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Neuroinflammatory fluid biomarkers in patients with Alzheimer's disease: a systematic literature review

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INTRODUCTION: Neuroinflammation is associated with both early and late stages of the pathophysiology of Alzheimer's disease (AD). Fluid biomarkers are gaining significance in clinical practice for diagnosis in presymptomatic stages, monitoring, and disease prognosis. This systematic literature review (SLR) aimed to identify fluid biomarkers for neuroinflammation related to clinical stages across the AD continuum and examined long-term outcomes associated with changes in biomarkers.
METHODS: The SLR was conducted per the Cochrane Handbook for Systematic Reviews of Interventions and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. We used PubMed®, Embase®, and Cochrane Collaboration databases to search for articles in English (between 2012 and 2022) on AD or mild cognitive impairment due to AD, using "neuroinflammation" or other "immune" search strings. Two independent reviewers screened titles and examined data from full-text articles for the SLR.
RESULTS: After the initial screening, 54 studies were prioritized for data extraction based upon their relevance to the SLR research questions. Nine studies for YKL-40, seven studies for sTREM2, and 11 studies for GFAP examined the relationship between the neuroinflammatory biomarkers and the clinical stage of the disease. Nine longitudinal studies further explored the association of fluid biomarkers with long-term clinical outcomes of disease. Cerebrospinal fluid (CSF) levels of YKL-40 were elevated in patients with AD dementia, while CSF sTREM2 levels were more strongly associated with preclinical and early symptomatic stages of AD. Plasma GFAP levels remained consistently elevated both in patients with AD dementia and individuals in preclinical stages with β-amyloid pathology. Longitudinal changes in plasma GFAP appeared to be predictive of cognitive decline in patients over time.
DISCUSSION: Neuroinflammatory biomarkers are associated with AD progression. More longitudinal studies in the preclinical and MCI stages of AD are needed to validate fluid biomarkers for diagnosis, disease monitoring, and prognosis in clinical practice.

INTRODUCTION

Alzheimer's disease (AD) is a chronic neurodegenerative disease characterized by brain pathologies that include extracellular β-amyloid (Aβ) plaques and intracellular neurofibrillary tangles, as well as neuronal and synaptic losses in the brain [1, 2]. Clinically, it is marked by a slow progressive impairment in cognition, function, and behavior of the patient [3]. The AD continuum refers to a seamless sequence of changes in brain pathology over time and space, from a preclinical phase, through a long mild cognitive impairment (MCI) phase, to the dementia stages of the disease (mild, moderate, and severe) [4]. During the preclinical stage, progressing brain pathology is reflected by subtle changes in disease biomarkers, whereas during the symptomatic phase, biomarker changes continue with eventual onset and worsening of cognitive and functional impairment over time [4].

Neuroinflammation is known to be a key player in pathophysiological development of AD [5, 6]. The first indication of the role of neuroinflammation in the pathogenesis of AD came from the early descriptions by Oskar Fischer in 1907. His work suggested the possibility of local inflammatory responses surrounding senile plaques, and the subsequent identification of complement proteins, acute-phase proteins, cytokines, astrocytes, and microglia surrounding amyloid plaques bolstered this idea [7, 8]. Microglia and astrocytes are the key cellular mediators of neuroinflammation in human brains with AD pathology. Microglia are the resident immune cells of the brain that are sensitive to changes in the brain microenvironment. Microglia exhibit various morphological/ultrastructural, transcriptional, metabolic, and functional states in both healthy and diseased central nervous systems [9]. Homeostatic microglia acquire a morphology with long, thin, ramified cellular processes and smaller cell bodies, whereas

reactive microglia assume more of an amoeboid cellular morphology, with thicker and shorter cellular processes [10]. In the brains of patients with AD, one can see both reactive microglia near Aβ plaques and homeostatic microglia away from amyloid plaques [5]. Astrocytes may undergo morphological, molecular, and functional changes in response to Aβ plaques' microenvironment in the brains of AD patients [11]. Reactive astrocytes can also be seen within the microenvironment surrounding the Aβ plaques next to reactive microglia, displaying hypertrophied cell bodies and increased expression of glial fibrillary acidic protein (GFAP) [5]. Microglia and astrocytes together serve as key cellular mediators of neuroinflammation and play a crucial role in disease progression from preclinical to symptomatic stages of AD.

Evidence from immunohistochemical and biochemical postmortem analyses showed diverse inflammatory processes and abnormal innate immune responses in brains of patients with AD [12]. Cytokines, chemokines, complement proteins, cyclooxygenases, coagulation and fibrinolytic factors, integrins, and other acute-phase proteins associated with inflammation were reported to be abnormally expressed in brains of patients with AD [13]. Evidence from genome-wide association studies (GWAS) revealed genes involved in inflammatory processes, such as clusterin gene (*CLU*), compliment receptor-1 gene (*CR1*), sialic acid-binding immunoglobulin-like lectin-3 gene (*CD33*), and triggering receptor expressed on myeloid cells 2 (*TREM2*), whose variants contribute to increased risk of AD [14]. AD risk genes associated with inflammation (apolipoprotein-E gene [*APOE*], *CD33*, and *TREM2*) identified from GWAS were enriched in distinct microglial subtypes in the brains of patients with AD [15]. Findings from aforementioned GWAS, along with data from epidemiological studies [16–18], further fortified the role of neuroinflammation in AD.

There is compelling evidence to suggest that neuroinflammation in brains of patients with AD begins in preclinical stages of disease, long before clinical symptoms become apparent [19–22]. The Honolulu–Asia Aging study reported increases in patient serum C-reactive protein more than two decades before diagnosis of dementia, suggesting an early involvement of immune activation in AD pathogenesis [23]. Evidence from neuropathological studies shows that onset of Aβ-associated neuroinflammatory responses begins in the early stages of AD pathology, before the onset of clinical dementia [8]. In addition, evidence from imaging studies showed increased levels of neuroinflammation, predominantly in the brain regions associated with early Aβ deposition in patients with MCI [24, 25], suggesting a role for neuroinflammation during early stages of AD pathogenesis. Neuroinflammation is known to trigger and promote Aβ and tau deposition, and could be the missing link between Aβ and tau pathologies in the brains of patients with AD [26–31].

Apart from AD, pathogenesis of other neurodegenerative diseases, such as Creutzfeldt–Jakob disease [32], frontotemporal dementia [33], and Parkinson's disease [34], also involves similar cellular and molecular mediators of neuroinflammation. The inflammatory proteins implicated in the above-mentioned conditions may thus lack specificity to a particular neurological condition. Hence, physicians need to be cautious with interpretation of clinical neuroinflammatory biomarker profiles, which could be driven by conditions other than AD, such as bacterial infection, Lyme disease, or multiple sclerosis. Nevertheless, the role of neuroinflammation and its cellular and molecular mediators is well established in AD pathogenesis and drug candidates targeting inflammation currently constitute a major class of drugs in the AD drug development pipeline [35].

Fluid biomarkers are gaining significance in AD clinical practice for diagnosis in presymptomatic stages, and for monitoring and disease prognosis in symptomatic stages due to their ease of use and lower cost. Biomarkers of neuroinflammation in cerebrospinal fluid (CSF) and blood can potentially inform us about the changes that take place within the microenvironment of brain tissue during the natural course of AD progression or in response to AD drug treatment [36]. The ATN classification system provides a conceptual framework to understand the relationship between pathology-based biomarker profile and the risk of dementia or cognitive decline in patients across the AD continuum [37]. The presence or absence of AD biomarkers related to amyloid (A), tau (T), neurodegeneration (N), and inflammation (I) would reflect pathomechanisms of a progressive disease defined by its biology and not by the clinical symptoms [38]. As symptoms are consequences of disease process and are not considered necessary to diagnose AD, a working group convened by the Alzheimer's Association (AA) in 2018 defined AD by its biology rather than by the clinical symptoms of impairment [38]. Post-2018, disease-targeting therapies for AD received regulatory approvals and several plasma biomarkers received clinical validation, hence the guidelines for diagnosis and staging of AD were revised by an AA working group in 2024 [39]. The revised criteria support the diagnosis of AD in living people by considering the presence of abnormalities in disease-specific core fluids or in imaging biomarkers, which include CSF hybrid ratios of pTau181/Aβ42, tTau/Aβ42, Aβ42/Aβ40, or plasma pTau217 or amyloid-positron emission tomography (PET) markers [39]. Non-specific inflammatory biomarkers such as plasma GFAP or CSF markers of neurodegeneration such as neurofilament light (NfL) can be used in addition to core Aβ, tau fluid, and PET biomarkers for staging, prognosis, or as indicator of biological treatment effect [39]. Additionally, for AD research and possible future clinical use, non-specific fluid biomarkers of neuroinflammation indicative of reactive astrogliosis and microglia such as CSF soluble triggering receptor expressed on myeloid cells 2 (sTREM2) were suggested [39].

Outside the brain, YKL-40 is secreted by macrophages, neutrophils, synovial cells, chondrocytes, vascular smooth muscle cells, and hepatic stellate cells [40]. In patients with degenerative and inflammatory joint disorders, serum YKL-40 levels are elevated [41], and in various malignancies including breast, colorectal, ovarian, kidney, small cell lung, and prostate carcinomas, elevated serum YKL-40 is linked to worse survival [40]. YKL-40 in the periphery is a non-specific marker for inflammatory diseases and malignant disorders. Inside the brain, YKL-40 is primarily expressed in reactive astrocytes, contributing to microglial activation induced by Aβ plaques [42, 43]. Immunohistochemical labeling of astrocyte with YKL-40 marker around Aβ plaques is suggestive of a role in Aβ plaque-induced neuroinflammation [44]. Further, the elevated plasma YKL-40 levels in patients with mild and MCI (Clinical Dementia Rating [CDR] 1 and CDR 0.5) compared with cognitively normal subjects (CDR 0) indicate its potential role in early preclinical stages of AD [44]. TREM2 is a transmembrane receptor protein found in tissue macrophages, including microglia in the brain and various macrophages outside the brain, such as osteoclasts in bones, and macrophages in the liver, adipose tissue, skin, gut, and tumors [45]. The extracellular domain of TREM2 is cleaved by the ADAM10 protease, producing sTREM2. This soluble form can be detected in CSF and may serve as an indicator of TREM2-mediated microglial functions [46]. GFAP is the primary cytoskeletal protein in astrocytes, crucial for maintaining the integrity of the blood–brain barrier. It is an effective immunohistochemical tool for studying astrocyte morphology and serves as a marker for reactive astrogliosis, which involves an increase in the number and size of astrocyte cell bodies [47, 48]. Blood and/or CSF biomarkers such as YKL-40, sTREM2, and GFAP have been substantiated for their potential role in reflecting AD pathogenesis, primarily via activation of astroglia- and microglia-mediated neuroinflammation [49, 50].

Apart from YKL-40, sTREM2, and GFAP, there are several other proteins markers of neuroinflammation in the brains of patients with AD. Cytokines are released by microglia and astroglia and mediate pro-inflammatory, anti-inflammatory, and bystander

neuronal injury responses in the brains of patients with AD [5]. The complement system is a major constituent of innate immune responses in the brains of AD patients, and microglia are a major source of complement proteins inside the brain. Early components of the classical pathway, such as C1q, C4, C3, and C1-esterase inhibitor proteins, were identified by immunostaining techniques from late-stage AD brains, suggesting the involvement of complement proteins in AD pathogenesis [5, 51]. With the advent of plasma biomarkers in the revised AA 2024 guidelines, there is a need to identify fluid biomarkers that have a strong association with neuroinflammation in AD and confirm their prognostic value. This would enable clinicians to predict the course of the disease and treatment outcomes. This systematic literature review (SLR) aimed to investigate the association of inflammatory fluid biomarkers with AD pathogenesis, and examined the long-term clinical outcomes and consequences of changes in these neuroinflammatory biomarkers in patients with AD. This study examined the peer-reviewed literature related to fluid biomarkers of neuroinflammation in patients with preclinical AD, MCI due to AD, and AD dementia. Specifically, studies on YKL-40, sTREM2, and GFAP biomarkers were reviewed for association of biomarkers with different clinical stages of AD and whether the studies showed potential for predicting long-term clinical outcomes of disease.

MATERIALS AND METHODS
Search strategy
The SLR was conducted as per the Cochrane Handbook for Systematic Reviews of Interventions and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [52]. Literature searches were conducted on February 6, 2023, using the OvidSP® platform through which the MEDLINE®, Embase®, and PsycINFO® databases were accessed. The databases were searched for English-language articles on AD or MCI due to AD, from February 2012 onwards. The searches were limited to the following Medical Subject Headings terms: "microglia," "triggering receptor expressed on myeloid cells 2 (TREM2)," "GFAP," "astrocytes," "neurovascular or blood–brain barrier (BBB)," "interleukin," "reactive oxygen species," "immune," and their related strings. Outcome measures were not included in the search strategy but were incorporated in the inclusion/exclusion criteria for study selection.

Selection criteria
All records identified through the literature searches were exported to EndNote® software and, after excluding duplicates, citations were exported to Microsoft (MS) Excel®. Two independent reviewers screened the titles and abstracts, and selected studies based on pre-determined selection criteria following the Patients, Intervention, Comparator, Outcomes, and Study (PICOS) design format [53]. The criteria for study selection were: (1) studies involving adult patients ≥ 18 years of age with a clinical diagnosis of MCI due to AD, dementia due to AD, or AD; (2) studies examining the association of neuroinflammation with AD or with long-term outcomes such as disease progression, memory impairment, executive functioning, or neuropsychiatric symptoms; (3) studies in the English language published between February 1, 2012, and February 7, 2023, without any geographical restrictions. Non-human studies, review articles, editorials, comments, case reports, and case series were excluded. Full-text studies retained after title/abstract review were again reviewed by two independent reviewers, and those lacking relevance were excluded. SLRs, meta-analyses, and network meta-analyses were included at the abstract review stage to identify relevant references. These publications were subsequently excluded during the full-text review. In case of disagreement among reviewers, consensus was reached either by reconciliation or through arbitration by a third

independent reviewer. In alignment with the revised AA 2024 guidelines regarding the inclusion of inflammation-related fluid biomarkers, we have restricted our analyses and discussions in this report to fluid biomarkers of neuroinflammation, specifically GFAP, sTREM2, and YKL-40.

Data extraction
Data extraction was performed by one reviewer and verified independently by another reviewer. Data were extracted from selected full-text studies using a standardized data-extraction template (in MS Excel®). From each selected record, key methodological features, patient demographics, clinical characteristics, outcome measures, and main findings were extracted and tabulated. No formal quality assessment of included studies was carried out. For cross-sectional studies, the biomarker levels reported across the respective study groups were tabulated and the ratio of mean/median values of biomarkers with respect to the control group were visualized using a bubble chart. For longitudinal studies, changes in biomarker levels across the AD continuum, along with follow-up time and main outcomes, were tabulated and visualized.
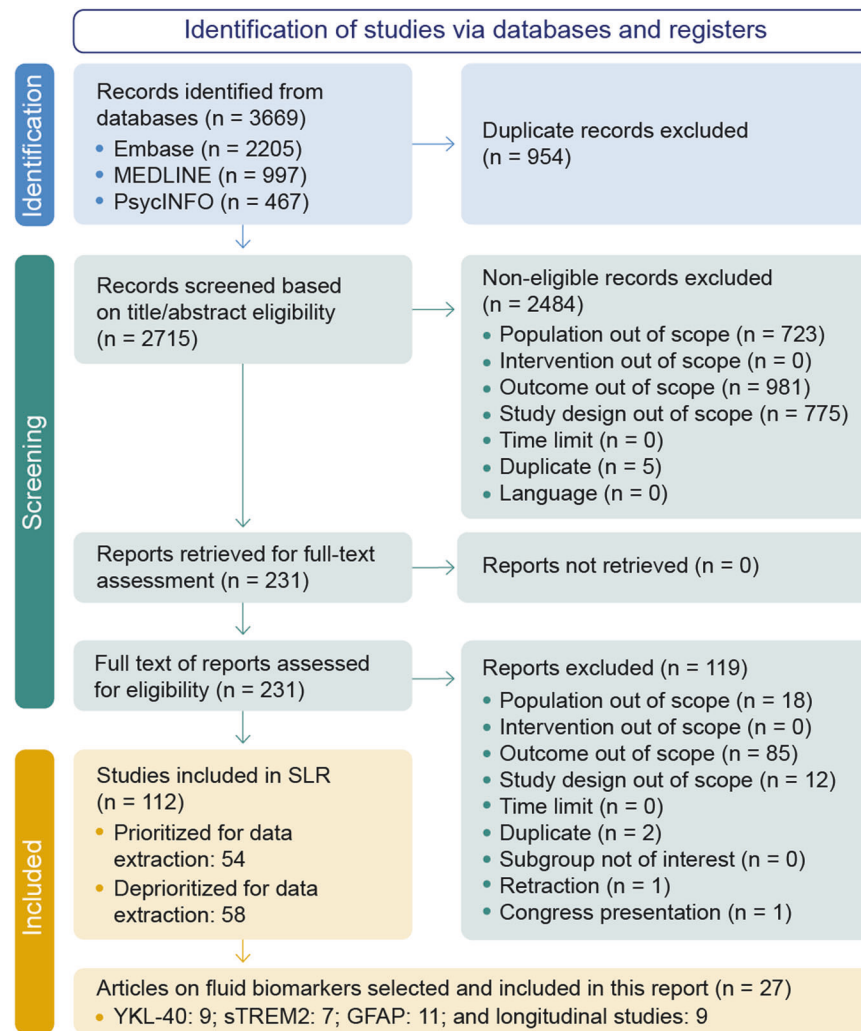
RESULTS
Literature search
The literature search identified 3669 records from the three databases (Medline®: 997; Embase®: 2205; Cochrane®: 467). After removing 954 duplicate publications, 2715 records were screened for title and abstract eligibility. Among the 2715 records screened, 231 records were selected for full-text review and 2484 records were excluded for being out of scope. Among the 231 records screened, full texts of 112 studies were found to be relevant and selected for data extraction, while 119 records were excluded for being out of scope. Of these 112 publications, data from 54 studies were prioritized for literature review because they provided the most detailed and relevant information pertaining to association of neuroinflammatory biomarkers with AD dementia and their long-term outcomes on cognition. The remaining 58 articles, which had limited data points, were deprioritized for literature review. The PRISMA diagram (Fig. 1) presents the results of the study selection process.

Study characteristics
Of the 54 studies included in the SLR, 43 were observational studies, four were randomized clinical trials, and seven did not report the study design. Among the 43 observational studies, four were case-control studies, 29 were cohort studies, and 10 were cross-sectional studies. Of the 54 included studies, 21 reported data from Europe, seven reported data from North America, four were from Asia, two were from Turkey, one was from Australia, and 19 did not report their study location. Supplementary Table 1 provides the details of the 54 studies included in the SLR.

Patient characteristics
The mean (standard deviation) age of patients in the included studies ranged from 52.0 (5.20) to 89.2 (1.63) years. The mean/median Mini-Mental State Examination (MMSE) score ranged from 10.7–24.6 in 20 studies, corresponding to MCI due to AD and mild and moderate dementia due to AD. In eight studies, mean/median MMSE score ranged from 25.4–28.60, corresponding to unimpaired cognitive function. The SLR captured studies involving patients with clinical syndromes across the AD continuum. Five studies included patients in preclinical stage, 18 studies comprised patients in the MCI stage, and 13 studies included patients with AD alongside patients with non-AD disorders such as prion disease, frontotemporal degeneration, dementia due to Lewy body disease, Creutzfeldt–Jakob disease, progressive supranuclear palsy, Parkinson's disease, and vascular dementia. Of the 54 studies

Fig. 1 PRISMA flowchart for identification, screening, and selection of studies for SLR. GFAP glial fibrillary acidic protein, PRISMA Preferred Reporting Items for Systematic Reviews and Meta-Analyses, sTREM2 soluble triggering receptor expressed on myeloid cells 2, SLR systematic literature review, YKL-40 chitinase-3-like protein 1.

captured by the SLR, 13 stratified patients by the presence or absence of AD biomarkers. The present report does not include findings from studies on imaging biomarkers of neuroinflammation. In the following subsections, we present findings from studies on fluid biomarkers of neuroinflammation captured in this SLR. Of the 27 studies on fluid biomarkers, nine studies on YKL-40, seven studies on sTREM2, and 11 studies on GFAP examined the relationship between the neuroinflammatory biomarkers and the clinical stage of the disease. Nine longitudinal studies in the SLR captured changes in the fluid biomarker levels and their association with long-term clinical outcomes.

YKL-40 as a neuroinflammatory biomarker of AD
Overall, nine YKL-40 studies published between 2012 and 2023, with sample sizes ranging from 52–419 participants and comprising 15 comparison groups across the AD continuum, were included in this report [54–62]. Seven studies determined YKL-40 levels in CSF, one in serum, and one in plasma. Table 1 provides detailed information about the studies and comparisons, along with the outcome. Overall, higher levels of YKL-40 were reported in eight of nine studies in patients at different clinical stages of cognitive impairment compared with cognitively unimpaired control subjects (Table 1 and Fig. 2A). Levels of CSF YKL-40 were

consistently higher (1.2-–1.7-fold) in patients with AD dementia compared with cognitively unimpaired control subjects (Fig. 2A). When measured in serum, YKL-40 levels were higher in the AD group compared with the control group, but no statistical significance was found [61]. Three studies compared YKL-40 levels among patients in the MCI stage (two in CSF, one in serum) of AD. While one study reported significantly higher levels of CSF YKL-40 (1.6-fold increase) in patients with MCI due to AD compared with the control group [54], another study found that the differences between the control group and patients with MCI due to AD or stable MCI were not statistically significant [59]. Likewise, the differences in the level of YKL-40 when measured in serum among controls and patients with all-cause MCI were not statistically significant [61]. Two studies evaluated YKL-40 levels during the preclinical phases of AD, and both reported no significant differences in comparison with the control groups [54, 61]. Subjects were stratified by core AD biomarkers in four studies (three in CSF, one in plasma). In two studies, cognitively impaired Aβ-positive (Aβ+) subjects showed significantly higher CSF YKL-40 levels compared with cognitively unimpaired Aβ-negative (Aβ−) subjects [57, 58], whereas in another study that measured YKL-40 levels in plasma, the differences between the groups as defined by core AD biomarkers were not statistically significant [62].
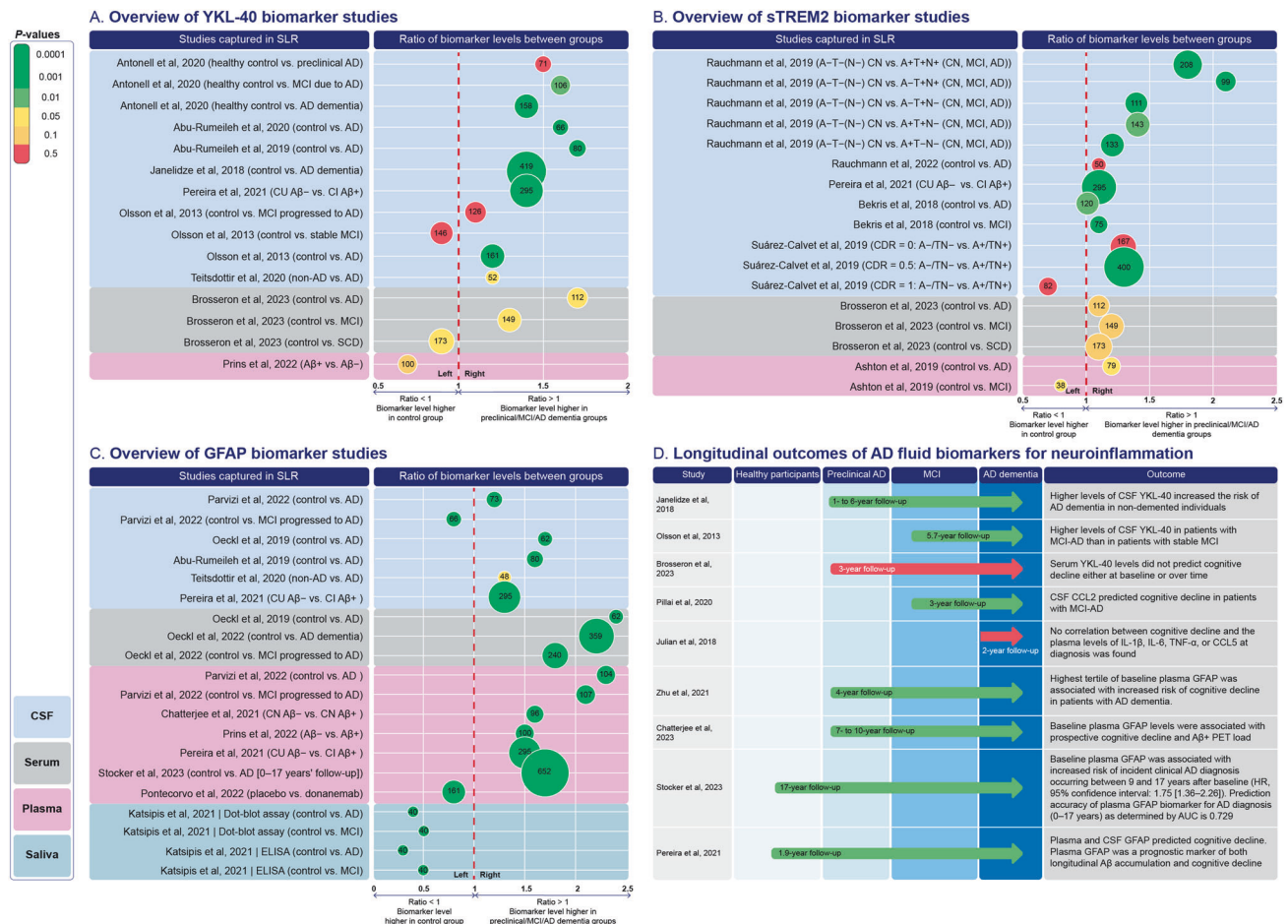
Table 1. Summary of studies for YKL-40.

Study no.	Study	Groups analyzed	Outcome measure	Magnitude of measure: mean (SD) or median (IQR)	Statistical analysis
1	Abu-Rumeileh et al. [56]	Control (n = 28) AD (n = 38)	CSF YKL-40 level	Control (147 [116–158]) ng/mL AD (240 [177–289])	$p < 0.001$ Kruskal–Wallis test
2	Abu-Rumeileh et al. [55]	Control (n = 40) AD (n = 40)	CSF YKL-40 level	Control (145 [115–161]) ng/mL AD (240 [176–293])	$p < 0.001$ Kruskal–Wallis test
3	Antonell et al. [54]	Healthy control (n = 50) Preclinical AD (n = 21) MCI due to AD (n = 56) AD dementia (n = 108)	CSF YKL-40 level	Control (217.23 [153.86–271.37]) ng/mL Preclinical AD (325.14 [237.24–363.73]) MCI due to AD (347.24 [257.71–397.06]) AD dementia (305.12 [247.33–396.56])	Preclinical AD vs. control ($p = 0.726$) MCI due to AD vs. control ($p = 0.025$) AD dementia vs. control ($p = 0.010$)
4	Brosseron et al. [61]	Control (n = 74) SCD (n = 99) MCI (n = 75) AD dementia (n = 38)	Serum levels of YKL-40	Control (83 ± 151 [23–1020]) ng/mL SCD (78 ± 332 [27–3178]) MCI (111 ± 100 [17–488]) AD dementia (138 ± 112 [22–514])	Kruskal–Wallis test followed by ANCOVA $p = 0.108$
5	Janelidze et al. [57]	Control–Aβ– (n = 362) Control–Aβ+ (n = 146) MCI–Aβ– (n = 114) MCI–Aβ+ (n = 142) AD dementia (n = 57)	CSF levels of YKL-40	Compared with the control–Aβ– group, the CSF levels of YKL-40 were increased in all groups with pathologic Aβ+ status (control–Aβ+[a], MCI–Aβ+[b], and AD dementia[c]) Furthermore, YKL-40 levels were higher in AD dementia than in control–Aβ+[d] and MCI–Aβ+[e]	One-way ANOVA [a]$p < 0.001$ [b]$p = 0.005$ [c]$p < 0.001$ [d]$p = 0.003$ [e]$p \leq 0.001$
6	Olsson et al. [59]	Control (n = 65) AD dementia (n = 96) MCI due to AD (n = 61) Stable MCI (n = 81)	CSF levels of YKL-40	Control (194,622 ± 76,326 ng/L) AD dementia (241,582 ± 100,701 ng/L) MCI due to AD (209,077 ± 74,859 ng/L) Stable MCI (171,687 ± 68,367 ng/L)	ANOVA $p < 0.01$
7	Pereira et al. [58]	Cognitively unimpaired Aβ– (n = 217) Cognitively unimpaired Aβ+ (n = 71) Cognitively impaired Aβ+ (n = 78) Cognitively impaired Aβ– (n = 63)	CSF levels of YKL-40	Cognitively unimpaired Aβ– (162.0 [38.3–458.2] ng/mL) Cognitively impaired Aβ+ (220.3 [63.9–523.5] ng/mL) Cognitively unimpaired Aβ+ (211.2 [80.9–374.8] ng/mL) Cognitively impaired Aβ– (184.6 [68.1–371.0] ng/mL)	Kruskal–Wallis test $p < 0.001$
8	Prins et al. [62]	Aβ+ (n = 50) Aβ– (n = 50)	Plasma levels of YKL-40	Aβ+ (54,662.3 ± 39,697.31 pg/mL for $n = 49$) Aβ– (82,947.1 ± 83,418.38 pg/mL for $n = 49$)	Independent t-test $p = 0.397$
9	Teitsdottir et al. [60]	CSF AD profile (n = 28) CSF non-AD profile (n = 24)	CSF levels of YKL-40	AD profile (203 [124–367] ng/mL) Non-AD profile (165 [83–399] ng/mL)	Mann–Whitney U test $p = 0.12$

The term "MCI" is "all-cause MCI", unless otherwise stated.
Aβ amyloid-beta pathology, *AD* Alzheimer's disease, *ANCOVA* analysis of covariance, *ANOVA* analysis of variance, *CSF* cerebrospinal fluid, *IQR* interquartile range, *MCI* mild cognitive impairment, *SCD* subjective cognitive decline, *SD* standard deviation, *YKL-40* chitinase-3-like protein 1.

Fig. 2 **Summary of biomarker studies and overview of key outcomes of the longitudinal studies captured by SLR.** Bubble charts in **A**, **B**, and **C** summarize biomarkers studies of YKL-40, sTREM2, and GFAP respectively. For each of the comparisons within the study, the position of the bubble corresponds to the ratio of mean/median values of biomarker with respect to the control group. If the bubble is on the left of the red dotted line (ratio < 1), biomarker levels are higher in the control group; if the bubble is on the right of the red dotted line (ratio > 1), biomarker levels are higher in the comparator group. The statistical significance of the differences in the mean/median values of biomarker levels between control and comparator group is denoted by the color and size of the bubble, and the numbers in the center of the bubbles (or to the side) denote the sample size of the groups that were compared in the study. **D** shows the longitudinal studies captured by SLR for fluid biomarkers of neuroinflammation, along with follow-up time and the main outcome of the study. Green arrows depict the studies that showed relationships between the change in biomarker levels and cognitive decline or brain pathology over time, while red arrows indicate studies that could not show such relationships. Note: The term "MCI" is "all-cause MCI", unless otherwise stated. Presence (+) or absence (−) of abnormal biomarkers of amyloid (A), tau (T), and neurodegeneration (N) as per A−T−N classification. Aβ amyloid-β pathology, AD Alzheimer's disease, AUC area under the ROC curve, CCL2 C-C motif chemokine ligand 2, CCL5 C-C motif chemokine ligand 5, CDR clinical dementia rating scale, CI cognitively impaired, CSF cerebrospinal fluid, CU cognitively unimpaired, ELISA enzyme-linked immunosorbent assay, GFAP glial fibrillary acidic protein, HR hazard ratio, IL interleukin, MCI mild cognitive impairment, MCI-AD MCI due to AD, PET positron emission tomography, ROC receiver operating characteristic, SLR systematic literature review, sTREM2 soluble triggering receptor expressed on myeloid cells 2, TNF-α tumor necrosis factor alpha, YKL-40 chitinase-3-like protein 1.

sTREM2 as a neuroinflammatory biomarker of AD

Seven studies of sTREM2 published between 2019 and 2023, comprising 17 comparison groups across the AD continuum with sample sizes ranging from 38–400 participants, were included in this report [46, 58, 61, 63–66]. Five studies determined sTREM2 levels in CSF, one in serum [61], and one in plasma [66]. Table 2 provides detailed information about the studies, along with group comparisons and study outcome. Significantly higher levels of sTREM2 were reported in four out of seven studies in patients with AD at different clinical stages of cognitive impairment compared with cognitively unimpaired control subjects (Table 2 and Fig. 2B) [46, 58, 63, 65]. Three studies compared cognitively unimpaired controls with patients with all-cause MCI or AD dementia and reported sTREM2 levels that were not statistically different across the groups [61, 64, 66]. One study by Bekris et al. measured

sTREM2 levels in both CSF and plasma between controls and all-cause MCI or AD groups. The study reported statistically higher CSF sTREM2 levels (1- to 1.1-fold) in patients with all-cause MCI and AD dementia compared with healthy controls [65], but plasma levels across the groups in this study were statistically no different. Another study compared serum sTREM2 levels between patients with subjective cognitive decline and cognitively unimpaired control patients, with no significant differences across the groups [61]. Three studies compared CSF sTREM2 levels among subjects stratified by A−T−N framework biomarkers [46, 58, 63]. In one study, CSF sTREM2 levels in subjects with biomarker profiles A+T+N+, A−T+N+, or A+T−N− were reported to be higher (1.8-fold for A+T+N+, 2.1-fold for A−T+N+, and 1.2-fold for A+T−N−) compared with cognitively unimpaired control patients bearing an A−T−N− biomarker profile [63]. Another study that included

Table 2. Summary of studies for sTREM2.

Study no.	Study	Groups analyzed	Outcome measure	Magnitude of measure: mean (SD)/median (IQR)	Statistical analysis
1	Pereira et al. [58]	Cognitively unimpaired Aβ− (n = 217)	CSF levels of sTREM2	Cognitively unimpaired Aβ− (10.3 [4.9–22.9] ng/mL)	Kruskal–Wallis test p < 0.001
		Cognitively impaired Aβ+ (n = 78)		Cognitively impaired Aβ+ (11.5 [5.5–29.6] ng/mL)	
		Cognitively unimpaired Aβ+ (n = 71)		Cognitively unimpaired Aβ+ (12.3 [4.7–21.9] ng/mL)	
		Cognitively impaired Aβ− (n = 63)		Cognitively impaired Aβ− (10.8 [6.2–24.7] ng/mL)	
2	Ashton et al. [66]	Controls (n = 20)	CSF levels of sTREM2	Controls: 7352 (5318)	ANCOVA p = 0.164
		MCI (n = 18)		MCI: 6204 (2572) ng/L	
		AD dementia (n = 59)		AD dementia: 8859 (5951) ng/L	
3	Bekris et al. [65]	HC (CSF: n = 37; plasma: n = 104)	CSF and plasma levels of sTREM2	CSF sTREM2 levels in MCI and AD dementia were significantly elevated compared with HC; Plasma sTREM2 levels were not significantly different between disease groups	Control and MCI (p = 0.0056) Control and AD dementia (p = 0.0249)
		MCI (CSF: n = 38; plasma: n = 35)			
		AD dementia (CSF: n = 83; plasma: n = 83)			
4	Brosseron et al. [61]	HC (n = 74)	Serum levels of sTREM2	Control (7.4 ± 9.1 [1.6–16.4] ng/mL)	Kruskal–Wallis test, p = 0.244
		SCD (n = 99)		SCD (7.9 ± 17.6 [2.2–14.0] ng/mL)	
		MCI (n = 75)		MCI (9.0 ± 16.9 [2.3–76.0] ng/mL)	
		AD dementia (n = 38)		AD dementia (8.3 ± 17.5 [1.9–75.6] ng/mL)	
5	Rauchmann et al. [64]	Control (n = 18)	CSF levels of sTREM2	Control (10.35 [3.00] ng/mL)	p = 0.37
		AD (n = 32)		AD (11.31 [3.49] ng/mL)	
6	Rauchmann et al. [63]	A−T−(N−) (CN) (n = 79)	CSF levels of sTREM3	A−T−(N−) (CN) (2572.10 [1596.09] pg/mL)	Kruskal–Wallis test p < 0.001
		A+T−N− (CN, MCI, AD dementia) (n = 54)		A+T−N− (CN, MCI, AD dementia) (3110.76 [1425.49] pg/mL)	
		A+T+N− (CN, MCI, AD dementia) (n = 64)		A+T+N− (CN, MCI, AD dementia) (3617.73 [1651.78] pg/mL)	
		A+T+N+ (CN, MCI, AD dementia) (n = 129)		A+T+N+ (CN, MCI, AD dementia) (4577.71 [2151.30] pg/mL)	
		A−T+N− (CN, MCI, AD dementia) (n = 32)		A−T+N− (CN, MCI, AD dementia) (3716.45 [2031.35] pg/mL)	
		A−T+N+ (CN, MCI, AD dementia) (n = 20)		A−T+N+ (CN, MCI, AD dementia) (5317.08 [2619.21] pg/mL)	
7	Suárez-Calvet et al. [46]	CDR = 0	CSF levels of sTREM2	CDR = 0 A−/TN− (3741 [1690]) pg/mL	p < 0.0001
		A−/TN− (n = 122)		A+/TN− (2835 [1524]) pg/mL	
		A+/TN− (n = 52)		A+/TN+ (4839 [2240]) pg/mL	
		A+/TN+ (n = 45)			
		CDR = 0.5		CDR = 0.5 A−/TN− (3436 [1754]) pg/mL	p < 0.0001
		A−/TN− (n = 118)			

Table 2. continued

Study no.	Study	Groups analyzed	Outcome measure	Magnitude of measure: mean (SD)/median (IQR)	Statistical analysis
		A+/TN− (n = 93)		A+/TN− (2791 [1292]) pg/mL	
		A+/TN+ (n = 282)		A+/TN+ (4441 [2211]) pg/mL	
	CDR = 1	A−/TN− (n = 2)	CDR = 1	A−/TN− (5660 [2008]) pg/mL	−
		A+/TN− (n = 15)		A+/TN− (3051 [1128]) pg/mL	
		A+/TN+ (n = 80)		A+/TN+ (3967 [2000]) pg/mL	
		AD (n = 31)			

The term "MCI" is "all-cause MCI", unless otherwise stated. Presence (+) or absence (−) of abnormal biomarkers of amyloid (A), tau (T), and neurodegeneration (N) as per A−T−N classification.
Aβ amyloid-beta, AD Alzheimer's disease, ANCOVA analysis of covariance, CDR clinical dementia rating scale, CN cognitively normal, CSF cerebrospinal fluid, HC healthy controls, IQR interquartile range, MCI mild cognitive impairment, SCD subjective cognitive decline, SD standard deviation, sTREM2 soluble triggering receptor expressed on myeloid cells 2.

presence or absence of Aβ biomarker reported statistically higher CSF sTREM2 levels among cognitively impaired Aβ+ subjects compared with Aβ− cognitively unimpaired controls [58]. In the study by Suárez-Calvet et al. [46], subjects in earliest asymptomatic preclinical phases of AD (CDR score = 0) bearing A+/TN− biomarker profile showed decreased CSF sTREM2 levels compared with those without Aβ and tau biomarker positivity (A−/TN−) (Table 2). Studies that measured sTREM2 levels in serum or plasma reported no statistical differences across comparisons [61, 66].

GFAP as a neuroinflammatory biomarker of AD
Eleven studies of GFAP published between 2019 and 2022, comprising 20 comparison groups across the AD continuum with sample sizes ranging from 40–652 participants, were included in this report [55, 58, 60, 62, 67–73]. Five studies determined GFAP levels in CSF [55, 58, 60, 67, 68], six in serum [58, 62, 67, 69–71], two in plasma [68, 72], and one in saliva [73]. Significantly higher levels of GFAP were reported in seven out of 11 studies in patients with AD at different clinical stages of cognitive impairment compared with cognitively unimpaired control subjects (Table 3 and Fig. 2C) [55, 58, 67–70, 72]. Five studies reported higher GFAP levels in patients with AD dementia compared with cognitively unimpaired control subjects [55, 67, 68, 70, 72]. Another study compared GFAP levels in patients with MCI due to AD and cognitively unimpaired controls using both plasma and CSF samples (Fig. 2C). This study reported higher levels of plasma biomarker in patients with MCI due to AD group relative to the control group (ratio > 1). Conversely, in CSF, the levels of biomarker in patients with MCI due to AD were lower than for controls (ratio < 1) [67]. One study measured GFAP levels in saliva using dot-blot and enzyme-linked immunosorbent assay methods. It reported significantly lower biomarker levels in AD and all-cause MCI groups (ratio < 1; Fig. 2C) compared with the control group [73]. Three studies reported GFAP levels in patients stratified by core AD biomarkers [58, 62, 69]. One study reported that plasma GFAP levels in Aβ+ patients with or without cognitive impairment were significantly elevated compared with Aβ− patients with or without cognitive impairment [58]. Similarly, in another study, plasma GFAP levels were significantly increased in patients with Aβ+ PET compared with patients with Aβ− PET [69].

Longitudinal studies on neuroinflammatory biomarkers of AD
The SLR identified nine longitudinal studies that evaluated long-term outcomes of changes in neuroinflammatory AD biomarkers [57–59, 61, 70, 74–77]. Table 4 lists the studies that assessed the relationship between biomarkers and clinical outcome over a period of time, and Fig. 2D visualizes the longitudinal studies and their outcomes spread across the AD continuum. Three studies examined YKL-40 levels longitudinally, of which two studies [57, 59] reported an association with changes in cognition, while the third study [61] did not show any relationship with cognitive performance. One study, with a follow-up period ranging 1–6 years, showed that higher levels of YKL-40 in patients without dementia increased the risk of dementia due to AD. Furthermore, the association of CSF YKL-40 with markers of neurodegeneration was stronger in Aβ+ individuals [57]. Likewise, Olsson et al. reported that patients with MCI who had a biomarker profile indicative of AD, and who developed AD later, had significantly higher CSF YKL-40 levels compared with patients with cognitively stable MCI [59]. Another longitudinal study of patients with all-cause MCI at baseline, with up to 36 months' follow-up, reported that cognitive decline in patients with MCI due to AD was best predicted by the inflammatory biomarker CSF C-C motif chemokine ligand 2 (CCL2) [75]. The discriminatory power of baseline CSF CCL2 was comparable with neurodegeneration markers (CSF NfL and magnetic resonance imaging [MRI]-based hippocampal volume) in predicting the highest quartile of clinical dementia rating–sum of boxes (CDR-SB) change over 2 years (≥3 CDR-SB) in

Table 3. Summary of studies for GFAP.

Study no.	Study	Groups analyzed	Outcome measure	Magnitude of measure: mean (SD)/median (IQR)	Statistical analysis
1	Abu-Rumeileh et al. [55]	AD (n = 40); Control (n = 40)	CSF GFAP level	AD (1.081 [0.534–1.422] ng/mL) (median); Control: 0.665 (0.409–0.978) ng/mL (median)	Kruskal–Wallis test p = 0.002
2	Teitsdottir et al. [60]	CSF AD profile (n = 28); CSF non-AD profile (n = 24)	CSF levels of GFAP	AD profile (1.3 [0.5–21.3] ng/mL); Non-AD profile (1.0 [0.1–7.1] ng/mL)	Mann–Whitney U test p = 0.09
3	Prins et al. [62]	Aβ– (n = 50); Aβ+ (n = 50)	Plasma levels of GFAP	Aβ+ (195.1 ± 87.13 pg/mL); Aβ– (134.0 ± 50.71 pg/mL)	Independent t-test p < 0.001
4	Pereira et al. [58]	Cognitively unimpaired Aβ– (n = 217); Cognitively unimpaired Aβ+ (n = 71); Cognitively impaired Aβ+ (n = 78)	CSF and plasma levels of GFAP	Cognitively impaired Aβ+: plasma (262.6 [94.0–650.7] pg/mL); CSF: (17.5 [5.5–35.6] pg/mL); Cognitively unimpaired Aβ– plasma (179.6 [31.1–534.9] pg/mL); CSF (13.5 [4.3–34.6] pg/mL); Cognitively impaired Aβ–: plasma (166.9 [24.5–476.0] pg/mL); CSF: (14.7 [5.4–31.2] pg/mL); Cognitively unimpaired Aβ+ plasma (252.1 [86.1–672.9] pg/mL); CSF: (16.1 [5.8–35.1] pg/mL)	Kruskal–Wallis test plasma: p < 0.001; Kruskal–Wallis test CSF: p < 0.001
5	Chatterjee et al. [69]	Cognitively normal Aβ– (n = 63); Cognitively normal Aβ+ (n = 33)	Plasma levels of GFAP	Aβ+ (240.12 ± 124.88 pg/mL); Aβ– (151.42 ± 58.49 pg/mL)	Student's t-test p ≤ 0.0001
6	Katsipis et al. [73]	Control (n = 20); MCI (n = 20); AD dementia (n = 20)	Saliva levels of GFAP	MCI (dot-blot: 6.50 ± 1.30[a], ELISA: 6.82 ± 2.10[a], both in terms of ng/mg of total protein); Controls (dot-blot: 11.88 ± 2.42; ELISA: 13.35 ± 3.03, both in terms of ng/mg of total protein); AD dementia (dot-blot: 4.57 ± 1.79[a,b], ELISA: 3.56 ± 2.24[a,c], both in terms of ng/mg of total protein)	[a]vs. control: p < 0.0001; [b]vs. MCI: p < 0.001; [c]vs. MCI: p < 0.0001
7	Oeckl et al. [72]	MCI-AD (n = 111); Control (n = 129); AD dementia (n = 230)	Serum levels of GFAP	MCI-AD (300 [232–433] pg/mL); Control (167 [108–234] pg/mL); AD dementia (375 [276–505] pg/mL)	p < 0.001; p < 0.001
8	Oeckl et al. [68]	AD (n = 28); Control (n = 34)	CSF and serum levels of GFAP	AD (serum: 376 [294–537]; CSF: 1396 [1007–2842] pg/mL); Control (serum: 157 [126–218]; CSF: 826 [628–1041] pg/mL)	p < 0.001
9	Parvizi et al. [67]	MCI-AD (n = 63; n = 30 for CSF); Control (n = 44; n = 36 for CSF); AD dementia (n = 60; n = 37 for CSF)	Plasma and CSF levels of GFAP	MCI-AD (plasma: 167.5 [93.8–256.3]; CSF in 30 patients: 8946.2 [7028.8–13,842.7] pg/mL); Control (plasma: 79 [53.7–120.6]; CSF in 36 patients: 11,145.3 [6980.5–14,373.8] pg/mL); AD dementia (plasma: 181.9 [129.6–269.6]; CSF in 37 patients: 13,663.5 [9945.4–21,059.1] pg/mL)	p < 0.001 for plasma; p < 0.01 for CSF
10	Pontecorvo et al. [71]	Donanemab (n = 131); Placebo (n = 126)	Plasma levels of GFAP at week 76 of treatment	Donanemab (189.99 [83.675]) for 83 patients pg/mL; Placebo (242.25 [87.293]) for 78 patients pg/mL	p < 0.001 vs. placebo
11	Stocker et al. [70]	AD dementia (0–9 years' follow-up; n = 51); AD dementia (9–17 years' follow-up; n = 94); AD dementia (0–17 years' follow-up; n = 145); Control (n = 507)	Plasma levels of GFAP	AD dementia (0–9 years) 151.4 ± 122.1 pg/mL; Control (78.2 [13.3–529.0] pg/mL for 504 subjects); AD dementia (9–17 years) 123.6 ± 56.2 pg/mL; AD dementia (0–17 years) 133.3 ± 86.0 pg/mL	p < 0.0001 vs. placebo; p < 0.0001 vs. controls; p < 0.0001 vs. controls; p < 0.0001 vs. controls

The term "MCI" is "all-cause MCI", unless otherwise stated.
Aβ amyloid-β pathology, AD Alzheimer's disease, CSF cerebrospinal fluid, ELISA enzyme-linked immunosorbent assay, GFAP glial fibrillary acidic protein, IQR interquartile range, MCI mild cognitive impairment, MCI-AD MCI due to AD, SD standard deviation.

Table 4. Longitudinal studies for fluid biomarkers.

Study	Patients and comparisons	Study outcomes
Janelidze et al. [57]	The study included CU elderly individuals ($n = 508$), patients with MCI ($n = 256$), and patients with AD dementia ($n = 57$). CSF samples were analyzed for YKL-40 (follow-up 3 years, range 1–6 years)	Higher levels of CSF YKL-40 increased risk of development of AD dementia in patients without dementia. High levels of YKL-40 were associated with increased CSF levels of total tau and phosphorylated tau. These associations were stronger in Aβ+ individuals
Zhu et al. [74]	56 patients with AD dementia and 83 CN individuals were compared. Mean follow-up period 3.9–4 years	The higher tertile of baseline plasma GFAP was associated with greater change in MMSE score and poor cognitive outcome during follow-up in AD dementia (1.20 points annually; HR 2.26, $p < 0.005$)
Pillai et al. [75]	48 patients with MCI-AD at baseline with a 15-month follow-up in whom the diagnosis of MCI-AD with CSF Aβ42 and pTau181 levels is consistent with a diagnosis of AD, and 134 ADNI MCI cohort with 36 months' follow-up	Cognitive decline in MCI-AD was best predicted by CSF CCL2 and baseline CSF CCL2 has comparable utility to markers of neurodegeneration (CSF NfL and hippocampal volume) in predicting the highest quartile of CDR-SB change over 2 years (≥3 CDR-SB)
Julian et al. [77]	109 patients with AD with MMSE and ADAS-cog scores at diagnosis were followed up to 2 years. Plasma values of IL-1β, IL-6, TNF-α, and CCL5 at diagnosis and during follow-up	After 2 years, mean MMSE scores and mean ADAS-cog scores worsened in subjects, suggestive of cognitive decline; however, during the 2 years of follow-up, no correlation between cognitive decline and the plasmatic value of IL-1β, IL-6, TNF-α, or CCL5 at diagnosis was found
Chatterjee et al. [76]	Aβ-PET negative CU (Aβ−, $n = 81$) and MCI (Aβ−, n = 26) patients were compared with Aβ+ PET patients across the AD continuum (CU Aβ+, $n = 39$; MCI Aβ+, $n = 33$; AD Aβ+, $n = 46$) Follow-up period 7–10 years	Longitudinally, plasma Aβ1–42/Aβ1–40, pTau181, and GFAP were altered in patients with MCI compared with CU individuals, and plasma GFAP and NfL were altered in patients with AD compared with CU individuals. Lower plasma Aβ1–42/Aβ1–40 and higher pTau181, GFAP, and NfL were associated with prospective cognitive decline
Olsson et al. [59]	The patients with AD dementia ($n = 96$), MCI due to AD ($n = 170$), and CN controls ($n = 65$) were included. YKL-40 was quantified and compared across groups. Follow-up period 5.7 years	When comparing patients with MCI who later developed AD (with AD-indicative Aβ and tau CSF biomarkers) with cognitively stable patients with MCI (with normal AD biomarkers), the former group had significantly higher CSF levels of YKL-40 than those who remained cognitively stable
Brosseron et al. [61]	Healthy controls ($n = 74$), patients with subjective cognitive decline ($n = 99$), MCI ($n = 75$), and AD dementia ($n = 38$) from the DELCODE cohort were followed up for an average of 3.1 years	Serum YKL-40 correlated to its CSF levels as well as with CSF neurodegeneration markers and structural MRI, but not with cognitive performance, clinical staging, or CSF biomarker-based schematics
Stocker et al. [70]	A community-based cohort, biomarker levels were measured at baseline in 768 subjects (aged 50–75 years) followed over 17 years	GFAP was associated with clinical AD incidence even more than a decade before diagnosis (9–17 years), while pTau181 and NfL were associated with more intermediate AD dementia risk (within 9 years)
Periera et al. [58]	This prospective study measured baseline plasma biomarkers (GFAP, YKL-40, sTREM2) in 504 individuals and a subsample was followed (median of 1.9 years) longitudinally for changes in amyloid load ($n = 196$) and cognition ($n = 185$)	Both plasma and CSF GFAP predicted cognitive decline, even after adjusting for longitudinal Aβ PET changes. Plasma GFAP was a prognostic marker of both longitudinal Aβ accumulation and cognitive decline

The term "MCI" is "all-cause MCI", unless otherwise stated. Some studies were in relation to imaging biomarkers, so have not been included. Amyloid (A), tau (T), and neurodegeneration (N) as per A−T−N classification.
Aβ amyloid-β pathology, *AD* Alzheimer's disease, *ADAS-cog* Alzheimer's Disease Assessment Scale–Cognitive subscale, *ADNI* Alzheimer's Disease Neuroimaging Initiative, *CCL2* C-C motif chemokine ligand 2, *CCL5* C-C motif chemokine ligand 5, *CDR-SB* clinical dementia rating–sum of boxes, *CN* cognitively normal, *CSF* cerebrospinal fluid, *CU* cognitively unimpaired, *GFAP* glial fibrillary acidic protein, *HR* hazard ratio, *IL* interleukin, *MCI* mild cognitive impairment, *MCI-AD* MCI due to AD, *MMSE* Mini-Mental State Examination, *MRI* magnetic resonance imaging, *NfL* neurofilament light, *PET* positron emission tomography, *sTREM2* soluble triggering receptor expressed on myeloid cells 2, *TNF-α* tumor necrosis factor alpha, *YKL-40* chitinase-3-like protein 1.

patients with MCI due to AD and AD dementia [75]. Four longitudinal studies suggested a potential for GFAP as biomarker to predict cognitive decline over time. In their study, which followed cognitively unimpaired subjects and subjects with AD dementia over time, Zhu et al. reported that those with highest tertile of baseline plasma GFAP levels, compared with lowest tertile, were associated with greater change in MMSE during follow-up; the highest tertile was also associated with increased risk of cognitive decline in patients with AD dementia [74]. Likewise, another longitudinal study by Chatterjee et al. compared plasma GFAP levels between Aβ− PET and Aβ+ PET subjects with unimpaired cognition, MCI due to AD, and AD dementia across the AD continuum. This study reported higher plasma GFAP levels in patients with MCI due to AD and AD dementia over 36 months, compared with cognitively unimpaired subjects. Further, baseline plasma GFAP levels were significantly associated with prospective cognitive decline in patients with MCI due to AD and AD dementia [76]. In another study, baseline plasma GFAP levels predicted the incidence of AD nearly a decade before the actual diagnosis [70], and in additional prospective study, baseline plasma GFAP levels predicted both Aβ accumulation as measured by PET and cognitive decline in patients over time [58].

DISCUSSION
Fluid biomarkers of neuroinflammation may help early detection of brain pathology during asymptomatic stages of AD, monitor disease progression over time, identify which asymptomatic

patients are at risk of developing AD dementia, and identify patients with AD who might respond best to treatment. This report presents the findings of an SLR targeting neuroinflammatory fluid biomarkers in patients across the AD continuum and explores the relationship of these biomarkers with long-term clinical outcomes related to core pathology and cognition. Among the 54 study records included in the SLR, a substantial number of studies centered around YKL-40, sTREM2, and GFAP as neuroinflammatory biomarkers. Furthermore, in the recent AA 2024 revised criteria, GFAP and sTREM2 were referred to as non-specific inflammatory biomarkers important in AD pathogenesis [39]. Consequently, we focused on these three fluid biomarkers. CSF levels of YKL-40 were elevated in patients with dementia due to AD, while high CSF sTREM2 levels were specifically detected in patients in the preclinical stages of AD who exhibited a biomarker profile characterized by the presence of Aβ pathology (A+T−N−). Furthermore, plasma GFAP levels remained consistently elevated not only in patients with AD dementia but also in those in preclinical stages with Aβ pathology, regardless of the presence or absence of cognitive impairment. Among the three biomarkers, longitudinal changes in plasma GFAP appeared to be useful in predicting cognitive decline in patients over time, even in those who were in asymptomatic preclinical stages of AD. These disease stage-related changes in biomarker levels of CSF YKL-40, CSF sTREM2, and plasma GFAP consolidate the role of neuroinflammation in the pathogenesis of AD and highlight the potential of these biomarkers for future applications in clinical practice and AD research.

Microglia and astroglia as cellular mediators of neuroinflammation release diverse pro-inflammatory and anti-inflammatory molecules, which define the inflammatory immune responses to Aβ deposits in the AD brain [49]. Evidence from neuropathological studies show that Aβ-associated neuroinflammatory responses in the neocortex occur during the early stages of AD pathology, preceding the stages associated with tau and clinical dementia [8]. Findings from imaging studies targeting neuroinflammation showed that patients with all-cause MCI exhibit increased neuroinflammation in areas of early Aβ deposition (frontal, occipital, parietal, and temporal lobes), suggesting a strong association between neuroinflammation and Aβ levels in early MCI. However, the association of neuroinflammation with tau is more evident during the late clinical stages of AD [24]. Several studies identified stage-specific biomarkers for detection of neuroinflammation in either CSF or blood [78]. Changes in these fluid biomarkers of neuroinflammation might help advance our knowledge about the insidious clinical progression of AD, unravel new drug targets for immunomodulation in AD, and enhance the ability to determine the responses to treatments targeting the immune processes in AD clinical trials [79]. The revised AA 2024 guidelines recommend the use of fluid biomarkers of neuroinflammation (GFAP), in addition to the core biomarkers of pathology (fluid biomarkers, Aβ42/40 ratio and pTau181 or PET imaging) for disease staging and monitoring of disease progression [39]. Additionally, the potential of CSF sTREM2 was referred to as a potential marker for microglial activation [39], thus presenting an opportunity to expand the 2018 AT(N) framework to ATX(N), where X can be "I" for neuroinflammatory biomarkers [38, 39, 80]. Inclusion of inflammatory biomarkers along with core biomarkers enabled clinicians and researchers to explore the preclinical asymptomatic phase [81] and MCI stages [25, 82, 83] of AD.

This SLR's findings about the YKL-40 biomarker reflect the evidence, diffused in published literature, of its association with AD dementia. In one study, baseline YKL-40 levels were reported to be higher in patients with MCI due to AD and AD dementia compared with cognitively unimpaired individuals; additionally, YKL-40 levels in MCI predicted progression to AD dementia [84]. In another study, the CSF YKL-40/Aβ42 ratio predicted risk of developing cognitive impairment (CDR 0 to CDR > 0 conversion)

after adjusting for age and gender [44]. A recent community-based cohort study of 6000 participants reported that higher plasma YKL-40 levels were associated with lower brain volume, poorer cognition, and higher risk of incident dementia over a median of 5.8 years of follow-up [85]. In contrast, one study that compared postmortem brain YKL-40 levels with antemortem CSF YKL-40 levels reported that CSF levels of YKL-40 were not reflective of YKL-40 changes within the AD brain [86]. This SLR could not find many studies that reliably showed elevated CSF YKL-40 levels in MCI or in preclinical stages of AD [54, 59, 61]. At least some of the discrepancies observed with YKL-40 levels in patients with AD can be explained by variants of the *CHI3L1* gene. One study reported that genetic variants in the *CHI3L1* locus were significantly associated with CSF YKL-40 levels, but not AD risk, age at onset, or disease progression [87]. It is important to account for *CHI3L1* variant status in the study subjects when interpreting YKL-40 data in the context of AD pathology. Therefore, YKL-40 may likely be a marker for ongoing pathology but may not have causal link to AD pathology. However, the long-term cognitive outcomes of elevated CSF YKL-40 remain to be established [61]. Regarding sTREM2, except for four studies [46, 61, 64, 66], all remaining studies consistently showed higher levels of sTREM2 in patients with AD dementia or in those with biomarkers consistent with AD dementia. One study with 659 cognitively unimpaired subjects reported lower CSF sTREM2 levels in subjects with Aβ pathology in the absence of tau deposition and neurodegeneration compared to those without Aβ or tau pathology. In contrast, those with tau pathology and neurodegeneration were associated with higher CSF sTREM2 levels [88]. This is consistent with the findings of a study captured by the SLR that reported lower CSF sTREM2 levels at the earliest asymptomatic phase when only abnormal Aβ pathology (A+) but no tau pathology or neurodegeneration (TN−) were present [46]. The sTREM2 biomarker has also been implicated in synaptic injury in a disease stage-specific manner. In one study comprising patients with Aβ pathology but without tau pathology or neurodegeneration (preclinical AD, A+T−N−), early synaptic injury was shown to be independently mediated by sTREM2, whereas later synaptic damage was additionally caused by astrogliosis and tau accumulation [89]. Furthermore, during preclinical stages, both YKL-40 and sTREM2 might play a role in neurodegeneration. Evidence for such interaction between neuroinflammation and accumulating neurodegeneration before the onset of symptoms was provided by elevated levels of CSF YKL-40 and sTREM2 in pre-dementia subjects with pathological levels of tau biomarkers [22].

As for GFAP, most studies in the SLR showed consistently higher levels of GFAP measured in CSF, plasma, and serum in patients with AD or in those with biomarker profiles consistent with AD. However, one study that measured GFAP in saliva showed lower levels of GFAP in patients with MCI due to AD and AD dementia [73]. This is consistent with a recent meta-analysis that evaluated GFAP as a peripheral biomarker and reported higher levels of GFAP in Aβ+ groups than in Aβ− groups, and in patients with AD dementia or MCI due to AD compared with cognitively unimpaired controls [90]. Another meta-analysis of 31 records comprising 3204 individuals reported CSF levels of GFAP significantly increased in patients with AD dementia compared with controls [91].

Some studies have shown the potential for use of GFAP as a prognostic and diagnostic biomarker. One study, in 300 cognitively unimpaired individuals who were followed up to 3 years, reported high baseline GFAP levels to be associated with higher risk of all-cause dementia, and further higher baseline GFAP levels were associated with steeper decline in the domains of memory attention and executive function, suggesting GFAP's potential for use as a prognostic biomarker [92]. In another study, plasma GFAP levels could distinguish patients with AD from controls and individuals with non-AD dementia; further, plasma GFAP levels

also distinguished Aβ cognitively unimpaired controls from subjects in preclinical and MCI stages of AD, suggesting its potential use as a diagnostic biomarker for AD [93]. However, caution is needed in interpreting the data as the longer half-life of GFAP, at about 24–48 h, suggests that even though it may be less prone to fluctuations, its ability to be released across the dysfunctional blood–brain barrier can make it less specific to AD; therefore, one must take into account the person's clinical context when interpreting the data [94, 95]. Nevertheless, noninvasive and less expensive blood biomarkers can be invaluable tools for longitudinal studies. Recent studies have further consolidated the potential of GFAP, NfL, and tau as blood biomarkers for predicting cognitive decline. In one longitudinal study, baseline levels of serum GFAP (β = −0.374, p = 0.004) and NfL (β = −0.422, p < 0.001) were significantly associated with the rate of cognitive decline, as measured by the MMSE [96]. In another longitudinal study, higher baseline GFAP levels predicted decline in performance on measures of delayed memory recall; however, in this study, only higher pTau181 at baseline predicted increased odds for worsening in CDR over time [97]. One study followed individuals with all-cause MCI for 4 years; it reported higher baseline plasma levels of pTau181, NfL, and GFAP among those who progressed to dementia due to AD in comparison to non-progressors [83]. The same study also reported that a combination of baseline pTau181 and GFAP levels best predicted clinical decline in individuals with all-cause MCI (area under the curve = 0.89) [83]. Finally, GFAP as a biomarker of early AD pathology is further confirmed in a longitudinal study that followed plasma GFAP levels over time in carriers and non-carriers of autosomal-dominant AD mutations. This study reported higher plasma GFAP levels in presymptomatic and symptomatic carriers compared with non-carriers, and further GFAP levels diverged 16 years before estimated onset of symptoms [98]. As for clinicopathological validation for GFAP as a biomarker, a single-center prospective study involving 139 patients with dementia examined the relationship between serum GFAP levels and postmortem neuropathology [99]. The study by Sánchez-Juan et al. demonstrated an association between serum GFAP levels and postmortem tau pathology, independent of amyloid deposits. This finding provides neuropathological validation for GFAP as a biomarker and supports its diagnostic use. Given the average time interval of 139 days between serum extraction and postmortem evaluation in this study, serum GFAP levels can be considered a proxy for tau pathology [99]. However, similar data for clinico-pathological validation of sTREM2 and YKL-40 biomarker levels in patients with AD are lacking. In the context of the three fluid biomarkers evaluated in this SLR, there is clearly a need for more longitudinal studies on CSF biomarker dynamics to further consolidate their clinical utility for predicting long-term cognitive outcomes. Future studies using imaging biomarkers like PET tracers specific for neuroinflammation and neurodegeneration can help us understand the predictive value of the changes observed in neuroinflammatory fluid biomarkers [100, 101]. Furthermore, discovery strategies using proteomic and multimodal omics approaches have identified additional potential fluid biomarkers related to neuroinflammation and neurodegeneration that change in the AD continuum, emphasizing the complex nature of AD [102–109].

The data extracted from the SLR showed a gradual increase in all fluid biomarkers evaluated across the AD continuum compared to healthy controls from cerebrospinal fluid (CSF), serum, and plasma samples. However, saliva samples showed a decrease in biomarker levels compared to healthy controls. It is important to note that the saliva findings require further replication and consolidation, as they are based on data from only two studies (Fig. 2C and Supplementary Fig. 1D). In CSF (Supplementary Fig. 1A), all three biomarkers—YKL-40, sTREM2, and GFAP—were elevated compared to healthy controls in both preclinical and symptomatic stages of AD. In plasma (Supplementary Fig. 1C), GFAP levels were consistently elevated compared to healthy controls across asymptomatic (preclinical), symptomatic, and dementia stages of AD. The findings from the SLR indicate YKL-40 and GFAP as potential candidates for AD staging, with sTREM2 as a sensitive biomarker in the late preclinical stages of the disease. This is in alignment with the revised AA 2024 criteria for the staging of AD, suggesting the use of plasma GFAP as inflammatory biomarker for AD staging [39]. Imaging biomarkers of neuroinflammation can be used to monitor adverse effects of therapeutic AD anti-Aβ antibodies like vasogenic edema and microhemorrhages, recognized as amyloid-related imaging abnormalities (ARIA), which are likely due to mobilization of plaque Aβ into the perivascular drainage system or from antibody targeting of vascular Aβ deposits [110]. Moreover, in vivo [^{11}C] PK11195 PET evidence for an association between microglial activation and the magnitude and severity of ARIA in patients with increased CSF concentration of anti-Aβ autoantibodies suggest a link between neuroinflammation driven by anti-Aβ immunothera-pies [111]. There is scope for studying the relationship between inflammatory fluid biomarkers and ARIA, which can help clinicians to identify patients with AD who are at risk of ARIA.

The findings of the SLR with regard to GFAP, sTREM2, and YKL-40 as potential biomarkers for the early diagnosis of AD are further strengthened by recent studies published in 2023 and 2024 (Supplementary Table 2). Two population-based prospective cohort studies with more than 13 years of follow-up showed elevated plasma GFAP levels to be associated with cognitive impairment and predictive of the risk of AD dementia [112, 113]. Another population-based cohort study, which included subjects with AD dementia and dementia-free individuals, revealed that plasma GFAP levels were significantly elevated in participants diagnosed with AD within 17 years. Plasma GFAP demonstrated the best discrimination between AD and controls and had a strong ability to predict clinical AD risk [114]. A longitudinal cohort study by Pelkmans et al. demonstrated plasma GFAP and CSF YKL-40 to be important contributors to AD progression, with plasma GFAP as a mediator for the association between soluble and insoluble Aβ in the early stages of AD, and CSF YKL-40 as a mediator for the association between Aβ and downstream Aβ-induced tau pathology and tau-induced neuronal injury during the later stages of AD [115]. Likewise, with regard to sTREM2, a recently published longitudinal study with a 4-year follow-up showed that in individuals with an A+/TN+ biomarker profile, baseline CSF sTREM2 is significantly associated with baseline tau-PET and Aβ-PET rate of change. In contrast, in individuals with an A+/TN− profile, higher rates of change in sTREM2 (slope) during the follow-up were significantly associated with lower rates of change in Aβ and tau-PET. This suggests that TREM2-related microglia activation and their relationships with AD markers and cognitive perfor-mance vary in the presence or absence of Aβ and tau pathology [116]. Additionally, a systematic review of 36 observational studies involving more than 3000 patients in each of the AD, MCI, and healthy control groups showed significantly higher CSF sTREM levels in the MCI and AD groups compared with healthy controls. It also found that increased plasma sTREM2 levels are associated with a higher risk of AD, suggesting that it may serve as a promising biomarker for diagnosing AD but is not effective for staging AD [117]. Regarding YKL-40, a recently published prospective analysis from four large community-based indepen-dent cohorts involving more than 6000 dementia-free participants showed that higher plasma YKL-40 levels were associated with lower brain volume and poorer cognition. The association between YKL-40 levels and incident dementia was independent of amyloid, tau, and neurodegeneration biomarker status, suggesting the potential for clinical uses of YKL-40 in determining the risk of dementia [85]. These recently published studies, further detailed in Supplementary Table 2, reinforce the rationale for

using these fluid biomarkers for diagnoses and staging AD, and clearly warrant more confirmatory studies.

Finally, one limitation of the SLR is that many of the studies captured did not have biomarker-supported diagnoses, which may suggest a risk of bias in interpretation of the findings. This is consistent with a recent meta-analysis that showed biomarker analysis was not routinely used in diagnostic practice [118]. Also, the SLR did not capture many longitudinal studies, which may have hampered us from evaluating their prognostic value. Focus on fluid biomarkers and exclusion of imaging studies from this report precluded us from discussing the studies that evaluated the congruence between the two diverse modalities of biomarker measurements in subjects.

Neuroinflammation plays a critical role in the pathogenesis of AD, and fluid biomarkers of neuroinflammation enable researchers to capture and follow ongoing disease processes in a stage-specific manner. The findings of the SLR invariably support the association of neuroinflammatory biomarkers with progression of AD. Findings varied across the specific biomarkers assessed and cognitive measurements used in the SLR. Even though studies on YKL-40, sTREM2, and GFAP were prominently captured by the SLR, imaging biomarkers (not explored in this report) may potentially facilitate understanding of the long-term consequences of neuroinflammation in the brains of patients with AD. Cross-sectional studies captured by the SLR supported the use of CSF/plasma/serum GFAP for segregating cognitively unimpaired individuals from those with preclinical AD, all-cause MCI, and different stages of AD dementia. Similarly, biomarker levels of CSF YKL-40 and CSF sTREM2 can potentially separate cognitively unimpaired people and those with AD. Longitudinal studies in diverse populations of AD are needed to consolidate the prognostic value of the biomarkers in clinical practice.

DATA AVAILABILITY
All data generated or analyzed during this study, which support the findings of this study, are included within this article and its supplementary information files. Any data not present in the manuscript will be available from the corresponding author upon reasonable request.

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AUTHOR CONTRIBUTIONS

MTH supervised the research, contributed to visualization and data presentation, and drafted, reviewed and edited the manuscript. SG contributed to visualization and data presentation, and drafted, reviewed and edited the manuscript. SAC conceptualized the data analysis, contributed to data curation, funding acquisition, project administration, visualization and data presentation, and drafted, reviewed and edited the manuscript. JHH-P conceptualized the data analysis and methodology, contributed to data curation, funding acquisition, and drafted, reviewed and edited the manuscript. MAB contributed to the methodology and validation, and drafted, reviewed and edited the manuscript. HZ contributed to data visualization, and drafted, reviewed and edited the manuscript. All authors have read and agreed to the publication of this manuscript.

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MTH serves on scientific advisory boards for Alector, Dementia Discovery Fund, UK DRI, and T3D Therapeutics. He has received honoraria for consultations and/or oral presentations from AC Immune, Biogen, Eisai, Novo Nordisk, and Roche. SG has served on scientific advisory boards for ADvantage Therapeutics, Alzheon, AmyriAD, Biogen Canada, Eisai Canada, Enigma, Lilly Canada, Lundbeck, Medesis, Roche Canada, Sharon Francis Foundation, and TauRx. SAC, JHH-P, and MAB are full-time employees of Novo Nordisk A/S. HZ has served on scientific advisory boards and/or as a consultant for AbbVie, Acumen, Alector, Alzinova, ALZpath, Annexon, Apellis, Artery Therapeutics, Inc., AZTherapies, Inc., Cognition Therapeutics, Inc., Denali Therapeutics, Eisai, NervGen, Novo Nordisk, OptoCeutics, Passage Bio, Pinteon Therapeutics, Prothena, Red Abbey Labs, reMYND, Roche, Samumed, Siemens Healthineers, Triplet Therapeutics, Inc., and Wave Life Sciences. He has given lectures in symposia sponsored by AlzeCure, Biogen, Cellectricon, Fujirebio, and Roche, and is a co-founder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program (outside submitted work). He is also a Wallenberg Scholar and a Distinguished Professor at the Swedish Research Council, supported by grants from the Swedish Research Council (#2023-00356; #2022-01018

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ADDITIONAL INFORMATION