Title: Clinical utility of cerebrospinal fluid biomarkers in the evaluation of cognitive

impairment: a systematic review and meta-analysis

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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, Web of Science research databases were conducted on 17th 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 (QALY).

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: 14–37), an increase in diagnostic confidence of 14% (95% CI: 9–18) and a pooled proportion of patients whose management changed of 31% (95% CI 12–50). CSF biomarkers were deemed cost effective, particularly in memory services, where pre-test AD prevalence is higher compared to 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[1], 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[2]. Biomarkers have been incorporated into the diagnostic framework of AD in clinical research[3]. A consensus "roadmap" was set out in 2017 to aid the incorporation of these biomarkers into the clinical setting to improve diagnostic accuracy[4].

Cerebrospinal fluid (CSF) biomarkers are currently used in the diagnostic investigation of AD at specialist tertiary Neurology Centres in the UK[5]. However, they are not routinely used in UK Memory Services[6,7]. CSF biomarkers have demonstrated analytical validity[8,9]. Validated AD CSF biomarkers include amyloid-β1-42, total-tau, and phosphorylated-tau181 (ptau-181)[10]. 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[11]. Many studies have demonstrated the correlation between CSF levels and neuropathology[12 13]. [14 15].. 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[16]. 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[17]. Several large multicentre studies have demonstrated that LP is a safe and tolerable procedure[17,18]. Further barriers to the routine use of LP in Memory Services include a lack of skills, training in this procedure[19].

Biomarkers may also assist clinicians in differentiating AD from non-AD dementias, and mild cognitive impairment (MCI) from early AD[20 21 22].

There have been several studies exploring the validity and diagnostic accuracy of CSF biomarkers in AD[23]. 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[24].

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 the 17th December 2021 using Medline, Embase, PsycINFO and Web of Science (WoS) databases, using the terms listed in the 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 & 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 (EPHPP)[25]. 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[26]. Sub-analyses were performed on the percentage change in AD diagnoses, i.e., changes in diagnosis from AD to non-AD and from non-AD to AD. The I^2 statistic was used to assess the degree of heterogeneity of the percentage change in diagnosis, confidence, and management across studies[27]. We followed Tu, YK 2016 methodology for testing the relationship between percentage change and baseline values, which uses a modified Pearson's test[28]. All analyses were performed using R Software R version 4.1.2; R Foundation for Statistical Computing[29].

Results

Study Identification

17 studies were identified for inclusion. The PRISMA flowchart is displayed in Figure 1. 5816 records were identified from 4 databases; Medline, EMBASE, PsycINFO, Web of Science. After removal of duplications, 3071 records were screened. 3031 records were excluded. Reasons for exclusion included: not relevant to diagnosis of dementia, did not involve relevant CSF markers, explored analytical validity of CSF markers. 40 reports were

assessed for eligibility. 23 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.

(Figure 1)

Study characteristics

Study characteristics are shown in Table 1 and Table 2 and in Supplemental Material Table 2

Table 1: Study characteristics

Author, Year of Publication	Country	Type of study	Referral setting	Intervention	Study Duration	Patient sample size (N)	Clinician sample size (N)	Patient inclusion criteria
Balasa et al, 2013	Spain	Prospective observational Study	Specialist Outpatient Clinic	LP for CSF Biomarkers: Aβ42, t-tau, and p-tau	2009-2013	157	NR	patients < 65 years
Boelaarts et al, 2020	The Netherlands	Prospective observational Study	Community geriatric outpatient clinic	LP for CSF Biomarkers: Aβ42, t-tau, and p-tau	2010-2016	69	NR	Patients <71 years
Cognat et al, 2019	France	Prospective observational Study	29 Secondary & Tertiary memory clinics	LP for CSF Biomarkers: Aβ42, t-tau, and p-tau	2012-2014	153	128	Initial diagnosis of MCI
Duits et al, 2015	The Netherlands	Prospective observational Study	Memory clinic	LP for CSF Biomarkers: Aβ42, t-tau, and p-tau	2011-2012	351	5	All patients visiting the clinic
E.M. van den Brink et al, 2020	Canada	Retrospective observational study	Specialist Memory Clinic	LP for CSF Biomarkers: Aβ42, t-tau, and p-tau & FDG-PET	2017-2019	28	NR	Atypical dementia presentations,
Falgas et al, 2019	Spain	Prospective observational study	Specialist Memory Clinic	Patients underwent biomarkers which included: MRI, LP for CSF Biomarkers: Aβ42, t-tau, and p-tau, FDG-PET, Amyloid PET	not reported	40	5	<65 years of age , MMSE score ≥ 18
Gjerum et al, 2021	Denmark	Retrospective observation incremental study	Memory Clinic	Patients randomised to addition of either 2-[18F]FDG-PET or CSF Biomarkers: Aβ42, t-tau, and p-tau	2015-2016	81	2	Cognitive impairment due to neurodegenerative disease, (MMSE ≥ 18, CDR ≥ 1.0, undergone T1-weighted MRI ≥ 1.5 Tesla, addition of CSF biomarkers deemed useful by clinician
Gooblar et al, 2015	USA	study using simulated clinical vignettes	Primary, Secondary and Tertiary Centres	Simulated CSF values	January-July 2013	2	193	2 Simulated clinical vignettes

Handels et al, 2017	The Netherlands	Cost-effectiveness analysis	NA	Simulated CSF values	NA	NA	NA	Simulated patients with MCI
Kester et al, 2010	The Netherlands	Prospective observational Study	One local hospital memory clinic	LP for CSF Biomarkers: Aβ42, t-tau, and p-tau	2005-2008	109	2	All patients visiting the clinic
Lee et al, 2017	Canada	Cost-effectiveness analysis	NA	Simulated CSF values	NA	NA	NA	Simulated patients with suspected AD
Mouton-Liger et al, 2014	France	Prospective observational study	secondary or tertiary memory centres	LP for CSF Biomarkers: Aβ42, t-tau, and p-tau	not specified	561	128	When a clinician considered a patient eligible for CSF biomarkers
Paquet et al, 2016	France	Prospective observational Study	29 Secondary & Tertiary memory clinics	LP for CSF Biomarkers: Aβ42, t-tau, and p-tau	2014-2016	69	128	Initial main diagnosis of a psychiatric disorder
Ramusino et al, 2019	Italy	Prospective Study	multicentre, 4 Memory Clinics	LP for CSF Biomarkers: Aβ42, t-tau, and p-tau & Amyloid-PET	2015-2017	71	2	MCI or mild dementia possibly due to AD, Age range 55-90 years, score < 4on the modified Hachinski ischemic scale At least 5 years of education
Stiffel et al, 2021	Canada	Prospective observational Study	A tertiary care memory clinic	LP for CSF Biomarkers: Aβ42, t-tau, and p-tau	2015-2020	262	NR	participants included if basic tertiary care work up, neuropsychological evaluation and FDG-PET did not provide conclusive diagnosis
Valcarcel-Nazco et al, 2014	Spain	Cost-effectiveness analysis- Economic evaluation	NA	Simulated CSF values	NA	NA	NA	Simulated patients with MCI & other dementias
Ye et al, 2021	China	Prospective observational Study	Neurology Clinic	LP for CSF Biomarkers: Aβ42, t-tau, and p-tau	2015-2019	137	not reported	All patients visiting the clinic

Abbreviations: MMSE - Mini Mental State Examination; CDR- Clinical Dementia Rating; LP-Lumbar Puncture; CSF- cerebrospinal Fluid; PET FDG- Fluorodeoxyglucose positron emission tomography; Aβ42- Amyloid Beta 42; T-tau- Total Tau; P-tau- Phospho-tau; AD- Alzheimer's Disease; NR- Not Reported

Table 1: Table of Study Characteristics Observational Studies

Table of Study Characteristics & Findings: Cost-effectiveness Analysis					
Author, Year of Publication	**Type of study**	**Aim**	**Outcome measure**	**Statistical analysis**	**Summary of findings**
Handels et al, 2017 The Netherlands	Cost-effectiveness analysis	To estimate the potential ICER of adding CSF biomarker testing to the standard diagnostic workup to determine the prognosis for patients with MCI	Accuracy of prognosis QALY Additional cost per patient ICER	Simulated data model using a merged dataset	Improved the accuracy of prognosis by 11% Average QALY gain of 0.046 €432 additional costs per patient ICER of €9416 per QALY gained
Lee et al, 2017 Canada	Cost-effectiveness analysis	To estimate the lifetime costs & 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	Additional cost per patient QALY ICER	Markov Model	AD pre-test probability of 12.7%: Average QALY gain of 0.015 ICER of $11,032 per QALY gained $165 additional costs per patient,
Valcarcel-Nazco et al, 2014 Spain	Cost-effectiveness analysis- Economic evaluation	To determine the cost-effectiveness of the CSF biomarkers to diagnose AD in MCI & dementia patients.	Cost & effectiveness	Probabilistic sensitivity analysis using 2nd order Monte Carlo simulations. Acceptability curves were calculated and ANCOVA models applied to simulation results	MCI Patients: lower average cost per patient of €1832.65 AD patients: higher average cost per patient of €1133.82 Dominant ICER for MCI patients
Abbreviations: ANCOVA- Analysis of Covariance; AD- Alzheimer's Disease; MCI- Mild Cognitive Impairment; ICER-Incremental Cost Effectiveness Ratio; QALY-Quality-adjusted life year; CSF-Cerebrospinal Fluid					

Table 2: Table of Study Characteristics & Findings- Cost-effectiveness Analysis Studies

Study design

Most (12 of 17, 71%) of the included studies were prospective observational studies [30–40].
One study was a survey of clinicians using simulated clinical scenarios [41]. Other study
designs included three cost-effectiveness analyses [42–44] and two retrospective observational
studies [45,46]. 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 multi-centre and two were
early-onset dementia clinics.

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[30,34]..

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 (SCD), MCI, AD dementia, frontotemporal lobe dementia
(FTLD), vascular dementia (VaD), dementia with Lewy bodies (DLB), 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 (CJD), Corticobasal
degeneration and Huntington's disease. Non-demented patients were categorized 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 specialty in Neurology, but only one study provided
detailed clinician demographics[41]

Outcome measures

Outcome measures are described in Supplementary Table 2. The majority (13 of 17, 76%) of studies required the clinician to complete a pre- and post-CSF results questionnaire, listing initial and final diagnoses respectively[30–34,36–41,46,47]. Of these studies, eight examined how CSF biomarker results changed diagnostic confidence [32–36,40,41,46], 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 [32–34,37,39,41,46].

Of the three studies that performed a cost-effectiveness analysis of CSF biomarkers to diagnose AD [42–44], two examined lifetime costs and quality-adjusted life-years (QALYs) [42,43] and one performed an economic evaluation[44]. Outcome measures are described in Table 2.

Quality assessment

Most (14 of 17, 83%) studies were assessed as being of moderate quality[30–41,45–47] and three studies were assessed as being of high quality[42–44]. No studies were assessed to be of low quality (Supplementary 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.

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 results [31–33,35–40,45,46], which ranged between 7–61%. The overall pooled percentage change in

diagnoses was 25% (95% CI: 14–37) and there was substantial heterogeneity (I^2 97%, p < 0.001) (Fig. 2a). Subgroup analyses found no significant change in diagnoses from initial AD to final non-AD or initial non-AD to final AD (Supplementary material Figure 1a & 1b).

(Fig. 2)

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 [46]. 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 [32–38,40], ranging from 5 to 22% (Supplementary Table 2). The overall pooled percentage change in confidence was 14% (95% CI: 9–18) and there was substantial heterogeneity (I^2 88%, p < 0.001) (Fig. 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 13-47%, and the overall pooled proportion of patients whose management changed was 31% (95% CI 12–50) with substantial heterogeneity (I^2: 97%, p < 0.001) (Fig. 2c). The most common management change was the commencement or stopping of cholinesterase inhibitors or other dementia medications (4 of 5 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[44], CSF biomarkers were reported to be an alternative, less expensive and more efficient diagnostic tool compared to standard diagnostic procedures in MCI patients, 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 dementia patients, despite higher uncertainty, CSF biomarkers were also a cost-effective alternative compared to standard clinical diagnostic criteria.

A second study[43] utilised a Markov model to estimate the lifetime costs and QALYs of CSF biomarkers in patients referred for cognitive assessment with suspected AD, where diagnosis remained unclear after neuroimaging. The study reported that the cost-effectiveness of CSF biomarkers depended on the prevalence of AD in the population, such that with a pre-test probability of AD of 12.7%, the addition of CSF biomarkers to neuroimaging had an incremental cost-effectiveness ratio (ICER) of $11,032 per QALY gained. However, at a lower prevalence such as in the general practice setting, CSF biomarkers were unlikely to be

cost-effective at a willingness-to-pay threshold of $50,000 per QALY gained. The study concluded that CSF biomarkers are likely to be cost effective in specialist memory clinics where pre-test prevalence may be greater than 15%.

The third study[42] found that the use of CSF biomarkers in an MCI population resulted in an ICER of €9,416, although there was a high degree of uncertainty. This was due to the uncertainty of input parameters computed in the model such as expert opinions and risk prediction coefficients.

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[34,38,45,46]. One study reported that CSF biomarkers and amyloid-PET results showed a good concordance and that there 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[34]. However, in another study amyloid-PET provided greater changes in diagnosis and diagnostic confidence than CSF biomarkers[38].

For participants correctly diagnosed patient with AD, CSF biomarkers had a significantly higher impact on diagnostic and a significant reduction in the need for further investigations when compared to FDG-PET[46]. One study reported that for 35% of patient participants FDG-PET and CSF-based diagnosis did not correspond [45],

Discussion

Previous systematic reviews have reported on the analytic or clinical validity of fluid biomarkers, or the clinical utility of imaging biomarkers such as amyloid PET[48–51]. In this review, we focussed 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 [48].

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[41], 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 to the impact of amyloid-PET where the change in confidence level reportedly ranged from 16 to 44%[48]. 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[31], 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%[48] , which represents a larger pooled effect size compared to 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[52]. Cost-effectiveness analyses revealed CSF biomarkers to be a cost-effective alternative to standard diagnostic work-up[42–44].

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

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[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[47]. 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[54]. Further studies are needed to establish if the clinical utility of blood-based biomarkers is comparable to CSF biomarkers and amyloid PET imaging. Blood-based biomarkers are simple to carry out and cost-effective[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[55]. It would be important to address this in future guidance, given the increasing proportion of people diagnosed as MCI in UK memory services[56].

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 generalizable to other clinician specialities 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[32].

No studies confirmed the final diagnosis with post-mortem 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[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 lumbar puncture 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.

References

1. Anna Dowrick A. Dementia 2014 opportunity for change report. *As Society, Editor*. Published online 2014.

2. Mulder C, Verwey NA, van der Flier WM, et al. Amyloid-β (1–42), total tau, and phosphorylated tau as cerebrospinal fluid biomarkers for the diagnosis of Alzheimer disease. *Clinical chemistry*. 2010;56(2):248-253.

3. Jack Jr CR, Bennett DA, Blennow K, et al. NIA-AA research framework: toward a biological definition of Alzheimer's disease. *Alzheimer's & Dementia*. 2018;14(4):535-562.

4. Frisoni GB, Boccardi M, Barkhof F, et al. Strategic roadmap for an early diagnosis of Alzheimer's disease based on biomarkers. *The Lancet Neurology*. 2017;16(8):661-676.

5. Keshavan A, O'Shea F, Chapman MD, et al. CSF biomarkers for dementia. *Practical Neurology*. Published online 2022.

6. Cook LD, Nichol KE, Isaacs JD. The London memory service audit and quality improvement programme. *BJPsych bulletin*. 2019;43(5):215-220.

7. Dunne RA, Aarsland D, O'Brien JT, et al. Mild cognitive impairment: the Manchester consensus. *Age Ageing*. 2021;50(1):72-80. doi:10.1093/ageing/afaa228

8. Blennow K, Hampel H, Weiner M, Zetterberg H. Cerebrospinal fluid and plasma biomarkers in Alzheimer disease. *Nature Reviews Neurology*. 2010;6(3):131-144.

9. Skillbäck T, Farahmand BY, Rosen C, et al. Cerebrospinal fluid tau and amyloid-β1-42 in patients with dementia. *Brain*. 2015;138(9):2716-2731.

10. Niemantsverdriet E, Valckx S, Bjerke M, Engelborghs S. Alzheimer's disease CSF biomarkers: Clinical indications and rational use. *Acta neurologica belgica*. 2017;117(3):591-602.

11. Wattmo C, Blennow K, Hansson O. Cerebro-spinal fluid biomarker levels: phosphorylated tau (T) and total tau (N) as markers for rate of progression in Alzheimer's disease. *BMC neurology*. 2020;20(1):1-12.

12. Strozyk D, Blennow K, White L, Launer L. CSF Aβ 42 levels correlate with amyloid-neuropathology in a population-based autopsy study. *Neurology*. 2003;60(4):652-656.

13. Schoonenboom NS, Reesink FE, Verwey NA, et al. Cerebrospinal fluid markers for differential dementia diagnosis in a large memory clinic cohort. *Neurology*. 2012;78(1):47-54.

14. Janelidze S, Mattsson N, Palmqvist S, et al. Plasma P-tau181 in Alzheimer's disease: relationship to other biomarkers, differential diagnosis, neuropathology and longitudinal progression to Alzheimer's dementia. *Nature medicine*. 2020;26(3):379-386.

15. Palmqvist S, Janelidze S, Quiroz YT, et al. Discriminative accuracy of plasma phospho-tau217 for Alzheimer disease vs other neurodegenerative disorders. *Jama*. 2020;324(8):772-781.

16. Henriksen K, O'Bryant SE, Hampel H, et al. The future of blood-based biomarkers for Alzheimer's disease. *Alzheimer's & Dementia*. 2014;10(1):115-131.

17. Duits FH, Martinez-Lage P, Paquet C, et al. Performance and complications of lumbar puncture in memory clinics: results of the multicenter lumbar puncture feasibility study. *Alzheimer's & Dementia*. 2016;12(2):154-163.

18. Shaw LM, Arias J, Blennow K, et al. Appropriate use criteria for lumbar puncture and cerebrospinal fluid testing in the diagnosis of Alzheimer's disease. *Alzheimer's & Dementia*. 2018;14(11):1505-1521.

19. Hampel H, Shaw LM, Aisen P, et al. State-of-the-art of lumbar puncture and its place in the journey of patients with Alzheimer's disease. *Alzheimer's dement*. 2021;(101231978). doi:10.1002/alz.12372

20. Toledo JB, Brettschneider J, Grossman M, et al. CSF biomarkers cutoffs: the importance of coincident neuropathological diseases. *Acta neuropathologica*. 2012;124(1):23-35.

21. Park JE, Choi KY, Kim BC, et al. Cerebrospinal fluid biomarkers for the diagnosis of prodromal Alzheimer's disease in amnestic mild cognitive impairment. *Dementia and geriatric cognitive disorders extra*. 2019;9(1):100-113.

22. Hampel H, Bürger K, Teipel SJ, Bokde AL, Zetterberg H, Blennow K. Core candidate neurochemical and imaging biomarkers of Alzheimer's disease. *Alzheimer's & Dementia*. 2008;4(1):38-48.

23. Lleo A, Cavedo E, Parnetti L, et al. Cerebrospinal fluid biomarkers in trials for Alzheimer and Parkinson diseases. *Nature Reviews Neurology*. 2015;11(1):41-55.

24. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *Bmj*. 2021;372.

25. Armijo-Olivo S, Stiles CR, Hagen NA, Biondo PD, Cummings GG. Assessment of study quality for systematic reviews: a comparison of the Cochrane Collaboration Risk of Bias Tool and the Effective Public Health Practice Project Quality Assessment Tool: methodological research. *Journal of evaluation in clinical practice*. 2012;18(1):12-18.

26. Van Houwelingen HC, Arends LR, Stijnen T. Advanced methods in meta-analysis: multivariate approach and meta-regression. *Statistics in medicine*. 2002;21(4):589-624.

27. Hardy RJ, Thompson SG. Detecting and describing heterogeneity in meta-analysis. *Statistics in medicine*. 1998;17(8):841-856.

28. Tu YK. Testing the relation between percentage change and baseline value. *Scientific reports*. 2016;6(1):1-8.

29. Team RC. R: A language and environment for statistical computing. Published online 2013.

30. Balasa M, Sánchez-Valle R, Antonell A, et al. Usefulness of biomarkers in the diagnosis and prognosis of early-onset cognitive impairment. *Journal of Alzheimer's Disease*. 2014;40(4):919-927.

31. Boelaarts L, de Jonghe JFM, Scheltens P. Diagnostic Impact of CSF Biomarkers in a Local Hospital Memory Clinic Revisited. *Dement Geriatr Cogn Disord*. 2020;49(1):2-7. doi:10.1159/000506332

32. Cognat E, Mouton Liger F, Troussiere AC, et al. 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. *BMJ Open*. 2019;9(5):e026380. doi:10.1136/bmjopen-2018-026380

33. Duits FH, Prins ND, Lemstra AW, et al. Diagnostic impact of CSF biomarkers for Alzheimer's disease in a tertiary memory clinic. *Alzheimer's dement*. 2015;11(5):523-532. doi:10.1016/j.jalz.2014.05.1753

34. Falgas N, Tort-Merino A, Balasa M, et al. Clinical applicability of diagnostic biomarkers in early-onset cognitive impairment. *Eur J Neurol*. 2019;26(8):1098-1104. doi:10.1111/ene.13945

35. Kester MI, Boelaarts L, Bouwman FH, et al. Diagnostic impact of CSF biomarkers in a local hospital memory clinic. *Dement Geriatr Cogn Disord*. 2010;29(6):491-497. doi:10.1159/000313534

36. Mouton-Liger F, Wallon D, Troussiere AC, et al. Impact of cerebro-spinal fluid biomarkers of Alzheimer's disease in clinical practice: a multicentric study. *J Neurol*. 2014;261(1):144-151. doi:10.1007/s00415-013-7160-3

37. Paquet C, Magnin E, Wallon D, et al. Utility of CSF biomarkers in psychiatric disorders: a national multicentre prospective study. *Alzheimers Res Ther*. 2016;8(101511643):27. doi:10.1186/s13195-016-0192-z

38. Ramusino MC, Costa A, Altomare D, et al. THE INCREMENTAL VALUE OF AMYLOID PET VERSUS CSF BIOMARKERS FOR THE DIAGNOSIS OF ALZHEIMER'S DISEASE (INDIA-FBB STUDY). *Alzheimer's Dementia*. 2018;14(7 Supplement):P17-P18. doi:10.1016/j.jalz.2018.06.2070

39. Stiffel M, Bergeron D, Mourabit Amari K, et al. Use of Alzheimer's Disease Cerebrospinal Fluid Biomarkers in A Tertiary Care Memory Clinic. *Can J Neurol Sci*. 2021;(cj9, 0415227):1-7. doi:10.1017/cjn.2021.67

40. Ye LQ, Gao PR, Zhang YB, et al. Application of Cerebrospinal Fluid AT(N) Framework on the Diagnosis of AD and Related Cognitive Disorders in Chinese Han Population. *Clin Interv Aging*. 2021;16(101273480):311-323. doi:10.2147/CIA.S294756

41. Gooblar J, Carpenter BD, Coats MA, Morris JC, Snider BJ. The influence of cerebrospinal fluid (CSF) biomarkers on clinical dementia evaluations. *Alzheimer's dement*. 2015;11(5):533-540.e2. doi:10.1016/j.jalz.2014.04.517

42. Handels RLH, Wimo A, Dodel R, et al. Cost-Utility of Using Alzheimer's Disease Biomarkers in Cerebrospinal Fluid to Predict Progression from Mild Cognitive Impairment to Dementia. *J Alzheimers Dis*. 2017;60(4):1477-1487. doi:10.3233/JAD-170324

43. Lee Y, Jang S, Kim E, et al. Cost-effectiveness of diagnostic technologies for dementia: A systematic review of economic evaluations. *Value Health*. 2017;20(9):A717. doi:10.1016/j.jval.2017.08.1911

44. Valcarcel-Nazco C, Perestelo-Perez L, Molinuevo JL, Mar J, Castilla I, Serrano-Aguilar P. Cost-effectiveness of the use of biomarkers in cerebrospinal fluid for Alzheimer's disease. *J Alzheimers Dis*. 2014;42(3):777-788. doi:10.3233/JAD-132216

45. Gauthier S, van den Brink SEM, El Amrani L, Rosa-Neto P, Vitali P. CLINICAL IMPACT OF CSF ASSESSMENT ON DIAGNOSTIC ACCURACY IN ATYPICAL DEMENTIAS IN QUEBEC, CANADA: PRELIMINARY RESULTS FROM A SPECIALIZED DEMENTIA CLINIC. *Alzheimer's Dementia*. 2019;15(7 Supplement):P1519. doi:10.1016/j.jalz.2019.08.079

46. Gjerum L, Andersen BB, Bruun M, et al. Comparison of the clinical impact of 2-[18F]FDG-PET and cerebrospinal fluid biomarkers in patients suspected of Alzheimer's disease. *PLoS ONE*. 2021;16(3):e0248413. doi:10.1371/journal.pone.0248413

47. Willemse EAJ, Scheltens P, Teunissen CE, Vijverberg EGB. A neurologist's perspective on serum neurofilament light in the memory clinic: a prospective implementation study. *Alzheimers Res Ther*. 2021;13(1):101. doi:10.1186/s13195-021-00841-4

48. Barker W, Greig-Gusto MT, Shea YF, Loewenstein DA, Duara R, Dekosky ST. Impact of Amyloid PET Imaging in the Memory Clinic: A Systematic Review and Meta-Analysis. *J Alzheimer's Dis*. 2018;64(1):323-335. doi:10.3233/JAD-180239

49. Carswell CJ, Win Z, Muckle K, et al. Clinical utility of amyloid PET imaging with (18)F-florbetapir: a retrospective study of 100 patients. *J Neurol Neurosurg Psychiatry*. 2018;89(3):294-299. doi:10.1136/jnnp-2017-316194

50. Fantoni ER, Chalkidou A, O' Brien JT, Farrar G, Hammers A. A Systematic Review and Aggregated Analysis on the Impact of Amyloid PET Brain Imaging on the Diagnosis, Diagnostic Confidence, and Management of Patients being Evaluated for Alzheimer's Disease. *J Alzheimers Dis*. 2018;63(2):783-796. doi:10.3233/JAD-171093

51. Ferreira D, Perestelo-Perez L, Westman E, Wahlund LO, Sarria A, Serrano-Aguilar P. Meta-Review of CSF Core Biomarkers in Alzheimer's Disease: The State-of-the-Art after the New Revised Diagnostic Criteria. *Front Aging Neurosci*. 2014;6(101525824):47. doi:10.3389/fnagi.2014.00047

52. Caselli RJ, Woodruff BK. Clinical impact of amyloid positron emission tomography—is it worth the cost? *JAMA neurology*. 2016;73(12):1396-1398.

53. Karikari TK, Pascoal TA, Ashton NJ, et al. Blood phosphorylated tau 181 as a biomarker for Alzheimer's disease: a diagnostic performance and prediction modelling study using data from four prospective cohorts. *The Lancet Neurology*. 2020;19(5):422-433.

54. Hansson O, Edelmayer RM, Boxer AL, et al. The Alzheimer's Association appropriate use recommendations for blood biomarkers in Alzheimer's disease. *Alzheimer's & Dementia*. 2022;n/a(n/a). doi:10.1002/alz.12756

55. Pink J, O'Brien J, Robinson L, Longson D. Dementia: assessment, management and support: summary of updated NICE guidance. *bmj*. 2018;361.

56. Welstead M, Luciano M, Muniz-Terrera G, Taylor AM, Russ TC. Prevalence of Mild Cognitive Impairment in the Lothian Birth Cohort 1936. *Alzheimer disease and associated disorders*. 2021;35(3):230.

Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart of selected papers

Fig. 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 (%).