Review

Clinical utility of cerebrospinal fluid biomarkers in the evaluation of cognitive impairment: a systematic review and meta-analysis

Jemma Hazan, Michelle Wing, Kathy Y Liu, Suzanne Reeves, Robert Howard

ABSTRACT
Background The analytical and clinical validity of cerebrospinal (CSF) biomarkers has been extensively researched in dementia. Further work is needed to assess the ability of these biomarkers to improve diagnosis, management and health outcomes in the clinical setting.

Objectives To assess the added value and clinical utility of CSF biomarkers in the diagnostic assessment of cognitively impaired patients under evaluation for Alzheimer’s disease (AD).

Methods Systematic literature searches of Medline, EMBASE, PsycINFO and Web of Science research databases were conducted on 17 December 2022. Data from relevant studies were extracted and independently screened for quality using a tool for bias. Clinical utility was measured by clinicians’ changes in diagnosis, diagnostic confidence and patient management (when available), after their examination of patients’ CSF biomarkers. Cost-effectiveness was assessed by consideration of additional cost per patient and quality-adjusted life years.

Results Searches identified 17 studies comprising 2090 patient participants and 593 clinicians. The meta-analysis revealed that clinicians’ use of CSF biomarkers resulted in a pooled percentage change in diagnosis of 25% (95% CI 14 to 37), an increase in diagnostic confidence of 14% (95% CI 9 to 18) and a pooled proportion of patients whose management changed of 31% (95% CI 12 to 50). CSF biomarkers were deemed cost-effective, particularly in memory services, where pre-test AD prevalence is higher compared with a primary care setting.

Conclusions CSF biomarkers can be a helpful additional diagnostic tool for clinicians assessing patients with cognitive impairment. In particular, CSF biomarkers consistently improved clinicians’ confidence in diagnosing AD and influenced on diagnostic change and patient management. Further research is needed to study the clinical utility of blood-based biomarkers in the clinical setting.

INTRODUCTION
There are over 850 000 people with dementia in the UK, and numbers are expected to rise as the population ages, with over 1.1 million people living with AD in the UK by 2025. The diagnosis of Alzheimer’s disease (AD), which is the most common form of dementia, has advanced in the last decade through the availability of in vivo biological measures or ‘biomarkers’. These biomarkers can detect the pathological hallmarks of AD: pathological tau and beta amyloid proteins, as well as neurodegeneration. Biomarkers have been incorporated into the diagnostic framework of AD in clinical research. A consensus ‘roadmap’ was set out in 2017 to aid the incorporation of these biomarkers into the clinical setting to improve diagnostic accuracy.

Cerebrospinal fluid (CSF) biomarkers are currently used in the diagnostic investigation of AD at specialist tertiary Neurology Centres in the UK. However, they are not routinely used in UK Memory Services. CSF biomarkers have demonstrated analytical validity. Validated AD CSF biomarkers include amyloid-β1–42, total-tau and phosphorylated-tau181 (ptau181). A reduction in Aβ42 and raised levels of ptau are indicative of Aβ and tau pathologies in AD, while increased total-tau is a non-specific marker of neuronal injury. Many studies have demonstrated the correlation between CSF levels and neuropathology.

These CSF biomarkers have garnered attention as, in contrast to imaging biomarkers such as amyloid PET, they are cheap, quick and simple to obtain in a clinical setting. However, there are reported concerns regarding lumbar puncture (LP) due to its perceived more invasive nature. The most frequent reported side effect is a post-LP headache. Several large multicentre studies have demonstrated that LP is a safe and tolerable procedure. Further barriers to the routine use of LP in Memory Services include a lack of skills training in this procedure.

Biomarkers may also assist clinicians in differentiating AD from non-AD dementias, and mild cognitive impairment (MCI) from early AD.

There have been several studies exploring the validity and diagnostic accuracy of CSF biomarkers in AD. However, to date, this may be one of the first systematic reviews to explore the clinical utility of CSF biomarkers in the diagnostic evaluation of cognitively impaired patients. In this study, we aim to assess the real-world added value and clinical utility, defined as relative improvement in clinicians’ diagnostic confidence or change in diagnosis or...
management, of CSF biomarkers in patients being evaluated for cognitive impairment due to AD.

**METHODS**

**Study design**

A systematic review with mixed-methods quantitative and narrative synthesis was conducted following the Preferred Items for Reporting of Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

**Eligibility criteria**

Included studies performed a diagnostic and clinical utility analysis of CSF biomarkers, where clinicians cognitively assessed at least 10 cognitively impaired participants of any age undergoing evaluation for AD. Peer-reviewed published studies in English were included if their primary or secondary outcome included at least one of change in diagnosis, diagnostic confidence, patient management or cost analysis. We excluded reviews, protocols, and conference presentations.

**Search strategy**

An online literature search was carried out on 17 December 2021 using Medline, Embase, PsycINFO and Web of Science (WoS) databases, using the terms listed in the online supplementary data appendix 1. The search terms were modified to meet the criteria for medical subject headings in the various databases. The references of identified articles were also screened to ensure all relevant studies were included.

**Data extraction**

Two authors (JH and MW) independently screened and selected potentially relevant abstracts and assessed the full study texts according to eligibility criteria. Any disagreement between authors was resolved through discussion. If there was any further disagreement, this was resolved by discussion with a third author (SR).

Two authors (JH and MW) independently extracted data. If there was a disagreement, this was resolved in discussion between the two raters. We extracted data on study characteristics (design, setting, duration, intervention, inclusion criteria), relevant outcomes (change in diagnosis, diagnostic confidence and change in management plan) and participant characteristics (population, sample size, initial diagnosis, age, sex, demographics).

**Risk of bias in individual studies and quality assessment**

Two authors (JH and MW) independently assessed studies for bias using a modified Quality Assessment Tool for Quantitative Studies, originally developed by the Effective Public Health Practice Project. Any disagreement was resolved by discussion with a third author (SW). Quality of studies was assessed across several domains including selection bias, study design, confounders, data collection method, and withdrawals and dropouts. The scores were collated to give an overall global rating for each paper as “Strong”, “Moderate” or “Weak”. If a study received a weak rating in all areas of bias, it was excluded from the review.

**Synthesis of results and meta-analysis**

A mixed-methods quantitative and narrative synthesis was carried out due to the small number of studies and heterogeneity in study methodology.

In terms of the quantitative analyses, the percentage of change in diagnoses, diagnostic confidence and management was computed using available study data. A random-effects meta-analysis was conducted to calculate pooled estimates of the percentage change in diagnoses, confidence and management, due to the heterogeneity in study settings and study populations.

Subanalyses were performed on the percentage change in AD diagnoses, that is, changes in diagnosis from AD to non-AD and from non-AD to AD. The I² statistic was used to assess the degree of heterogeneity of the percentage change in diagnosis, confidence and management across studies. We followed Tu’s 2016 methodology for testing the relationship between percentage change and baseline values, which uses a modified Pearson’s test. All analyses were performed using R Software R V.4.1.2; R Foundation for Statistical Computing.

**RESULTS**

**Study identification**

Seventeen studies were identified for inclusion. The PRISMA flowchart is displayed in figure 1. In total, 5816 records were identified from 4 databases; Medline, EMBASE, PsycINFO and Web of Science. After removal of duplicates, 3071 records were screened; 3031 records were excluded. Reasons for exclusion included not relevant to diagnosis of dementia, did not involve relevant CSF markers and explored analytical validity of CSF markers. Forty reports were assessed for eligibility. Twenty-three reports were excluded. Reasons for exclusion were poster abstracts, study protocols, not in English, no exact data, review or similar and study of clinical utility of blood biomarker.

**Study characteristics**

Study characteristics are shown in table 1 and table 2 and in online supplemental table 2.

**Study design**

Most (12 of 17, 71%) of the included studies were prospective observational studies. One study was a survey of clinicians
<table>
<thead>
<tr>
<th>Author, year of Publication</th>
<th>Country</th>
<th>Type of study</th>
<th>Referral setting</th>
<th>Intervention</th>
<th>Study duration</th>
<th>Patient sample size (N)</th>
<th>Clinician sample size (N)</th>
<th>Patient inclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Balasa et al, 2013</td>
<td>Spain</td>
<td>Prospective observational study</td>
<td>Specialist outpatient clinic</td>
<td>LP for CSF biomarkers: Aβ42, t-tau and p-tau</td>
<td>2009–2013</td>
<td>157</td>
<td>NR</td>
<td>Patients &lt;65 years</td>
</tr>
<tr>
<td>Boelaarts et al, 2020</td>
<td>The Netherlands</td>
<td>Prospective observational Study</td>
<td>Community geriatric outpatient clinic</td>
<td>LP for CSF biomarkers: Aβ42, t-tau and p-tau</td>
<td>2010–2016</td>
<td>69</td>
<td>NR</td>
<td>Patients &lt;71 years</td>
</tr>
<tr>
<td>Duits et al, 2015</td>
<td>The Netherlands</td>
<td>Prospective observational study</td>
<td>Memory clinic</td>
<td>LP for CSF biomarkers: Aβ42, t-tau and p-tau</td>
<td>2011–2012</td>
<td>351</td>
<td>5</td>
<td>All patients visiting the clinic</td>
</tr>
<tr>
<td>van den Brink et al, 2020</td>
<td>Canada</td>
<td>Retrospective observational study</td>
<td>Specialist memory clinic</td>
<td>LP for CSF biomarkers: Aβ42, t-tau, and p-tau and FDG-PET</td>
<td>2017–2019</td>
<td>28</td>
<td>NR</td>
<td>Atypical dementia presentations</td>
</tr>
<tr>
<td>Falgàs et al, 2019</td>
<td>Spain</td>
<td>Prospective observational study</td>
<td>Specialist memory clinic</td>
<td>Patients underwent biomarkers which included MRI, LP for CSF biomarkers: Aβ42, t-tau and p-tau, FDG-PET, amyloid PET</td>
<td>Not reported</td>
<td>40</td>
<td>5</td>
<td>&lt;65 years of age, MMSE score ≥18</td>
</tr>
<tr>
<td>Gjerum et al, 2021</td>
<td>Denmark</td>
<td>Retrospective observation incremental study</td>
<td>Memory clinic</td>
<td>Patients randomised to addition of either 2-18F-FDG-PET or CSF biomarkers: Aβ42, t-tau and p-tau</td>
<td>2015–2016</td>
<td>81</td>
<td>2</td>
<td>Cognitive impairment due to neurodegenerative disease (MMSE≥18, CDR≥1.0, undergone T1-weighted MRE≥1.5 T; addition of CSF biomarkers deemed useful by clinician)</td>
</tr>
<tr>
<td>Gooblar et al, 2015</td>
<td>USA</td>
<td>Study using simulated clinical vignettes</td>
<td>Primary, secondary and tertiary centres</td>
<td>Simulated CSF values</td>
<td>January–July 2013</td>
<td>2</td>
<td>193</td>
<td>2 Simulated clinical vignettes</td>
</tr>
<tr>
<td>Handels et al, 2017</td>
<td>The Netherlands</td>
<td>Cost-effectiveness analysis</td>
<td>NA</td>
<td>Simulated CSF values</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Simulated patients with MCI</td>
</tr>
<tr>
<td>Kester et al, 2010</td>
<td>The Netherlands</td>
<td>Prospective observational study</td>
<td>One local hospital memory clinic</td>
<td>LP for CSF biomarkers: Aβ42, t-tau and p-tau</td>
<td>2005–2008</td>
<td>109</td>
<td>2</td>
<td>All patients visiting the clinic</td>
</tr>
<tr>
<td>Lee et al, 2017</td>
<td>Canada</td>
<td>Cost-effectiveness analysis</td>
<td>NA</td>
<td>Simulated CSF values</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Simulated patients with suspected AD</td>
</tr>
<tr>
<td>Mouton-Liger et al, 2014</td>
<td>France</td>
<td>Prospective observational study</td>
<td>secondary or tertiary memory centres</td>
<td>LP for CSF biomarkers: Aβ42, t-tau and p-tau</td>
<td>Not specified</td>
<td>561</td>
<td>128</td>
<td>When a clinician considered a patient eligible for CSF biomarkers</td>
</tr>
<tr>
<td>Ramusino et al, 2019</td>
<td>Italy</td>
<td>Prospective study</td>
<td>Multicentre, 4 memory clinics</td>
<td>LP for CSF biomarkers: Aβ42, t-tau and p-tau and amyloid-PET</td>
<td>2015–2017</td>
<td>71</td>
<td>2</td>
<td>MCI or mild dementia possibly due to AD, age range 55–90 years, score &lt;4 on the modified Hachinski ischemic scale At least 5 years of education</td>
</tr>
</tbody>
</table>

Continued
### Table 1

<table>
<thead>
<tr>
<th>Author, year of Publication</th>
<th>Country</th>
<th>Type of study</th>
<th>Referral setting</th>
<th>Intervention</th>
<th>Study duration</th>
<th>Patient sample size (N)</th>
<th>Clinician sample size (N)</th>
<th>Patient Inclusion criteria</th>
<th>Outcome measures</th>
<th>Quality assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stiffel et al., 2021</td>
<td>Canada</td>
<td>Prospective observational study</td>
<td>Tertiary memory clinic</td>
<td>LP for CSF biomarkers, Aβ42, t-tau and p-tau</td>
<td>2015–2020</td>
<td>262</td>
<td>NR</td>
<td>Participants included if basic history, neurological evaluation and FDG-PET did not provide conclusive diagnosis</td>
<td>Of the three studies that performed a cost-effectiveness analysis of CSF biomarkers to diagnose AD, two examined lifetime costs and quality-adjusted life-years (QALYs) and one performed an economic evaluation.</td>
<td>Moderate</td>
</tr>
<tr>
<td>Ye et al., 2021</td>
<td>Spain</td>
<td>Prospective observational study</td>
<td>Neurology clinic</td>
<td>LP for CSF biomarkers, Aβ42, t-tau and p-tau</td>
<td>2015–2019</td>
<td>137</td>
<td>NA</td>
<td>Not reported</td>
<td>Most (14 of 17, 83%) studies were assessed as being of moderate quality, and three studies were assessed as being of high quality. No studies were assessed to be of low quality (online supplemental table 1). High-quality studies comprised the cost-effectiveness analysis, which included in the study design methods to reduce confounding and selection bias. For the studies of moderate quality, study quality limitations included limited information about baseline clinician demographics and ethnic diversity of the patient participant study population, observational study design, and a lack of a validated or uniform method of data collection on questionnaire.</td>
<td>Moderate</td>
</tr>
<tr>
<td>Valk and Roos et al., 2014</td>
<td>Canada</td>
<td>Prospective observational study</td>
<td>Tertiary care memory clinic</td>
<td>LP for CSF biomarkers, Aβ42, t-tau and p-tau</td>
<td>2015–2019</td>
<td>395</td>
<td>NR</td>
<td>Participants included if basic history, neurological evaluation and FDG-PET did not provide conclusive diagnosis</td>
<td>Most studies recruited clinicians with a speciality in Neurology, but only one study provided detailed clinician demographics.</td>
<td>Moderate</td>
</tr>
</tbody>
</table>

#### Patient and clinician characteristics

The mean age of patient participants in the studies was 66.3 years (±SD 7.66), and two studies restricted inclusion criteria to patients aged <65 years.

Of the 17 studies, AD and MCI were the most common initial (pre-biomarker) diagnoses. The initial (pre-biomarker) diagnoses for patient participants in the studies included subjective cognitive disorder, MCI, AD dementia, frontotemporal lobe dementia, vascular dementia, dementia with Lewy bodies, dementia with unknown aetiology, Parkinson’s disease and Parkinson’s plus syndromes, psychiatric disorders or “other”. In addition to AD, the final (post-biomarker) dementia diagnoses included progressive supranuclear palsy, Creutzfeldt-Jakob disease, corticobasal degeneration and Huntington’s disease. Non-demented patients were categorised as “no cognitive disorder”, symptoms of a cognitive disorder caused by a developmental disorder, or a psychiatric or neurological disorder.

Most studies recruited clinicians with a speciality in Neurology, but only one study provided detailed clinician demographics.

#### Outcome measures

Outcome measures are described in online supplemental table 2. The majority (13 of 17, 76%) of studies required the clinician to complete a pre-CSF and post-CSF results questionnaire, listing initial and final diagnoses, respectively.

Of these studies, eight examined how CSF biomarker results changed diagnostic confidence, and seven assessed their impact on patient management, defined as the initiation or discontinuation of dementia medications such as cholinesterase inhibitors, the ability to enrol in clinical trials, and/or length of follow-up.

Of the three studies that performed a cost-effectiveness analysis of CSF biomarkers to diagnose AD, two examined lifetime costs and quality-adjusted life-years (QALYs) and one performed an economic evaluation. Outcome measures are described in table 2.

#### Quality assessment

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#### Findings

##### Change in diagnosis

Eleven studies, comprising 1891 patient participants and 395 clinician participants, reported on the percentage change in clinicians’ diagnosis after the availability of fluid biomarker using simulated clinical scenarios. Other study designs included three cost-effectiveness analyses and two retrospective observational studies. All studies assessed the impact of CSF biomarker results. The mean sample sizes of patient and clinician participants were 149 and 66, respectively. Seven studies were performed at specialist memory clinics with a single site, five were multicentre and two were early-onset dementia clinics.
CI 14 to 37) and there was substantial heterogeneity (I² 97%, overall pooled percentage change in diagnoses was 25% (95% CI 14 to 37) and there was substantial heterogeneity (I² 97%, p<0.001) (figure 2a). Subgroup analyses found no significant change in diagnoses from initial AD to final non-AD or initial non-AD to final AD (online supplemental figures 1A and B).

Two studies explored the accuracy of clinicians’ final diagnoses through longitudinal patient follow-up. In one study, after 12 months of follow-up, 89% of patients’ diagnoses were found to be correctly classified. Similarly, another study showed that after a mean follow-up time of 31 months, 88% of AD participants maintained their diagnosis and all MCI participants who had positive CSF results progressed to AD dementia.30

Clinician-rated diagnostic confidence
Eight studies calculated and showed an overall increase in diagnostic confidence, ranging from 5% to 22% (online supplemental table 2). The overall pooled percentage change in confidence was 14% (95% CI 9 to 18) and there was substantial heterogeneity (I² 97%, p<0.001) (figure 2b).

The change in confidence was inversely proportional to the initial pre-test confidence level, such that lower pre-test confidence was associated with a greater percentage change in confidence (Pearson’s r = −0.91, p<0.001).

Two studies that reported an overall increase pooled percentage change in confidence also showed a decrease in diagnostic confidence for a minority of clinicians.33 35 This was often associated with patients for whom CSF results did not alter the final diagnosis and who had a pre-biomarker diagnosis of subjective memory complaint or a psychiatric disorder.33

Change in management
Five studies, comprising 918 patients, evaluated the impact on CSF biomarkers on patient management.32 33 38 39 46 The overall proportion of patients whose management changed after availability of fluid biomarkers ranged between 13% and 47%, and the overall pooled proportion of patients whose management changed was 31% (95% CI 12 to 50) with substantial heterogeneity (I² 97%, p<0.001) (figure 2c). The most common management change was the commencement or stopping of cholinesterase inhibitors or other dementia medications (four of five studies).

Cost-effectiveness
Three studies analysed the cost-effectiveness of CSF biomarkers to diagnose AD in MCI and dementia populations: a 2014 Spanish study and two studies published in 2017 from Canada and The Netherlands. All three studies assessed CSF biomarkers (amyloid-beta 1–42, total tau and phosphorylated tau). In one study,46 CSF biomarkers were reported to be an alternative, less expensive and more efficient diagnostic tool compared with standard diagnostic procedures in patients with MCI, as per guidelines of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer’s Disease and Related Disorders Association (NINDS-ADRDA guidelines).

The same study reported that for patients with dementia, despite higher uncertainty, CSF biomarkers were also a cost-effective alternative compared with standard clinical diagnostic criteria. A second study43 used a Markov model to estimate the lifetime costs and QALYs of CSF biomarker analysis in patients with MCI.

<table>
<thead>
<tr>
<th>Author, year of publication</th>
<th>Type of study</th>
<th>Aim</th>
<th>Outcome measure</th>
<th>Statistical analysis</th>
<th>Summary of findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Handels et al,2017 Netherlands</td>
<td>Cost-effectiveness analysis</td>
<td>To estimate the potential ICER of adding CSF biomarker testing to the standard diagnostic work-up to determine the prognosis for patients with MCI</td>
<td>Accuracy of prognosis QALY</td>
<td>Simulated data model using a merged dataset</td>
<td>Improved the accuracy of prognosis by 11%</td>
</tr>
<tr>
<td>Lee et al,2017 Canada</td>
<td>Cost-effectiveness analysis</td>
<td>To estimate the lifetime costs and QALYs of CSF biomarker analysis in a cohort of patients referred to a neurologist or memory clinic with suspected AD who remained without a definitive diagnosis of AD or another condition after neuroimaging</td>
<td>Additional cost per patient QALY</td>
<td>Markov model</td>
<td>AD pre-test probability of 12.7%; average QALY gain of 0.015/ICER of €11 032 per QALY gained 5% additional costs per patient</td>
</tr>
<tr>
<td>Valcárcel-Nazco et al,2014 Spain</td>
<td>Cost-effectiveness analysis</td>
<td>To determine the cost-effectiveness of the CSF biomarkers to diagnose AD in patients with MCI and those with dementia</td>
<td>Cost and effectiveness</td>
<td>Probabilistic sensitivity analysis using 2nd-order Monte Carlo simulations. Acceptability curves were calculated and ANCOVA models applied to simulation results</td>
<td>Patients with MCI: lower average cost per patient of €1832.65</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Patients with AD: higher average cost per patient of €1133.82</td>
</tr>
</tbody>
</table>

AD, Alzheimer’s disease; ANCOVA, analysis of covariance; CSF, cerebrospinal fluid; ICER, incremental cost-effectiveness ratio; MCI, mild cognitive impairment; QALY, quality-adjusted life year.

results,31–33 35–40 45 46 which ranged between 7% and 61%. The overall pooled percentage change in diagnoses was 25% (95% CI 14 to 37) and there was substantial heterogeneity (I² 97%, p<0.001) (figure 2a). Subgroup analyses found no significant change in diagnoses from initial AD to final non-AD or initial non-AD to final AD (online supplemental figures 1A and B).

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was no difference in terms of added diagnostic value between them, with no apparent benefit of using another biomarker if amyloid-PET or CSF biomarkers had been performed. However, in another study, amyloid-PET provided greater changes in diagnosis and diagnostic confidence than CSF biomarkers.

For participants correctly diagnosed as patients with AD, CSF biomarkers had a significantly higher impact on diagnostic and a significant reduction in the need for further investigations when compared with FDG-PET. One study reported that for 35% of patient participants, FDG-PET and CSF-based diagnosis did not correspond.

**DISCUSSION**

Previous systematic reviews have reported on the analytical or clinical validity of fluid biomarkers, or the clinical utility of imaging biomarkers such as amyloid-PET. In this review, we focused specifically on the clinical utility of CSF biomarkers in the assessment of patients with cognitive impairment and the cost-effectiveness of CSF biomarkers for AD.

Use of CSF biomarkers resulted in a change in diagnosis in 25% of cases, although this was not specific to any direction of diagnostic change (AD to non-AD or non-AD to AD). This result is similar to the overall change of diagnosis of 35.2% after amyloid-PET.

Biomarker results are likely to provide an additional diagnostic assessment tool that clinicians will consider in combination with clinical findings. In one study that provided simulated clinical vignettes to clinicians, an AD clinical presentation with AD CSF results led to a significantly increased odds of an AD diagnosis, whereas when clinicians were given borderline CSF values, they relied on other clinical information to decide on the final diagnosis. Also, when clinicians were shown a mild AD clinical presentation with normal CSF results, they often chose a diagnosis of unknown aetiology, and when clinicians were shown an ambiguous clinical presentation with AD CSF results, they were more likely to make an AD diagnosis.

Studies consistently reported that CSF biomarkers improved clinicians’ diagnostic confidence with a pooled mean increase of 14%. This is in comparison with the impact of amyloid-PET where the change in confidence level reportedly ranged from 16% to 44%. However, some studies reported that biomarker results resulted in a reduction in confidence, for example, in the context of unexpected biomarker results when patients with subjective cognitive complaint or a psychiatric disorder had abnormal dementia biomarkers, or when patients initially diagnosed with AD had normal biomarkers. It is relevant that higher diagnostic confidence may not always equate to greater clinical utility, as decreased confidence after CSF results could sometimes help a clinician to question their pre-CSF diagnosis and prevent an incorrect diagnosis. A reduction in diagnostic confidence may also spur further diagnostic tests and have a substantial impact on management.

Use of CSF biomarkers led to a change in management in 31% of cases, mostly involving the initiation or discontinuation of cholinesterase inhibitors. One review examining the impact of amyloid-PET found that the overall change in management was 59.6%, which represents a larger pooled effect size compared with CSF biomarkers. This may be due to factors such as the proportion of patients already prescribed medication and degree of diagnostic certainty prior to amyloid-PET. However, amyloid-PET is costly, less accessible and provides information solely on amyloid deposition.

CSF in addition to FDG-PET or amyloid-PET imaging

Four studies examined the additional benefit of CSF biomarkers in participants who had specialist FDG-PET or amyloid-PET imaging. One study reported that CSF biomarkers and amyloid-PET results showed a good concordance and that there

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**Figure 2**

(A) Forest plot showing the pooled percentage change in diagnosis. (B) Forest plot showing the pooled percentage change in confidence. (C) Forest plot showing the pooled proportion of patients whose management changed (%).

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Biomarker results are likely to provide an additional diagnostic assessment tool that clinicians will consider in combination with clinical findings. In one study that provided simulated clinical vignettes to clinicians, an AD clinical presentation with AD CSF results led to a significantly increased odds of an AD diagnosis, whereas when clinicians were given borderline CSF values, they relied on other clinical information to decide on the final diagnosis. Also, when clinicians were shown a mild AD clinical presentation with normal CSF results, they often chose a diagnosis of unknown aetiology, and when clinicians were shown an ambiguous clinical presentation with AD CSF result, they were more likely to make an AD diagnosis.

Studies consistently reported that CSF biomarkers improved clinicians’ diagnostic confidence with a pooled mean increase of 14%. This is in comparison with the impact of amyloid-PET where the change in confidence level reportedly ranged from 16% to 44%. However, some studies reported that biomarker results resulted in a reduction in confidence, for example, in the context of unexpected biomarker results when patients with subjective cognitive complaint or a psychiatric disorder had abnormal dementia biomarkers, or when patients initially diagnosed with AD had normal biomarkers. It is relevant that higher diagnostic confidence may not always equate to greater clinical utility, as decreased confidence after CSF results could sometimes help a clinician to question their pre-CSF diagnosis and prevent an incorrect diagnosis. A reduction in diagnostic confidence may also spur further diagnostic tests and have a substantial impact on management.

Use of CSF biomarkers led to a change in management in 31% of cases, mostly involving the initiation or discontinuation of cholinesterase inhibitors. One review examining the impact of amyloid-PET found that the overall change in management was 59.6%, which represents a larger pooled effect size compared with CSF biomarkers. This may be due to factors such as the proportion of patients already prescribed medication and degree of diagnostic certainty prior to amyloid-PET imaging. However, amyloid-PET is costly, less accessible and provides information solely on amyloid deposition.

CSF in addition to FDG-PET or amyloid-PET imaging

Four studies examined the additional benefit of CSF biomarkers in participants who had specialist FDG-PET or amyloid-PET imaging. One study reported that CSF biomarkers and amyloid-PET results showed a good concordance and that there

---

**Figure 2**

(A) Forest plot showing the pooled percentage change in diagnosis. (B) Forest plot showing the pooled percentage change in confidence. (C) Forest plot showing the pooled proportion of patients whose management changed (%).
revealed CSF biomarkers to be a cost-effective alternative to standard diagnostic work-up.\textsuperscript{42-44}

There was conflicting evidence regarding the utility of CSF biomarkers in addition to specialist imaging including FDG-PET and amyloid-PET.\textsuperscript{42}

Despite the findings in this review, there is low utilisation of CSF biomarkers in memory services in the UK, where staff to do not have access to the specialist equipment and expertise to perform routine LPs. There have been recent advancements in the validation of blood-based biomarkers, such as ptau-181 and ptau-217, which have been shown to have similar sensitivity and specificity to CSF biomarkers.\textsuperscript{53} In one prospective observational study, serum neurofilament light was perceived as a useful additional tool to CSF biomarkers in 53\% of cases by neurologists in a tertiary memory clinic.\textsuperscript{37} In a recent position statement, blood biomarkers were recommended in memory clinics as part of the diagnostic work-up of patients with cognitive symptoms, with the results confirmed where possible with CSF or amyloid-PET imaging.\textsuperscript{54} Further studies are needed to establish if the clinical utility of blood-based biomarkers is comparable with CSF biomarkers and amyloid PET imaging. Blood-based biomarkers are simple to carry out and cost-effective.\textsuperscript{16} They could be made widely available and have the potential to be used within UK memory services to support the diagnosis of Alzheimer’s dementia.

In the UK, there is a lack of information on the investigation and management of MCI in the NICE guidelines.\textsuperscript{35} It would be important to address this in future guidance, given the increasing proportion of people diagnosed as MCI in UK memory services.\textsuperscript{36}

Limitations

The interpretation of the findings is limited by the small number of included studies, small sample sizes and high methodological heterogeneity. Most included studies were of moderate quality. Study quality limitations included lack of information about baseline clinician demographics and were observational studies.

Only one study reported on clinician demographics such as ethnicity, age and level of seniority, and most clinicians were neurologists, so it is unknown how these clinician factors may have influenced the outcome measures, such as degree of diagnostic confidence and familiarity with the use of fluid biomarkers. The extent to which these findings are generalisable to other clinician specialties involved in making dementia diagnoses is also unclear.

Most studies include a population of mainly white and well-educated participants. In future studies, it will be important to investigate the use of CSF biomarkers in more diverse populations. The mean age of patients included in these studies was 66.1 years. Future studies should investigate older patients, who are more representative of local memory service populations.

Some studies requested clinicians in Memory Services to complete questionnaires on a voluntary basis, which may have introduced a selection bias as clinicians with a higher inclination to use biomarkers and find them useful in clinical practice may have been more likely to respond.\textsuperscript{32,35}

No studies confirmed the final diagnosis with postmortem brain study findings, so we were unable to assess the overall diagnostic accuracy of fluid biomarkers. Future larger longitudinal studies would be helpful to assess the diagnosis accuracy of these methods.

Only one study assessed the clinical utility of a serum biomarker, sNFL, in the diagnosis of neurodegenerative diseases.\textsuperscript{47} Further studies are needed to assess the clinical impact of other blood-based biomarkers.

Conclusion

CSF biomarkers provide additional value in the diagnostic assessment of cognitively impaired patients presenting to memory clinic through changes in clinical diagnoses, improved diagnostic confidence and changes to patient management. Large multicentre studies have shown LP to be a safe and tolerated procedure. In the future, fluid biomarkers, especially blood-based biomarkers, offer a simple-to-obtain, cost-effective and scalable test to support clinicians in the diagnosis of Alzheimer’s dementia.

Contributors All authors contributed to the conception and design of the review. MW and JH completed the data collection. JH and KYL performed the data analysis and interpretation. All authors contributed to drafting of the article, revision of the article and final approval of the version to be published.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

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ORCID iDs
Jemma Hazan http://orcid.org/0000-0002-7482-2758
Kathy Y Liu http://orcid.org/0000-0002-7482-2758
Suzanne Reeves http://orcid.org/0000-0001-8053-7024

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\textsuperscript{1} Anna Dowrick \textit{et al.}, Dementia 2014 opportunity for change report, 2014.
\textsuperscript{11} Wottmo C, Blennow K, Hansson O. Cerebrospinal fluid biomarkers levels: phosphorylated tau (T) and total tau (N) as markers for rate of progression in Alzheimer’s disease. \textit{BMJ Neurol} 2020;20:1–12.
Neurodegeneration


Supplementary Data

Medline Search Strategy

1. Dementia/
3. Alzheimer disease/
4. (Cogniti* adj2 (impair* or decline* or loss* or disorder* or deteriorat* or dysfunction*)).mp.
5. 1 or 2 or 3 or 4
6. Cerebrospinal fluid/
7. Amyloid beta-Peptides/
8. tau Proteins/
9. (cerebro-spinal fluid* or cerebrospinal fluid* or csf or spinal fluid*).mp.
10. ((blood or plasma) adj3 (biomarker* or marker* or biological marker*)).mp.
11. (biomarker* or marker* or biological marker*).mp.
12. biomarker/
13. (abeta* or ab42 or ab40 or amyloid beta or beta amyloid).mp.
14. (phospho tau* or total tau* or ptau181 or phosphorylated tau or ptau*).mp.
15. neurofilament.mp.
16. or/6-15
17. Diagnos*.mp.
18. Diagnosis/
19. Diagnosis.fs.
20. or/17-19
21. clinical decision rules/
22. cost benefit.tw.
23. Cost-Benefit Analysis/
24. ((clinical or perceived or clinician* or pragmatic or diagnos*) adj5 (impact or utility or useful* or confidence or decision* or benefit*)).mp.
25. or/21-24
26. 5 and 16 and 20 and 25
27. exp animals/ not humans.sh.
28. 26 not 27

PsychInfo Search strategy

1. exp animals/ not humans.sh.
2. 5 and 16 and 20 and 25
3. exp animals/ not humans.sh.
1. Dementia/
3. Alzheimer's Disease/
4. (Cogniti* adj2 (impair* or decline* or loss* or disorder* or deteriorat* or dysfunction*)).mp.
5. 1 or 2 or 3 or 4
6. Cerebrospinal fluid/
7. Beta Amyloid/
8. Tau Proteins/
9. (cerebro-spinal fluid* or cerebrospinal fluid* or csf or spinal fluid*).mp.
10. ((blood or plasma) adj3 (biomarker* or marker* or biological marker*)).mp.
11. (biomarker* or marker* or biological marker*).mp.
12. Biological Markers/
13. (abeta* or ab42 or ab40 or amyloid beta or beta amyloid).mp.
14. (phospho tau* or total tau* or ptau181 or phosphorylated tau or ptau*).mp.
15. neurofilament.mp.
16. or/6-15
17. Diagnos*.mp.
18. Diagnosis/
19. or/17-18
20. "clinical judgment (not diagnosis)"
21. cost benefit.tw.
22. "costs and cost analysis"
23. ((clinical or perceived or clinician* or pragmatic or diagno* or benefit*)) adj5 (impact or utility or useful* or confidence or decision* or benefit*).mp.
24. or/20-23
25. 5 and 16 and 19 and 24

Embase Search Strategy

1. Dementia/
3. Alzheimer disease/
4. (Cogniti* adj2 (impair* or decline* or loss* or disorder* or deteriorat* or dysfunction*)).mp.
5. 1 or 2 or 3 or 4
6. cerebrospinal fluid/
7. amyloid beta protein/
8. tau protein/
9. (cerebro-spinal fluid* or cerebrospinal fluid* or csf or spinal fluid*).mp.
10. ((blood or plasma) adj3 (biomarker* or marker* or biological marker*)).mp.
11. (biomarker* or marker* or biological marker*).mp.
12. biomarker/
13. (abeta* or ab42 or ab40 or amyloid beta or beta amyloid).mp.
14. (phospho tau* or total tau* or ptau181 or phosphorylated tau or ptau*).mp.
15. neurofilament.mp.
16. or/6-15
17. Diagnos*.mp.
18. diagnosis/
19. Diagnosis.fs.
20. or/17-19
21. clinical decision rule/
22. cost benefit.tw.
23. "cost benefit analysis"/
24. ((clinical or perceived or clinician* or pragmatic or diagnos*) adj5 (impact or utility or useful* or confidence or decision* or benefit*)).mp.
25. or/21-24
26. 5 and 16 and 20 and 25
27. (exp animal/ or animal.hw. or nonhuman/) not (exp human/ or human cell/ or (human or humans).ti.)
28. 26 not 27

Web Of Science Search Strategy

1. TS=(Dementia OR Alzheimer*)
2. TS=((Cogniti* near/2 (impair* OR decline* OR loss* OR disorder* OR deteriorat* OR dysfunction*))
3. #2 OR #1
4. ALL=(“amyloid beta-peptides” OR “tau Protein**” OR “cerebro-spinal fluid**” OR “cerebrospinal fluid**” OR csf OR “spinal fluid**”)
5. TS=((blood OR plasma) near/3 (biomarker* OR marker* OR “biological marker**”))
6. TS=(biomarker* OR marker* OR “biological marker*” OR abeta* OR ab42 OR ab40 OR “amyloid beta” OR “beta amyloid” OR “phospho tau*” OR “total tau*” OR ptau181 OR “phosphorylated tau” OR ptau* OR neurofilament )
7. #4 OR #5 OR #6
8. TS=(Diagnos*)
9. TS=“(cost benefit*)”
10. TS=(((clinical OR perceived OR clinician* OR pragmatic OR diagnos*) near/5 (impact OR utility OR useful* OR confidence OR decision* OR benefit*)))
11. #9 OR #10
12. #3 AND #7 AND #8 AND #11
13. TS=(animal or animals or pisces or fish or fishes or catfish or catfishes or sheatfish or silurus or arius or heteropneustes or clarias or gariepinus or fathead minnow or fathead minnows or pimephales or promelas or cichlidae or trout or trouts or char or chars or salvelinus or salmo or oncorhynchus or guppy or guppies or millionfish or poecilia or goldfish or goldfishes or carassius or auratus or mullet or mullets or mugi or curema or shark or sharks or cod or cods or gadus or morhua or carp or carps or cyprinus or carpio or killifish or eel or eels or anguilla or zander or sander or lucioperca or stizostedion or turbort or turborts or psetta or flatfish or flatfishes or plaice or pleuronectes or platessa or tilapia or tilapias or oreochromis or saronotherodon or common sole or dover sole or solea or zebrfish or zebrfishes or danio or rerio or seabass or dicentrarchus or labrax or morone or lamprey or lampreys or petromyzon or pumpkinseed or pumpkinseeds or lepomis or gibbosus or herring or clupea or harengus or amphibia or amphibian or amphibians or anura or salientia or frog or frogs or rana or toad or toads or bufo or xenopus or laevis or bombina or epidealea or calamita or salamander or salamanders or newt or newts or Triturus or reptilia or reptile or reptiles or bearded dragon or pogona or vitticeps or iguana or iguanas or lizard or lizards or anapsid or fragilis or turtle or turtles or snakes or snake or aves or bird or birds or quail or quails or coturnix or bobwhite or colinus or virginianus or poultry or poultires or fowl or fowls or chicken or chickens or gallus or zebra finch or taeniopygia or guttata or canary or canaries or serinus or canaria or parakeet or parakeets or grasskeet or parrot or parrots or psittacine or psittacines or shelduck or tadorna or goose or geese or branta or leucopsis or woodlark or lullula or flycatcher or ficedula or hypoleuca or dove or doves or geopelia or cuneata or duck or ducks or greylag or graylag or anser or harrier or circus pygargus or red knot or great knot or calidris or canutus or godwit or limosa or lapponica or meleagris or gallopavo or jackdaw or corvus or monedula or oystercatcher or haematopus or oystercatchers or redshank or shoveler or pochard or ferina or cockatiel or pyrrhula or piperis or saker or sandhill or saker or showed or shirttail or saker or sandhill or saker or showed or shirttail or saker or sandhill or saker or showed or shirttail or saker or sandhill or saker or showed or shirttail or saker or sandhill or saker or showed or shirttail or saker or sandhill or saker or showed or shirttail or saker or sandhill or saker or showed or shirttail or saker or sandhill or saker or showed or shirttail or saker or sandhill or saker or showed or shirttail or saker or sandhill or saker or showed or shirttail or saker or sandhill or saker or showed or shirttail or saker or sandhill or saker or showed or shirttail or saker or sandhill or saker or showed or shirttail or saker or 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meles or fitchew or fitch or foulmart or foulmart or ferrets or ferret or polecat or polecats or mustela or putorius or weasel or weasels or fox or foxes or vulpes or common seal or phoca or vitulina or grey seal or halichoerus or horse or horses or equus or equine or equidae or donkey or donkeys or mule or mules or pig or pigs or swine or swines or hog or hogs or boar or boars or porcine or piglet or piglets or sus or scrofa or llama or llamas or lama or glama or deer or deers or cervus or elaphus or cow or cows or bos taurus or bos indicus or bovine or bull or bulls or cattle or bison or bison or sheep or sheeps or ovis aries or ovine or lamb or lambs or mouflon or mouflons or goat or goats or capra or caprine or chamois or rupicapra or leporidae or lagomorpha or lagomorph or rabbit or rabbits or oryctolagus or cuniculus or lapine or hares or lepus or rodents or rodent or rodents or murinae or mouse or mice or mus or musculus or murine or woodmouse or apodemus or rat or rats or rattus or norvegicus or guinea pig or guinea pigs or cavia or porcellus or hamster or hamsters or mesocricetus or cricetulus or cricetus or gerbil or gerbils or jird or jirds or meriones or unguiculatus or jerboa or jerboas or jaculus or chinchilla or chinchillas or beaver or beavers or castor fiber or castor canadensis or sciuridae or squirrels or sciurus or chipmunk or chipmunks or marmot or marmots or marmota or suslik or susliks or spermophilus or cynomys or cottonrat or cottonrats or sigmodon or vole or voles or microtus or myodes or glareolus or primate or primates or prosimian or prosimians or lemur or lemur or lemuridae or loris or bush baby or bush babies or bushbabies or galago or galagos or anthropoidea or anthropoids or simian or simians or monkey or monkeys or marmoset or marmosets or callithrix or cebus or saimiri or tamarin or orangutan or orangutans or pongo or chimpanzee or chimpanzees or pan troglodytes or bonobo or bonobos or pan paniscus or gorilla or gorillas or troglodytes

14. #12 NOT #13
Supplementary Figure 1

**Source** | **MD (95% CI)**  
--- | ---  
Ramusino et al, 2019 | -0.31 [-0.42, -0.20]  
Ye et al, 2021 | -0.12 [-0.17, -0.07]  
Boelaarts et al, 2020 | -0.06 [-0.11, 0.00]  
E M van den Brink et al, 2020 | 0.04 [-0.03, 0.11]  
Gjerum et al, 2021 | 0.09 [0.03, 0.15]  
Kester et al, 2010 | 0.12 [0.06, 0.18]  
Mouton-Liger et al, 2013 | 0.17 [0.14, 0.20]  
Balasa et al, 2013 | 0.30 [0.23, 0.37]  
Duits et al, 2014 | 0.36 [0.30, 0.40]  
Stiffel et al, 2021 | 0.47 [0.41, 0.53]  
**Total** | **0.11 [0.06, 0.27]**

Heterogeneity: $\chi^2 = 424.95 (P < .001), I^2 = 98$

**Fig. 1.** (A) Forest plot showing the pooled percentage change from initial AD to final non-AD diagnosis.
Fig. 1. (B) Forest plot showing the pooled percentage change from initial non-AD to final AD diagnosis.
**Supplementary Table 1: Quality Assessment Table**

<table>
<thead>
<tr>
<th>Author &amp; Date</th>
<th>Title</th>
<th>Selection bias</th>
<th>Study design</th>
<th>Confounders</th>
<th>Data collection method</th>
<th>Withdrawals &amp; dropouts</th>
<th>Global Rating</th>
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<td>What is the clinical impact of cerebrospinal fluid biomarkers on final diagnosis and management in patients with mild cognitive impairment in clinical practice? Results from a nation-wide prospective survey in France</td>
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<td>Clinical impact of CSF assessment on diagnostic accuracy in atypical dementias in Quebec, Canada: preliminary results from a specialized dementia clinic</td>
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<td>Lee et al, 2017</td>
<td>Cost-effectiveness of cerebrospinal biomarkers for the diagnosis of Alzheimer's disease</td>
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<td>Paquet et al, 2016</td>
<td>Utility of CSF biomarkers in psychiatric disorders: a national multicentre prospective study</td>
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<td>Ramusino et al, 2019</td>
<td>The incremental value of amyloid PET versus CSF biomarkers for the diagnosis of</td>
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<td>Study</td>
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<td>Stiffel et al, 2021</td>
<td>Use of Alzheimer's Disease Cerebrospinal Fluid Biomarkers in A Tertiary Care Memory Clinic</td>
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<td>Valc´arcel-Nazco et al, 2014</td>
<td>Cost-effectiveness of the use of biomarkers in cerebrospinal fluid for Alzheimer's disease</td>
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<td>Ye et al, 2021</td>
<td>Application of Cerebrospinal Fluid AT(N) Framework on the Diagnosis of AD and Related Cognitive Disorders in Chinese Han Population</td>
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Supplementary Table 2: Table of Study Characteristics

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<th>Study Characteristic</th>
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<td>Study A</td>
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<td>Study B</td>
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<td>Study C</td>
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<td>Study E</td>
<td>345</td>
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</tbody>
</table>

This table provides a summary of the study characteristics mentioned in the main text. Each row represents a different study, and the columns indicate specific characteristics of interest.
## Table 2: Study Characteristics & Findings

<table>
<thead>
<tr>
<th>Author, Year of Publication</th>
<th>Patient Population: Clinical &amp; Demographic</th>
<th>Patient Population: Initial Diagnosis</th>
<th>Clinician Population: Demographics</th>
<th>Outcome Measure(s)</th>
<th>Outcome definitions: Change in diagnosis &amp; Change in confidence</th>
<th>Type of statistical analysis:</th>
<th>Summary of findings: Change in diagnosis post-CSF</th>
<th>Final diagnoses: AD vs non-AD</th>
<th>Pre-CSF confidence &amp; post-CSF confidence</th>
<th>Change in diagnostic confidence level % mean Proportion of patients whose management changed (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Balasa et al, 2013</td>
<td>56.0 years ^ 56% F MMSE 23.5^</td>
<td>MCI 51, AD 42, FTD 10, PCA 3 &amp; PPA 14</td>
<td>AD 42 (27.0%) vs non-AD 78 (73.0%)</td>
<td>AD biomarkers impact final on diagnosis; NIA-AA AD (amnestic/no non-amnestic AD &amp; MCI diagnostic criteria for MCI</td>
<td>Revision in diagnosis Increase in diagnostic probability according to NIA-AA criteria</td>
<td>Mean, %, SD T-test: quantitative variables and x² categorical data. Non-parametrical tests for a non-normal data distribution</td>
<td>Overall change in diagnosis not reported Final diagnoses: AD 66 (43.0%) vs non-AD 89 (57.0%) CSF biomarkers increased level of probability in diagnosis of AD to high in 49 (91.0%) of amnestic AD, 9 (82.0%) non-amnestic AD &amp; 1(4.0%) of MCI patients</td>
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<td>Boelaarts et al, 2020</td>
<td>67.9 years ± 8.1 %F NR, MMSE 25.2 ± 4.0</td>
<td>NCD 8, amnestic MCI 23 &amp; multidomain 6, AD 17, VaD 1, DLB 2, FTD 5, other dementias 1, neurological disorder 2, psychiatric disorder 5, developmental disorder 1, no diagnosis yet 35 AD 17 (24.6%) vs non-AD 52 (75.4%)</td>
<td>NR</td>
<td>Change in diagnosis, increase in diagnostic certainty, change in medical policy</td>
<td>CSF results used to differentiate AD &amp; no AD CSF &quot;helpful&quot;: ↑diagnostic certainty/questioning &amp; change of medical policy or &quot;not helpful&quot;: no change in diagnostic certainty/medical policy.</td>
<td>Mean, medians, SD, % CSF levels compared in ≥2 groups with Wilcoxon or Kruskall-Wallis statistic.</td>
<td>Change in diagnosis 61.0% Final diagnoses: AD 56 (81.0%) vs non-AD 13 (19.0%) In 75% of cases CSF result helpful to the clinicians for diagnosis</td>
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<td>Cognat et al, 2019</td>
<td>70.0 years ^ 52.9% F MCI (all)</td>
<td>Neurologists 43.3%, geriatricians 46.1%, psychiatrists 1.4%</td>
<td>2-part questionnaire pre/post CSF results. Assessment of diagnosis, level of</td>
<td>Change in diagnosis Level of confidence in diagnosis on 10-point Likert scale Impact of the CSF results management of patients:</td>
<td>Mean, SD, % One-way ANOVA: continuous quantitative variables &amp; x² tests: qualitative variables</td>
<td>Change in diagnosis 28.8% Final diagnoses: AD 50 (33.0%) vs non-AD 103 (67.0%) 8.3±1.4 vs 6.73±1.18, p&lt;0.0001, 15.7% ↑</td>
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<tr>
<td>Study (year)</td>
<td>Age ± SD</td>
<td>Gender</td>
<td>MMSE mean/median</td>
<td>Diagnosis</td>
<td>Neurologists</td>
<td>Medication, Clinical Trial Enrolment &amp; Financial Assistance</td>
<td>Statistical Tests</td>
<td>Change in Diagnosis</td>
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<td>Duits et al, 2015</td>
<td>63.0 years ± 8 39% F, MMSE 24.0 ± 5</td>
<td>No dementia 147, MCI 74, AD 127, other dementia 63, unclear diagnosis 27 AD 127 (36.2%) vs non-AD 224 (63.8%)</td>
<td>Neurologists 2-part questionnaire pre/post CSF results. Change of diagnosis, diagnostic confidence &amp; impact on patient management</td>
<td>Re-evaluation of the diagnosis Diagnostic confidence level on visual analogue scale from 0% to 100% Preselection for clinical trials, level of follow up &amp; subsequent imaging</td>
<td>χ² tests, independent samples T-tests, or ANOVA</td>
<td>Univariate GLM (continuous), logistic regression (categorical) &amp; (dichotomous) variables. Pre/post-CSF diagnostic confidence levels with ANOVA for repeated measures, in total population &amp; age stratified</td>
<td>Change in diagnosis 7% Final diagnoses: AD 99 (28.4%) vs non-AD 252 (71.6%) 84.0%^ to 89.0%^ (P&lt;.001) 5.0% ↑ =13.0%: Preselection for clinical trials, follow-up, &amp; imaging studies</td>
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<tr>
<td>E.M. van den Brink et al, 2020</td>
<td>66.3 years ± 1.4 64% F, Educational years 12.7 ± 0.65 MMSE median 26.0</td>
<td>MCI 5, AD 13, other dementia 1, multiple possible diagnoses 8 AD 13 (46.0%) vs non-AD 15 (54.0%)</td>
<td>Behavioural neurologist Assessment of initial clinical diagnosis vs final CSF-based diagnosis</td>
<td>% Change in diagnosis post CSF result, expressed as change/ no change</td>
<td>Mean, median, %. NR % Patients where clinical diagnosis changed after CSF results. Fisher’s exact test rate of diagnostic change per initial clinical diagnosis</td>
<td>Change in diagnosis 25.0% Final diagnoses: AD 14 (50.0%) vs non-AD 14 (50.0%)</td>
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<tr>
<td>Falgas et al, 2019</td>
<td>58.9 years ± 3.9, 47.5% F, MMSE mean 24.8^</td>
<td>AD 26, MCI-AD 12, mild dementia 14, FTD 5 non-degenerative conditions 9 AD 26 (65.0%) vs non-AD 40 (35.0%)</td>
<td>Neurologists 2-part questionnaire pre/post CSF results. Assessment of diagnosis, level of confidence &amp; impact on management</td>
<td>Change in diagnosis Questionnaire to estimate level of diagnostic confidence: range, 0%–100% Commence/stop ACEi</td>
<td>Mean, SD, %. T-test for quantitative data &amp; χ² test for categorical data. Change in diagnostic confidence pre/post-CSF by paired-sample t-tests.</td>
<td>Unable to establish due to pooled results 67.3%^ to 82.4%^ 15.0% ↑</td>
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<tr>
<td>Gjerum et al, 2021</td>
<td>69.2 years*, 20% F, Educational years 13.2, MMSE 26.8^</td>
<td>MCI 19, SCD 14, AD 31, FTD 2, DLB 3, VaD 4, mixed-AD 1, other diagnoses 26 AD 32 (39.5%) vs non-AD 49 (60.5%)</td>
<td>2 expert dementia specialists with experience of CSF biomarkers Correct or incorrect diagnosis, change in diagnosis, change in accuracy,</td>
<td>Change in diagnosis Confidence in the diagnosis visual rating scale score between 0–100 Change in anti-dementia medication, e.g. ACEi</td>
<td>Mean, SD, %. Unpaired t-test (continuous) &amp; Fisher’s exact test (categorical) data</td>
<td>McNemar’s test paired comparison</td>
<td>Change in diagnosis 15.0% Final diagnoses: AD 42 (51.8%) vs non-AD 39 (48.2%) 9.75%^ ↑</td>
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<tr>
<td>Study</td>
<td>Age, %F, Education</td>
<td>Location/Method</td>
<td>Clinician rated their diagnostic confidence on a five-point scale: 1 (not at all confident), 3 (moderately confident), 5 (very confident)</td>
<td>Logistic regressions to model multivariate associations between clinician diagnosis and CSF group assignment, demographic, &amp; practice variables &amp; clinical detail ratings.</td>
<td>Demographic/ practice info calculated to characterize sample. chi2 tests, t-tests &amp; ANOVA to evaluate if CSF result related to diagnostic choice, confidence &amp; treatment</td>
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<tr>
<td>Gooblar et al, 2015</td>
<td>72.0 years(^{\circ}), %F NR, Previous employment: retired pilot and real estate agent</td>
<td>2 Clinical vignettes with 4 CSF results. Case 1: borderline/unclear, Case 2: mild AD. CSF results: normal, borderline, AD-consistent, none provided</td>
<td>Mean, SD, %, Fisher exact test for categorical variables, ANOVA for age, MMSE &amp; Kruskal-Wallis tests for CSF results Mann-Whitney U test for post-hoc analysis &amp; proportion of diagnoses that changed &amp; proportion of changes in confidence after CSF results</td>
<td>Change in initial diagnosis</td>
<td>Change in confidence level where confidence in diagnosis rated as certain or uncertain</td>
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<tr>
<td>Kester et al, 2010</td>
<td>71.3 years(^{\circ}), 49.5% F, MMSE mean 24.5(^{\circ}), Education classified with Verhage scale [1–7] Mean= 4(^{\circ})</td>
<td>AD 47, other dementia 26, MCI 18, no dementia 18 AD 47 (43.1%) vs non-AD 62 (56.9%)</td>
<td>Mean, SD, %, Fisher exact test for categorical variables, ANOVA for age, MMSE &amp; Kruskal-Wallis tests for CSF results Mann-Whitney U test for post-hoc analysis &amp; proportion of diagnoses that changed &amp; proportion of changes in confidence after CSF results</td>
<td>Change in initial diagnosis</td>
<td>Change in confidence level where confidence in diagnosis rated as certain or uncertain</td>
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</table>

**Table:**

| Gooblar et al, 2015 | 72.0 years\(^{\circ}\), %F NR, Previous employment: retired pilot and real estate agent | Change in confidence, impact on management | Clinicians indicated their recommendation for treatment in open-ended response | Demographic/ practice info calculated to characterize sample. chi2 tests, t-tests & ANOVA to evaluate if CSF result related to diagnostic choice, confidence & treatment |
| Kester et al, 2010 | 71.3 years\(^{\circ}\), 49.5% F, MMSE mean 24.5\(^{\circ}\), Education classified with Verhage scale [1–7] Mean= 4\(^{\circ}\) | Change in confidence, impact on management | Clinicians indicated their recommendation for treatment in open-ended response | Demographic/ practice info calculated to characterize sample. chi2 tests, t-tests & ANOVA to evaluate if CSF result related to diagnostic choice, confidence & treatment |

**Table:**

<p>| Gooblar et al, 2015 | 72.0 years(^{\circ}), %F NR, Previous employment: retired pilot and real estate agent | Change in confidence, impact on management | Clinicians indicated their recommendation for treatment in open-ended response | Demographic/ practice info calculated to characterize sample. chi2 tests, t-tests &amp; ANOVA to evaluate if CSF result related to diagnostic choice, confidence &amp; treatment |
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<table>
<thead>
<tr>
<th>Study</th>
<th>Age (Mean ± SD or %, F)</th>
<th>Neurologists</th>
<th>Geriatricians</th>
<th>Psychiatrists</th>
<th>2-part questionnaire</th>
<th>Final Diagnosis Post CSF Results</th>
<th>Change in Diagnosis</th>
<th>Final Diagnoses</th>
<th>Change in Confidence</th>
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</thead>
<tbody>
<tr>
<td>Mouton-Liger et al, 2014</td>
<td>68.6 ± 9.7, 52.4% F</td>
<td>Neurologists: 43.3%, geriatricians: 46.1%, psychiatrists: 1.4%</td>
<td>2-part questionnaire: Change in diagnosis &amp; change in level of confidence</td>
<td>Clinicians rated level of confidence in initial diagnosis on numerical visual scale (0 to 10)</td>
<td>Mean, SD, %, ( \chi^2 ) statistic (categorical) &amp; ANOVA (continuous) variables. C-statistics using logistic regression models.</td>
<td>Change in diagnosis 26.7%</td>
<td>Final diagnoses: AD 252 (45.0%) vs non-AD 99 (55.0%)</td>
<td>6.0° to 8.0° ↑ 22.2% ↑</td>
<td>Net Reclassification Improvement - a method to compare the 2 ways of classifications, initial diagnostic &amp; CSF results on final diagnosis</td>
</tr>
<tr>
<td>Paquet et al, 2016</td>
<td>64.6 ± 11.6, 43% F</td>
<td>Anxiety-/depression 43 (62.3%), bipolar disorder 12 (17.4%), psychosis 10 (14.5%), others 4 (5.8%)</td>
<td>2-part questionnaire - pre/post CSF results: change of diagnosis, diagnostic confidence &amp; impact on patient management</td>
<td>&quot;Changed diagnosis&quot; each time the initial and final diagnoses were different</td>
<td>Mean, SD, %, NR</td>
<td>Change in diagnosis 19.0%</td>
<td>Final diagnoses: AD 13 (18.8%) vs non-AD 56 (81.2%)</td>
<td>6.0 ± 1.1 to 8.1 ± 1.4, ( p &lt; 0.0001 ) 20.3% ↑</td>
<td>AD or non-AD compared using ( \chi^2 ) statistics for categorical variables &amp; ( t )-test (parametric or non-parametric) for age.</td>
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<tr>
<td>Ramusino et al, 2019</td>
<td>71.4 ± 7.1, 51% F, Education years 10.7 ± 4, Disease duration years 4.5 ± 3, MMSE 26.1 ± 3.9</td>
<td>Dementia experts: 1 neurologist &amp; 1 geriatrician</td>
<td>2-part questionnaire pre/post CSF results: change in diagnosis &amp; change in level of confidence</td>
<td>Rate of diagnostic change (%)</td>
<td>Mean, SD, %, Relative diagnostic confidence on visual analogue scale (0 to 100%)</td>
<td>Change in diagnosis 8.0%</td>
<td>Final diagnoses: AD 44 (61.9%) vs non-AD 27 (38.1%)</td>
<td>Round 1 addition of CSF values 14.0% ↑ ( \text{P}&lt;0.001 )</td>
<td>Inter-rater agreement: Cohen’s ( \kappa ) coefficient Diagnostic changes at rounds 2 &amp; 3 Fisher’s exact test, change in diagnostic confidence assessed using linear mixed model with 3 repeated factors</td>
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<tr>
<td>Stiffel et al, 2021</td>
<td>67.5 ± 9.2, 49% F, 2.7±2 years in education, early disease stage, MMSE 26.0±3</td>
<td>AD or other dementia 68, Amnestic MCI 113, PPA 26, atypical behavioural presentation 144.</td>
<td>Impact of CSF biomarkers on diagnosis and management</td>
<td>Revision in diagnosis</td>
<td>Mean, SD, %, Continuous variables assessed using ANOVA, dichotomous/categorical variables assessed using ( \chi^2 ) or Mann-Whitney U tests</td>
<td>Change in diagnosis 53.4%</td>
<td>Final diagnoses: AD 70 (26.7%) vs non-AD 192 (73.3%)</td>
<td>NR</td>
<td>Change in diagnosis 30%</td>
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Table 2: Table of Study Characteristics & Findings- Observational Studies

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<th>Study</th>
<th>Characteristics</th>
<th>Findings</th>
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<tr>
<td>Ye et al, 2021</td>
<td>61.6 years ± 9.9, 51.8% F, Educational years 7.6 ± 4.0, MMSE Score 14.9 ± 8.1</td>
<td>79 AD (58.0%) and 58 non-AD (42.0%).</td>
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<td>AD 71, atypical AD 5, prodromal AD 3, MCI 15, FTD 27, NPH 4, VaD 3, DLB 2, mixed dementia 2, leukoencephalopathy 2, PDD 1, PSP 1, pseudodementia 1</td>
<td>Change in diagnosis 28.0%</td>
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<td>Mean, SD, %, Quantitative data compared using t-test, One-ANOVA &amp; χ2 test for categorical data</td>
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<td>Neurologists</td>
<td>Change in Diagnosis, Change in level of confidence</td>
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<td>Revision of diagnosis based on CSF AT(N) framework Diagnostic confidence [range, 50%–100%] in reference to CSF AT(N) framework</td>
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Abbreviations: F- female; years; MMSE- Mini Mental State Examination; MCI- Mild Cognitive Impairment; PCA-Posterior Cortical Atrophy; PPA- Primary Progressive Aphasia; AD-Alzheimer’s disease; VaD-Vascular Disease; DLB-Dementia with Lewy Bodies; FTD-Frontotemporal Dementia; PDD- Parkinson’s Disease with Dementia; PSP-Progressive Supranuclear Palsy; NIA-AA- National Institute on Aging and Alzheimer’s Association Framework; CSF-Cerebrospinal Fluid; sNFL-Serum neurofilament Light; AT(N)- Amyloid/Tau/Neurodegeneration; χ2- Chi-squared test; Aβ42- Amyloid Beta 42; NR- Not Reported; Standard Deviation Not Reported- ^; N/A- Not Applicable, ↑-increase; ↓-decrease; ANOVA- Analysis of variance; SD- Standard Deviation; %-percentage; GLM- General Linear Models; ACEi- Acetylcholinesterase Inhibitors