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Biomarkers for Alzheimer's disease across diverse biological domains: an umbrella review and evidence map

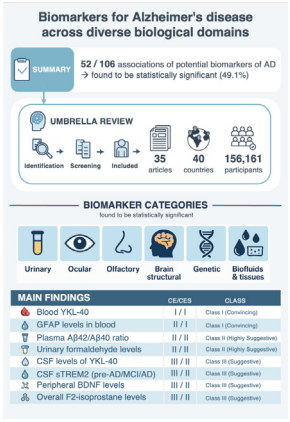
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HIGHLIGHTS

- Review of 35 *meta*-analyses involving over 156,161 participants identified 106 candidate biomarkers for Alzheimer's disease.
- A total of 52 biomarkers were statistically significant, with 26 exhibiting high credibility.
- The findings advocate a multimodal biomarker approach to enhance early diagnosis and monitoring of Alzheimer's disease.
- Non-invasive assays based on urine, saliva, and plasma are highlighted as promising early detection tools.
- The review underscores the need for rigorous, high-quality studies to validate these biomarker associations.

GRAPHICAL ABSTRACT



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ABSTRACT

Background: This study aimed to systematically assess the quality, biases, and credibility of associations between potential Alzheimer's disease (AD) biomarkers through an umbrella review of existing *meta*-analyses.

Methods: We systematically searched PubMed/MEDLINE, Embase, CINAHL, and Google Scholar up to December 18, 2024, for *meta*-analyses of observational studies examining biomarkers for AD. Two reviewers independently screened studies and extracted data. We recalculated effect sizes using random-effects models and converted all estimates to equivalent standardized mean differences or ratio of means. The quality of included reviews was assessed using AMSTAR2, and the credibility of each association was graded using predefined criteria (Class I–IV).

Results: A total of 35 articles provided 106 unique *meta*-analyses covering 1,277 original studies and 156,161 participants across 40 countries. Of these, 52 biomarkers showed statistically significant associations with AD upon re-analysis. Among them, 30 associations included more than 1,000 participants, 49 showed substantial heterogeneity ($I^2 > 50$ %), and 17 had prediction intervals that excluded the null. Only one biomarker (blood YKL-40) reached Class I (convincing) evidence. Eleven associations were classified as highly suggestive (Class II), 14 as suggestive (Class III), and 26 as weak (Class IV) evidence levels. Biomarkers with high credibility (Class I–III) included urine formaldehyde, macular RNFL (optical coherence tomography), olfactory scores, plasma Aβ42/Aβ40 ratio, blood and CSF YKL-40, sTREM2, GFAP, ApoA-I, peripheral BDNF, and F2-isoprostane levels.

Conclusions: This umbrella review provides a comprehensive evidence map of AD-related biomarkers. While 52 biomarkers were identified as statistically significant, only a subset met high credibility thresholds, emphasizing the need for large-scale, prospective studies to validate their clinical utility.

Study registration: PROSPERO CRD42024567136.

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Introduction

Alzheimer's disease (AD) has emerged as a significant global public health issue, especially in aging societies [1]. It profoundly impacts the quality of life through cognitive decline and memory impairments, higher disease burdens to patients and their families, and imposes considerable socioeconomic costs [2]. According to the Global Burden of Disease Study, the global economic burden of AD-related dementias was estimated at $2.8 trillion in 2019, with projections suggesting an increase to $16.9 trillion by 2050 [2]. The number of dementia patients worldwide is expected to rise from 57.4 million in 2019 to 152.8 million by 2050 [1].

The significant and growing disease burden attributed to AD is partly due to increasing life expectancy, leading to a significant rise in cases of AD. However, the mechanisms of AD remain complex and not fully understood, resulting in the absence of effective therapeutics or treatments [3]. Although some therapeutics can ameliorate symptoms of AD, the lack of accurate early diagnosis often delays intervention, reducing the effectiveness of treatments. Therefore, there is an urgent need for early and effective biomarkers for AD, as reliable early diagnosis would enable timely and successful treatment and disease monitoring.

Currently, there is no independent and definitive method for diagnosing AD. Physicians and neurologists typically use a combination of biomarker tests, cognitive assessments (such as the Mini-Mental State Examination and the Montreal Cognitive Assessment), and imaging studies to conduct a comprehensive evaluation and estimate the severity and progression of cognitive impairment [4,5]. The guidelines from the National Institute on Aging and the Alzheimer's Association (NIA-AA) provide a diagnostic framework, most recently updated in 2024, integrating biomarkers and clinical symptoms [6]. This includes cerebrospinal fluid (CSF) levels of amyloid-beta and tau proteins, plasma biomarkers, and imaging techniques like positron emission tomography (PET) scans to identify amyloid plaques and neurofibrillary tangles [6]. To further refine these guidelines, personalized, predictive models for diagnosing and managing AD could be considered, similar to approaches in oncology [7]. However, in neuropsychiatric fields, including AD, there are few validated multivariate predictive models [8–10].

Therefore, to capture the full spectrum of AD pathology, candidate biomarkers were organized into six domains: genetics, brain structure, biofluids/tissues, ocular, urinary, and olfactory. Unlike previous umbrella reviews that focused solely on individual compartments such as ocular markers [11], our study uniquely synthesizes and directly compares evidence across all six domains, thereby filling a critical gap in the field. Based on extensive existing *meta*-analyses, this study aimed to provide a comprehensive overview of currently reported biomarkers for AD, applying quantitative criteria to grade their evidence levels and offering practical insights for clinical practice and policy-making.

Methods

Literature search strategy and selection criteria

This study is an umbrella review conducted according to PRISMA 2020 guidelines and registered in PROSPERO (registration number: CRD42024567136) [12]. Two independent investigators (JK and YS) performed the screening, data extraction, and methodological appraisal. We independently searched PubMed/MEDLINE, Embase, CINAHL, and Google Scholar systematic review databases up to May 26, 2024, to identify eligible articles. We also manually reviewed the references of relevant studies to identify additional eligible articles. We also manually reviewed the reference lists of all included reviews and relevant articles identified through database searching to capture additional eligible studies not indexed under standardized terms.

We included systematic reviews, including *meta*-analyses of observational studies, such as cohort, case-control, and cross-sectional studies. The search strategy was as follows: (Alzheimer's disease [Title/Abstract]) AND ((systematic review [Title/Abstract]) OR (meta [Title/Abstract])) and their variants. The study selection process also involved manually searching the bibliographies of selected articles and reviewing titles, abstracts, and full texts.

Studies were excluded if they were duplicates, focused on single gene polymorphisms as biomarkers of AD, involved scoring systems for AD, reported duplicate results, or were non-English language articles. Non-English articles were excluded to ensure

consistent data interpretation and to avoid bias due to language-based information loss. A biological domain was defined as the anatomical compartment or measurement modality in which a biomarker is assessed. We categorized eligible AD-related biomarkers into the following main domains: urinary, ocular, olfactory, brain structural, genetic, and biofluid and tissue biomarkers (including saliva, blood, serum, cerebrospinal fluid, and brain tissue samples). Ocular biomarkers were categorized into five principal domains according to their anatomical origin and imaging-modality relevance (**Supplementary** Fig. 1). To avoid duplication, when multiple *meta*-analyses covered the same topic, only one was selected. If two or more *meta*-analyses had the same evaluation score, the *meta*-analysis with the highest number of included studies was chosen.

Data extraction

For each *meta*-analysis, we extracted the following information: the name of the first author, the year of publication, the biomarker of interest, the total number of participants, the maximum adjusted individual study estimate, and the corresponding 95 % confidence interval (CI). We also recorded the metrics used in the analysis, such as the area under the curve (AUC), Cohen's d, effect size, Hedge's g, mean difference (MD), ratio of means (RoM), and standardized mean difference (SMD). Also, we summarized the individual study design, including whether the study followed a cohort or case-control design.

Data analysis

This study aimed to reassess the robustness and consistency of various biomarkers associated with AD by reanalyzing eligible *meta*-analyses. This reanalysis was based on individual study estimates from existing *meta*-analyses. Two independent authors (JK and YS) conducted an initial screening of titles and abstracts, followed by a full-text analysis to select articles that met the objectives of this study. Key data extracted from the selected articles included the year of publication, number of studies, biomarkers, country of study, number of cases and participants, study design, effect estimation model (random or fixed effects), degree of heterogeneity, maximum adjusted effect, and 95 % CIs.

To assess the methodological quality of the included studies, we utilized the A Measurement Tool to Assess Systematic Reviews 2 checklist for grading. In case of disagreement, another researcher (DKY and/or CJN) was involved in the discussion to reach a consensus [13].

Both fixed and random effects models were used to produce summary effect estimates and p-values, with statistical significance set at *P*-value < 0.05. Egger's regression asymmetry test was applied to detect the presence of small study effects, considering Egger's *P*-value < 0.1 as indicative of such effects. For statistically significant *meta*-analyses, we reviewed potential excess significance bias by comparing the number of individual studies with expected statistical significance to assess publication bias [13]. Publication bias and selective reporting bias were evaluated using *P*-curve analysis, which analyzes the distribution of statistically significant *P*-values. A right-skewed *P*-curve indicates a true effect, while a flat or left-skewed *P*-curve suggests selective reporting or publication bias. We increased the transparency of our study design and conducted our analyses according to a pre-registered protocol. We also used a variety of statistical approaches to ensure the consistency and reliability of our findings.

Each *meta*-analysis was reanalyzed using DerSimonian and Laird's random and fixed effects models [14]. For each association identified in observational studies, we obtained the effect sizes from the individual studies included in the *meta*-analyses and recalculated the pooled effect sizes along with their 95 % confidence intervals, using random-effects models. Specifically, we applied the DerSimonian and Laird method for analyses involving 10 or more studies, and the Hartung, Knapp, Sidik, and Jonkman method for analyses with fewer than 10 studies to minimize type I error [15]. We used the I^2 statistic to determine the presence of heterogeneity, considering I^2 values greater than 50 % to indicate significant heterogeneity.

P-curve analyses were performed to detect possible *P*-hacking, and the 95 % prediction interval (PI) indicated the uncertainty of the observed estimates and suggested directions of future research using Bayesian statistics. Egger's test was used to assess publication bias if the *P*-value was ≤ 0.1. To ensure comparability across studies reporting different effect measures, pooled effect sizes were recalculated by converting metrics such as AUC, Cohen's d, effect size, Hedge's g, and MD into equivalent SMD (eSMD) or RoM, as appropriate. The detailed formulas and transformation procedures are provided in **Table S5** [16–18]. All statistical tests in this study were two-tailed, and the 'meta' package of R software (version 4.2.2; R Foundation, Vienna, Austria) was used for analysis. A two-sided *P*-value of 0.05 or less was considered statistically significant.

Credibility of evidence

This study utilized a series of statistical tests developed from previous umbrella reviews to assess the credibility of evidence (CE) for each AD biomarker [19]. The strength of evidence was categorized into five levels based on established criteria: convincing (class I), highly suggestive (class II), suggestive (class III), weak (class IV), and not significant (NS). Each level of evidence was determined based on several criteria, including the *P*-value under a random-effects model, the number of AD cases, the statistical significance of the largest study, the I^2 statistic, the presence of small study effects, the presence of excessive significance bias, the summary estimate of the random effect under a 10 % confidence upper bound, and the 95 % PIs. The classification criteria were as follows [16,20,21]:

- Class I: *P*-value of $< 10^{-6}$ under a random effects model, at least 1000 AD cases, a *P*-value of < 0.05 for the largest study, I^2 statistic indicating heterogeneity less than 50 %, no small study effects or excessive significance bias, and a 95 % PIs excluding zero.
- Class II: *P*-value of $< 10^{-6}$ with at least 1000 AD cases, and the largest study must have a p-value of < 0.05. At this level, additional criteria for heterogeneity, small study effects, excessive significance bias, and PIs are not required.
- Class III: *P*-value of 10^{-3} and more than 1000 AD cases. This level does not require statistical significance of the largest study or other additional criteria.
- Class IV: *P*-value of < 0.05 and the number of AD with no requirement for the number of AD cases to exceed 1000. Criteria for heterogeneity, small study effect, and excessive significance bias do not apply, nor is there a requirement for the *P*-value of the largest study.
- NS: *P*-value of ≥ 0.05, indicating no statistical significance, regardless of the number of AD cases or other criteria.

This evidence and quality assessment criteria play an instrumental role in increasing the reliability and accuracy of AD biomarkers in diagnosis and treatment. This evidence and quality assessment criteria play an instrumental role in increasing the reliability and accuracy of AD biomarkers in diagnosis and treatment. All thresholds and classification rules for credibility levels were based on previously established criteria from Ioannidis et al. [19]

and subsequent umbrella reviews, ensuring methodological transparency and reproducibility. To assess the robustness of the credibility classifications, we performed leave-one-out sensitivity analyses for all biomarkers initially categorized as Class II or III. We then re-evaluated the credibility levels after excluding each study one at a time and reported the updated classification as credibility of evidence for sensitivity analysis (CES). This approach enabled us to verify whether the observed credibility was dependent on any single influential study.

Results

From database inception to Dec 18, 2024, we identified 8461 articles, 35 of which were eligible for inclusion after duplicate removal and screening of titles/abstracts or full-text (Fig. 1). Excluded study characteristics are shown in **Table S1**. The eligible *meta*-analyses were published between 2015 and 2024. A total of 1277 original articles across 40 countries (Argentina, Australia, Austria, Belgium, Bosnia and Herzegovina, Brazil, Canada, Chile, China, Colombia, Croatia, Czech Republic, Denmark, Finland, France, Germany, Greece, Hong Kong, Hungary, India, Iran, Ireland, Italy, Japan, Lithuania, Mexico, Netherlands, Norway, Poland, Portugal, Singapore, South Korea, Spain, Sweden, Switzerland, Taiwan, Thailand, Turkey, the United Kingdom, and the United States) and five continents (Asia, Europe, North America, Oceania, and South America) were included (Table 1) [22–58].

The 35 eligible articles provided 106 unique *meta*-analyses for biomarkers (3 urinary biomarkers, 5 ocular biomarkers, 5 olfactory biomarkers, 6 brain structural biomarkers, 3 genetic biomarkers, and 84 biomarkers from biofluids and tissues), covering over 156,161 participants. Of 35 original *meta*-analysis articles on biomarkers, 24 (68.6 %) were graded as high quality and 11 (31.4 %) low or critically low, mainly because the article did not report the protocol for the systematic review (Table 1 and **Table S2**). The number of original studies included in the pooled analyses was 10 on the median, ranging from one to 61. (Table 2). Effect metrics used were either AUC, Cohen's d, Effect size, Hedge's g, MD, RoM, and SMD, which were converted into eSMD and RoM. Our re-analyses showed that 49.1 % (52/106) associations were statistically significant under the random effects model.

30 (57.7 %) of 52 statistically significant associations included more than 1000 participants per association (Table 2). 49 (94.2 %) of 52 associations exhibited significant heterogeneity (I^2 > 50). Using Egger's regression test, there are no small study effects or statistical evidence of publication bias in 23.1 % (12/52) of the studies. The 95 % PIs excluded the null in 17 (32.7 %) of 52 associations. Based on the evaluated CE and CES levels for each biomarker, 1.9 % (1/52) *meta*-analytical effects were the convincing evidence (class I), 21.2 % (11/52) *meta*-analytical effects were the highly suggestive evidence (class II), 26.9 % (14/52) effects were suggestive evidence (class III), and 50.0 % (26/52) effects were weak evidence (class IV) among statistically significant associations. The detailed classification of the certainty of evidence is shown in the supplementary information (**Table S3**). The forest plot, Funnel plot, and P-curve for each biomarkers are presented in Supplementary Materials (Supplementary Figs. 2-106).

As urinary biomarkers, formaldehyde levels were higher in patients with AD and graded at the highly suggestive level of evidence (eSMD, 1.63 [95 % CI, 1.05 to 2.21]; CE/CES = II/II; Fig. 2 and Table 3). Among five ocular biomarkers, three biomarkers had significant associations with AD and were graded as suggestive or weak evidence: structural thickness (optical coherence tomography [OCT]) (eSMD, −0.23 [95 % CI, −0.30 to −0.17]; CE/CES = III/III), microvascular density (optical coherence tomography angiography [OCTA]) (eSMD, −0.12 [95 % CI, −0.17 to −0.07]; CE/CES = III/III), and microvascular density (eSMD, −0.26 [95 % CI, −0.50 to −0.02]; CE = IV).

After re-analysis, five olfactory biomarkers showed statistical significance and were graded as from weak to highly suggestive evidence, respectively: lower olfactory identification score (eSMD, −2.04 [-2.24 to −1.84]; CE/CES = II/III), lower olfactory threshold score (eSMD, −0.73 [-1.12 to −0.33]; CE/CES = III/III), lower olfactory discrimination score (eSMD, −1.22 [-1.50 to −0.94]; CE = IV), olfactory function (TDI) score (eSMD, −1.46 [-1.78 to −1.14]; CE = IV), and poor odor identification ability (−1.75 [-2.36 to −1.14]; CE/CES = III/III). There are three significant brain structural biomarkers with weak evidence: higher quantitative susceptibility mapping (QSM) values in the putamen (eSMD, 1.28 [0.52 to 2.04]; CE = IV), higher QSM values in the caudate nucleus (0.72 [0.25 to 1.20]; CE = IV), and lower callosal midsagittal area changes (−0.85 [-1.01 to −0.69]; CE = IV). Only long non-coding RNAs (lncRNAs) between 3 genetics biomarkers had statistically significant diagnostic accuracy in patients with AD (0.70 [0.38 to 1.03]; CE/CES = III/III).

All 39 biomarkers from biospecimens, including saliva, blood, CSF, serum, and tissue samples, had statistically significant associations for diagnosis of AD, with various evidence levels ranging from weak to convincing evidence (Figs. 2 and 3 and Table 3): salivary Aβ1-42 (RoM, 1.92 [95 % CI, 1.23 to 2.99]; CE = IV), CSF levels of Aβ42 (eSMD, −2.09 [95 % CI, −2.56 to −1.62]; CE = II/II), neurogenic exosome Aβ42 levels (eSMD, 1.71 [1.21 to 2.20]; CE = IV), blood p-tau 181; RoM, 1.80 [95 % CI, 1.64 to 1.98]; CE/CES = II/II), blood p-tau 231; RoM, 1.97 [95 % CI, 1.74 to 2.23]; CE = IV), plasma Aβ42 levels (eSMD, −0.60 [-0.83 to −0.37]; CE/CES = III/III), plasma Aβ42/Aβ40 ratio (eSMD, −1.44 [-1.98 to −0.90]; CE/CES = II/II), platelet Aβ precursor protein (AβPP) ratio levels (eSMD, −1.88 [-2.34 to −1.42]; CE = IV), neutrophil to lymphocyte ratio (eSMD, 0.10 [0.06 to 0.13]; CE/CES = II/II), blood chitinase-3-like protein 1 (YKL-40) (eSMD, 0.38 [0.27 to 0.49]; CE/CES = I/I), CSF levels of YKL-40 (eSMD, 0.89 [0.67 to 1.12]; CE/CES = III/II), overall levels of YKL-40 (eSMD, 0.61 [0.27 to 0.94]; CE/CES = III/III), plasma neurofilament light chain levels (eSMD, 0.20 [0.17 to 0.22]; CE/CES = II/I), CSF soluble triggering receptor expressed on myeloid cells 2 (sTREM2) levels (pre-AD, mild cognitive impairment [MCI], and AD dementia versus control groups; eSMD, 0.41 [0.24 to 0.58]; CE/CES = III/II), CSF sTREM2 levels (AD versus control groups; eSMD, 0.40 [0.18 to 0.63]; CE/CES = III/II), glial fibrillary acidic protein (GFAP) levels in the blood (eSMD, 1.15 [0.82 to 1.48]; CE/CES = II/I), CSF levels of synaptosomal-associated protein 25 (SNAP-25) (ROM, 1.50 [1.29 to 1.74]; CE = IV), CSF levels of adaptor-related protein complex 2 subunit β1 (AP2B1) (eSMD, 0.54 [0.19 to 0.89]; CE = IV), CSF levels of flotillin-1 (FLOT1) (eSMD, −0.49 [-0.62 to −0.35]; CE = IV), CSF levels of GM2 ganglioside activator (GM2A) (eSMD, 0.51 [0.05 to 0.97]; CE = IV), CSF levels of cathepsin B (CTSB) (eSMD, 0.20 [0.03 to 0.38]; CE = IV), CSF levels of cathepsin Z (CTSZ) (eSMD, −0.16 [-0.31 to −0.01]; CE = IV), CSF levels of lysosome-associated membrane glycoprotein 1 (LAMP1) (eSMD, 0.77 [0.06 to 1.48]; CE = IV), CSF levels of lysosome-associated membrane glycoprotein 2 (LAMP2) (eSMD, 0.50 [0.14 to 0.85]; CE = IV), serum levels of apolipoprotein A-I (ApoA-I) (eSMD, −1.15 [-1.72 to −0.59]; CE/CES = III/III), peripheral blood levels of ApoA-I (eSMD, −1.15 [-1.63 to −0.67]; CE/CES = III/III), interleukin-17 (IL-17) levels (eSMD, −0.38 [-0.54 to −0.21]; CE = IV), CSF neurogranin ratio (RoM, 1.62 [1.50 to 1.75]; CE/CES = II/I), CSF visinin-like protein 1 (VILIP-1) levels (RoM, 1.35 [1.28 to 1.43]; CE/CES = II/II), total cholesterol levels in blood (eSMD, 0.17 [0.01 to 0.32]; CE = IV), triglyceride levels in blood (eSMD, 0.17 [0.01 to 0.32; CE = IV), neurofilament concentration in CSF (RoM, 2.12 [95 % CI, 1.86 to 2.41]; CE/CES = II/II), peripheral brain-derived neurotrophic factor (BDNF) levels (eSMD, −0.73 [-1.07 to −0.39]; CE/CES = III/II), brain aluminum levels (eSMD,

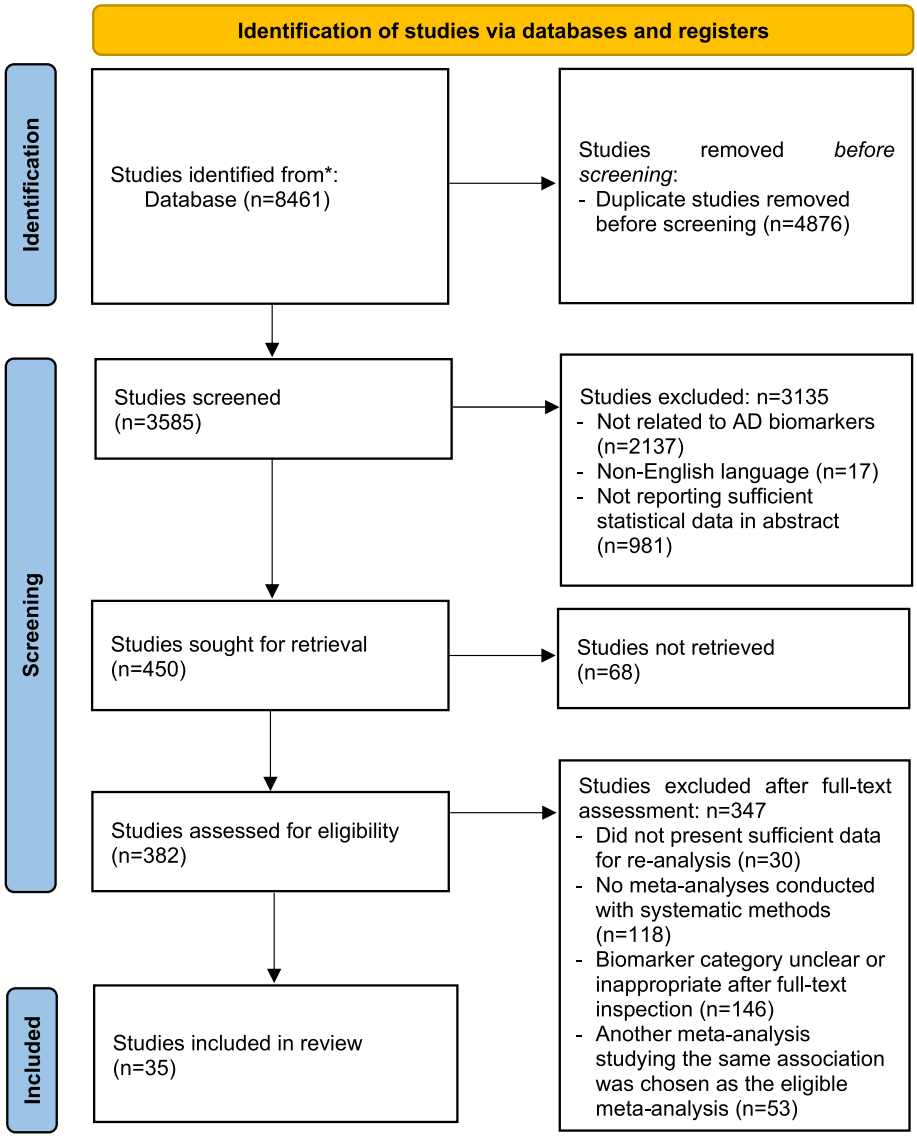


Fig. 1. PRISMA 2020 flow diagram. *Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers). *From:* Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. https://doi.org/10.1136/bmj.n71.

0.92 [0.30 to 1.53]; CE = IV), serum aluminum levels (eSMD, 0.28 [0.30 to 0.54]; CE = IV), CSF levels of F2-isoprostane (eSMD, 1.56 [0.91 to 2.21]; CE = IV), 8-iso prostaglandin F 2α (8-*iso*-PGF2α) levels in frontal lobe tissue samples (eSMD, 1.93 [0.98 to 2.88]; CE = IV), and overall levels of F2-isoprostane (eSMD, 1.01 [0.69 to 1.32]; CE/CES = III/II).

Discussion

Key findings

This study is the first umbrella review to systematically and quantitatively assess the certainty and strength of evidence (CE and CES) for potential biomarkers of AD. Based on 35 eligible *meta*-analyses including over 156,161 participants from 1277 original studies across 40 countries, we identified 106 unique pooled analyses for biomarkers related to the diagnosis or pathology of AD. After re-analysis, 52 out of 106 associations (49.1 %) were found to be statistically significant under a random-effects model. These included one urinary biomarker, three ocular biomarkers, five olfactory biomarkers, three brain structural biomarkers, one genetic biomarker, and 39 biomarkers from biofluids and tissues. Among these, 29 biomarkers showed high-credibility evidence, classified as convincing (class I), highly suggestive (class II), or suggestive (class III). Specifically, these included: urinary formaldehyde levels (CE/CES = II/II); macular retinal nerve fiber layer thickness measured via OCT (CE/CES = III/III); microvascular density measured by OCTA (CE/CES = III/III); lower odor identification score (CE/CES = II/III); lower olfactory threshold score (CE/CES = III/III); poor odor identification ability (CE/CES = III/III); diagnostic accuracy of lncRNAs (CE/CES = III/III); plasma Aβ42 levels (CE/CES = III/III); plasma Aβ42/Aβ40 ratio (CE/CES = II/II); blood YKL-40 (CE/CES = I/I); CSF levels of YKL-40 (CE/CES = III/II); overall levels of YKL-40 (CE/CES = III/III); CSF sTREM2 levels in pre-AD, MCI, and AD dementia groups (CE/CES = III/II); CSF sTREM2 levels in AD versus control groups (CE/CES = III/II); GFAP levels in blood (CE/CES = II/I); serum ApoA-I (CE/CES = III/III); peripheral ApoA-I (CE/CES = III/III); peripheral BDNF levels (CE/CES = III/II); and overall F2-isoprostane levels (CE/CES = III/II). These findings underscore the existence of multiple statistically significant and highly

Table 1
Characteristics of *meta*-analysis to investigate the potential biomarker for Alzheimer's diseases.

	First author	Included countries
1. Urinary biomarkers		
Urine formaldehyde levels	Chen F et al., 2022	China
F2-isoprostane (urine samples)	Trares K et al., 2022	Spain, Sweden, US
8-*iso*-PGF2α (urine samples)	Trares K et al., 2022	Italy, South Korea, Spain, Sweden, US
2. Ocular		
Structural thickness (OCT)	Ashraf G et al., 2023	Australia, Italy, Netherlands, Poland, Portugal, South Korea, Spain, US
Microvascular density (OCTA)	Ashraf G et al., 2023	Australia, Italy, Netherlands, Poland, Portugal, South Korea, Spain, US
Macrovascular calibre (Fundus)	Ashraf G et al., 2023	Australia, Japan, Netherlands, South Korea
Microvascular density	Yeh TC et al., 2022	China, Germany, Italy, Netherlands, Poland, Singapore, Turkey, US
Choroidal thickness	Yeh TC et al., 2022	Netherlands, Turkey, US
3. Olfactory biomarkers		
Olfactory identification score	Bouhaben J et al., 2024	Australia, Canada, China, Croatia, Czech Republic, France, Germany, Greece, Iran, Italy, Japan, Korea, Lithuania, Netherlands, Poland, UK, USA
Olfactory threshold score	Bouhaben J et al., 2024	Canada, China, France, Germany, Italy, Korea, Netherlands, UK, USA
Olfactory discrimination score	Bouhaben J et al., 2024	Canada, Germany, Italy, Korea, Netherlands, USA
Olfactory function (TDI) score	Bouhaben J et al., 2024	Canada, Germany, Italy, Korea, Netherlands
Odor identification ability	Kotecha AM et al., 2018	Australia, Canada, Germany, UK, US
4. Brain structural biomarkers		
Quantitative susceptibility mapping values in the putamen	Ghaderi S et al., 2024	Canada, China, Germany, Japan, South Korea
Quantitative susceptibility mapping values in the globus pallidus	Ghaderi S et al., 2024	Canada, China, South Korea
Quantitative susceptibility mapping values in the caudate nucleus	Ghaderi S et al., 2024	Canada, China, Germany, South Korea
Quantitative susceptibility mapping values in the thalamus	Ghaderi S et al., 2024	Canada, China, South Korea
Cerebral blood flow in the hippocampus	Kapasouri EM et al., 2022	China, Netherlands
Callosal midsagittal area changes	Wang XD et al., 2015	Austria, Canada, China, Danmark, France, Germany, Japan, Netherlands, Portland, US
5. Genetic biomarkers		
Diagnostic accuracy of lncRNAs	Shobeiri P et al., 2023	China, Iran
Diagnostic accuracy of BACE1-AS lncRNA	Shobeiri P et al., 2023	China
APOE ε4	Gurjeet K et al., 2020	Australia, Colombia, Germany, UK, USA
6. Biofluids and tissues (saliva, blood, CSF, serum, and tissue sample)		
Salivary Aβ1-42	Fan Z et al., 2023	Brazil, Canada, Chile, Greece, Spain, US
Salivary t-tau	Fan Z et al., 2023	Brazil, Chile, South Korea, Spain, Sweden, UK, US
Salivary p-tau	Fan Z et al., 2023	Greece, South Korea, Spain, US
CSF levels of Aβ42	Zhang X et al., 2023	Denmark, France, Germany, Netherlands, Norway, Spain, Sweden, US
Neurogenic exosome Aβ42	Zhang X et al., 2023	Canada, China, Singapore, South Korea, US
Neurogenic exosome t-tau	Zhang X et al., 2023	Canada, China, South Korea, US
Neurogenic exosome p-tau181	Zhang X et al., 2023	Canada, China, South Korea, US
Blood p-tau (p-tau181, p-tau-217, p-tau231)	Chen L et al., 2022	Canada, China, England, Finland, Italy, Japan, Singapore, Spain, Sweden, Taiwan, US
Blood p-tau-181	Chen L et al., 2022	Canada, China, England, Finland, Italy, Japan, Singapore, Spain, Sweden, Taiwan, US
Blood p-tau-217	Chen L et al., 2022	Spain, Sweden, US
Blood p-tau-231	Chen L et al., 2022	Canada
Plasma Aβ40 levels (PET-positive versus PET-negative)	Cheng L et al., 2022	Australia, Belgium, China, France, Germany, Japan, Netherlands, South Korea, Sweden, Taiwan, UK, US
Plasma Aβ42 levels (PET-positive versus PET-negative)	Cheng L et al., 2022	Australia, Belgium, China, France, Germany, Japan, Netherlands, Sweden, Taiwan, UK, US
Plasma Aβ42/Aβ40 ratio (PET-positive versus PET-negative)	Cheng L et al., 2022	Australia, Belgium, China, Germany, Japan, Netherlands, South Korea, Spain, Sweden, Taiwan, UK, US
Plasma p-T181-tau levels	Kim KY et al., 2021	China, South Korea, US
Plasma p-S396-tau levels	Kim KY et al., 2021	US
Platelet AβPP ratio levels	Shi Y et al., 2017	Brazil, Italy, Mexico, Sweden, Taiwan, Thailand, US
ApoE levels	Talwar P et al., 2016	Canada, Finland, France, Germany, India, Japan, Sweden, UK, US
Blood S100B levels	Holper S et al., 2024	Brazil, Germany, India, USA
Neutrophil to lymphocyte ratio	Mohammadi A et al., 2024	Australia, China, Germany, Japan, Turkey, USA
Serum VEGF concentrations	Zakariaee SS et al., 2024	Brazil, China, Europe, Germany, Italy, Korea, Singapore, Spain
CSF VEGF concentrations	Zakariaee SS et al., 2024	Germany, Netherlands, Sweden, USA
Salivary AChE	Fan Z et al., 2023	Iran, UK
Blood YKL-40 levels	Holper S et al., 2024	Germany, Korea, Norway, Poland, USA
CSF levels of YKL-40	Zhang Y et al., 2023	Denmark, France, Germany, Netherlands, Norway, Spain, Sweden, US
Overall levels of YKL-40	Zhang Y et al., 2023	China, Denmark, France, Germany, Japan, Netherlands, Norway, South Korea, Spain, Sweden, US

Table 1 (*continued*)

	First author	Included countries
Plasma neurofilament light chain levels	Fan Z et al., 2023	Canada, China, Europe, Germany, Spain, Sweden, US
CSF sTREM2 levels (pre-AD, MCI, and AD dementia versus control groups)	Zhou W et al., 2023	China, Germany, Italy,Norway, Spain, Sweden, UK, US
CSF sTREM2 levels (AD versus control groups)	Zhou W et al., 2023	Germany, Italy, Norway, Spain, Sweden, UK, US
GFAP levels in the blood	Kim KY et al., 2023	Australia, Canada, Finland, France, Germany, Greece, Italy, Netherlands, Poland, Spain, Sweden, UK, US
CSF synaptosomal-associated protein 25 (SNAP-25) levels	Liu Q et al., 2022	Argentina, Australia, Canada, China, France, Germany, Japan, UK, US
CSF endocytosis markers (AP2B1)	Krance SH et al.,	Denmark, Germany, Italy, Sweden, Switzerland, UK, US
CSF endocytosis markers (FLOT1)	Krance SH et al.,	Japan, US
CSF intra-lysosomal markers (GM2A)	Krance SH et al.,	Denmark, Germany, Italy, South Korea, Sweden, Switzerland, UK, US
CSF intra-lysosomal markers (CTSB)	Krance SH et al.,	Denmark, Germany, Italy, South Korea, Sweden, Switzerland, UK, US
CSF intra-lysosomal markers (CTSZ)	Krance SH et al.,	Denmark, Germany, Italy, South Korea, Sweden, Switzerland, UK, US
CSF lysosomal membrane proteins (LAMP1)	Krance SH et al.,	Denmark, Germany, Italy, Sweden, Switzerland, UK, US
CSF lysosomal membrane proteins (LAMP2)	Krance SH et al.,	Denmark, Germany, Italy, South Korea, Sweden, Switzerland, UK, US
CSF autophagy marker (LC3B)	Krance SH et al.,	Denmark, Germany, Sweden, Switzerland, UK, US
Serum ApoA-I levels	Tong JH et al., 2022	China, France, Japan, South Korea
Plasma ApoA-I levels	Tong JH et al., 2022	Canada, China, Japan, Netherlands, US
Peripheral blood ApoA-I levels	Tong JH et al., 2022	Canada, China, France, Japan, Netherlands, South Korea, US
CSF ApoA-I levels	Tong JH et al., 2022	Belgium, Japan, Netherlands, US
Plasma p-Y-IRS-1 levels	Kim KY et al., 2021	US
Plasma HSP levels	Kim KY et al., 2021	Spain, US
Plasma/serum insulin-like growth factor-1 (IGF-1) levels	Xu LZ et al., 2021	China, European, France, Germany, Italy, Japan, Spain, Sweden, UK
CSF IGF-1 levels	Xu LZ et al., 2021	European, Sweden
TNF-α levels	Anuradha U et al., 2022	Brazil, Belgium, China, Germany, Greece, India, Italy, Poland, South Korea, Spain, Turkey, US
IL-6 levels	Anuradha U et al., 2022	Brazil, Germany, Greece, Hungary, India, Italy, South Korea, Sweden, Taiwan, Turkey, US
IL-1β levels	Anuradha U et al., 2022	Brazil, India, Italy, Spain, Turkey, US
IL-18 levels	Anuradha U et al., 2022	India, Italy, South Korea, Turkey, US
IL-12 levels	Anuradha U et al., 2022	Germany, Italy, South Korea, US
IL-8 levels	Anuradha U et al., 2022	Italy, South Korea, Sweden, US
IFN-gamma levels	Anuradha U et al., 2022	Germany, Italy, Sweden
IP-10 levels	Anuradha U et al., 2022	Brazil, South Korea
IL-16 levels	Anuradha U et al., 2022	Italy, South Korea
IL-7 levels	Anuradha U et al., 2022	India, South Korea, US
IL-5 levels	Anuradha U et al., 2022	India, South Korea, US
CRP levels	Anuradha U et al., 2022	Bosnia and Herzegovina, Ireland, Italy, Sweden, Turkey, US
MCP-1 levels	Anuradha U et al., 2022	Brazil, Italy, South Korea
MIP-1α levels	Anuradha U et al., 2022	Brazil, India, South Korea, US
RANTES levels	Anuradha U et al., 2022	South Korea, Sweden
GM-CSF levels	Anuradha U et al., 2022	South Korea, US
IL-4 levels	Anuradha U et al., 2022	South Korea, Sweden
IL-10 levels	Anuradha U et al., 2022	Brazil, India, US
TGF-β1 levels	Anuradha U et al., 2022	Italy
IL-1α levels	Anuradha U et al., 2022	Brazil, South Korea
CSF neurogranin (Ng) ratio	Dulewicz M et al., 2020	Belgium, Brazil, China, France, Germany, Ireland, Italy, Netherlands, Poland, Spain, Sweden, UK, US
CSF visinin-like protein 1 (VILIP-1) ratio	Dulewicz M et al., 2020	Canada, China, Germany, Netherlands, Poland, Singapore, US
Total cholesterol levels in blood	Tang Q et al., 2020	China, Germany, India, Iran, Italy, Japan, Netherlands, Portugal, Spain, Switzerland, Turkey, US
HDL-C levels in blood	Tang Q et al., 2020	China, India, Iran, Japan, Turkey
LDL-C levels in blood	Tang Q et al., 2020	China, India, Iran, Japan, Turkey
Triglyceride levels in blood	Tang Q et al., 2020	China, Germany, India, Iran, Italy, Japan, Netherlands, Portugal, Spain, Switzerland, Turkey, US
Neurofilament (NfL) concentration in CSF	Forgrave LM et al., 2019	Argentina, Austria, Belgium, China, France, Germany, Hungary, Italy, Netherlands, Spain, Sweden, Switzerland, UK, US
Peripheral BDNF levels	Xie B et al., 2020	NA
Brain aluminum levels	Virk SA et al., 2015	Australia, Canada, Hungary, Japan, Singapore, Switzerland, UK, US

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Table 1 (*continued*)

	First author	Included countries
Serum aluminum levels	Virk SA et al., 2015	China, France, Hong Kong, Italy, Spain, Sweden, UK, US
CSF aluminum levels	Virk SA et al., 2015	France, Greece, Sweden, US
F2-isoprostane (blood samples)	Trares K et al., 2022	US
8-*iso*-PGF2α (blood samples)	Trares K et al., 2022	Bosnia and Herzegovina, France, Italy, Norway, Turkey
F2-isoprostane (CSF samples)	Trares K et al., 2022	Taiwan, US
8-*iso*-PGF2α (CSF samples)	Trares K et al., 2022	US
F2-isoprostane (Frontal lobe tissue samples)	Trares K et al., 2022	US
8-*iso*-PGF2α (Frontal lobe tissue samples)	Trares K et al., 2022	US
F2-isoprostane levels	Trares K et al., 2022	Bosnia and Herzegovina, France, Italy, Norway, South Korea, Spain, Sweden, Taiwan, Turkey, US

Abbreviations.
AD, Alzheimer's disease; BDNF, brain-derived neurotrophic factor; CSF, cerebrospinal fluid; eSMD, equivalent standardized mean differences; FLOT1, Flotillin-1; GFAP, glial fibrillary acidic protein; IL-7, Interleukin 7; LAMP1, Lysosomal-associated membrane protein 1; MCI, mild cognitive impairment; OCT, optical coherence tomography; PET, positron emission tomography; RNFL, retinal nerve fiber layer; RoM, ratio of means; sTREM2, triggering receptor expressed on myeloid cells 2.

credible biomarkers across diverse biological domains, supporting their potential role in the early diagnosis and mechanistic understanding of AD.

Comparisons with previous studies

Recent reviews and original experimental studies have enhanced our understanding of AD pathology, broadening the scope of biological and molecular markers associated with its pathological process and diagnosis [59–61]. Previous review articles primarily highlighted the critical roles of Aβ and tau proteins, suggesting a strong relationship between these protein levels and the pathological process of AD [61]. These proteins have even been utilized as markers in recent clinical trials to assess the effects of new pharmacological therapeutics and interventions.[62,63] More recent research has expanded to include various pathologies and in-depth mechanisms, such as neuroinflammation, glial activation, brain structural changes (such as atrophy), systemic inflammation, alterations in biological mechanisms (such as endocytosis and lysosomal function), and olfactory functions as potential biomarkers [22,24–30,32,34–36,38–40,42–48,50–57]. These findings indicate the necessity of a biomarker panel rather than reliance on a single indicator.

While there is a previous umbrella review that has exclusively focused on ocular biomarkers [11], it is crucial to provide a more comprehensive overview and summary of systematic biomarkers. Hampel et al. emphasized the advantages of integrating biomarkers with neuroimaging techniques, showing that combining CSF and plasma biomarkers with PET and magnetic resonance imaging (MRI) scan data significantly improves diagnostic accuracy [64]. This integrative approach is supported by other studies highlighting the diagnostic value of combining multiple biomarker modalities [65]. Thus, while previous studies have built a robust foundation for biomarker research in AD, recent advancements underscore the importance of multi-modal and integrative approaches. However, previous studies on biomarkers have predominantly been narrative reviews,[61,66] *meta*-analyses focusing on specific biomarkers [22–52], or umbrella reviews exclusively covering ocular biomarkers [11]. Therefore, our study holds significant value by comprehensively overviewing existing biomarkers and systematically quantifying and assessing the hierarchy of evidence for potential AD biomarkers.

Plausible mechanisms

Our study identified 52 statistically significant associations between biomarkers and AD and systematically quantified and assessed the hierarchy of credibility of existing evidence. This umbrella review aims to provide an overview and summary of potential biomarkers for diagnosing AD. We seek to provide plausible mechanisms for each biomarker based on previous studies, as detailed below.

a. Urinary biomarkers.

Urinary formaldehyde levels were higher in patients with AD, suggesting its potential as a biomarker for AD with highly suggestive evidence. Formaldehyde is a marker for inflammation and oxidative stress [67]. Significant accumulation of formaldehyde has been reported in both AD mouse models and patients with AD [68]. When formaldehyde was injected into the hippocampus, it induced neuronal death, memory impairments, and exaggerated amyloidopathy and tauopathy [22]. Endogenous formaldehyde is normally excreted in urine [63]. However, the altered metabolic capacity of endogenous formaldehyde due to aging or the pathological process of AD can lead to DNA damage, impaired mitochondrial function, and neuronal apoptosis, thereby contributing to AD pathogenesis or accelerating the pathology of AD [22,68]. These findings are supported by higher urinary formaldehyde levels in patients with AD compared to healthy controls, suggesting its potential as an early diagnostic marker [22].

b. Ocular biomarkers.

AD is a neurogenerative disorder that can cause damage to the optic nerve and retina [69]. Evidence from preclinical models and postmortem studies suggests that retrograde neurodegeneration can induce apoptosis of retinal ganglion cells (RGC) and axonal loss. Recent studies indicate that Aβ may directly induce changes in RGCs [11,70]. Since Aβ and hyperphosphorylated tau contributed to neurodegeneration in the brain, their accumulation in the retina may similarly contribute to the degeneration of RGCs, synaptic dysfunction, and, ultimately, neuronal cell death [11,23]. Particularly, decreased thickness of the macular retinal nerve fiber layer (RNFL) and peripapillary RNFL, both measured by OCT and categorized as structural thickness biomarkers, indicated axonal loss in the optic nerve, which is associated with the neurodegenerative pathology in AD, supported by suggestive evidence levels.

In addition to structural thickness, we observed significantly lower microvascular density in various retinal layers (e.g., total macula, superficial and deep layers) measured by OCTA, supporting their potential as ocular biomarkers for AD. The observed reduction in retinal vascular density in patients with AD is associated with blood flow changes in the brain and retina.[24] Reduced cerebral blood flow can affect retinal vessels, with more pronounced effects in the deep capillary layer [71]. In addition, the accumulation of Aβ plaques, a hallmark of AD pathology, can deposit in the vascular walls and impair vascular function, which

Table 2
Reanalysis of estimated effect using DerSimonian and Laird's methods (DL) and Hartung-Knapp-Sidik-Jonkman (HKSJ) method, and CE on biomarker of Alzheimer's diseases.

Biomarkers	Included studies	Metrics	Total sample	Reported summary estimated effect (95 % CI); Random effect model	Re-analysed summary estimated effect (95 % CI) DL method			Re-analysed summary estimated effect (95 % CI) HKSJ method; random effect model	Heterogeneity I^2 (%)	Egger's p-value	Tau square, τ	95 % prediction interval	CE/ CES*
					Fixed-effect model	Random effect model	Largest study						
1. Urinary biomarkers													
Urine formaldehyde levels	12	SMD	1451	**1.63 (1.05 to 2.21)**	**1.18 (1.06 to 1.31)**	**1.63 (1.05 to 2.21)**	**0.62 (0.30 to 0.93)**	**1.68 (0.76 to 2.60)**	95.39	0.01	0.99	(−0.69, 3.95)	II/II
F2-isoprostane (urine samples)	5	Hedge's g	410	0.60 (−0.01 to 1.21)	**0.46 (0.22 to 0.70)**	0.60 (−0.01 to 1.22)	0.28 (−0.15 to 0.71)	0.63 (−0.33 to 1.60)	84.20	0.29	0.40	(−1.65, 2.85)	NS
8-*iso*-PGF2 (urine samples)	5	Hedge's g	365	0.68 (−0.05 to 1.41)	**0.64 (0.42 to 0.86)**	0.68 (−0.05 to 1.40)	−0.24 (−0.67 to 0.19)	0.68 (−0.30 to 1.66)	90.91	0.54	0.62	(−2.09, 3.45)	NS
2. Ocular biomarkers													
Structural thickness (OCT)	58	SMD, Cohen's d	12,827	N/A	**−0.23 (−0.30 to −0.17)**	**−0.23 (−0.32 to −0.13)**	0.00 (−0.22 to 0.22)	**−0.23 (−0.32 to −0.13)**	45.57	0.96	0.06	(−0.72, 0.26)	III/III
Microvascular density (OCTA)	123	SMD, Cohen's d	8013	N/A	**−0.12 (−0.17 to −0.07)**	**−0.14 (−0.22 to −0.06)**	**−0.10 (−0.43 to 0.24)**	**−0.14 (−0.22 to −0.06)**	59.01	0.06	0.11	(−0.81, 0.54)	III/ III
Macrovascular calibre (Fundus)	27	SMD, Cohen's d	2663	N/A	**−0.11 (−0.20 to −0.03)**	−0.10 (−0.27 to 0.07)	−0.01 (−0.35 to 0.34)	−0.10 (−0.29 to 0.09)	73.82	0.27	0.15	(−0.90, 0.70)	NS
Microvascular density	32	Cohen's d	2361	N/A	**−0.25 (−0.33 to −0.16)**	**−0.26 (−0.50 to −0.02)**	0.00 (−0.22 to 0.22)	−0.26 (−0.59 to 0.07)	86.84	0.73	0.37	(−1.52, 0.99)	IV
Choroidal thickness	3	Cohen's d	764	−0.58 (−1.26 to 0.10)	**−0.47 (−0.66 to −0.28)**	**−0.57 (−1.12 to −0.02)**	**−0.46 (−0.69 to −0.24)**	−0.61 (−2.20 to 0.98)	83.01	0.75	0.19	(−7.2, 6.06)	NS
3. Olfactory biomarkers													
Olfactory identification score	61	Hedges' g	6123	**−2.06 (−2.31 to −1.82)**	**−1.70 (−1.76 to −1.64)**	**−2.04 (−2.24 to −1.84)**	**−1.61 (−1.79 to −1.42)**	**−2.07 (−2.33 to −1.81)**	89.65	0.00	0.52	(−3.5, −0.58)	II/III
Olfactory threshold score	12	Hedges' g	1186	**−0.74 (−1.19 to −0.29)**	**−0.60 (−0.71 to −0.48)**	**−0.73 (−1.12 to −0.33)**	**−0.49 (−0.70 to −0.29)**	**−0.77 (−1.29 to −0.25)**	89.25	0.42	0.41	(−2.22, 0.76)	III/III
Olfactory discrimination score	8	Hedges' g	565	**−1.21 (−1.45 to −0.96)**	**−1.16 (−1.35 to −0.98)**	**−1.20 (−1.44 to −0.97)**	**−0.99 (−1.32 to −0.66)**	**−1.22 (−1.50 to −0.94)**	33.38	0.08	0.04	(−1.76, −0.64)	IV
Olfactory function (TDI) score	8	Hedges' g	582	**−1.45 (−1.72 to −1.17)**	**−1.44 (−1.62 to −1.26)**	**−1.45 (−1.72 to −1.18)**	**−1.69 (−2.05 to −1.33)**	**−1.46 (−1.78 to −1.14)**	51.22	0.65	0.08	(−2.2, −0.7)	IV
Odor identification ability	9	SMD	1212	**−1.63 (−1.95 to −1.31)**	**−1.55 (−1.68 to −1.42)**	**−1.64 (−1.97 to −1.32)**	**−1.53 (−1.72 to −1.34)**	**−1.75 (−2.36 to −1.14)**	76.51	0.45	0.16	(−2.67, −0.62)	III/III
4. Brain structural biomarkers													
Quantitative susceptibility mapping values in the putamen	8	SMD	436	**1.23 (0.62 to 1.84)**	**0.97 (0.77 to 1.18)**	**1.23 (0.68 to 1.77)**	**0.50 (0.04 to 0.96)**	**1.28 (0.52 to 2.04)**	84.74	0.00	0.51	(−0.65, 3.1)	IV
Quantitative susceptibility mapping values in the globus pallidus	6	SMD	335	**0.79 (0.07 to 1.52)**	**0.61 (0.38 to 0.84)**	**0.79 (0.15 to 1.43)**	0.40 (−0.08 to 0.89)	0.82 (−0.16 to 1.80)	86.57	0.02	0.55	(−1.46, 3.04)	NS
Quantitative susceptibility mapping values in the caudate nucleus	6	SMD	324	**0.72 (0.39 to 1.06)**	**0.72 (0.49 to 0.96)**	**0.73 (0.39 to 1.06)**	**0.81 (0.31 to 1.30)**	**0.72 (0.25 to 1.20)**	50.58	0.99	0.09	(−0.23, 1.68)	IV
Quantitative susceptibility mapping values in the thalamus	6	SMD	346	1.00 (−0.42 to 2.43)	**0.46 (0.22 to 0.70)**	**0.92 (0.06 to 1.78)**	**0.66 (0.16 to 1.16)**	1.06 (−0.94 to 3.06)	92.05	0.26	1.04	(−2.16, 4)	NS
Cerebral blood flow in the hippocampus	4	SMD	308	**−2.82 (−5.04 to −0.60)**	**−1.30 (−1.57 to −1.02)**	**−2.82 (−5.03 to −0.61)**	**−0.36 (−0.69 to −0.03)**	−2.85 (−6.03 to 0.34)	97.62	0.31	4.92	(−13.53, 7.89)	NS
Callosal midsagittal area changes	20	SMD	970	**−0.85 (−1.00 to −0.69)**	**−0.84 (−0.98 to −0.70)**	**−0.85 (−1.01 to −0.69)**	**−0.80 (−1.24 to −0.37)**	**−0.85 (−1.02 to −0.68)**	22.29	0.14	0.03	(−1.24, −0.46)	IV
5. Genetic biomarkers													
Diagnostic accuracy of lncRNAs	11	AUC	1482	**0.71 (0.62 to 0.80)**	**0.72 (0.61 to 0.83)**	**0.70 (0.38 to 1.03)**	**0.36 (0.11 to 0.58)**	**0.70 (0.34 to 1.06)**	88.58	0.81	0.24	(−0.47, 1.88)	III/III
Diagnostic accuracy of BACE1-AS lncRNA	3	AUC	294	**0.81 (0.62 to 0.99)**	**0.84 (0.55 to 1.13)**	**0.83 (0.46 to 1.20)**	**1.00 (0.62 to 1.47)**	0.82 (−1.57 to 3.21)	37.68	N/A	0.03	(−2.35, 4.02)	NS
APOE ε4	4	OR	259	**1.72 (1.01 to 2.91)**	**1.72 (1.01 to 2.91)**	**1.72 (1.01 to 2.91)**	2.33 (0.89 to 6.14)	1.93 (0.81 to 4.63)	0.00	0.31	0.00	(0.56, 6.66)	NS
6. Biofluids and tissues (saliva, blood, CSF, serum, and tissue sample)													
Salivary Aβ1-42	7	Ratio of means	760	**1.90 (1.28 to 2.81)**	**2.04 (2.00 to 2.07)**	**1.90 (1.28 to 2.82)**	**2.45 (2.40 to 2.50)**	**1.92 (1.23 to 2.99)**	99.60	0.47	0.26	(0.45, 8.13)	IV
Salivary t-tau	5	Ratio of means	576	0.94 (0.67 to 1.31)	**0.67 (0.64 to 0.70)**	0.94 (0.68 to 1.31)	**0.65 (0.62 to 0.67)**	0.97 (0.62 to 1.50)	84.77	0.02	0.11	(0.27, 3.44)	NS
Salivary p-tau	4	Ratio of means	291	0.91 (0.56 to 1.45)	**0.67 (0.59 to 0.77)**	0.91 (0.57 to 1.45)	**0.54 (0.46 to 0.62)**	0.93 (0.50 to 1.73)	87.86	0.02	0.19	(0.09, 9.56)	NS
CSF levels of Aβ42	10	SMD	1123	**−2.09 (−2.56 to −1.61)**	**−1.74 (−1.88 to −1.60)**	**−2.09 (−2.56 to −1.62)**	**−1.02 (−1.28 to −0.76)**	**−2.13 (−2.73 to −1.52)**	90.17	0.11	0.51	(−3.82, −0.35)	II/II
Neurogenic exosome Aβ42	12	SMD	842	**1.70 (1.20 to 2.20)**	**1.53 (1.37 to 1.69)**	**1.71 (1.21 to 2.20)**	**1.41 (1.07 to 1.75)**	**1.77 (1.11 to 2.43)**	88.71	0.37	0.65	(−0.18, 3.59)	IV
Neurogenic exosome t-tau	5	SMD	446	**1.02 (0.27 to 1.77)**	**1.14 (0.94 to 1.35)**	**1.02 (0.27 to 1.77)**	**0.66 (0.29 to 1.04)**	1.00 (−0.13 to 2.13)	91.82	0.81	0.66	(−1.84, 3.88)	NS
Neurogenic exosome p-tau181	10	SMD	604	**1.75 (1.16 to 2.35)**	**1.70 (1.51 to 1.90)**	**1.76 (1.16 to 2.36)**	**1.70 (1.30 to 2.11)**	**1.81 (1.08 to 2.54)**	88.36	0.59	0.79	(−0.41, 3.93)	IV
Blood p-tau-181	29	Ratio of means	6058	**1.80 (1.63 to 2.00)**	**1.73 (1.69 to 1.78)**	**1.80 (1.64 to 1.98)**	**1.59 (1.47 to 1.71)**	**1.87 (1.66 to 2.08)**	92.03	0.32	0.06	(1.14, 3.08)	II/II
Blood p-tau-217	5	Ratio of means	912	**3.49 (2.02 to 6.03)**	**4.16 (3.76 to 4.61)**	**3.52 (1.86 to 6.63)**	**1.78 (1.42 to 2.22)**	4.26 (0.81 to 2.21)	96.06	0.50	0.48	(1.55, 7.96)	NS
Blood p-tau-231	1	Ratio of means	201	**1.97 (1.74 to 2.23)**	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	IV
Plasma Aβ40 levels (PET-positive versus PET-negative)	10	SMD	2323	−0.76 (−0.61 to 2.14)	**0.15 (0.06 to 0.24)**	0.75 (−0.02 to 1.51)	0.13 (−0.07 to 0.33)	0.77 (−0.83 to 2.37)	98.49	0.05	1.48	(−2.2, 3.69)	NS
Plasma Aβ42 levels (PET-positive versus PET-negative)	9	SMD	1986	**−0.60 (−0.80 to −0.41)**	**−0.63 (−0.72 to −0.54)**	**−0.60 (−0.79 to −0.41)**	**−0.45 (−0.65 to −0.25)**	**−0.60 (−0.83 to −0.37)**	72.66	0.92	0.06	(−1.21, 0.01)	III/III

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Table 2 (*continued*)

Biomarkers	Included studies	Metrics	Total sample	Reported summary estimated effect (95 % CI); Random effect model	Re-analysed summary estimated effect (95 % CI) DL method			Re-analysed summary estimated effect (95 % CI) HKSJ method; random effect model	Heterogeneity I^2 (%)	Egger's p-value	Tau square, τ	95 % prediction interval	CE/ CES*
					Fixed-effect model	Random effect model	Largest study						
Plasma Aβ42/Aβ40 ratio (PET-positive versus PET-negative)	14	SMD	2628	**−1.44 (−2.17 to −0.72)**	**−1.25 (−1.34 to −1.16)**	**−1.44 (−1.98 to −0.90)**	**−1.10 (−1.31 to −0.89)**	**−1.45 (−2.25 to −0.64)**	97.07	0.38	1.01	(−3.71, 0.83)	II/II
Plasma p-T181-tau levels	8	SMD	586	**4.04 (2.31 to 5.76)**	**1.49 (1.25 to 1.73)**	**4.05 (2.33 to 5.77)**	**1.71 (1.33 to 2.10)**	4.69 (−1.07 to 10.46)	97.56	0.17	5.63	(−2.14, 10.25)	NS
Plasma p-S396-tau levels	4	SMD	188	**2.51 (0.80 to 4.23)**	**1.69 (1.33 to 2.05)**	**2.54 (0.83 to 4.26)**	**1.96 (1.51 to 2.41)**	3.06 (−2.65 to 8.76)	93.30	0.73	2.63	(−5.39, 10.48)	NS
Platelet AβPP ratio levels	16	SMD	952	**−1.87 (−2.33 to −1.41)**	**−1.56 (−1.71 to −1.41)**	**−1.88 (−2.34 to −1.42)**	**−1.88 (−2.24 to −1.53)**	**−1.96 (−2.52 to −1.39)**	88.58	0.06	0.74	(−3.8, 0.03)	IV
ApoE levels	24	MD	2402	−0.30 (−0.69 to 0.09)	0.08 (−0.03 to 0.19)	−0.30 (−0.70 to 0.09)	**1.30 (1.02 to 1.58)**	−0.38 (−0.93 to 0.18)	90.43	0.05	0.74	(−2.14, 1.53)	NS
Blood S100B levels	4	Hedge g	488	0.46 (−0.43 to 1.34)	**0.26 (0.08 to 0.44)**	0.43 (−0.26 to 1.13)	**0.67 (0.39 to 0.96)**	0.50 (−1.02 to 2.02)	92.34	0.64	0.44	(−2.83, 3.68)	NS
Neutrophil to lymphocyte ratio	10	MD	3175	**0.59 (0.38 to 0.80)**	**0.58 (0.50 to 0.66)**	**0.59 (0.37 to 0.80)**	**0.42 (0.24 to 0.60)**	**0.59 (0.32 to 0.85)**	83.23	0.96	0.09	(−0.14, 1.32)	II/II
Serum VEGF concentrations	21	SMD	6492	0.23 (−0.27 to 0.73)	**0.21 (0.15 to 0.28)**	0.24 (−0.27 to 0.75)	**0.34 (0.23 to 0.44)**	0.86 (−2.36 to 4.07)	98.04	0.75	1.31	(−2.22, 2.7)	NS
CSF VEGF concentrations	10	SMD	1180	−0.13 (−0.42 to 0.16)	**−0.25 (−0.37 to −0.13)**	**−0.13 (−0.42 to 0.17)**	**−0.40 (−0.65 to −0.16)**	−0.10 (−0.50 to 0.30)	80.59	0.14	0.16	(−1.12, 0.87)	NS
Salivary AChE	3	Ratio of means	135	0.83 (0.24 to 2.88)	**0.46 (0.43 to 0.49)**	0.83 (0.24 to 2.87)	**0.42 (0.39 to 0.46)**	0.86 (0.15 to 4.94)	97.67	0.57	0.87	N/A	NS
Blood YKL-40 levels	16	Hedge g	2517	**0.38 (0.28 to 0.49)**	**0.38 (0.29 to 0.47)**	**0.38 (0.27 to 0.49)**	**0.25 (0.08 to 0.43)**	**0.38 (0.26 to 0.50)**	17.85	0.81	0.01	(0.15, 0.61)	I/I
CSF levels of YKL-40	13	SMD	1346	**0.89 (0.67 to 1.12)**	**0.93 (0.81 to 1.04)**	**0.89 (0.67 to 1.12)**	**1.30 (1.03 to 1.56)**	**0.89 (0.65 to 1.13)**	72.90	0.76	0.12	(0.09, 1.7)	III/II
Overall levels of YKL-40	18	SMD	1811	**0.61 (0.27 to 0.94)**	**0.73 (0.63 to 0.82)**	**0.61 (0.27 to 0.94)**	**1.30 (1.03 to 1.56)**	**0.60 (0.17 to 1.02)**	90.93	0.60	0.46	(−0.88, 2.09)	III/III
Plasma neurofilament light chain levels	19	MD	5616	**14.33 (12.42 to 16.24)**	**13.27 (12.29 to 14.25)**	**14.34 (12.43 to 16.25)**	**7.70 (5.05 to 10.35)**	**15.26 (12.75 to 17.78)**	69.75	0.01	11.32	(6.95, 21.73)	II/I
CSF sTREM2 levels (pre-AD, MCI, and AD dementia versus control groups)	28	SMD	4463	**0.41 (0.24 to 0.58)**	**0.37 (0.30 to 0.43)**	**0.41 (0.24 to 0.58)**	−0.08 (−0.24 to 0.09)	**0.41 (0.21 to 0.61)**	84.46	0.77	0.16	(−0.44, 1.26)	III/II
CSF sTREM2 levels (AD versus control groups)	16	SMD	2021	**0.40 (0.18 to 0.63)**	**0.40 (0.31 to 0.50)**	**0.40 (0.18 to 0.63)**	**0.77 (0.55 to 0.99)**	**0.40 (0.06 to 0.75)**	81.22	0.96	0.16	(−0.48, 1.28)	III/II
GFAP levels in the blood	14	SMD	4566	**1.15 (0.82 to 1.48)**	**0.67 (0.60 to 0.74)**	**1.15 (0.82 to 1.48)**	**0.19 (0.09 to 0.29)**	**1.16 (0.85 to 1.46)**	94.47	0.10	0.36	(−0.2, 2.5)	II/I
CSF synaptosomal-associated protein 25 (SNAP-25) levels	8	Ratio of means	887	**1.50 (1.30 to 1.74)**	**1.56 (1.49 to 1.64)**	**1.50 (1.30 to 1.73)**	**2.06 (1.87 to 2.28)**	**1.50 (1.29 to 1.74)**	87.53	0.16	0.04	(0.9, 2.49)	IV
CSF endocytosis markers (AP2B1)	6	SMD	376	**0.51 (0.26 to 0.77)**	**0.49 (0.29 to 0.70)**	**0.52 (0.26 to 0.78)**	0.28 (−0.09 to 0.66)	**0.54 (0.19 to 0.89)**	32.00	0.13	0.03	(−0.1, 1.14)	IV
CSF endocytosis markers (FLOT1)	3	SMD	86	**−0.49 (−0.92 to −0.06)**	**−0.49 (−0.90 to −0.08)**	**−0.49 (−0.90 to −0.08)**	−0.52 (−1.15 to 0.11)	**−0.49 (−0.62 to −0.35)**	0.00	0.30	<0.01	(−3.15, 2.18)	IV
CSF intra-lysosomal markers (GM2A)	10	SMD	810	**0.50 (0.04 to 0.95)**	**0.27 (0.13 to 0.42)**	**0.51 (0.05 to 0.97)**	**0.27 (0.04 to 0.50)**	0.77 (−0.57 to 2.11)	88.56	0.72	0.46	(−1.14, 2.16)	IV
CSF intra-lysosomal markers (CTSB)	11	SMD	928	**0.20 (0.03 to 0.37)**	**0.18 (0.05 to 0.31)**	**0.20 (0.03 to 0.38)**	0.06 (−0.17 to 0.28)	0.20 (0.00 to 0.41)	32.27	0.94	0.03	(−0.21, 0.62)	IV
CSF intra-lysosomal markers (CTSZ)	10	SMD	1355	**−0.16 (−0.30 to −0.01)**	**−0.17 (−0.28 to −0.06)**	**−0.16 (−0.31 to −0.01)**	**−0.30 (−0.48 to −0.11)**	−0.16 (−0.33 to 0.01)	27.03	0.37	0.01	(−0.48, 0.16)	IV
CSF lysosomal membrane proteins (LAMP1)	9	SMD	729	**0.60 (0.27 to 0.93)**	**0.41 (0.27 to 0.56)**	**0.62 (0.28 to 0.96)**	**0.25 (0.02 to 0.47)**	**0.77 (0.06 to 1.48)**	75.46	0.12	0.18	(−0.47, 1.71)	IV
CSF lysosomal membrane proteins (LAMP2)	12	SMD	914	**0.48 (0.13 to 0.83)**	**0.32 (0.18 to 0.46)**	**0.50 (0.14 to 0.85)**	0.18 (−0.04 to 0.41)	0.77 (−0.28 to 1.83)	80.83	0.30	0.28	(−0.75, 1.74)	IV
CSF autophagy marker (LC3B)	3	SMD	129	**0.65 (0.18 to 1.12)**	**0.65 (0.29 to 1.00)**	**0.65 (0.18 to 1.12)**	0.55 (0.00 to 1.09)	0.65 (−0.44 to 1.74)	41.98	N/A	0.07	(−3.94, 5.24)	NS
Serum ApoA-I levels	14	SMD	1782	**−1.16 (−1.72 to −0.59)**	**−1.19 (−1.30 to −1.08)**	**−1.15 (−1.72 to −0.59)**	−0.16 (−0.43 to 0.11)	**−1.15 (−1.80 to −0.50)**	96.01	1.00	1.11	(−3.53, 1.22)	III/III
Plasma ApoA-I levels	6	SMD	702	**−1.13 (−2.05 to −0.21)**	**−0.35 (−0.52 to −0.18)**	**−1.13 (−2.05 to −0.22)**	0.00 (−0.21 to 0.21)	−1.20 (−2.93 to 0.53)	94.63	0.13	1.20	(−4.44, 2.18)	NS
Peripheral blood ApoA-I levels	20	SMD	2484	**−1.15 (−1.63 to −0.66)**	**−0.94 (−1.03 to −0.84)**	**−1.15 (−1.63 to −0.67)**	0.00 (−0.21 to 0.21)	**−1.16 (−1.75 to −0.57)**	96.07	0.67	1.14	(−3.45, 1.15)	III/III
CSF ApoA-I levels	6	SMD	671	0.20 (−0.16 to 0.56)	**0.22 (0.06 to 0.39)**	0.20 (−0.16 to 0.57)	**0.22 (0.01 to 0.43)**	0.19 (−0.36 to 0.74)	68.96	0.89	0.13	(−0.93, 1.34)	NS
Plasma p-Y-IRS-1 levels	3	SMD	152	−2.40 (−5.26 to 0.46)	−0.07 (−0.27 to 0.13)	−2.40 (−5.25 to 0.45)	**0.33 (0.11 to 0.55)**	−2.46 (−9.95 to 5.03)	98.50	0.30	6.17	(−38.96, 34.16)	NS
Plasma HSP levels	2	SMD	86	−0.25 (−3.20 to 2.69)	**−0.65 (−1.15 to −0.15)**	−0.25 (−3.19 to 2.69)	**−1.74 (−2.38 to −1.10)**	−0.24 (−19.33 to 18.85)	96.89	N/A	4.36	N/A	NS
Plasma/serum insulin-like growth factor-1 (IGF-1) levels	17	SMD	2264	−0.01 (−0.35 to 0.32)	**−0.18 (−0.26 to −0.09)**	−0.01 (−0.35 to 0.33)	−0.15 (−0.34 to 0.04)	0.02 (−0.49 to 0.52)	92.57	0.30	0.44	(−1.47, 1.45)	NS
CSF IGF-1 levels	3	SMD	285	**−2.40 (−4.36 to −0.43)**	−0.04 (−0.29 to 0.21)	**−2.44 (−4.44 to −0.45)**	0.09 (−0.22 to 0.40)	−3.14 (−17.08 to 10.80)	97.45	0.30	2.76	(−27.18, 22.3)	NS
TNF- levels	17	SMD	1045	−0.43 (−1.08 to 0.22)	−0.13 (−0.27 to 0.01)	−0.43 (−1.08 to 0.21)	**0.42 (0.03 to 0.82)**	−0.45 (−1.27 to 0.37)	95.11	0.04	1.73	(−3.32, 2.46)	NS
IL-6 levels	14	SMD	718	0.34 (−0.26 to 0.95)	**0.20 (0.04 to 0.36)**	0.35 (−0.26 to 0.95)	−0.14 (−0.58 to 0.29)	0.38 (−0.53 to 1.29)	92.73	0.45	1.21	(−2.14, 2.84)	NS
IL-1β levels	10	SMD	982	0.71 (−0.44 to 1.86)	**1.22 (1.07 to 1.38)**	0.71 (−0.44 to 1.86)	**2.94 (2.68 to 3.20)**	0.71 (−0.37 to 1.79)	97.90	0.72	3.31	(−3.7, 5.12)	NS
IL-18 levels	6	SMD	383	0.00 (−0.66 to 0.66)	−0.06 (−0.27 to 0.16)	0.00 (−0.65 to 0.65)	**−0.50 (−0.93 to −0.07)**	0.00 (−0.85 to 0.86)	88.97	0.26	0.59	(−2.33, 2.33)	NS
IL-12 levels	4	SMD	172	−0.49 (−3.78 to 2.79)	**−1.28 (−1.65 to −0.92)**	−1.18 (−2.65 to 0.29)	**−1.97 (−2.58 to −1.35)**	−1.18 (−3.69 to 1.34)	93.63	0.68	2.10	(−8.79, 5.83)	NS
IL-8 levels	5	SMD	497	1.32 (−0.67 to 3.32)	**−0.68 (−0.90 to −0.47)**	1.32 (−0.64 to 3.28)	**−1.22 (−1.47 to −0.98)**	1.40 (−2.54 to 5.34)	97.54	0.09	4.82	(−6.36, 9)	NS
IFN-gamma levels	4	SMD	222	−0.27 (−0.60 to 0.07)	−0.27 (−0.60 to 0.06)	−0.44 (−1.93 to 1.05)	0.18 (−0.33 to 0.70)	−0.44 (−3.30 to 2.41)	94.86	1.00	2.19	(−7.6, 6.72)	NS
IP-10 levels	2	SMD	77	3.44 (−2.56 to 9.44)	**0.89 (0.34 to 1.43)**	3.44 (−2.55 to 9.44)	0.47 (−0.11 to 1.04)	3.53 (−35.35 to 42.41)	96.77	N/A	18.12	N/A	NS
IL-16 levels	2	SMD	100	−1.11 (−3.38 to 1.16)	**−1.27 (−1.75 to −0.80)**	−1.11 (−3.38 to 1.17)	**−2.26 (−2.90 to −1.62)**	−1.10 (−15.84 to 13.64)	95.50	N/A	2.57	N/A	NS
IL-7 levels	2	SMD	129	−0.38 (−0.76 to 0.01)	−0.38 (−0.75 to 0.00)	−0.38 (−0.75 to 0.00)	−0.37 (−0.80 to 0.07)	**−0.38 (−0.54 to −0.21)**	0.00	N/A	0.00	N/A	IV
IL-5 levels	2	SMD	129	−0.24 (−0.62 to 0.14)	−0.24 (−0.62 to 0.13)	−0.24 (−0.62 to 0.13)	−0.17 (−0.60 to 0.26)	−0.24 (−1.96 to 1.47)	0.00	N/A	0.00	N/A	NS
CRP levels	6	SMD	720	−0.37 (−1.59 to 0.86)	0.07 (−0.10 to 0.24)	**−0.37 (0.86 to 0.56)**	−0.20 (−0.47 to 0.06)	−0.49 (−4.04 to 3.06)	97.63	1.00	2.22	(−4.85, 4.12)	NS

Table 2 (*continued*)

Biomarkers	Included studies	Metrics	Total sample	Reported summary estimated effect (95 % CI); Random effect model	Re-analysed summary estimated effect (95 % CI) DL method			Re-analysed summary estimated effect (95 % CI) HKSJ method; random effect model	Heterogeneity I^2 (%)	Egger's p-value	Tau square, τ	95 % prediction interval	CE/ CES*
					Fixed-effect model	Random effect model	Largest study						
MCP-1 levels	3	SMD	153	0.20 (−0.73 to 1.13)	0.02 (−0.38 to 0.42)	0.20 (−0.72 to 1.12)	**−0.61 (−1.19 to −0.03)**	0.23 (−1.65 to 2.12)	79.77	0.30	0.53	(−10.79, 11.18)	NS
MIP-1 levels	3	SMD	182	−0.26 (−1.70 to 1.90)	**−0.57 (−0.90 to −0.24)**	−0.26 (−1.70 to 1.19)	**−1.61 (−2.09 to −1.12)**	−0.23 (−3.27 to 2.81)	94.35	0.30	1.53	(−18.53, 18.02)	NS
RANTES levels	2	MD	340	−4.38 (−14.19 to 6.03)	**−8.77 (−9.28 to −8.25)**	−4.37 (−14.78 to 6.04)	**−8.80 (−9.34 to −8.26)**	−3.40 (−72.01 to 65.21)	81.92	N/A	47.78	N/A	NS
GM-CSF levels	2	SMD	45	0.14 (−0.46 to 0.74)	0.14 (−0.43 to 0.71)	0.14 (−0.43 to 0.71)	0.11 (−0.69 to 0.91)	0.14 (−0.30 to 0.58)	0.00	N/A	0.00	N/A	NS
IL-4 levels	2	SMD	83	−0.38 (−1.02 to 0.26)	**−0.43 (−0.84 to −0.01)**	−0.37 (−1.01 to 0.27)	**−0.66 (−1.19 to −0.13)**	−0.34 (−4.53 to 3.85)	54.53	N/A	0.12	N/A	NS
IL-10 levels	3	SMD	179	0.10 (−0.35 to 0.55)	0.05 (−0.27 to 0.37)	0.11 (−0.34 to 0.56)	−0.23 (−0.66 to 0.21)	0.16 (−0.76 to 1.09)	44.22	1.00	0.07	(−4.35, 4.58)	NS
TGF-β1 levels	2	SMD	141	**3.09 (0.72 to 5.47)**	**2.58 (2.11 to 3.04)**	**3.09 (0.72 to 5.46)**	**1.91 (1.33 to 2.44)**	3.12 (−12.25 to 18.49)	95.20	N/A	2.79	N/A	NS
IL-1 levels	2	SMD	82	**0.90 (0.43 to 1.38)**	**0.90 (0.44 to 1.37)**	**0.90 (0.44 to 1.37)**	**0.99 (0.38 to 1.59)**	0.90 (−0.51 to 2.32)	0.00	N/A	0.00	N/A	NS
CSF neurogranin (Ng) ratio	28	Ratio of means	3908	**1.62 (1.50 to 1.75)**	**1.38 (1.37 to 1.39)**	**1.62 (1.50 to 1.75)**	**1.37 (1.36 to 1.39)**	**1.62 (1.48 to 1.77)**	76.44	0.00	0.02	(1.18, 2.23)	II/I
CSF visinin-like protein 1 (VILIP-1) ratio	11	Ratio of means	1568	**1.34 (1.28 to 1.41)**	**1.31 (1.30 to 1.31)**	**1.35 (1.28 to 1.43)**	**1.35 (1.34 to 1.37)**	**1.35 (1.23 to 1.49)**	98.18	0.87	0.01	(1.12, 1.63)	II/II
Total cholesterol levels in blood	25	SMD	4920	**0.17 (0.01 to 0.32)**	**0.16 (0.10 to 0.22)**	**0.17 (0.01 to 0.32)**	−0.14 (−0.31 to 0.02)	0.17 (−0.01 to 0.34)	82.25	0.34	0.11	(−0.55, 0.88)	IV
HDL-C levels in blood	18	SMD	3968	−0.15 (−0.34 to 0.05)	**−0.16 (−0.22 to −0.09)**	−0.15 (−0.34 to 0.05)	**−0.21 (−0.39 to −0.03)**	−0.14 (−0.38 to 0.09)	86.95	0.60	0.15	(−0.99, 0.7)	NS
LDL-C levels in blood	17	SMD	3862	0.18 (−0.02 to 0.38)	**0.18 (0.11 to 0.25)**	0.18 (−0.02 to 0.38)	0.08 (−0.10 to 0.25)	0.18 (−0.05 to 0.41)	86.64	0.88	0.14	(−0.65, 1.02)	NS
Triglyceride levels in blood	25	SMD	4920	**0.17 (0.01 to 0.32)**	**0.16 (0.10 to 0.22)**	**0.17 (0.01 to 0.32)**	−0.14 (−0.31 to 0.02)	0.17 (−0.01 to 0.34)	82.25	0.34	0.11	(−0.55, 0.88)	IV
Neurofilament (NfL) concentration in CSF	29	Ratio of means	4368	**2.12 (1.85 to 2.42)**	**1.99 (1.92 to 2.06)**	**2.12 (1.86 to 2.41)**	**1.41 (1.29 to 1.55)**	**2.12 (1.85 to 2.42)**	90.95	0.24	0.10	(1.08, 4.13)	II/II
Peripheral BDNF levels	28	SMD	3481	**−0.51 (−59.00 to −0.44)**	**−0.51 (−0.59 to −0.44)**	**−0.73 (−1.07 to −0.39)**	0.06 (−0.14 to 0.25)	**−0.77 (−1.22 to −0.31)**	95.00	0.10	0.76	(−2.55, 1.09)	III/II
Brain aluminum levels	20	SMD	386	**0.88 (0.25 to 1.51)**	**0.58 (0.37 to 0.80)**	**0.92 (0.30 to 1.53)**	0.17 (−0.51 to 0.84)	1.92 (−0.43 to 4.27)	86.12	0.05	1.55	(−1.78, 3.61)	IV
Serum aluminum levels	12	SMD	708	**0.28 (0.03 to 0.54)**	**0.26 (0.11 to 0.41)**	**0.28 (0.03 to 0.54)**	**0.66 (0.29 to 1.03)**	**0.29 (0.01 to 0.57)**	62.84	0.41	0.12	(−0.54, 1.11)	IV
CSF aluminum levels	4	SMD	124	**0.48 (0.03 to 0.93)**	**0.45 (0.09 to 0.81)**	**0.47 (0.01 to 0.93)**	0.28 (−0.25 to 0.81)	0.48 (−0.34 to 1.30)	32.59	1.00	0.07	(−1.06, 2.01)	NS
F2-isoprostane (blood samples)	4	Hedge's g	374	0.91 (−0.14 to 1.96)	**0.50 (0.25 to 0.75)**	0.92 (−0.14 to 1.97)	−0.20 (−0.59 to 0.20)	0.95 (−1.06 to 2.96)	93.82	0.06	1.08	(−4.12, 5.95)	NS
8-*iso*-PGF2α (blood samples)	6	Hedge's g	464	**0.68 (0.05 to 1.32)**	**0.64 (0.44 to 0.83)**	**0.69 (0.04 to 1.33)**	0.03 (−0.34 to 0.40)	0.69 (−0.21 to 1.58)	90.48	0.70	0.58	(−1.62, 3)	NS
F2-isoprostane (CSF samples)	6	Hedge's g	170	**1.48 (0.97 to 1.98)**	**1.35 (1.03 to 1.67)**	**1.49 (0.99 to 1.99)**	**0.77 (0.22 to 1.33)**	**1.56 (0.91 to 2.21)**	56.09	0.01	0.21	(0.02, 2.96)	IV
8-*iso*-PGF2α (CSF samples)	2	Hedge's g	209	0.40 (−0.06 to 0.86)	**0.34 (0.07 to 0.61)**	0.42 (−0.05 to 0.89)	0.27 (−0.02 to 0.56)	0.50 (−2.89 to 3.89)	40.42	N/A	0.06	N/A	NS
F2-isoprostane (Frontal lobe tissue samples)	4	Hedge's g	94	**1.98 (0.77 to 3.20)**	**1.92 (1.44 to 2.41)**	**1.97 (0.77 to 3.17)**	**1.20 (0.24 to 2.15)**	1.98 (−0.06 to 4.02)	83.52	0.63	1.25	(−3.51, 7.44)	NS
8-*iso*-PGF2α (Frontal lobe tissue samples)	1	Hedge's g	27	**1.93 (0.98 to 2.88)**	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	IV
F2-isoprostane levels	25	Hedge's g	1627	**1.00 (0.69 to 1.32)**	**0.71 (0.61 to 0.82)**	**1.01 (0.69 to 1.32)**	0.27 (−0.02 to 0.56)	**1.05 (0.67 to 1.44)**	87.87	0.00	0.54	(−0.55, 2.56)	III/II

Abbreviations: AD, Alzheimer's disease; BDNF, brain-derived neurotrophic factor; CSF, cerebrospinal fluid; eSMD, equivalent standardized mean differences; FLOT1, Flotillin-1; GFAP, glial fibrillary acidic protein; IL-7, Interleukin 7; LAMP1, Lysosomal-associated membrane protein 1; MCI, mild cognitive impairment; OCT, optical coherence tomography; PET, positron emission tomography; RNFL, retinal nerve fiber layer; RoM, ratio of means; sTREM2, triggering receptor expressed on myeloid cells 2.

The bold indicated statistical significance (*P*-value < 0.05).

* Class and quality of evidence: CE = class of evidence (convincing (I), highly suggestive (II), suggestive (III), weak (IV)); CES = class of evidence after leave-one-out sensitivity analysis.

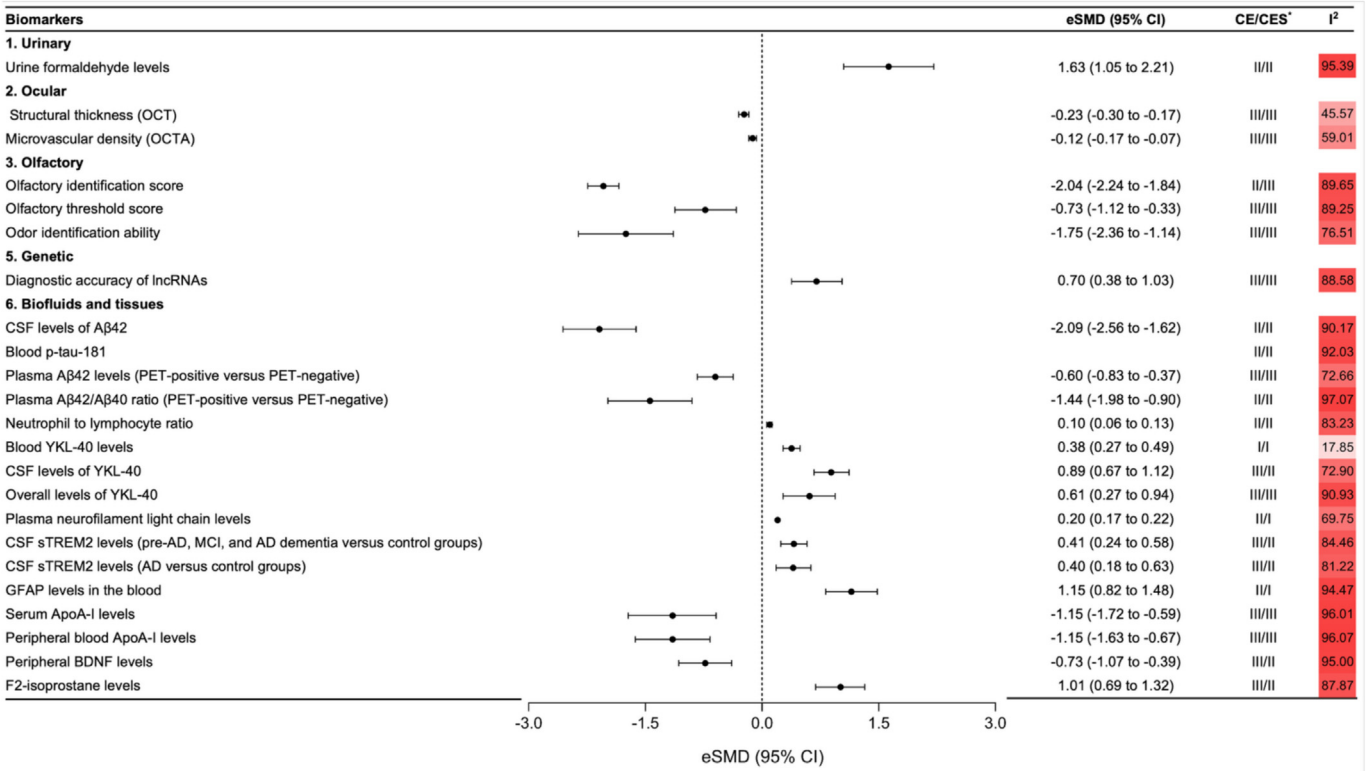


Fig. 2. Summary estimates of *meta*-analyses of potential biomarkers for Alzheimer's disease; only associations for which an eSMD was available are displayed. *Abbreviations*: AD, Alzheimer's disease; BDNF, brain-derived neurotrophic factor; CE, credibility of evidence; CES, credibility of evidence for sensitivity analysis; CI, confidence interval; CSF, cerebrospinal fluid; eSMD, equivalent standardized mean difference; GFAP, glial fibrillary acidic protein; lncRNA, long non-coding RNA; MCI, mild cognitive impairment; OCT, optical coherence tomography; OCTA, optical coherence tomography angiography; PET, positron emission tomography; TREM2, triggering receptor expressed on myeloid cells 2; YKL-40, chitinase-3-like protein 1. *CE = class of evidence (convincing (I), highly suggestive (II), suggestive (III), weak (IV)); CES = class of evidence after removing each study one at a time for sensitivity analysis.

may be related to the decreased microvascular density in the retina [24,71]. Therefore, these changes in ocular vessels, evidenced by lower vessel density of superficial capillary plexus and deep capillary plexus vessels, have the potential to act as ocular biomarkers for AD.

c. Olfactory biomarkers.

Throughout the pathological process of AD, patients showed anatomical and pathological changes in critical brain regions related to olfactory functions (e.g., peripheral and central olfactory cortex, olfactory bulb and tract regions, layers II and III of the entorhinal cortex, and the horn of Ammon) [26]. Deficits in these key olfactory areas lead to impaired odor detection, recognition, and discrimination in patients with AD [72]. These olfactory dysfunctions have appeared before cognitive impairments occur in patients with AD [73]. Our studies also showed impaired odor identification ability in patients with AD compared to healthy controls, suggesting its potential as an olfactory biomarker for AD with highly suggestive evidence level.

However, previous studies have indicated that olfactory loss, hyposmia, and anosmia can also be part of normal aging, complicating the interpretation of olfactory deficits in clinical practice [26]. Therefore, the viability of olfactory biomarkers for AD depends on distinguishing between aging-related olfactory decline and olfactory impairments due to AD [26]. Previous studies suggested that patients with AD reported lower olfactory identification scores compared to individuals with mild cognitive impairment (MCI), indicating that olfactory function decline may capture the transition from MCI to AD [25].

Although our umbrella review did not identify a standardized statistical threshold at which olfactory loss predicts progression from MCI to AD, converging neuropathological evidence suggests that tau and amyloid pathologies begin early in olfactory-associated regions such as the olfactory bulb and entorhinal cortex [74]. These pathologies may underlie olfactory dysfunction specific to AD rather than aging [74]. Thus, future clinical trials should aim to identify diagnostic thresholds that differentiate between MCI, AD, and normal aging in olfactory testing, which could improve early detection of AD by detecting the transition from MCI to AD.

d. Brain structural biomarkers.

Patients with AD showed significant pathological iron deposition in the basal ganglia, specifically in the putamen and caudate nucleus, evidenced by higher QSM values in these regions of patients compared to healthy controls. This substantial increase in QSM values is consistent with previous studies, suggesting that QSM is a key imaging biomarker for detecting brain iron accumulation in neurodegenerative diseases like AD [28]. Iron plays a role in promoting oxidative stress, inflammation, amyloidopathy, and tauopathy [75]; therefore, increased iron levels in the basal ganglia can result in neuronal damage and synaptic loss observed in AD pathology. In addition, iron is important in dopamine metabolism, a neurotransmitter downregulated in AD [75]. Disruption of iron homeostasis in the putamen and caudate nucleus can affect dopamine metabolism and dopaminergic neurons, leading to impaired behavioral symptoms such as impaired motor, emotional, and cognitive functions [76]. Iron is also essential for myelin production, the lipid-rich substance that insulates neurons and facilitates

Table 3
Evidence maps of the umbrella review on biomarkers of Alzheimer's diseases.

	eSMD (95 % CI)	RoM (95 % CI)	Direction	CE/CES*
1. Urinary biomarkers				
Urine formaldehyde levels	**1.63 (1.05 to 2.21)**		Association	II/II
F2-isoprostane (urine samples)	0.63 (−0.33 to 1.60)		No association	NS
8-*iso*-PGF2α (urine samples)	0.68 (−0.30 to 1.66)		No association	NS
2. Ocular biomarkers				
Structural thickness (OCT)	**−0.23 (−0.30 to −0.17)**		Association	III/III
Microvascular density (OCTA)	**−0.12 (−0.17 to −0.07)**		Association	III/III
Macrovascular calibre (Fundus)	−0.10 (−0.27 to 0.07)		No association	NS
Microvascular density	**−0.26 (−0.50 to −0.02)**		Association	IV
Choroidal thickness	−0.61 (−2.20 to 0.98)		No association	NS
3. Olfactory biomarkers				
Olfactory identification score	**2.04 (−2.24 to −1.84)**		Association	II/III
Olfactory threshold score	**−0.73 (−1.12 to −0.33)**		Association	III/III
Olfactory discrimination score	**−1.22 (−1.50 to −0.94)**		Association	IV
Olfactory function (TDI) score	**−1.46 (−1.78 to −1.14)**		Association	IV
Odor identification ability	**−1.75 (−2.36 to −1.14)**		Association	III/III
4. Brain structural biomarkers				
Quantitative susceptibility mapping values in the putamen	**1.28 (0.52 to 2.04)**		Association	IV
Quantitative susceptibility mapping values in the globus pallidus	0.82 (−0.16 to 1.80)		No association	NS
Quantitative susceptibility mapping values in the caudate nucleus	**0.72 (0.25 to 1.20)**		Association	IV
Quantitative susceptibility mapping values in the thalamus	1.06 (−0.94 to 3.06)		No association	NS
Cerebral blood flow in the hippocampus	−2.85 (−6.03 to 0.34)		No association	NS
Callosal midsagittal area changes	**−0.85 (−1.01 to −0.69)**		Association	IV
5. Genetic biomarkers				
Diagnostic accuracy of lncRNAs	**0.70 (0.38 to 1.03)**		Association	III/III
Diagnostic accuracy of BACE1-AS lncRNA	0.82 (−1.57 to 3.21)		No association	NS
APOE ε4	1.93 (0.81 to 4.63)		No association	NS
6. Biofluids and tissues (saliva, blood, CSF, serum, and tissue sample)				
Salivary Aβ1-42		**1.92 (1.23 to 2.99)**	Association	IV
Salivary t-tau		0.97 (0.62 to 1.50)	No association	NS
Salivary p-tau		0.93 (0.50 to 1.73)	No association	NS
CSF levels of Aβ42	**−2.09 (−2.56 to −1.62)**		Association	II/II
Neurogenic exosome Aβ42	**1.71 (1.21 to 2.20)**		Association	IV
Neurogenic exosome t-tau	1.00 (−0.13 to 2.13)		No association	NS
Neurogenic exosome p-tau181	**1.76 (1.16 to 2.36)**		Association	IV
Blood p-tau-181		**1.80 (1.64 to 1.98)**	Association	II/II
Blood p-tau-217		4.26 (0.81 to 2.21)	No association	NS
Blood p-tau-231		**1.97 (1.74 to 2.23)**	Association	IV
Plasma Aβ40 levels (PET-positive versus PET-negative)	0.75 (−0.02 to 1.51)		No association	NS
Plasma Aβ42 levels (PET-positive versus PET-negative)	**−0.60 (−0.83 to −0.37)**		Association	III/III
Plasma Aβ42/Aβ40 ratio (PET-positive versus PET-negative)	**−1.44 (−1.98 to −0.90)**		Association	II/II
Plasma p-T181-tau levels	4.69 (−1.07 to 10.46)		No association	NS
Plasma p-S396-tau levels	3.06 (−2.65 to 8.76)		No association	NS
Platelet AβPP ratio levels	**−1.88 (−2.34 to −1.42)**		Association	IV
ApoE levels	−0.03 (−0.07 to 0.01)		No association	NS
Blood S100B levels	0.50 (−1.02 to 2.02)		No association	NS
Neutrophil to lymphocyte ratio	**0.10 (0.06 to 0.13)**		Association	II/II
serum VEGF concentrations	0.86 (−2.36 to 4.07)		No association	NS
CSF VEGF concentrations	−0.13 (−0.42 to 0.17)		No association	NS
Salivary AChE		0.86 (0.15 to 4.94)	No association	NS
Blood YKL-40 levels	**0.38 (0.27 to 0.49)**		Association	I/I
CSF levels of YKL-40	**0.89 (0.67 to 1.12)**		Association	III/II
Overall levels of YKL-40	**0.61 (0.27 to 0.94)**		Association	III/III
Plasma neurofilament light chain levels	**0.20 (0.17 to 0.22)**		Association	II/I
CSF sTREM2 levels (pre-AD, MCI, and AD dementia versus control groups)	**0.41 (0.24 to 0.58)**		Association	III/II
CSF sTREM2 levels (AD versus control groups)	**0.40 (0.18 to 0.63)**		Association	III/II
GFAP levels in the blood	**1.15 (0.82 to 1.48)**		Association	II/I
CSF synaptosomal-associated protein 25 (SNAP-25) levels		**1.50 (1.29 to 1.74)**	Association	IV
CSF endocytosis markers (AP2B1)	**0.54 (0.19 to 0.89)**		Association	IV
CSF endocytosis markers (FLOT1)	**−0.49 (−0.62 to −0.35)**		Association	IV
CSF intra-lysosomal markers (GM2A)	**0.51 (0.05 to 0.97)**		Association	IV
CSF intra-lysosomal markers (CTSB)	**0.20 (0.03 to 0.38)**		Association	IV
CSF intra-lysosomal markers (CTSZ)	**−0.16 (−0.31 to −0.01)**		Association	IV
CSF lysosomal membrane proteins (LAMP1)	**0.77 (0.06 to 1.48)**		Association	IV
CSF lysosomal membrane proteins (LAMP2)	**0.50 (0.14 to 0.85)**		Association	IV
CSF autophagy marker (LC3B)	0.65 (−0.44 to 1.74)		No association	NS
Serum ApoA-I levels	**−1.15 (−1.72 to −0.59)**		Association	III/III
Plasma ApoA-I levels	−1.20 (−2.93 to 0.53)		No association	NS
Peripheral blood ApoA-I levels	**−1.15 (−1.63 to −0.67)**		Association	III/III
CSF ApoA-I levels	0.19 (−0.36 to 0.74)		No association	NS
Plasma p-Y-IRS-1 levels	−2.46 (−9.95 to 5.03)		No association	NS
Plasma HSP levels	−0.24 (−19.33 to 18.85)		No association	NS
Plasma/serum insulin-like growth factor-1 (IGF-1) levels	−0.01 (−0.35 to 0.33)		No association	NS
CSF IGF-1 levels	−3.14 (−17.08 to 10.80)		No association	NS

(*continued on next page*)

Table 3 (*continued*)

	eSMD (95 % CI)	RoM (95 % CI)	Direction	CE/CES*
TNF-α levels	−0.43 (−1.08 to 0.21)		No association	NS
IL-6 levels	0.35 (−0.26 to 0.95)		No association	NS
IL-1β levels	0.71 (−0.44 to 1.86)		No association	NS
IL-18 levels	0.00 (−0.85 to 0.86)		No association	NS
IL-12 levels	−1.18 (−3.69 to 1.34)		No association	NS
IL-8 levels	1.40 (−2.54 to 5.34)		No association	NS
IFN-gamma levels	−0.44 (−3.30 to 2.41)		No association	NS
IP-10 levels	3.53 (−35.35 to 42.41)		No association	NS
IL-16 levels	−1.10 (−15.84 to 13.64)		No association	NS
IL-7 levels	**−0.38 (−0.54 to −0.21)**		Association	IV
IL-5 levels	−0.24 (−1.96 to 1.47)		No association	NS
CRP levels	−0.49 (−4.04 to 3.06)		No association	NS
MCP-1 levels	0.23 (−1.65 to 2.12)		No association	NS
MIP-1α levels	−0.23 (−3.27 to 2.81)		No association	NS
RANTES levels	−0.01 (−0.11 to 0.10)		No association	NS
GM-CSF levels	0.14 (−0.30 to 0.58)		No association	NS
IL-4 levels	−0.34 (−4.53 to 3.85)		No association	NS
IL-10 levels	0.16 (−0.76 to 1.09)		No association	NS
TGF-β1 levels	3.12 (−12.25 to 18.49)		No association	NS
IL-1α levels	0.90 (−0.51 to 2.32)		No association	NS
CSF neurogranin (Ng) ratio		**1.62 (1.50 to 1.75)**	Association	II/I
CSF visinin-like protein 1 (VILIP-1) ratio		**1.35 (1.28 to 1.43)**	Association	II/II
Total cholesterol levels in blood	**0.17 (0.01 to 0.32)**		Association	IV
HDL-C levels in blood	−0.15 (−0.34 to 0.05)		No association	NS
LDL-C levels in blood	0.18 (−0.02 to 0.38)		No association	NS
Triglyceride levels in blood	**0.17 (0.01 to 0.32)**		Association	IV
Neurofilament (NfL) concentration in CSF		**2.12 (1.86 to 2.41)**	Association	II/II
Peripheral BDNF levels	**−0.73 (−1.07 to −0.39)**		Association	III/II
Brain aluminum levels	**0.92 (0.30 to 1.53)**		Association	IV
Serum aluminum levels	**0.28 (0.03 to 0.54)**		Association	IV
CSF aluminum levels	0.48 (−0.34 to 1.30)		No association	NS
F2-isoprostane (blood samples)	0.95 (−1.06 to 2.96)		No association	NS
8-*iso*-PGF2α (blood samples)	0.69 (−0.21 to 1.58)		No association	NS
F2-isoprostane (CSF samples)	**1.56 (0.91 to 2.21)**		Association	IV
8-*iso*-PGF2α (CSF samples)	0.50 (−2.89 to 3.89)		No association	NS
F2-isoprostane (Frontal lobe tissue samples)	1.98 (−0.06 to 4.02)		No association	NS
8-*iso*-PGF2α (Frontal lobe tissue samples)	**1.93 (0.98 to 2.88)**		Association	IV
F2-isoprostane levels	**1.01 (0.69 to 1.32)**		Association	III/II

Abbreviations: AD, Alzheimer's disease; BACE1-AS, β-site APP-cleaving enzyme 1 antisense RNA; BDNF, brain-derived neurotrophic factor; CSF, cerebrospinal fluid; eSMD, equivalent standardized mean differences; FLOT1, Flotillin-1; GFAP, glial fibrillary acidic protein; IL-7, Interleukin 7; LAMP1, Lysosomal-associated membrane protein 1; MCI, mild cognitive impairment; NS, not significant; OCT, optical coherence tomography; PET, positron emission tomography; RNFL, retinal nerve fiber layer; RoM, ratio of means; sTREM2, triggering receptor expressed on myeloid cells 2.
Color represented the levels of eSMD or RoM in data with statistical significance (*P*-value < 0.05).
* Class and quality of evidence: CE = class of evidence (convincing (I), highly suggestive (II), suggestive (III), weak (IV)); CES = class of evidence after leave-one-out sensitivity analysis.

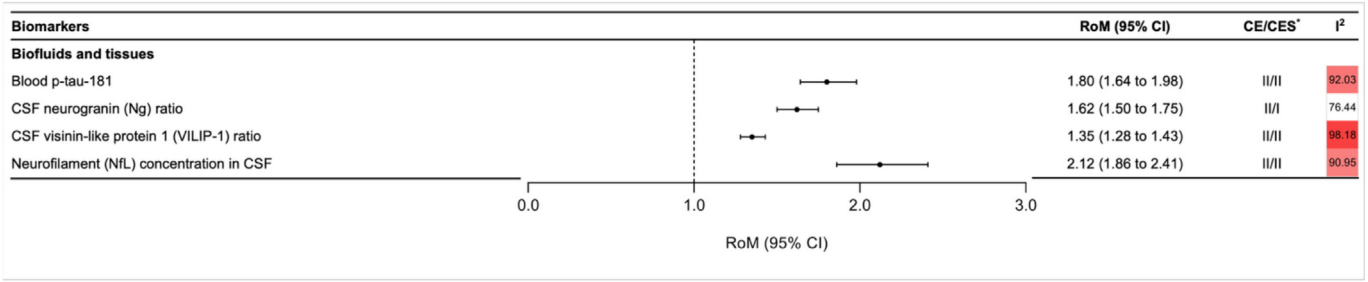


Fig. 3. Summary estimates of *meta*-analyses of potential biomarkers for Alzheimer's disease; only associations for which an RoM was available are displayed. *Abbreviations*: CE, credibility of evidence; CES, credibility of evidence for sensitivity analysis; CI, confidence interval; CSF, cerebrospinal fluid; RoM, Ratio of means. *CE = class of evidence (convincing (I), highly suggestive (II), suggestive (III), weak (IV)); CES = class of evidence after removing each study one at a time for sensitivity analysis.

electrical signal transmission [75]; thus, excess iron accumulation may be a consequence of decreased myelin production and neuronal cell death in patients with AD.

Apart from iron accumulation, we found a reduced callosal midsagittal area in patients with AD, suggesting its potential as a brain structural biomarker.[30] The corpus callosum plays a critical role in the hemispheric integration and communication of perceptual, cognitive, and volitional information [77,78]. Patients with AD frequently show atrophy of the corpus callosum, particularly in the callosal midsagittal area [77,78]. Reduction in the area of the corpus callosum results in impaired interhemispheric functional connectivity, ultimately leading to cognitive deficits [79]. Our study

suggests that increased QSM levels in the putamen and caudate nucleus, along with a reduced callosal midsagittal area, could serve as biomarkers for AD.

e. Genetic biomarkers.

lncRNAs have been reported to be involved in the pathogenesis of neurodegenerative diseases such as AD. Previous studies have suggested that exosomal lncRNAs in plasma could serve as potential biomarkers for AD. Our re-analysis findings also supported that lncRNAs had higher diagnostic accuracy in identifying AD, backed by a suggestive level of evidence, indicating their potential as promising diagnostic biomarkers for AD [27]. We also performed a post-hoc analysis for apolipoprotein E (APOE) ε4 [58], a well-established genetic risk for AD in several previous studies. However, our re-analysis did not identify a statistically significant association between APOE ε4 and AD diagnosis under the Ioannidis framework, and thus it was not included in the final credibility classification. This discrepancy highlights that even widely recognized biomarkers may not fulfill stringent statistical thresholds in umbrella reviews of observational *meta*-analyses. Furthermore, although several individual lncRNAs, such as β-site APP-cleaving enzyme 1 antisense RNA (πτ), nuclear enriched abundant transcript 1, and metastasis associated lung adenocarcinoma transcript 1 —, have been suggested in previous studies, including Shobeiri et al., our re-analysis did not find statistically significant associations for any specific lncRNA after applying the predefined criteria [27].

f. Biofluids and tissues (CSF, blood, serum, saliva, and tissue samples).

Amyloidopathy and tauopathy are two well-known major pathological processes of AD. Patients with AD exhibit extracellular accumulation of Aβ plaques and intracellular neurofibrillary tangles [80]. Aβ primarily consists of Aβ40 and Aβ42, both derived from AβPP, but they differ in lengths of amino acids. Compared to Aβ40, Aβ42 is more prone to aggregation into amyloid plaques in the brain, and its oligomers are highly neurotoxic [80]. Conversely, Aβ40 may have antioxidative and anti-amyloidogenic effects, and it is mainly present in cerebral amyloid angiopathy. [33,80] Thus, Aβ42 aggregates form amyloid plaques in the brains of patients with AD, reducing the amount secreted into the extracellular space or CSF [81]. The blood–brain barrier (BBB) regulates the passage of Aβ42 between the central nervous system and blood [81]. As AD progresses, CSF Aβ42 levels significantly decrease while Aβ40 levels remain within the normal range. The Aβ42/Aβ40 ratio can be effectively normalized to individual differences, and a lower plasma Aβ42/Aβ40 ratio in patients with AD indicates the selective deposition of Aβ42 in the brain as insoluble amyloid plaques, predicting dementia onset [82]. Our study found significantly lower CSF Aβ42 levels, lower plasma Aβ42 levels, and a lower Aβ42/Aβ40 ratio, supported by highly suggestive evidence levels.

Our umbrella review also revealed that unlike CSF and plasma Aβ42 levels, saliva and neurogenic exosome Aβ42 levels increased. Neurogenic exosomes are small vesicles involved in intercellular signaling, and in patients with AD, stressed neuronal cells may attempt to remove Aβ42, resulting in higher Aβ42 levels in neurogenic exosomes [33]. Similarly, elevated Aβ42 levels in saliva may reflect peripheral accumulation or active clearance from the brain, particularly under early neuroinflammatory stress. Similarly, elevated Aβ42 levels in saliva may reflect peripheral accumulation or active clearance from the brain, particularly under early neuroinflammatory stress. Previous study suggested that salivary Aβ42 may reflect AD pathology and has been proposed as a potential non-invasive biomarker [31]. However, further studies are needed to validate its diagnostic sensitivity and temporal dynamics relative to central biomarkers [83]. Platelet AβPP, which is directly associated with amyloidopathy as a precursor protein of Aβ, also shows potential as a biomarker. Reduced platelet AβPP ratios in patients are an outcome driven by abnormal processing and increased accumulation of Aβ [49].

In addition to amyloidopathy, tauopathy-associated biomarkers show significant associations. In AD, tau protein becomes hyperphosphorylated and aggregates into neurofibrillary tangles within neurons, disrupting normal cell function and contributing to neuronal death [84]. When neurons are damaged and die, p-tau is released into the extracellular space, entering the bloodstream or being encapsulated in exosomes. Exosomes help remove damaged or excess proteins from neurons.[85] In AD, increased neuronal damage results in more p-tau-containing exosomes being released into the blood.[85] Dysfunction of the BBB also contributes to increased leakage of tau protein from the brain into the blood, increasing plasma p-tau levels.[86].

Neuroinflammation is a hallmark pathological process in AD, with astroglia and microglia playing critical roles in mediating this response. Prior studies suggested that AD pathology is accompanied by significant functional and morphological changes in both microglia and astrocytes [87]. YKL-40, a glycoprotein secreted by reactive astrocytes and microglia, plays a key role in extracellular matrix remodeling and chronic neuroinflammation [88]. GFAP, an intermediate filament protein, is a hallmark of astrogliosis and reflects astrocytic reactivity in response to neuronal injury [89]. sTREM2, expressed on microglial surfaces, regulates microglial activation, phagocytosis, and lipid metabolism. These glial biomarkers, YKL-40, GFAP, and sTREM2, interact along shared pathways, representing a networked immune response to neuronal damage in AD pathology [35,36]. Their simultaneous elevation in patients with AD suggests co-activation of astrocytic and microglial processes, providing a more comprehensive and biologically plausible indicator of disease progression than any single biomarker alone. In addition, neurofilament levels in CSF and plasma, indicative of axonal injury, may complement glial markers in capturing broader neurodegenerative changes.

Importantly, in our main analysis, blood YKL-40 was the only biomarker reaching Class I credibility (convincing evidence). YKL-40 reflects chronic glial activation and neuroinflammation. Through additional sensitivity analysis (CES), we identified two more biomarkers reaching Class I credibility: blood GFAP and CSF VILIP-1 ratio. GFAP reflects reactive astrocytic responses following pathological changes, while VILIP-1, a calcium sensor protein expressed in neurons, is associated with disrupted calcium signaling and neuronal damage in AD [90]. The robustness of these findings across sensitivity analyses supports their potential as core biomarkers for AD diagnosis and monitoring.

Here, we also suggested several markers related to endosomal-lysosomal and autophagy pathways, which are associated with the progression of AD. Upon re-analysis, among several candidate proteins, seven (AP2B1, GM2A, CTSB, CTSZ, LAMP1, LAMP2, and FLOT1) showed statistically significant associations with AD. Increased AP2B1 is related to heightened endocytosis and attempts to remove abnormal proteins such as Aβ [39]. Elevated LAMP1 levels may reflect the accumulation of dysfunctional lysosomes and impaired autophagic flux, which are known pathological features of AD [39]. Preclinical studies showed that lysosomal function is crucial for Aβ clearance in cells [91]. Conversely, decreased FLOT1 levels are associated with abnormalities in cell membrane structure and signaling, as well as disruptions in the endocytic pathway [39]. These findings suggest their potential as biomarkers for AD.

Moreover, we identified various other biomarkers associated with AD. Decreased levels of the proinflammatory cytokine IL-7 suggest changes in immune response and altered neuroinflammation [44]. Reduced levels of peripheral BDNF are related to decreased neuronal survival, neurodegeneration, and cognitive

decline, as BDNF plays a crucial role in neuronal differentiation, survival, and synaptic plasticity.[92] Increased serum aluminum levels are associated with neurotoxicity, oxidative stress, and enhanced inflammatory responses.[93] Elevated levels of F2-isoprostane and 8-*iso*-PGF2, biomarkers of lipid peroxidation, indicate increased oxidative stress and neuronal damage [94]. Increased SNAP-25 levels suggest synaptic damage and the reorganization of neural connections, as SNAP-25 can regulate spine morphogenesis [95]. Elevated neurogranin levels are associated with synaptic dysfunction and impaired neural signaling [96,97]. Higher VILIP-1 levels indicate neuronal damage and disrupted calcium signaling [45]. These findings provide a comprehensive overview of potential biomarkers for AD, highlighting their roles in various pathological processes, including neuroinflammation, synaptic damage, oxidative stress, and neuronal survival. This multifaceted approach underscores the complexity of AD and the need for a diverse array of biomarkers to improve diagnosis and understanding of disease progression.

Lastly, AD is only one of several pathological causes of dementia, and the findings of this review had room for interpretation within the broader context of dementia [98]. Dementia encompasses various etiologies, and this umbrella review specifically focused on potential biomarkers for AD. While we sought to include only *meta*-analyses investigating groups of patients diagnosed with AD, some studies included mixed populations, such as those with MCI or other types of dementia [99]. Given the need for additional confirmation of AD through clinical assessment (neurological examination, MRI/CT scans, etc.) and biomarkers (e.g., CSF testing, PET scans), it is possible that some included groups may have encompassed individuals with other neurological disorders or types of dementia, such as Parkinson's disease, vascular dementia, and dementia with Lewy bodies. Moreover, many of the biomarkers reported in this review are frequently observed in other neurodegenerative disorders or types of dementia, such as Lewy body dementia [100]. This may limit the specificity of our findings, but also underscores the clinical relevance of these biomarkers in real-world diagnostic settings. Reliance on a single biomarker is insufficient to improve diagnostic accuracy and differentiate AD from other forms of dementia. Instead, a comprehensive approach utilizing multiple biomarkers, as highlighted in this review, is critical for enhancing the precision of AD diagnosis.

Although all phosphorylated tau epitopes reflect tauopathy, they differ in their biochemical properties, phosphorylation sites, and potential clinical utility. For example, p-tau181 and p-tau231 are involved in early tau phosphorylation processes and are more consistently detectable in peripheral samples [101], contributing to their statistically significant associations with AD in our analysis. In contrast, p-tau217, despite being highly specific in some clinical contexts, showed no significant association in our results. This discrepancy may reflect differences in assay sensitivity, sample heterogeneity, or variability in peripheral expression and clearance dynamics. Moreover, p-tau217 may rise later in the disease course or under specific conditions not fully captured in the included *meta*-analyses [101]. These findings emphasize the importance of considering individual p-tau epitopes separately rather than treating p-tau as a single, uniform biomarker.

Clinical policy implications

Understanding the mechanisms of AD remains complex and inconclusive, necessitating ongoing research into the underlying processes. Although therapeutics are being developed to ameliorate the symptoms of AD, safety issues from side effects (e.g., amyloid-related imaging abnormalities) [102] and a lack of accurate early diagnosis often result in later interventions, limiting their efficacy. Therefore, there is an urgent need for early and/or effective biomarkers for AD. Reliable early diagnosis would enable more timely and successful treatment and disease monitoring. Currently, there is no independent definitive method for diagnosing AD [4]. Physicians and neurologists typically conduct comprehensive evaluations by combining biomarker tests, cognitive assessments (e.g., Mini-Mental State Examination and Montreal Cognitive Assessment), and imaging studies to make an accurate diagnosis and estimate the severity and progression of cognitive impairment.

Guidelines from the NIA-AA provide a diagnostic framework, most recently updated in 2024, incorporating biomarkers and clinical symptoms [6]. This includes CSF levels of Aβ and tau proteins, plasma biomarkers, and imaging techniques such as PET scans to identify amyloid plaques and neurofibrillary tangles. These criteria aim to improve the accuracy of diagnosing and staging AD. International guidelines from organizations such as the European Federation of Neurological Societies and the International Working Group are similar [103,104].

For biomarkers to contribute to more accurate diagnosis, several limitations in present biomarkers must be overcome. Ideal biomarkers for AD should be affordable, specific, sensitive, reliable, and not solely reliant on judgment from specialized clinicians. CSF is considered an optimal source for biomarker development in neurodegenerative diseases like AD due to its direct contact with the brain and ability to reflect molecular changes. However, CSF collection is a significantly invasive procedure, making it less suitable for widespread use in screening or early diagnosis. Based on our findings, non-invasive and accessible biomarkers derived from urine, saliva, or plasma could address some of these limitations and play a supplementary role in early detection.

To enhance clinical translation, the "A/T/N" classification system has emerged as a practical framework. This system categorizes biomarkers into three binary groups: A (amyloid) for amyloid pathology (e.g., amyloid PET or CSF Aβ42); T (tau) for tau pathology (e.g., CSF phosphorylated tau or tau PET); and N (neurodegeneration) for neuronal damage (e.g., fluorodeoxyglucose-PET, structural MRI, or CSF total tau) [105]. Each category is assessed as positive or negative, enabling a biologically grounded staging model of AD. Our findings suggest that several high-credibility biomarkers from biofluids, such as plasma Aβ42/Aβ40, GFAP, YKL-40, p-tau 181/231, and neurofilament light chain, could be integrated within or alongside the A/T/N system as complementary markers. For instance, GFAP and YKL-40 may strengthen the "N" domain by capturing astroglial and inflammatory changes not reflected by conventional neurodegeneration markers. To ensure clinical applicability, future studies should validate these combinations through longitudinal studies in biomarker-confirmed cohorts, ideally using platforms like the Alzheimer's Disease Neuroimaging Initiative. In doing so, statistical associations may be translated into clinically actionable diagnostic panels. We proposed that a multimodal strategy, combining these novel biomarkers with established diagnostic frameworks such as the NIA-AA 2024 criteria [6], has the potential to significantly enhance the precision, accessibility, and early detection capabilities of AD diagnostics.

Future directions

Future studies should prioritize the identification and validation of biomarkers that are not only diagnostically robust but also practical for early detection, monitoring the progression from MCI to AD, and assessing treatment response. Among the candidates identified in this umbrella review, blood YKL-40, plasma GFAP, and CSF VILIP-1 ratio, each supported by Class I or II evidence, emerge as promising biomarkers that could serve these purposes [106]. These markers represent complementary biological pathways (e.g., neuroinflammation, reactive astrocytosis, and neuronal degradation)

and are detectable in peripheral biofluids, making them suitable for longitudinal tracking and scalable screening.

In addition, future studies should also aim to develop more effective diagnostic algorithms that combine a select set of high-credibility biomarkers to improve diagnostic specificity and clinical applicability. Given the overlap of pathological characteristics between AD and other neurodegenerative conditions such as Parkinson's disease and Lewy body dementia, a combinatorial approach, rather than reliance on any single biomarker, is essential to solely identify AD more precisely [107]. For instance, detecting abnormalities in two or more Class I–II biomarkers, potentially integrated with supportive imaging or CSF findings, may offer a feasible framework for early-stage diagnosis and differential classification of AD. Ultimately, translating these biomarkers into real-world tools will require validation of their cost-effectiveness, temporal dynamics, and utility in diverse clinical settings, including low-resource environments. Multimodal diagnostic approaches that incorporate various biomarkers may further enhance diagnostic accuracy, sensitivity, and specificity, enabling more effective monitoring of disease progression [108].

Limitations

While our study provides valuable evidence on various biomarkers for AD, our umbrella review has some limitations. First, the umbrella review relies entirely on existing *meta*-analyses.[109] Second, most of the included studies had observational nature, which limits the ability to infer causality due to potential residual confounding. Despite statistical adjustment in original studies, unmeasured variables, such as lifestyle factors, medication use, or genetic susceptibility, may bias the reported associations. Third, some biomarkers analyzed in our study (e.g., olfactory identification score, BDNF levels) may be influenced by demographic or clinical covariates such as age, sex, or comorbid conditions (e.g., sinusitis, Parkinson's disease, or depression). Follow-up studies should perform stratified analyses to verify whether observed biomarker signals persist across different subgroups and to improve diagnostic precision [109,110]. Fourth, since our umbrella review is based on existing *meta*-analyses, we tried to focus on patients with AD and compare them to healthy controls. However, we cannot completely ignore the heterogeneity in the definitions of groups from the existing *meta*-analyses and original studies [13]. We only addressed associations reported in published *meta*-analyses, which implies we might have missed or underestimated biomarkers not evaluated in other *meta*-analyses [19]. Fifth, we employed the Ioannidis framework, one of the most widely applied approaches for evaluating evidence credibility in umbrella reviews of observational *meta*-analyses [15]. Nonetheless, we acknowledge that certain clinically important biomarkers may have been underestimated due to the strict thresholds of this framework. For example, well-established biomarkers such as the plasma Aβ42/Aβ40 ratio or CSF sTREM2 were categorized into lower credibility classes despite their strong clinical relevance. Moreover, we caution that the absence of statistical significance in certain biomarkers should not be interpreted as evidence of no diagnostic value. Some biomarkers may have failed to meet credibility thresholds due to limited sample sizes, underpowered *meta*-analyses, or insufficient research attention, rather than a true lack of association. These biomarkers may still hold clinical potential and warrant further investigation in future well-designed studies. Sixth, we aimed to exclusively investigate biomarkers for AD by using search terms such as "(Alzheimer's disease [Title/Abstract]) AND ((systematic review [Title/Abstract]) OR (meta [Title/Abstract])" and their variants to focus on prior *meta*-analyses specifically addressing AD. However, we cannot completely exclude the possibility that some included studies were based on clinically diagnosed dementia rather than pathologically confirmed AD. The diagnostic accuracy of clinically diagnosed AD is varied based on diagnostic methods, and approximately 70 % sensitivity and specificity based on CSF tests of Aβ42, Aβ40, Aβ42/Aβ40 ratio, and p-tau, which may introduce bias in interpreting biomarker specificity for AD [99]. Seventh, although we aimed to include studies diagnosing AD, most included *meta*-analyses relied on clinical rather than pathological diagnoses. This limitation reflects the nature of existing evidence in observational biomarker studies, where pathological confirmation is rarely feasible. While clinical diagnostic criteria have moderate sensitivity and specificity, the absence of pathological confirmation may reduce the specificity of associations. Future umbrella reviews should prioritize stratified analyses by diagnostic method where possible to enhance diagnostic confidence. Lastly, the quality of the *meta*-analyses included in our review might not have been directly assessed, which could affect the reliability of our findings. Although we used well-established methodologies in the umbrella review, further modifications in statistical methods could alter the results and certainty of the evidence, introducing potential bias [111,112].

Conclusion

In this umbrella review, we reassessed 106 *meta*-analyzed associations and confirmed 52 statistically significant relationships. Convincing evidence (class I) emerged only for elevated circulating YKL-40. Highly suggestive evidence (class II) supported eleven biomarkers, such as urinary formaldehyde, CSF Aβ42, blood p-tau 181, the plasma Aβ42/Aβ40 ratio, the neutrophil-to-lymphocyte ratio, plasma neurofilament light chain, blood GFAP, the CSF neurogranin ratio, CSF VILIP-1, and CSF neurofilament concentration. An additional fourteen biomarkers, including macular retinal-nerve-fibre-layer thinning on OCT, retinal microvascular rarefaction on OCTA, reduced olfactory identification and threshold scores, CSF YKL-40, CSF sTREM2, serum and peripheral ApoA-I, peripheral BDNF, and total F2-isoprostanes, provided suggestive evidence (class III). The remaining significant associations were graded as weak (class IV). Collectively, these findings delineate a concise panel of AD biomarkers with the highest current credibility, yet the predominance of heterogeneous or small studies highlights the need for large, protocol-driven prospective investigations to establish causality, define clinical cut-offs, and guide future diagnostic guidelines and therapeutic monitoring.

Ethical statement

This systematic review article does not require Institutional Review Board approval. Our systematic review and *meta*-analysis protocol was registered with PROSPERO (Registration No. CRD42024567136).

Contributors

Drs. CJN and DKY had full access to all of the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis. All authors approved the final version of the manuscript before submission. *Study concept and design*: JK, YS, YY, DKY, and CJN; *acquisition, analysis, or interpretation of data*: JK, YS, YY, DKY, and CJN; *drafting of the manuscript*: JK, YS, YY, DKY, and CJN; *critical revision of the manuscript for important intellectual content*: all authors; *statistical analysis*: JK, YS, YY, DKY, and CJN; *study supervision*: CJN and DKY. CJN and DKY supervised the study and served as guarantors. JK, YS, and YY contributed equally as the first authors. CJN and DKY contributed

equally as corresponding authors. The corresponding author attests that all listed authors meet the authorship criteria and that no one meeting the criteria has been omitted.

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The authors declare that they have no financial interests related to the material in the manuscript. This research was conducted independently of any business or financial relationships that could be construed as a potential conflict of interest.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jare.2025.07.022.

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