versus HC comparisons received a high grade; while the studies that compared the AD-HC group received a moderate grade. The studies that compared the left ALPS index in the AD and HC cohorts were highly graded, but received moderate and low grades for the AD versus MCI and MCI versus HC comparison studies. The studies of the right ALPS index comparing the AD and HC and AD and MCI cohorts received a moderate grade, but a low grade for the MCI versus HC comparison studies.

Groups		Summary estimate						Heterogeneity		Grade									GRADE score
		Number of Studies	Number of participants in the studies	Mean ALPS index ± standard deviation	Mean difference (95% CI)	Standardized Mean Difference (95% CI)	P-value of SMD	I^2 statistic	P-value of Q test	Downgrades					Upgrades				
										Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Effect size	Dose response	Adjusted for confounders		
Overall	AD vs HC	12	537/891	AD (1.23±0.17), HC (1.39±0.16)	-0.16 (-0.2, -0.12)	-1.07 (-1.57, -0.56)	*<0.001*	93.44	*<0.001*	☐	■	☐	☐	■	■	☐	☐	⊕⊕⊕◯ Moderate
	AD vs MCI	8	385/547	AD (1.18±0.16), MCI (1.24±0.15)	-0.04 (-0.06, -0.02)	-0.25 (-0.4, -0.1)	*0.01*	2.39	0.58	☐	☐	☐	☐	☐	☐	☐	☐	⊕⊕⊕⊕ High
	MCI vs HC	9	570/816	MCI (1.24±0.15), HC (1.34±0.16)	-0.11 (-0.16, -0.06)	-0.81 (-1.57, -0.06)	*0.04*	95.91	*<0.001*	☐	■	☐	☐	☐	■	☐	☐	⊕⊕⊕⊕ High
Left	AD vs HC	10	363/623	AD (1.28±0.15), HC (1.41±0.2)	-0.14 (-0.17, -0.1)	-0.71 (-0.93, -0.5)	*<0.001*	45.95	0.06	☐	☐	☐	☐	☐	■	☐	☐	⊕⊕⊕⊕ High
	AD vs MCI	6	297/376	AD (1.23±0.17), MCI (1.30±0.17)	-0.03 (-0.05, 0.00)	-0.15 (-0.33, 0.03)	0.09	0.00	0.56	☐	☐	☐	■	☐	☐	☐	☐	⊕⊕⊕◯ Moderate
	MCI vs HC	7	399/523	MCI (1.3±0.15), HC (1.4±0.17)	-0.12 (-0.16, -0.08)	-0.78 (-1.64, 0.08)	0.07	94.04	*<0.001*	☐	■	☐	■	☐	■	☐	☐	⊕ ⊕◯◯ Low
Right	AD vs HC	10	363/623	AD (1.3±0.17), HC (1.4±0.2)	-0.12 (-0.15, -0.08)	-0.61 (-0.84, -0.38)	*<0.001*	51.91	0.05	☐	■	☐	☐	■	■	☐	☐	⊕⊕⊕◯ Moderate
	AD vs MCI	6	297/376	AD (1.3±0.16), MCI (1.3±0.19)	-0.02 (-0.05, 0.00)	-0.13 (-0.27, 0.01)	0.06	0.00	0.77	☐	☐	☐	■	☐	☐	☐	☐	⊕⊕⊕◯ Moderate
	MCI vs HC	7	399/523	MCI (1.3±0.18), HC (1.35±0.18)	-0.1 (-0.12, -0.08)	-0.6 (-1.35, 0.16)	0.1	90.63	*<0.001*	☐	■	☐	■	☐	■	☐	☐	⊕ ⊕◯◯ Low

Supplementary Table 3. Summary of the studies included in the systematic review.

ID	Study Design	Type of center	Reference test for AD confirmation	Population	Imaging protocol	Outcomes	Limitations
Sacchi, Luca et al. 2024, Italy [4]	Prospective cross sectional	Single	Clinical	87 participants (AD: 47, MCI: 17, CU: 23)	3.0 T MR Philips Achieva dStream (TE = 85 ms, TR = 8400, matrix = 96 × 96, slice thickness = 2.5 mm, number of slices = 60, FoV = 240 × 240 mm^2)	A lower DTI-ALPS index may represent a significant marker of disease progression in Alzheimer's Disease (AD).	• Small sample size and single-center study.
Li, Y., et al. 2024, China [5]	Cross sectional	Multi	Clinical, PET	654 SILCODE participants (215 normal controls [NC], 194 SCD, 153 MCI, and 92 AD) and 650 ADNI participants (197 NC, 191 SCD, 158 MCI, and 104 AD)	3.0 T MR system, GE, SIEMENS, and Philips machines	A reduced ALPS index was associated with a higher likelihood of progression to cognitive impairment.	• Small sample size.
Sun, Y. W et al. 2024, China [6]	Cross sectional	Single	Clinical, CSF, and PET	41 subjects (23 MCI patients and 18 HC)	3.0 T Philips Healthcare (Ingenia Elition scanner), 32-channel head coil TR/TE = 3950/96 ms, FOV = 224 mm × 224 mm, matrix size = 112 × 110, flip angle = 90°, slice thickness = 2 mm	Lower ALPS index values were significantly associated with disrupted brain structure-function coupling in patients with MCI due to AD.	• Small sample size and single-center study.
Zhou, Liangdong et al. 2024, USA [7]	Cross sectional	Single	Clinical, amyloid PET	50 subjects, 24/50 were Aß positive.	3.0 T Siemens, 98 directions, TR/TE=3230/89.20ms, Flip angle=78°, FOV=21×21cm, matrixsize=140×140, voxel size=1.5×1.5×1.5mm,92axialslices,3b-val-ues=0,1500, and3000s/mm^2, multiband factor=6	DTI-ALPS has a higher correlation with severe Aß deposition, supporting a lower DTI-ALPS index in AD	• Small sample size and single-center study.
Kim, Minjae et al. 2024, Republic of Korea [8]	Cross sectional	Single	Clinical, amyloid PET	80 participants (AD (n = 65) and CN (n = 15))	3.0 T Philips, TR: 9900 ms; TE: 77 ms; slice thickness, 2 mm; flip angle, 90◦, FOV: 224×224mm^2; acquisition matrix, 112×112.	The ALPS index in the AD group was significantly lower.	• Small sample size and single-center study.
Zhang, Xue et al. 2024, China [9]	Cross sectional	Single	Clinical, amyloid PET	30 (AD-MCI (n = 15) and AD-D (n = 15)) AD patients (16 men and 14 women) and 26 NCs (11 men and 15 women)	3.0 T Siemens	A lower ALPS index was observed in patients with AD.	• Small sample size and single-center study.
Hong, Hui et al. 2024, China [10]	Cross sectional	Multi/ Dataset (ADNI)	Clinical, amyloid PET	133 participants (40 CN Aß− , 48 CN Aß + , 26 MCI Aß+ , and 19 AD Aß + participants)	3.0 T Siemens, DTI images: TR = 7200 ms, TE = 56 ms, voxel size = 2.0 × 2.0 × 2.0 mm^3, Acquisition matrix = 116 × 116 mm^2.	Inverse association between ALPS index and amyloid load and white matter hyperintensity (WMH) burden.	• Participants from 17 different centers.
Huang, Shu-Yi et al. 2024, China [11]	Cross sectional	Multi/ Dataset (ADNI, theUKBiobank (UKB))	Clinical, CSF, and amyloid PET	419 participants (235 CN, 137 MCI, and 47 AD participants)	3.0 T Siemens, DTI images: TR = 7200 ms, TE = 56 ms, voxel size = 2.0 × 2.0 × 2.0 mm^3, Acquisition matrix = 116 × 116 mm^2.	Decreased ALPS index correlated with lower CSF Aß42 and may precede amyloid pathology.	• NA
Matsushita, Shu et al. 2024, Japan [12]	Cross sectional	Multi/ Dataset (OASIS-3)	Clinical, amyloid PET	58 participants (29 CN, and 29 AD participants)	3.0 T Siemens, b value of 1000 sec/mm^2, along with a single b value = 0 sec/mm^2 image, with TR/TE = 11,000/87 msec, flip angle = 90, matrix size = 96 × 96, and slice thickness = 2.5 mm without an interslice gap.	MRI-based glymphatic measures associated with aging.	• Small sample size and single-center study.
Zhong, Jiayi et al. 2023, China [13]	Cross sectional	Single	Clinical	300 (subjects, including 111 NC participants, 120 MCI and 69 AD patients)	3.0 T Siemens, TR = 2,400 ms, TE = 71 ms, Slice Thickness = 2 mm, 112 × 112 matrix, 90°filp angle, voxel size = 2 × 2 × 2 mm^3	ALPS index progressively decreased with cognitive decline.	• Small sample size and single-center study.
Zhong, Jiayi et al. 2023, China (Conference Abstract) [14]	Cross sectional	Single	Clinical	159 (65 NC participants, 58 MCI patients, and 36 AD patients)	3.0 T Siemens, b = 1000, b = 2000s/mm^2 (echo planar imaging, TR=2400 ms, TE=71 ms, Fov=224 mm, 76 slices, Slice Thickness=2 mm, 112×112 matrix, 90°filp angle, voxel size = 2×2×2 mm^3).	Significant ALPS index differences between cognitive groups.	• Small sample size and single-center study.
Saito, Yuya et al. 2023, Japan [15]	Cross sectional	Multi/ Dataset (ADNI)	Clinical, amyloid PET	23 participants (2 AD, 15 MCI, and 6 CNs)	3.0 T Siemens, DTI images: TR = 7200 ms, TE = 56 ms, voxel size = 2.0 × 2.0 × 2.0 mm^3, Acquisition matrix = 116 × 116 mm^2.	Vector-based ALPS showed higher reproducibility than standard ALPS.	• Small sample size. • The current study did not stratify the patients and healthy controls.
Saito, Yuya et al. 2023, Japan [16]	Cross sectional	Multi/ Dataset (ADNI)	Clinical, amyloid PET	45 patients with AD and 82 CN participants	3.0 T (Prisma Fit Siemens, Signa HDxt, and MR750 GE)	ALPS index is associated with cognition and amyloid burden.	• Small sample size. • Differences in scanner models on the ALPS index.

Liang, Tian et al. 2023, China [17]	Cross sectional	Single	Clinical	105 participants (38 AD, 18 MCI, and 28 CNs)	3.0 T GE, TR/ TE = 15800/77 ms; FOV = 25.6 cm; Matrix = 128×128; The voxel size = 2×2×2.5 mm^3; NEX = 3, and 55 pieces have no gap; B value = 1000 s/mm^2.	DTI-ALPS index was significantly lower in individuals with MCI and AD compared to cognitively unimpaired.	• Small sample size.
Hsu, Jung-Lung et al. 2023, Taiwan [18]	Cross sectional	Single	Clinical, amyloid PET	50 participants (13 NCs and 37 patients with AD)	b = 1,000s/mm^2 with an echo planar imaging sequence with TR = 8,800 ms, TE = 91 ms, matrix = 116, FOV = 256 mm^2, 70 slices, slice thickness = 2.2mm	ALPS index was inversely correlated with amyloid and tau deposition. ALPS index demonstrated positive associations with global cognitive performance.	• Small sample size and single-center study.
Kamagata, Koji et al. 2022, Japan [2]	Cross sectional	Multicenter / Dataset (ADNI)	Clinical, CSF, and amyloid PET	111 patients (36 patients with AD, 44 patients with MCI, and 31 HC)	NA	Reduced ALPS index in AD may indicate impaired glymphatic clearance.	• NA
Ota, Miho et al. 2022, Japan [19]	Prospective cross sectional	Single	Clinical, amyloid PET	57 patients (21 patients with AD and 36 healthy subjects)	3.0-T Siemens, TR/ TE = 17,700/93 ms, FOV 224 × 224 mm, matrix 114 × 114, slice thickness 2mm with no interslice gap.	ALPS index showed potential as a biomarker for amyloid/tau pathology and neuroinflammation.	• Small sample size and single-center study. • Did not include the patients with MCI in this study.
Steward, Christopher E et al. 2021, Australia [20]	Cross sectional	Multicenter /Datasets (VEL015, AIBL Active)	Clinical	20 older volunteers with subjective memory complaints or MCI, 16 AD patients from the VEL015 trial,	3.0-T Siemens, TR/ TE = 8,700/92 ms, FOV 240 × 240 mm, matrix 96 × 96, b = 1,000 s/mm2, voxel size 2.5 mm^3, 30 directions	ALPS index demonstrated positive associations with global cognitive performance.	• Small sample size. • Retrospective nature of the study. • Beta-amyloid status was not available.
Taoka, Toshiaki et al. 2017, Japan [21]	Cross sectional	Single	Clinical	31 patients (14 males and 17 females; age range 51–89 years old; mean 75 years; median 76 years)/ 16 with AD, 9 MCI, and 6 with SCI [MMSE range 12–30]	3.0-T Siemens, DTI sets with b = 0, b = 1000, and b = 2000 s/mm^2 (Echo planer, TR = 6600 ms, TE = 89 ms, MPG = 30 directions, FOV = 230 mm, matrix = 94 × 94, slice thickness = 3 mm)	significant negative correlation between diffusivity along the projection fibres and association fibres" in DTI-ALPS studies supports the method's ability to detect glymphatic system dysfunction by revealing altered water movement patterns in brain tissue. ALPS index demonstrated positive associations with global cognitive performance.	• Small sample size and single-center study.

Alzheimer’s disease (AD), mild cognitive impairment (MCI), subjective cognitive impairment (SCI), and mini-mental state examination (MMSE). Alzheimer’s Disease Assessment Scale–Cognitive Subscale (ADAS-Cog11), signal to noise ratio (SNR), NC, normal control; AD-MCI, mild cognitive impairment due to Alzheimer’s disease; AD-D, Alzheimer’s disease dementia; SD, standard deviation; CDR, Clinical Dementia Rating; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; AQ, The Alzheimer’s Questionnaire; NPI, Neuropsychiatric Inventory; BNT, Boston Naming Test; DST, Digit Span Test; SDMT, Symbol Digit Modalities Test; RAVLT, Rey Auditory Verbal Learning Test; TMT A, Trail Making Test A; TMT B, Trail Making Test B; CDT, Clock Drawing Test; PET, positron emission tomography; CSF, cerebrospinal fluid.

APPENDIX III: Meta-analysis results

Assessing publication bias related to small studies

The possibility of publication bias was assessed by the Egger test and plot, the counter and Doi funnel plots for variables that had at least 10 studies, and trim-and-fill plots. The initial analysis showed no publication bias for outcomes, except in the studies that reported MMSE and MoCA scores. The trim-and-fill analysis indicated no significant evidence of missing studies. However, slight asymmetries observed in some trim-and-fill plots (e.g., ALPS-index comparisons for AD-HC and AD-MCI) suggest the possibility of minor bias, though it is unlikely to impact the overall conclusions (see Supplementary Table below). However, publication bias may still be possible. The Doi plot showed that there was minor asymmetry (LFK = -1.47) for the overall ALPS index in the AD versus HC comparison studies, which was demonstrated in the counter funnel plot. The Doi plot only showed subtle asymmetry (LFK = -0.97) for the left ALPS index in the AD versus HC comparison studies, which was demonstrated in the counter funnel plot. The Doi plot showed that there was minor asymmetry (LFK = -1.07) for the right ALPS index in the AD versus HC comparison studies, which was demonstrated in the counter funnel plot (see Supplementary Figure below).

Supplementary Table 4. Summary presented, following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines.

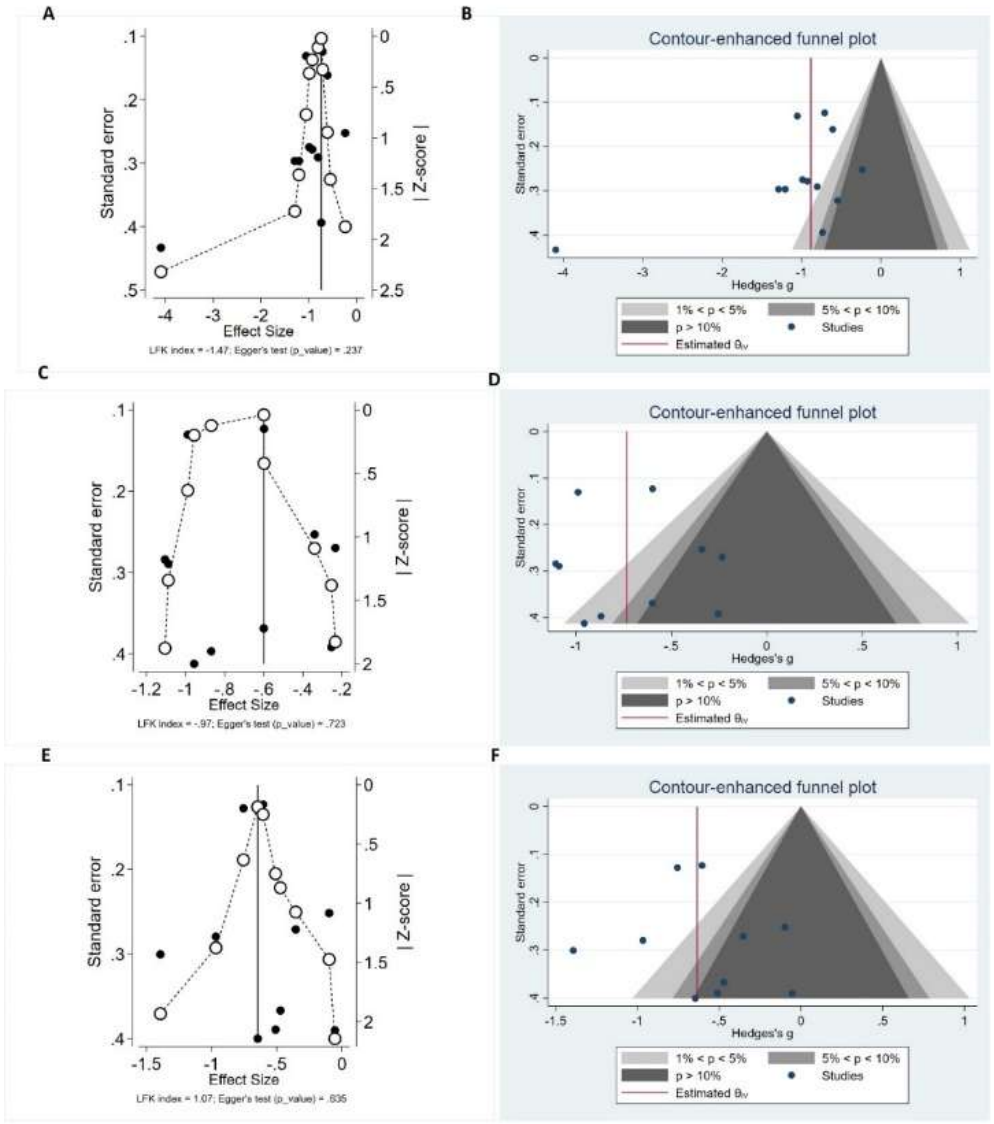
Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	1
INTRODUCTION			
Rationale	3	Rationale	2
Objectives	4	Objectives	2
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	2
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	2
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Supplemental files
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Supplemental files
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Supplemental files
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Supplemental files
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Supplemental files-table
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Supplemental files
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Supplemental files
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Supplemental files
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Supplemental files
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Supplemental files
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Supplemental files
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Supplemental files
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Supplemental files
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Supplemental files

Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Supplemental files
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Supplemental files
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	7, Supplemental files-table
Study characteristics	17	Cite each included study and present its characteristics.	7
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	7, Supplemental files-figures
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	7, Supplemental files-table
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	7
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	7
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	7
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	7
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Table 1
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Supplemental files Table 1
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	8, 9
	23b	Discuss any limitations of the evidence included in the review.	8, 9
	23c	Discuss any limitations of the review processes used.	8, 9
	23d	Discuss implications of the results for practice, policy, and future research.	8, 9
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	2
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	2
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	NA
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	9
Competing interests	26	Declare any competing interests of review authors.	1
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Supplemental files

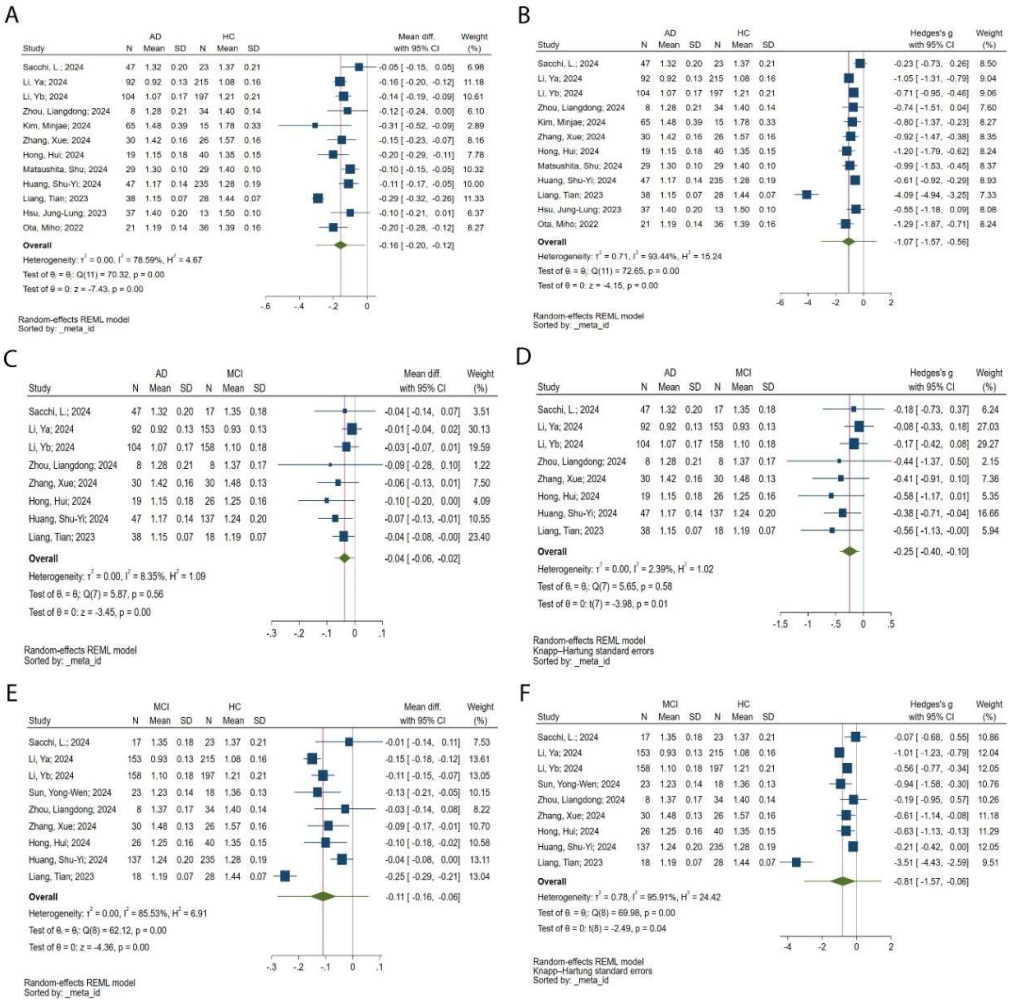
Supplementary Table 5. This table presents the results of Egger's tests conducted to assess the possibility of small study effects (publication bias) in various comparisons among the Alzheimer's disease (AD), mild cognitive impairment (MCI), and healthy control (HC) groups. Egger's test examines the asymmetry of funnel plots, which may indicate bias due to small study effects.

Groups		z	P-value
Overall	AD – HC	-1.96	0.05
	AD - MCI	-1.7	0.09
	MCI - HC	-1.53	0.12
Left	AD – HC	0.24	0.81
	AD - MCI	-0.79	0.43
	MCI - HC	-0.6	0.55
Right	AD – HC	0.45	0.65
	AD - MCI	-1.1	0.27
	MCI - HC	0.29	0.77
MMSE		3.86	< *0.001*
MOCA		4.2	< *0.001*

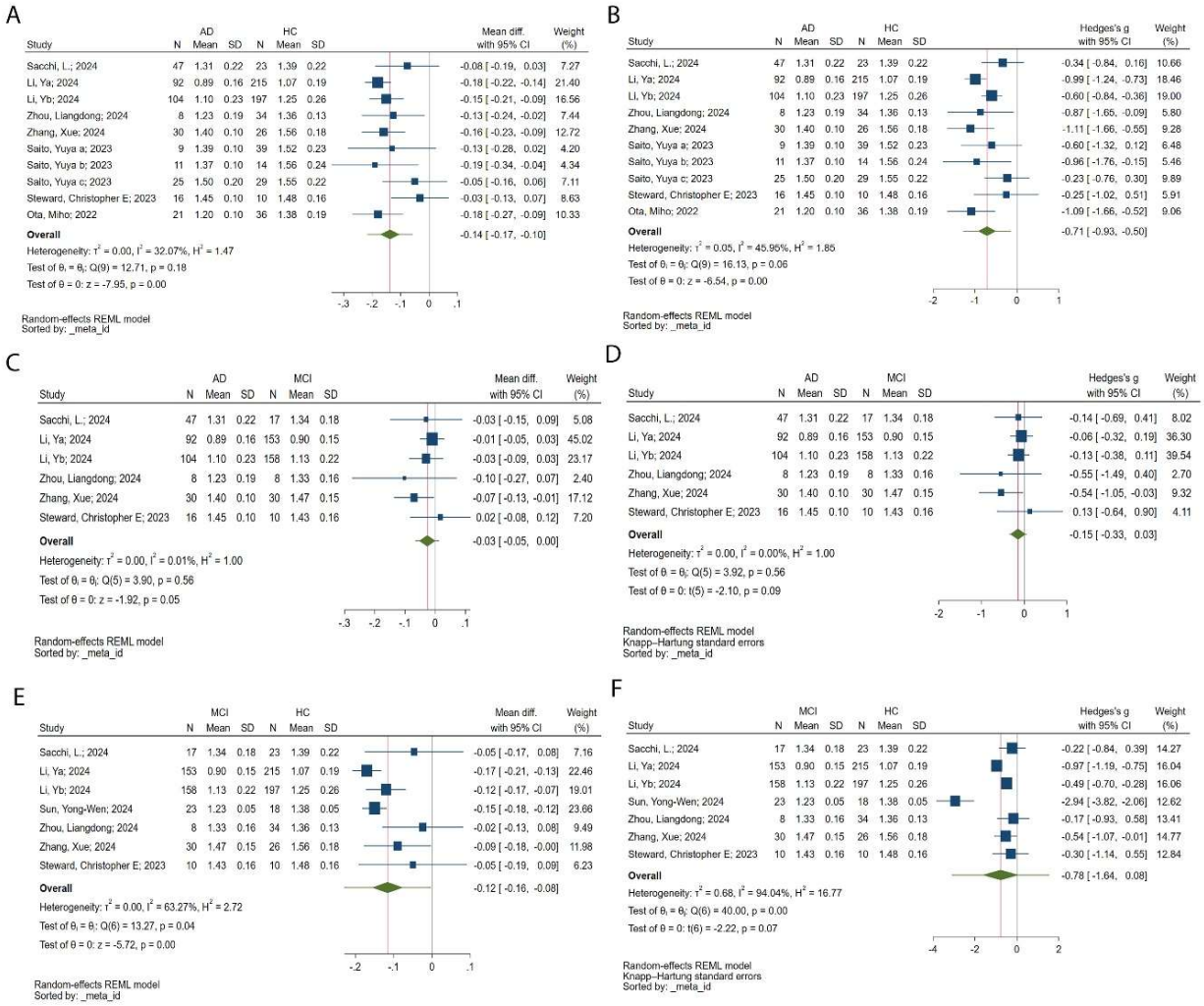
Supplementary Figure 1. Funnel plots assessing the possibility of publication bias in the studies included in the meta-analysis. Publication bias was evaluated using the Egger test, Doi plot, and counter funnel plots. The initial analysis suggested minimal publication bias for most variables, except for studies reporting Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA) scores. The trim-and-fill analysis did not indicate any missing studies. However, the Doi plots revealed minor asymmetry, suggesting potential publication bias. For the overall Analysis Along the Perivascular Space (ALPS) index in the comparison between Alzheimer's disease (AD) and healthy controls (HC), a slight asymmetry was observed. Similarly, minor asymmetry was also seen in the left and right ALPS indices in the comparison between AD and HC, as demonstrated by the Doi plots and corresponding counter funnel plots. A) shows the Doi plot of the overall ALPS index, B) shows the enhanced counter funnel plot of the overall ALPS index, C) shows the Doi plot of the left ALPS index, D) shows the enhanced counter funnel plot of the left ALPS index, E) shows the Doi plot of the right ALPS index, and F) shows the enhanced counter funnel plot of the right ALPS index.



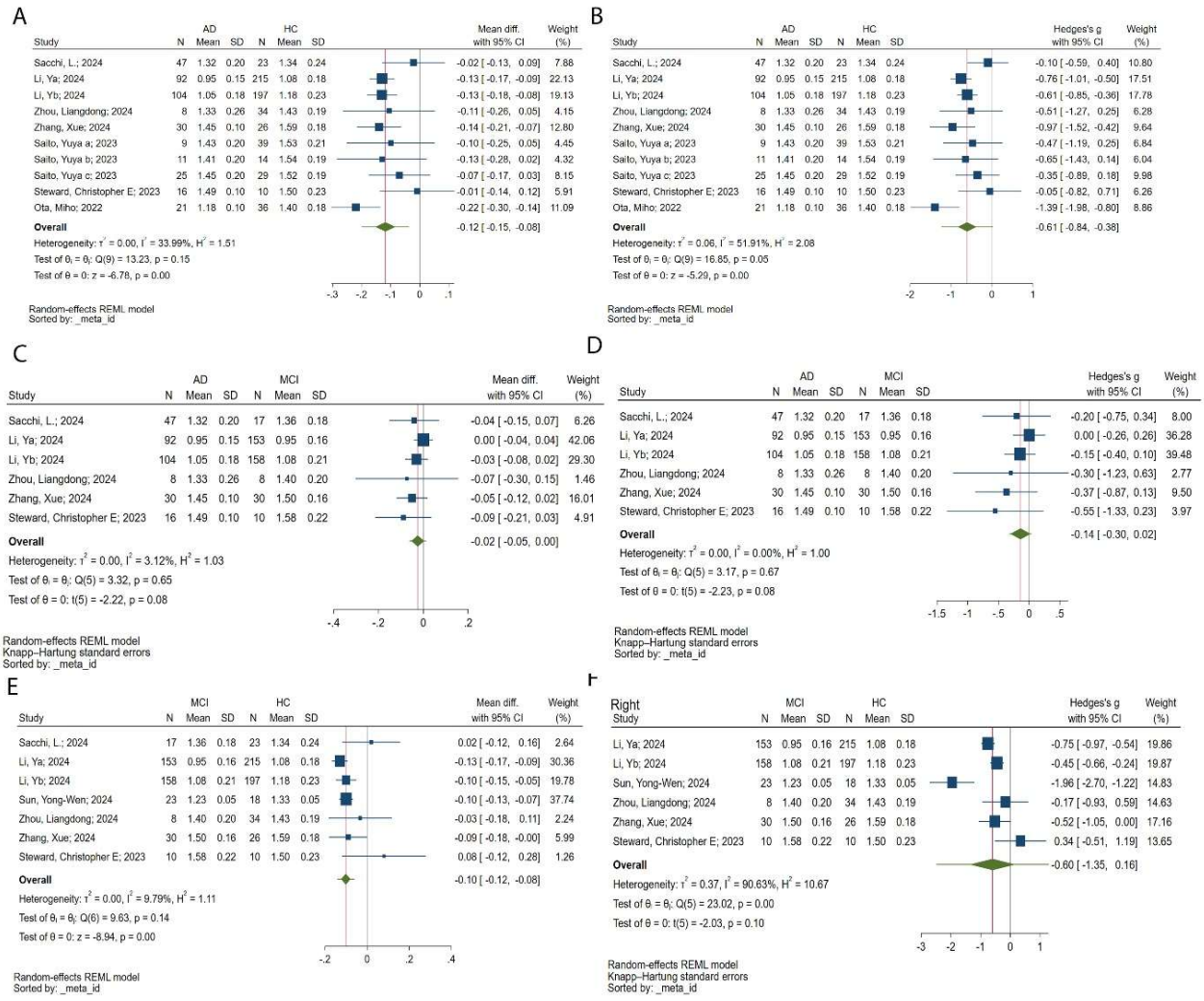
Supplementary Figure 2. Forest plots illustrating the meta-analysis results for the Analysis Along the Perivascular Space (ALPS) index across Alzheimer's disease (AD), mild cognitive impairment (MCI), and healthy control (HC) cohorts. Comparisons between AD and HC show a significantly lower ALPS index in AD, with the mean difference (MD) and standardized mean difference (SMD) indicating substantial reductions. Similarly, AD versus MCI comparisons reveal a modest but significant decrease in the ALPS index in AD. Furthermore, the MCI group shows a clear reduction in the ALPS index compared to HC. These findings collectively underscore the ALPS index's potential as a biomarker for altered cerebral interstitial fluid dynamics associated with the progression from HC to MCI and AD. The plots detail the MD and SMD across these groups: A) MD between AD and HC, B) SMD between AD and HC, C) MD between AD and MCI, D) SMD between AD and MCI, E) MD between MCI and HC, and F) SMD between MCI and HC.



Supplementary Figure 3. Forest plots illustrating the meta-analysis results comparing the left Analysis Along the Perivascular Space (ALPS) index across Alzheimer's disease (AD), mild cognitive impairment (MCI), and healthy control (HC) groups. When comparing AD and HC cohorts, the analysis revealed a significant difference, with AD participants showing a lower left ALPS index. In contrast, the comparison between AD and MCI groups indicated a slight, nonsignificant trend toward a reduced left ALPS index in AD. Similarly, the MCI versus HC analysis show a nonsignificant trend toward a lower left ALPS index in MCI participants compared to HC. The plots detail the mean difference (MD) and standardized mean difference (SMD) across these groups for the left ALPS index: A) MD between AD and HC, B) SMD between AD and HC, C) MD between AD and MCI, D) SMD between AD and MCI, E) MD between MCI and HC, and F) SMD between MCI and HC.

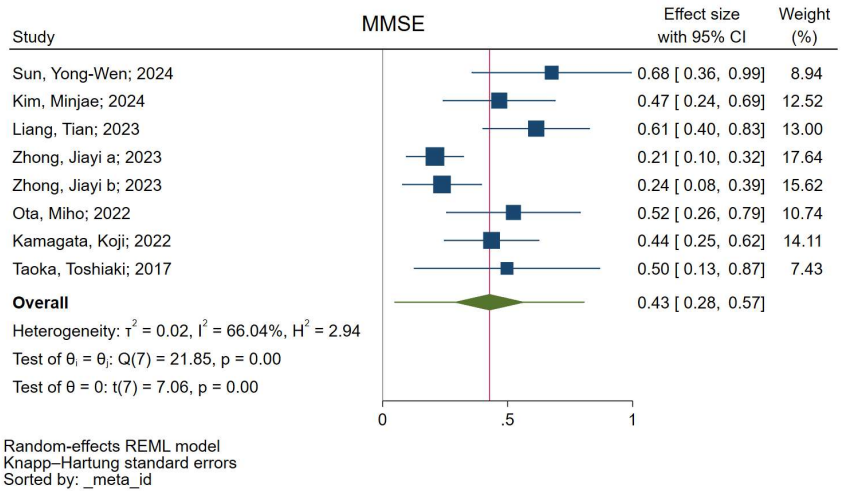


Supplementary Figure 4. Forest plots illustrating the meta-analysis results of the right Analysis Along the Perivascular Space (ALPS) index in Alzheimer's disease (AD), mild cognitive impairment (MCI), and healthy control (HC) groups. The comparison between Alzheimer's disease (AD) and healthy controls (HC) shows a significant difference in the right ALPS index. The comparison between AD and mild cognitive impairment reveals a nonsignificant trend for a lower right ALPS index in AD. Similarly, the comparison between mild cognitive impairment and HC shows a nonsignificant trend for a lower right ALPS index in mild cognitive impairment. The plots detail the mean difference (MD) and standardized mean difference (SMD) across these groups for the right ALPS index: A) MD between AD and HC, B) SMD between AD and HC, C) MD between AD and MCI, D) SMD between AD and MCI, E) MD between MCI and HC, and F) SMD between MCI and HC.

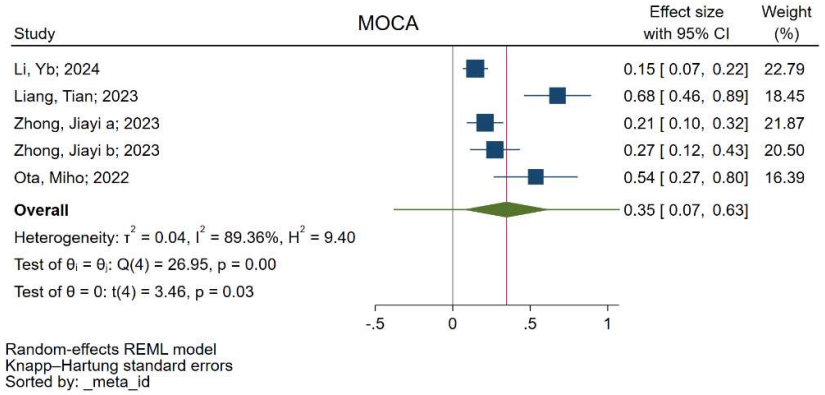


Supplementary Figure 5. Forest plots illustrating the meta-analysis of correlations between the overall Analysis Along the Perivascular Space (ALPS) index and cognitive assessments across Alzheimer's continuum. A) The comparison between the ALPS index and the Mini-Mental State Examination (MMSE) scores shows a significant positive correlation. B) The comparison between the ALPS index and the Montreal Cognitive Assessment (MoCA) scores.

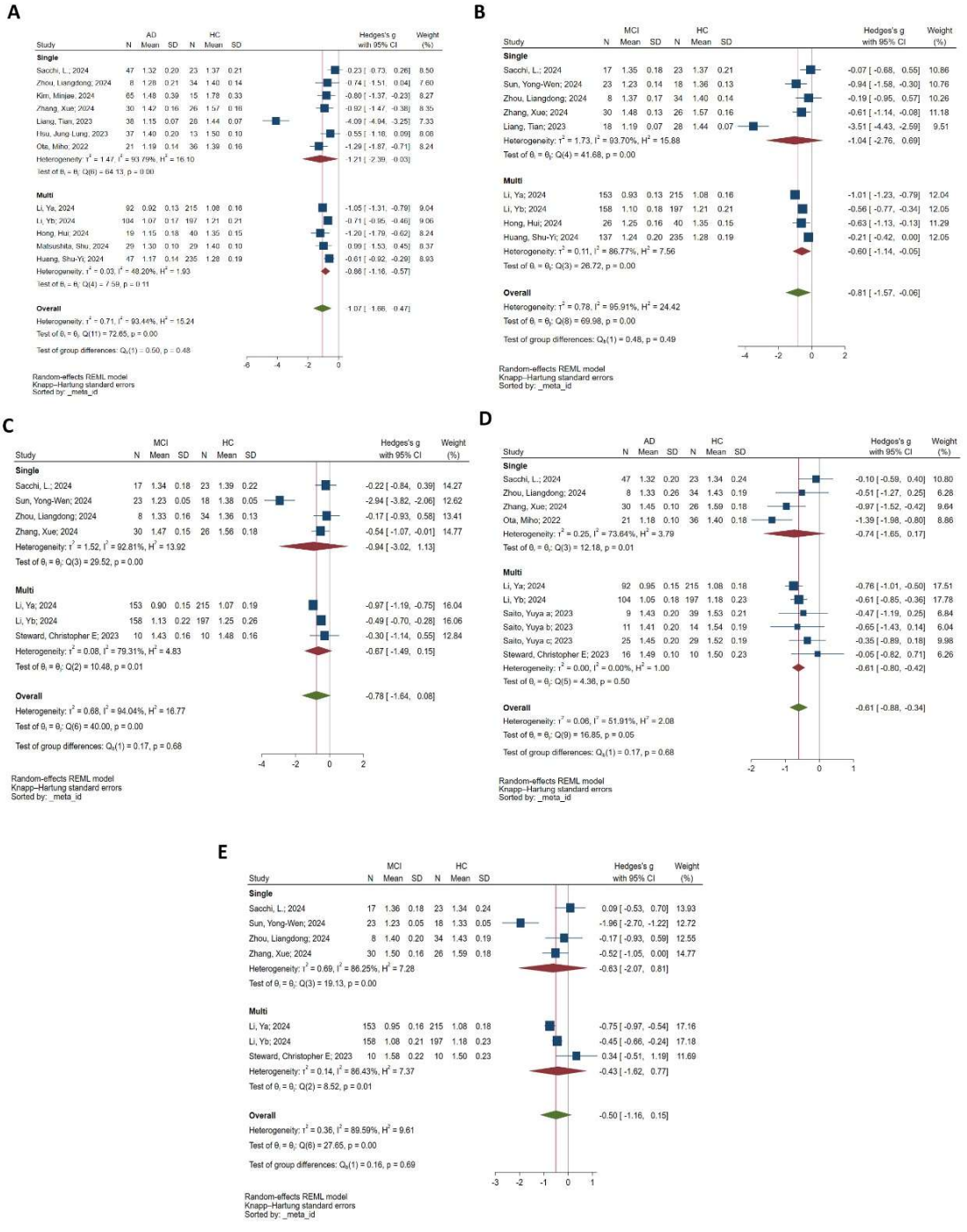
A



B

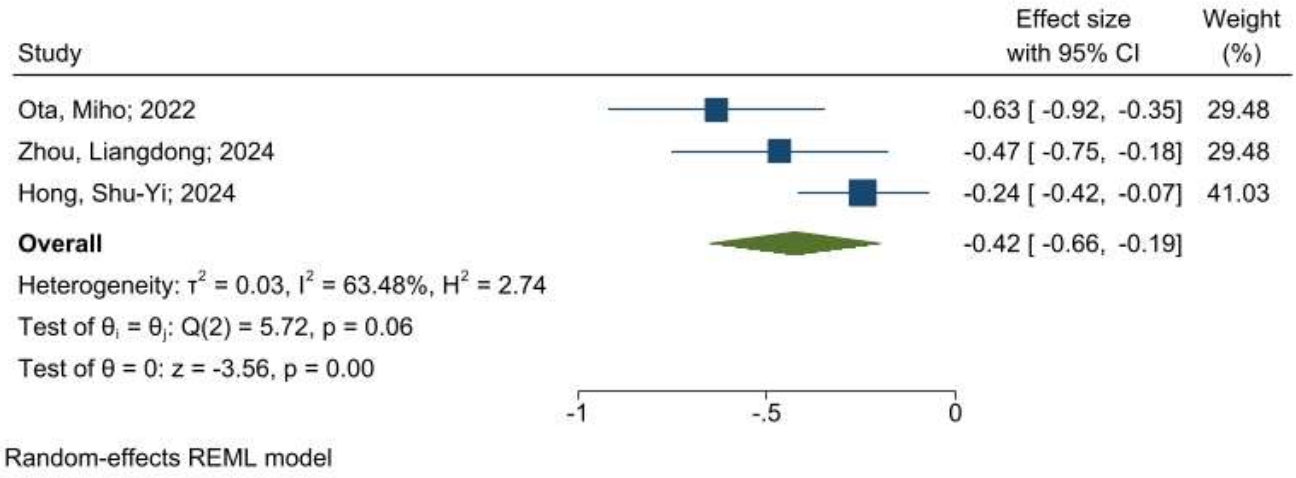


Supplementary Figure 6. Forest plots illustrating the impact of study design—single-center versus multicenter—on heterogeneity in the analysis of the Analysis Along the Perivascular Space (ALPS) index. Substantial heterogeneity was observed in several comparisons, including those between Alzheimer's disease (AD) and healthy controls (HC), mild cognitive impairment (MCI) and HC, and between the left and right ALPS indices. When the studies were divided into single-center and multicenter groups, a significant reduction in heterogeneity was noted in the multicenter studies for both the overall ALPS index comparing AD and healthy controls and the right ALPS index comparing AD and HC. A) shows the overall ALPS index between AD and HC, B) shows the overall ALPS index between MCI and HC, C) shows the left ALPS index between MCI and HC, D) shows the right ALPS index between AD and HC, E) shows the overall ALPS index between MCI and HC.

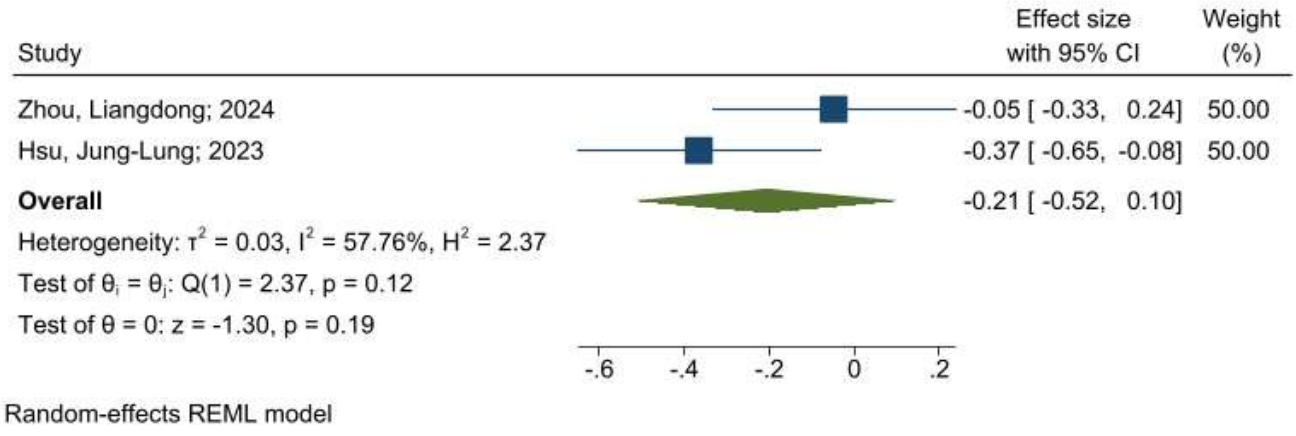


Supplementary Figure 7. Forest plots illustrating the summary of studies examining the association between Analysis Along the Perivascular Space (ALPS) Index and amyloid deposition. A) Pooled results from a subset of studies showed a significant negative correlation between the ALPS index and amyloid deposition, although heterogeneity across studies was substantial. Most studies reported a negative association between the ALPS index and amyloid PET positivity. B) Another subset of studies also assessed the relationship between the ALPS index and standardized uptake value ratio (SUVR), with findings suggesting a modest, non-significant negative correlation and moderate heterogeneity.

A)

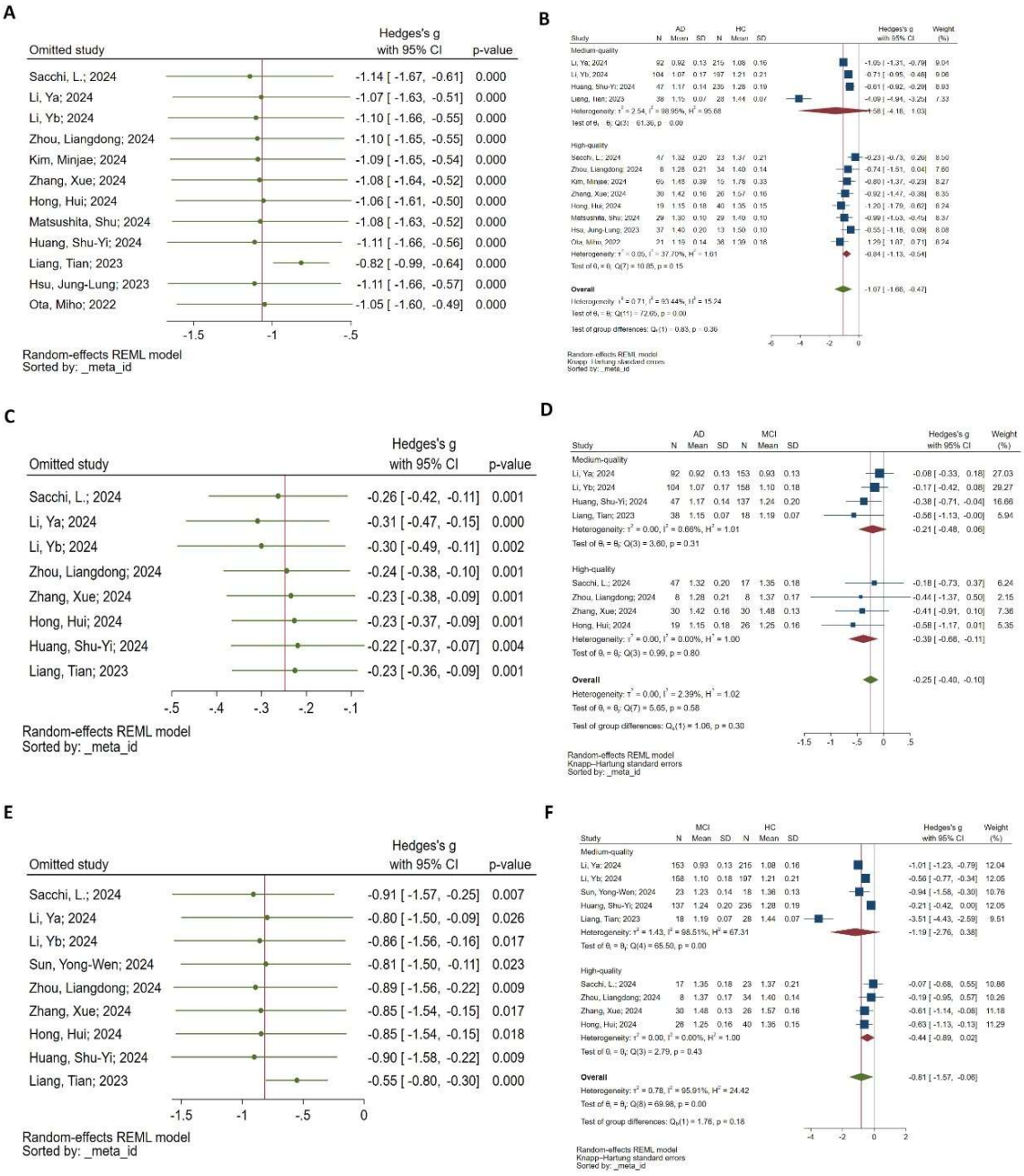


B)

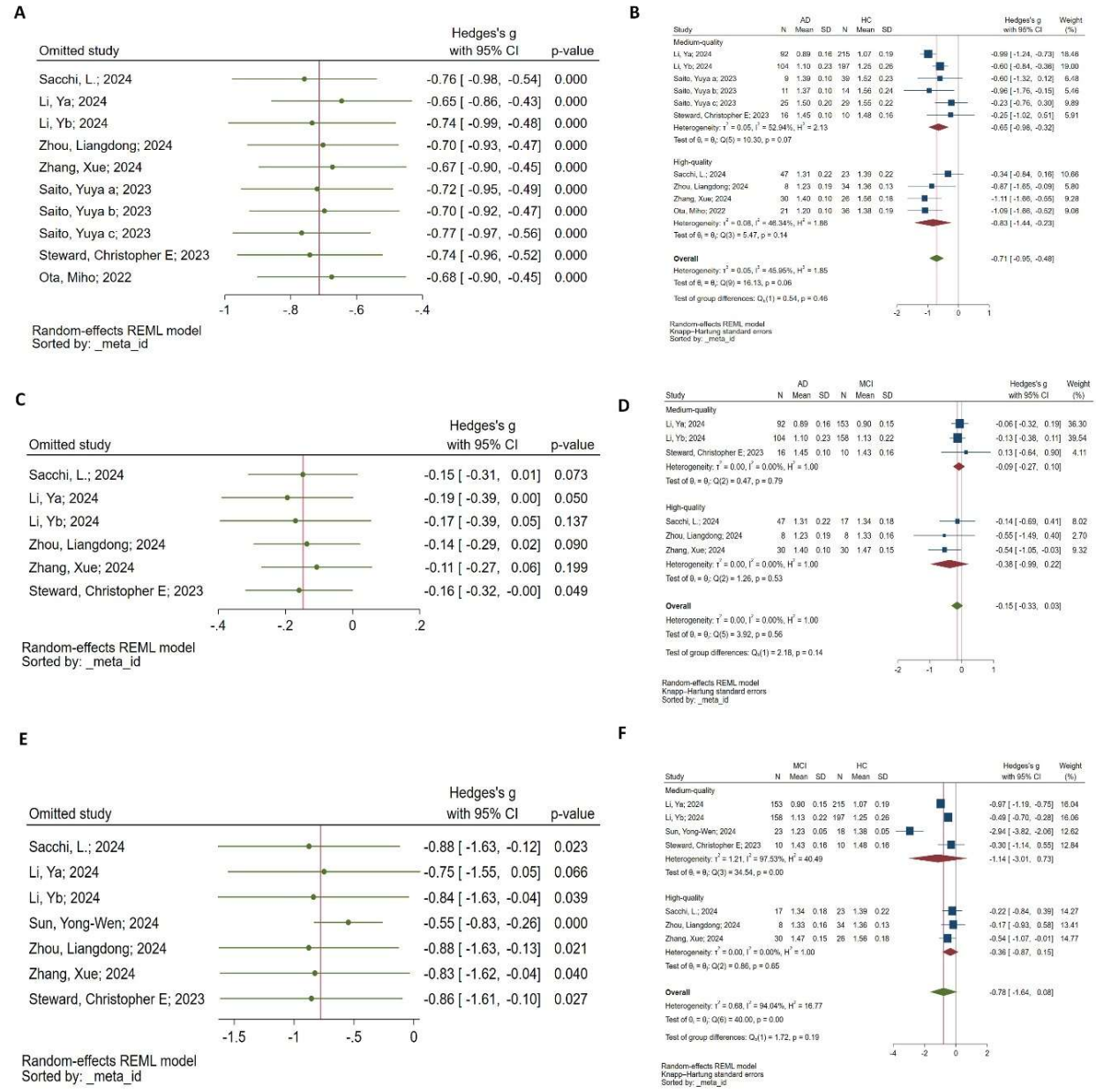


APPENDIX IV: Sensitivity analysis results

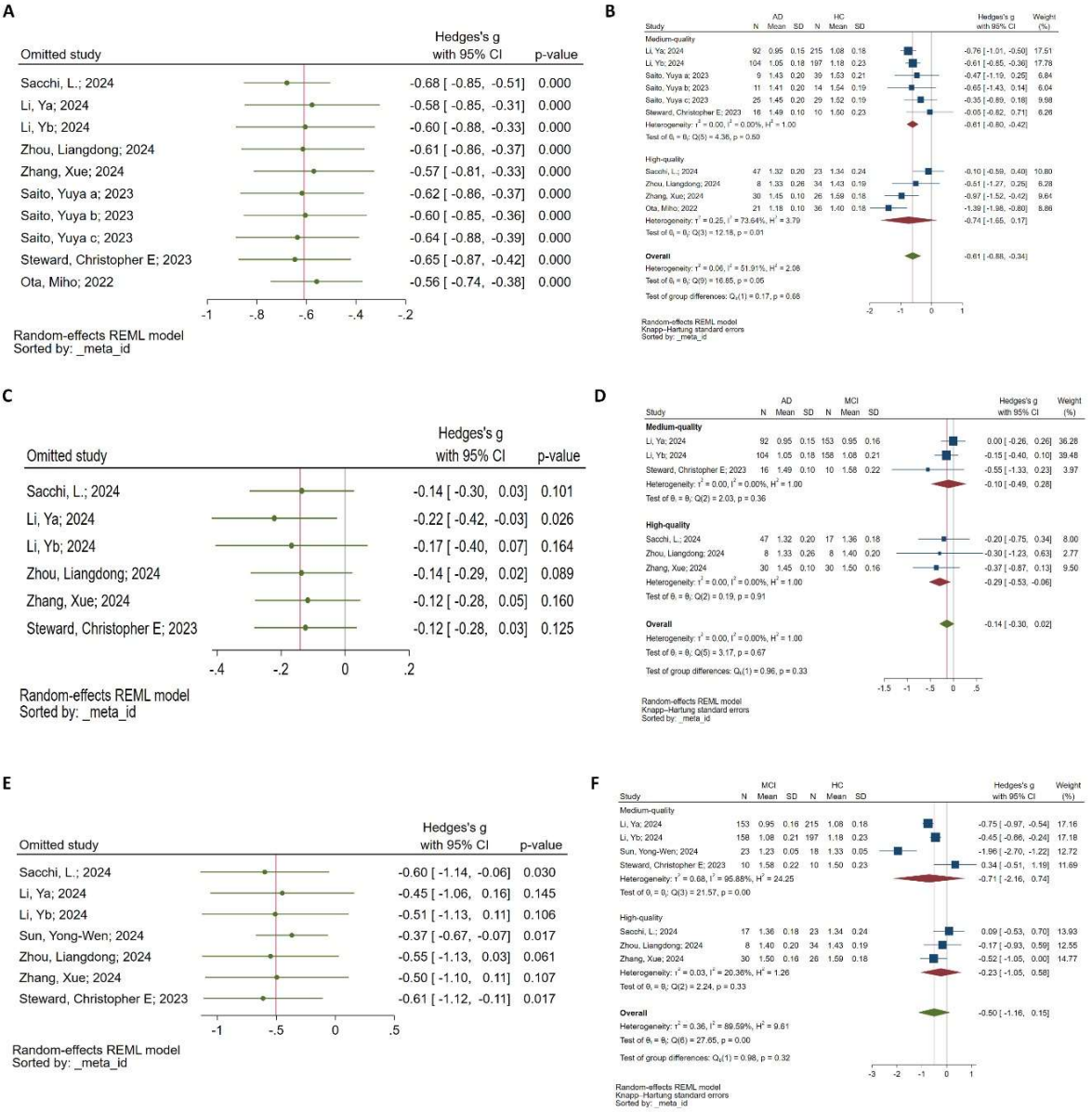
Supplementary Figure 8. Sensitivity analysis using the leave-one-out removal method and subgroups based on the NOS quality assessment score (High-quality, Medium-quality, and Low-quality). **A.** The leave-one-out removal method for the overall Analysis Along the Perivascular Space (ALPS) index in the AD versus HC group, **B.** The subgroups based on the NOS quality assessment score for the overall ALPS index in the AD versus HC group, **C.** The leave-one-out removal method for the overall ALPS index in the AD versus MCI group, **D.** The subgroups based on the NOS quality assessment score for the overall ALPS index in the AD versus MCI group, **E.** The leave-one-out removal method for the overall ALPS index in the MCI versus HC group, and **F.** The subgroups based on the NOS quality assessment score for the overall ALPS index in the MCI versus HC group.



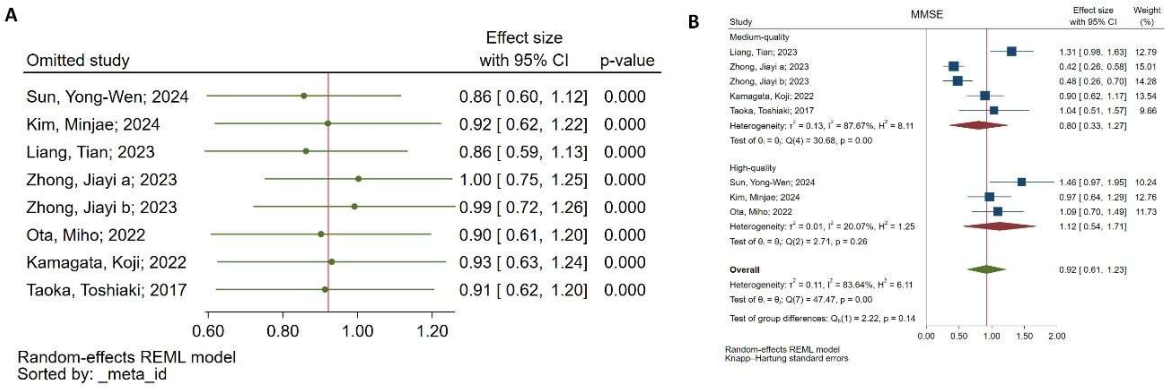
Supplementary Figure 9. Sensitivity analysis using the leave-one-out removal method and subgroups based on the NOS quality assessment score (High-quality, Medium-quality, and Low-quality). **A.** The leave-one-out removal method for the left Analysis Along the Perivascular Space (ALPS) index in the AD versus HC group, **B.** The subgroups based on the NOS quality assessment score for the left ALPS index in the AD versus HC group, **C.** The leave-one-out removal method for the left ALPS index in the AD versus MCI group, **D.** The subgroups based on the NOS quality assessment score for the left ALPS index in the AD versus MCI group, **E.** The leave-one-out removal method for the left ALPS index in the MCI versus HC group, and **F.** The subgroups based on the NOS quality assessment score for the left ALPS index in the MCI versus HC group.



Supplementary Figure 10. Sensitivity analysis using the leave-one-out removal method and subgroups based on the NOS quality assessment score (High-quality, Medium-quality, and Low-quality). **A.** The leave-one-out removal method for the right Analysis Along the Perivascular Space (ALPS) index in the AD versus HC group, **B.** The subgroups based on the NOS quality assessment score for the right ALPS index in the AD versus HC group, **C.** The leave-one-out removal method for the right ALPS index in the AD versus MCI group, **D.** The subgroups based on the NOS quality assessment score for the right ALPS index in the AD versus MCI group, **E.** The leave-one-out removal method for the right ALPS index in the MCI versus HC group, and **F.** The subgroups based on the NOS quality assessment score for the right ALPS index in the MCI versus HC group.

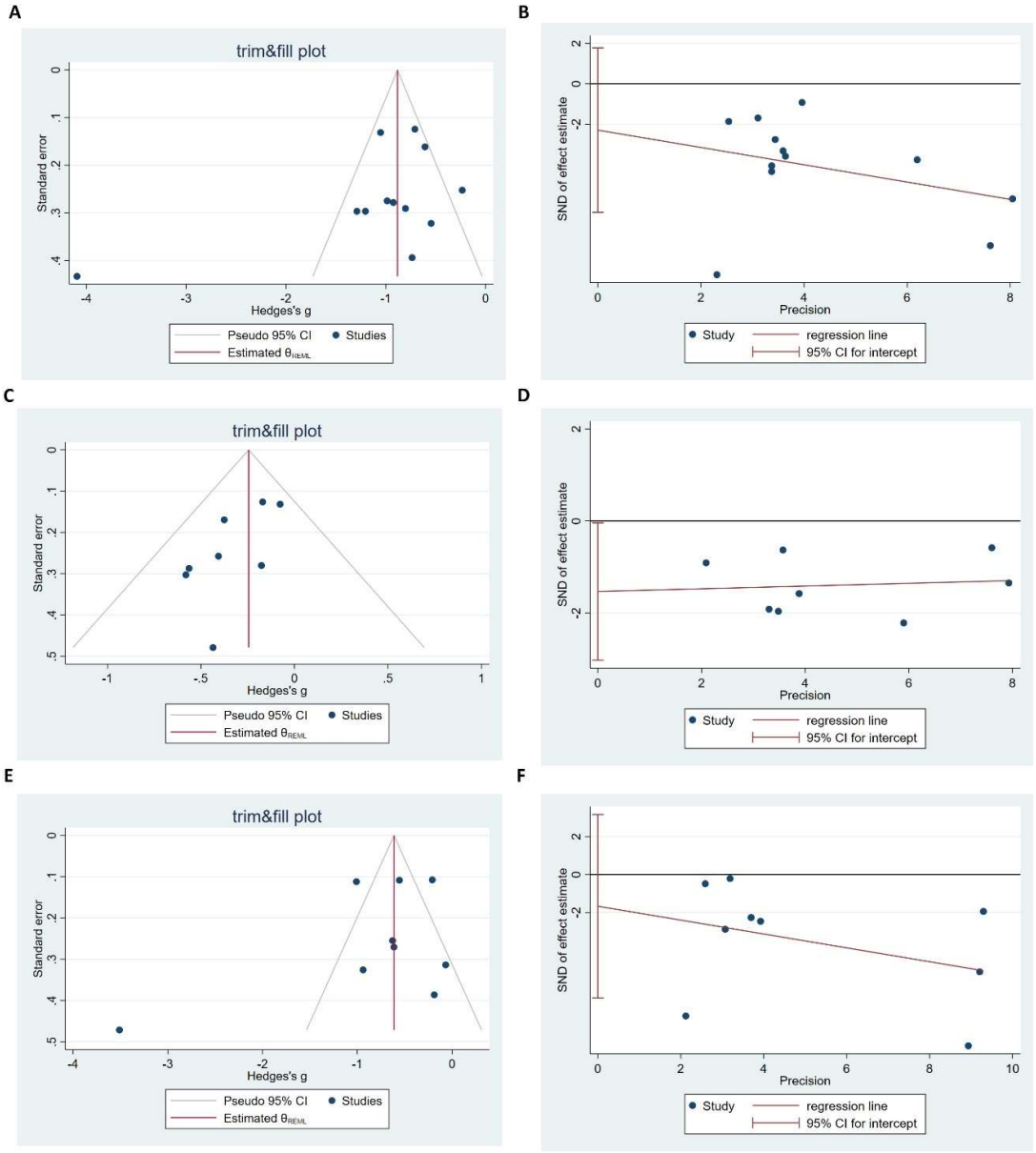


Supplementary Figure 11. Sensitivity analysis using the leave-one-out removal method and subgroups based on the NOS quality assessment score (High-quality, Medium-quality, and Low-quality). **A.** The leave-one-out removal method for MMSE correlated to the Analysis Along the Perivascular Space (ALPS) index in the AD versus HC group, **B.** The subgroups based on the NOS quality assessment score for MMSE correlated to the ALPS index in the AD versus HC group, **C.** The leave-one-out remove method for MOCA correlated to the ALPS index in the AD versus MCI group.

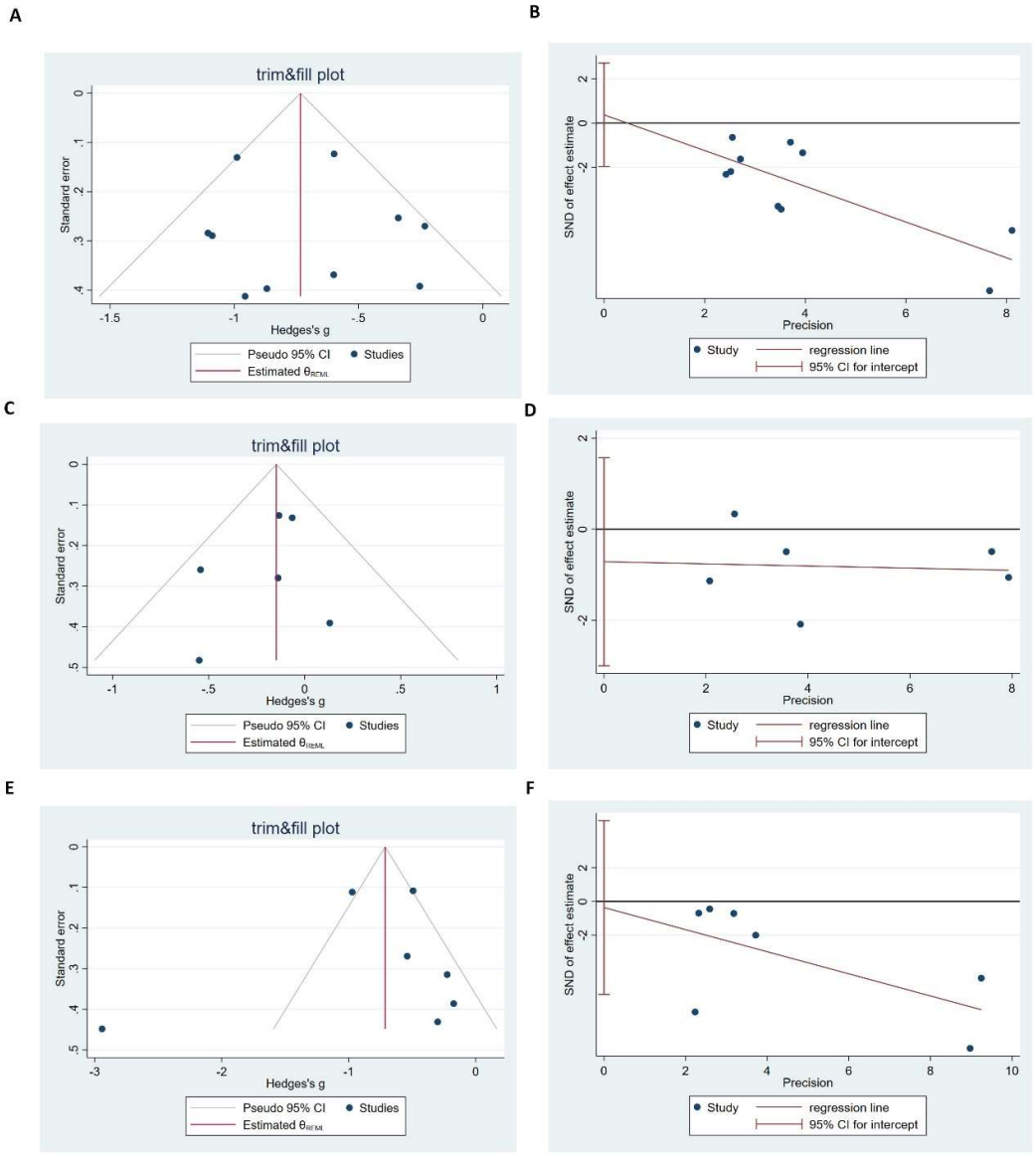


APPENDIX VI: Publication bias assessment using Egger's tests, Egger's graphs, and trim-and-fill plots.

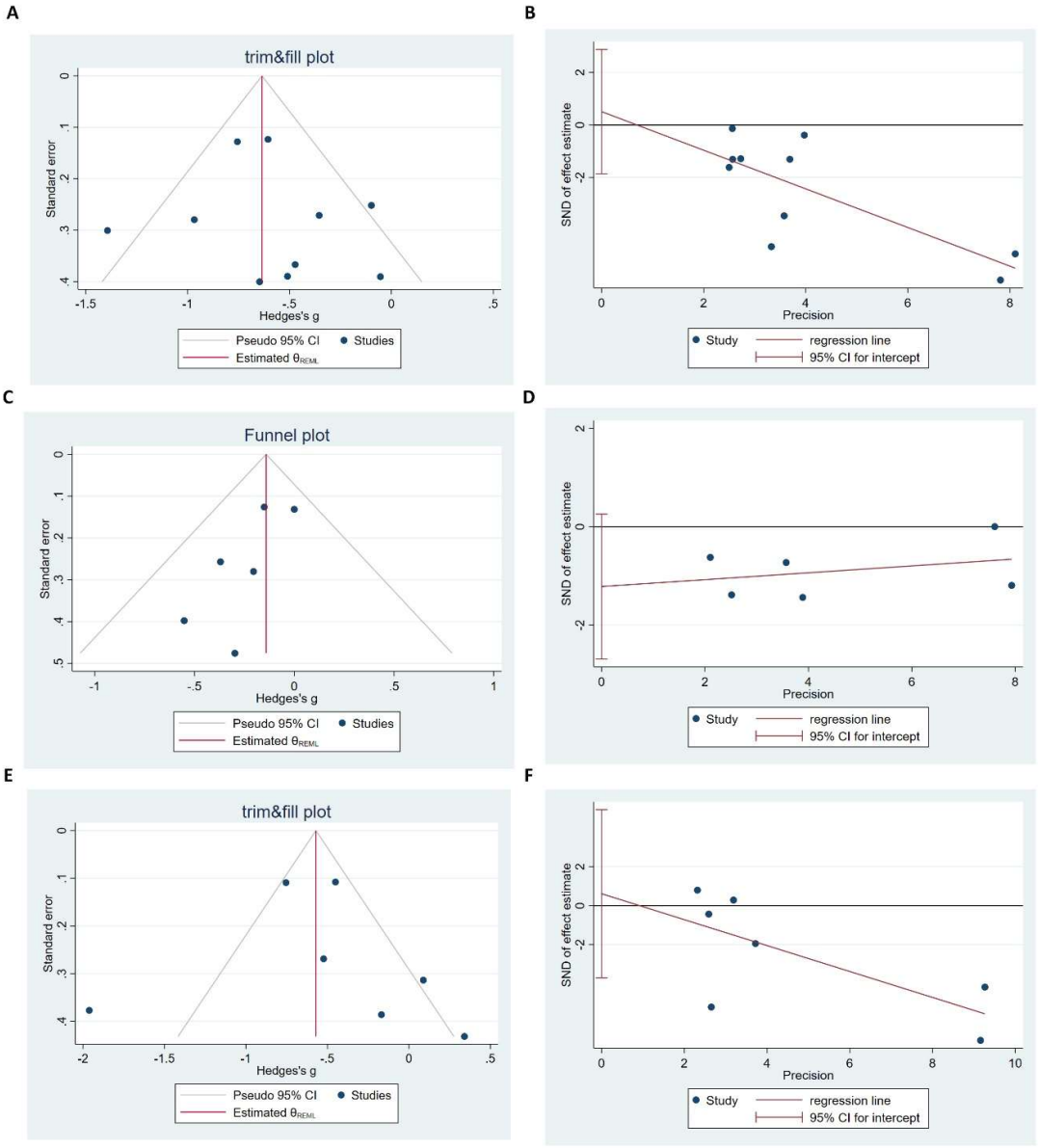
Supplementary Figure 12. Publication bias assessment using Egger's graphs and trim-and-fill plots. **A.** The trim-and-fill plot for the overall Analysis Along the Perivascular Space (ALPS) index in the AD versus HC group, **B.** The Egger's graph for the selected comparisons for the overall ALPS index in the AD versus HC group, **C.** The trim-and-fill plot for the overall ALPS index in the AD versus MCI group, **D.** The Egger's graph for the selected comparisons for the overall ALPS index in the AD versus MCI group, **E.** The trim-and-fill plot for the overall ALPS index in the MCI versus HC group, and **F.** The Egger's graph for the selected comparisons for the overall ALPS index in the MCI versus HC group.



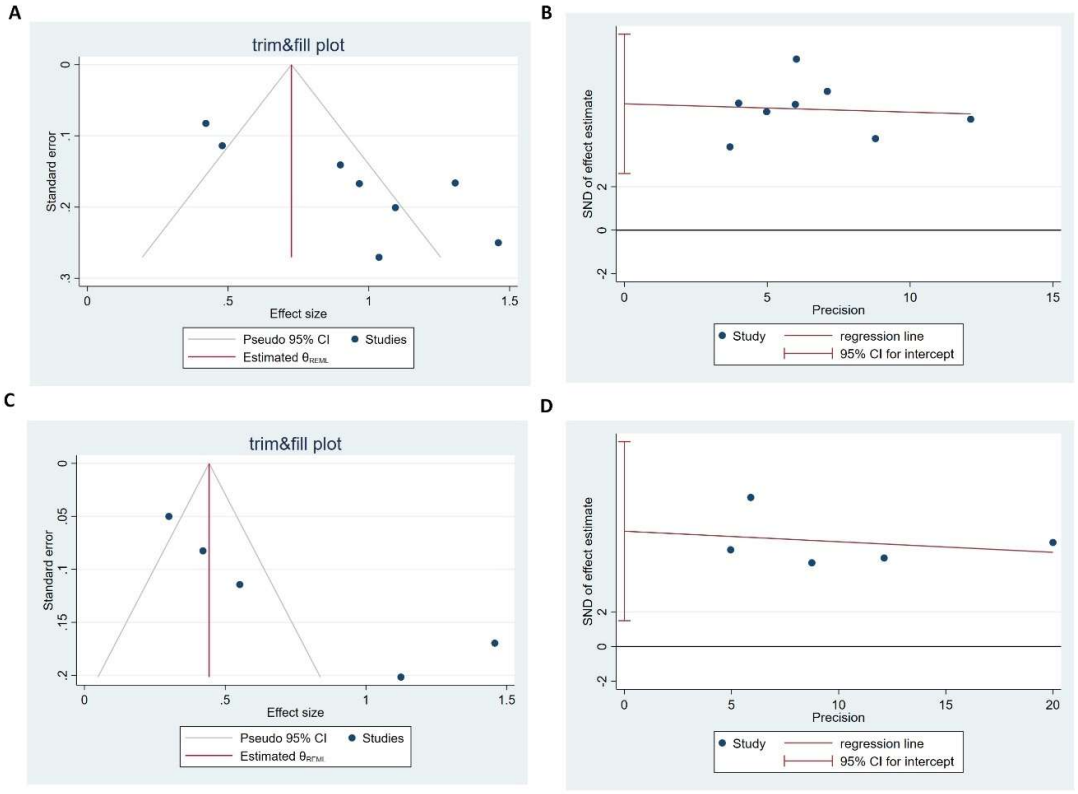
Supplementary Figure 13. Publication bias assessment using Egger's graphs and trim-and-fill plots. **A.** The trim-and-fill plot for the left Analysis Along the Perivascular Space (ALPS) index in the AD versus HC group, **B.** The Egger's graph for the selected comparisons for the left ALPS index in the AD versus HC group, **C.** The trim-and-fill plot for the left ALPS index in the AD versus MCI group, **D.** The Egger's graph for the selected comparisons for the left ALPS index in the AD versus MCI group, **E.** The trim-and-fill plot for the left ALPS index in the MCI versus HC group, and **F.** The Egger's graph for the selected comparisons for the left ALPS index in the MCI versus HC group.



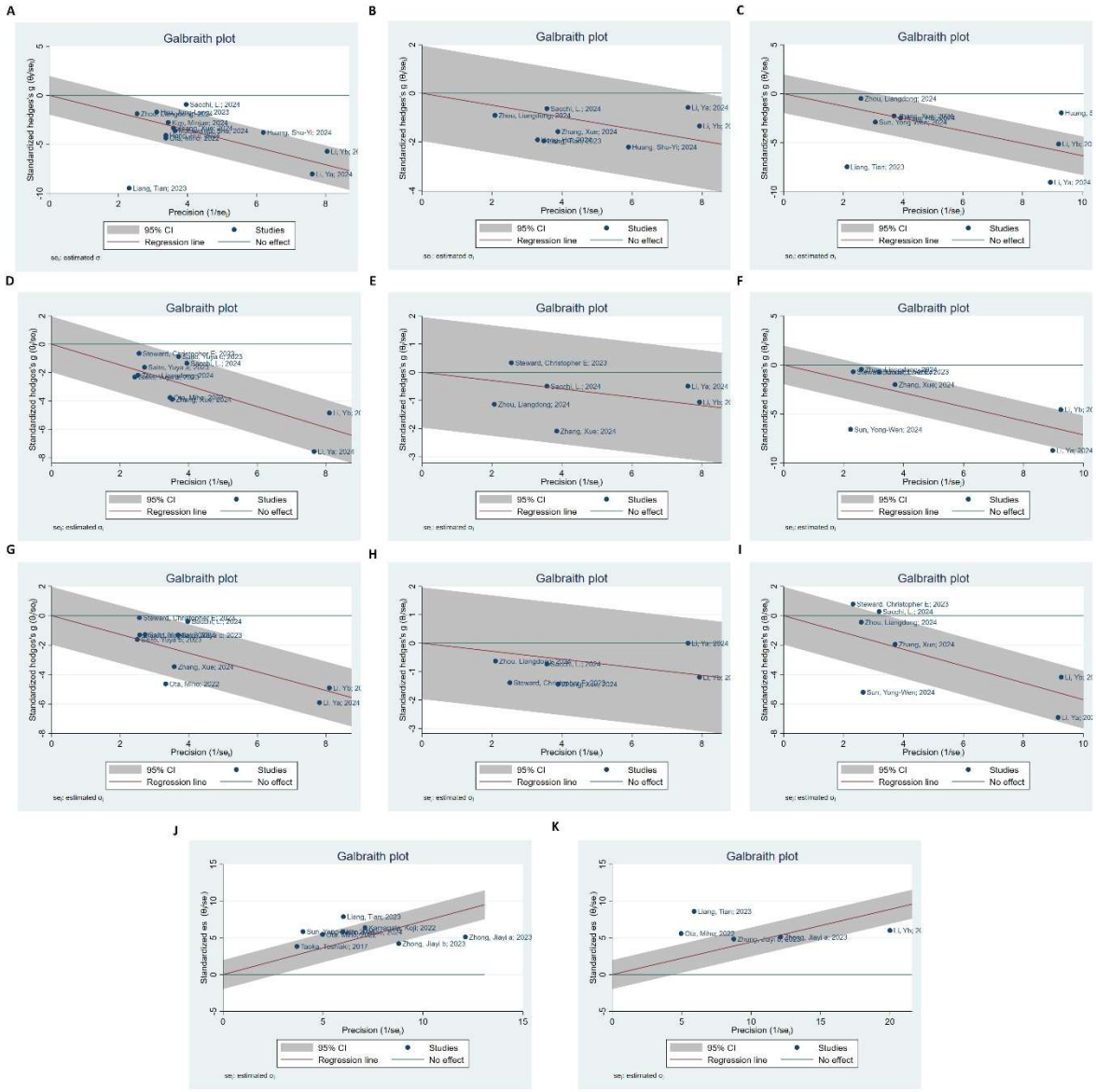
Supplementary Figure 14. Publication bias assessment using Egger's graphs and trim-and-fill plots. **A.** The trim-and-fill plot for the right Analysis Along the Perivascular Space (ALPS) index in the AD versus HC group, **B.** The Egger's graph for the selected comparisons for the right ALPS index in the AD versus HC group, **C.** The trim-and-fill plot for the right ALPS index in the AD versus MCI group, **D.** The Egger's graph for the selected comparisons for the right ALPS index in the AD versus MCI group, **E.** The trim-andill plot for the right ALPS index in the MCI versus HC group, and **F.** The Egger's graph for the selected comparisons for the right ALPS index in the MCI versus HC group.



Supplementary Figure 15. Publication bias assessment using Egger's graphs, and trim-and-fill plots. **A.** The trim-and-fill plot for the MMSE score correlation with the Analysis Along the Perivascular Space (ALPS) index, **B.** The Egger's graph for the selected comparisons for MMSE score correlation with the ALPS index, **C.** The trim-and-fill plot for MOCA score correlation with the ALPS index, **D.** The Egger's graph for the selected comparisons for MOCA score correlation with the ALPS index.



Supplementary Figure 16. Galbraith plots to assess the possibility of heterogeneity. **A.** The overall Analysis Along the Perivascular Space (ALPS) index in the AD versus HC group, **B.** The overall ALPS index in the AD versus MCI group, **C.** The overall ALPS index in the MCI versus HC group, **D.** The left ALPS index in the AD versus HC group, **E.** The left ALPS index in the AD versus MCI group, **F.** The left ALPS index in the MCI versus HC group, **G.** The right ALPS index in the AD versus HC group, **H.** The right ALPS index in the AD versus MCI group, **I.** The right ALPS index in the MCI versus HC group, **J.** MMSE score correlation with the ALPS index, **K.** MOCA score correlation with the ALPS index.



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