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REVIEW ARTICLE

Systematic review of health economic models for assessment and diagnosis of dementia

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Abstract

INTRODUCTION: Timely diagnosis of dementia is a public health priority to enable risk modification and treatment access. This study systematically identifies and critically appraises health economic models of dementia assessment and diagnosis.

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METHODS: Inclusion criteria were: any dementia stage; evaluated strategy(ies) for initial assessment/diagnosis of dementia; health economic evaluation using decision modeling. Ten databases were searched for 2000–2024. Philips checklist was applied for quality assessment. Narrative synthesis appraised methodological features and issued decision-making recommendations.

RESULTS: Thirty-two studies were included. Six evaluated cerebrospinal fluid (CSF); 11 neuroimaging including amyloid-targeting positron emission tomography; three blood-based biomarkers; two genetic testing; and 10 early assessment/diagnosis strategies. Methodological limitations included non-consideration of capacity constraints. Decision-making recommendations generally affirmed current clinical guidelines: for example, CSF to confirm Alzheimer's disease is cost-effective (incremental cost-effectiveness ratio of £10,150 per quality-adjusted life-year gained vs. no use).

DISCUSSION: Methodological appraisal and decision-making recommendations should assist model development and evidence-based dementia diagnosis.

KEYWORDS
blood-based biomarkers of Alzheimer's disease, decision modeling, dementia, diagnosis, health economic evaluation, mild cognitive impairment, neuroimaging

1 | INTRODUCTION

Dementia describes a range of cognitive and behavioral symptoms that includes memory loss, problems with reasoning and communication, change in personality, and impaired ability to carry out activities of daily living.[1] It is the outcome of neurodegenerative diseases including Alzheimer's disease (AD) which accounts for 60%–80% of dementia cases, making it the most common cause of the dementia syndrome.[2,3] With the ageing of global populations, the number of dementia cases worldwide is projected to increase from 55 million in 2019 to 139 million in 2050, while the annual cost associated with dementia is expected to double from US$1.3 trillion in 2019 to US$2.8 trillion in 2030.[4] In the United Kingdom, the annual cost of dementia (in 2015 prices) amounted to £4.9 billion for National Health Service (NHS) healthcare, £15.7 billion for social care (£9 billion of which was paid privately by patients and their families), and £13.9 billion for unpaid care provided by informal caregivers.[5] The formal and informal care cost of dementia is projected to increase substantially faster than that of cancer, coronary heart disease, and stroke.[6] The impact of dementia on patients' and their informal caregivers' health-related quality of life (HRQoL) also is substantial.[7,8]

Improving diagnosis of dementia is therefore a public health priority to enable timely access to pharmacological treatments and care support, motivate lifestyle changes to modify risk factors that exacerbate disease progression, and allow for advanced legal, financial, and care planning.[9,10] In the United Kingdom and in other similar health economies, the diagnosis of dementia typically occurs in two steps. The first assessment is conducted in an initial assessment at non-specialist settings such as at a general practitioner (GP) visit, and typically entails examining clinical history, conducting cognitive tests using validated brief cognitive instruments (e.g., 6-item cognitive impairment test [6CIT][11]), and undertaking blood and urine tests.[1] Upon suspected dementia, a referral to specialist settings is implemented, with this more detailed assessment including neuropsychological testing to confirm cognitive impairment, structural imaging (e.g., magnetic resonance imaging [MRI] and computed tomography [CT]) to rule out reversible causes of cognitive decline and assist diagnosis of dementia subtypes, and further tests according to the suspected dementia subtype (e.g., cerebrospinal fluid (CSF) test to identify beta-amyloid (Aβ) or tau levels as biomarkers of AD subtype).[1] Thus, multiple diagnostics and physician types are incorporated in an initial assessment and diagnosis, and are components of a clinical pathway that should be included in evaluations of the effectiveness and cost-effectiveness of a given dementia diagnostic strategy.

Regarding the AD subtype in particular, evolved understanding of the disease has led to the recommendation to use biomarkers in its diagnosis in research settings. Since 2011, AD is to be defined and diagnosed by abnormally elevated levels of biomarkers Aβ (A+) and tau (T+)–detected in vivo by CSF,[12] positron emission tomography (PET)[13] or, most recently, plasma assay[14]–rather than by manifest clinical symptoms only.[15,16] This scheme distinguishes between three stages of disease progression: (1) preclinical AD where elevated biomarker levels (A+T- or A+T+) are yet unaccompanied by clinical symptoms; (2) mild cognitive impairment (MCI) due to AD or prodromal AD where elevated biomarker levels are accompanied by cognitive decline which does not yet affect daily functioning; and (3) AD dementia where daily functioning is significantly impaired.[17,18] AD biomarkers thus enable the confirmation or the ruling out of AD pathology[19] as well as the prediction of the emergence and progression of clinical symptoms of AD.[20–23] Once the symptoms occur, they can be grouped as those

affecting cognition, behavior and function and staged according to severity (e.g., mild, moderate, and severe).[24]

This capacity to detect AD biologically rather than clinically raises the prospect of early prevention and treatment of AD prior to the emergence of clinical symptoms. This is further enhanced by the recent US regulatory approval of lecanemab and donanemab, which are amyloid-targeting treatments (ATTs) targeting the Aβ pathology of AD, and which have demonstrated efficacy in reducing brain Aβ levels and cognitive and functional declines in randomized controlled trial (RCT) setting.[25,26] Of 32 investigational drugs undergoing phase 3 trial in January 2024, 21 (66%) target the underlying cause, and 95 of 164 (58%) trials target cognitively normal or early AD (MCI or mild AD) subjects.[27] Potential availability of effective ATTs and other disease-modifying therapies (DMTs) raises the importance of differential diagnosis of dementia subtype and precise staging of patients in trial and clinical practice settings.

Decision modeling is a vehicle of health economic evaluation well-suited for assessing the cost-effectiveness and broader benefits of dementia interventions that range from prevention to initial assessment, diagnosis, and post-diagnostic care.[28,29] Key strengths of decision modeling include the ability to compare and evaluate multiple intervention strategies and "what if" intervention scenarios and to conduct the evaluation at the broader (national or local) population level rather than for the samples of individual clinical studies.[30] However, the modeling of AD, and of dementia more broadly, poses specific methodological challenges such as the need to characterize the broad continuum of disease and symptom progression and to capture the wide range of outcomes including the value of informal care.[31] This in turn has generated a wide spectrum of methodological assumptions and practices that makes comparison between the methods and results of existing models difficult.[29,32] Models that incorporate dementia diagnostic pathways face additional challenges in that characterizing the accuracies of sequential diagnostic tests and identifying the relevant diagnostic accuracy data are essential modeling steps.[33]

Given these methodological challenges, a systematic review is an ideal study design to identify, synthesize, and critically appraise the methodological features of existing economic models of dementia diagnosis.[34] The review of previous modeling methods and data sources is also a pre-requisite for the development of a *de novo* model that is structurally valid, methodologically robust, and relevant to decision-making.[35] While a sizeable number of reviews have been published on dementia economic models since 2006,[29,34,36–48] only one[41] focused on models of diagnostic strategies for AD and identified only eight decision models for the period up to March 2011.

Overall, there is a need for an up-to-date systematic review of model-based economic evaluations of initial assessment and diagnostic strategies for dementia which takes into account the recent advances in diagnostic techniques, new strategies for implementing initial assessment in routine clinical practice, and the latest modeling techniques to address the methodological challenges inherent in evaluating these interventions. Accordingly, this study aims to systematically identify health economic models of initial assessment and diagnostic strategies for dementia, synthesize their key methodological features, and issue decision-making recommendations for dementia diagnostic investments based on health economic evidence.

HIGHLIGHTS

- We conducted an up-to-date review of health economic models of dementia diagnosis.
- Twenty-two studies evaluated cerebrospinal fluid (CSF), blood, neuroimaging, and genetic diagnostic biomarkers.
- Ten studies evaluated strategies for initial assessment before specialist referral.
- Diagnosis-related methodological limitations of existing models were appraised.
- Models should consider broader benefit/harm from diagnosis and capacity constraint.

2 | METHODS

The protocol for this systematic literature review[49] was registered with Prospective Register of Ongoing Systematic Reviews (PROSPERO), registration number: CRD42017073874. This protocol had set out a broad scope, covering the full spectrum of neurodegeneration from cognitively normal to dementia incidence and progression, and all intervention types across the spectrum.[49] Here we present the results of a subset of the planned review, focusing only on decision models evaluating initial assessment and diagnostic strategies for dementia. The review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guideline.[50] See the Appendix for the PRISMA checklist.

2.1 | Eligibility criteria

2.1.1 | Target population

This review focused on adults in community or any care setting and covers all dementia types and the full spectrum of dementia, including pre-dementia stages with underlying neurodegenerative disease (e.g., cognitively normal, subjective memory complaints, MCI), dementia of all severity stages, and end of life.

2.1.2 | Intervention and comparator

Any intervention strategy for the target population which included an initial assessment and/or diagnosis of dementia was included. Any comparator strategy was acceptable, including "do nothing", "usual care", and alternative assessment and diagnostic strategies.

2.1.3 | Study design

We only included model-based economic evaluations, which meant excluding economic evaluations conducted alongside trials or other clinical studies. Only full health economic evaluations were included, namely those that compared two or more intervention strategies in terms of both costs and consequences.[51] This excluded models that solely tracked outcomes (e.g., number of disease cases prevented) or intervention costs. All types of full health economic evaluations were eligible, including cost-utility analysis (CUA), cost-effectiveness analysis (CEA), and cost-benefit analysis (CBA). We included studies that reported an adaptation of an existing economic model. Previous reviews, conference abstracts, dissertations, and preprints were excluded.

2.2 | Search strategy

The following electronic databases were searched to identify papers published between January 1, 2000, and March 6, 2024: Ovid Medline, Ovid Embase, Economic Literature Database (EconLit), National Health Service Economic Evaluation Database (NHS EED), Cochrane Library, Cost-effectiveness Analysis Registry (CEA Registry), Research Papers in Economics (RePEc), Database of Abstracts of Reviews of Effectiveness (DARE), Science Citation Index (SCI), Turning Research Into Practice (TRIP) and Open Grey. The search terms are described in the published protocol.[49] In addition, a manual search of the reference lists of studies included in the review was performed.

The search did not cover the period prior to 2000 since high-quality systematic reviews covering it already exist. According to Handels et al.,[41] there was only one study by Simon and Lubin,[52] published in 1985, that conducted a model-based health economic evaluation of a dementia diagnostic strategy, comparing routine CT scan to selective CT and to MRI. The above database search was run twice: the first run covered the period from January 1, 2000, to February 28, 2019; the update run covered the period from March 1, 2019, to March 6, 2024. Open Grey was not covered in the update since it was no longer available.

2.3 | Study selection

All references obtained from the database search were downloaded to EndNote X7 (first run) and Covidence (update run). The duplicates were then removed. All remaining titles and abstracts were each screened independently by two reviewers. Full text articles were obtained for studies that appeared to meet the inclusion criteria or where a decision could not be made based on the title and abstract alone. Studies that did not fulfil the inclusion criteria were excluded, and the reasons for exclusion were recorded. At both title/abstract and full text screening stages, disagreements between two reviewers were resolved by a third reviewer.

2.4 | Data extraction and synthesis

Two reviewers independently extracted data from each of the included studies and recorded the information in Excel; any discrepancies were resolved by a third reviewer.

2.4.1 | Main characteristics extracted from included models

The following model characteristics were prioritized for extraction and synthesis:

1. Main study characteristics–study aim, country, dementia type (e.g., AD, non-AD dementia), target population, initial assessment and diagnostic strategy, comparator strategy.
2. Model and evaluation characteristics–type of analysis (e.g., CEA, CUA), perspective (e.g., societal), model type, model start/end point, cycle length (if applicable), time horizon, evaluation outcomes.
3. Disease characteristics and health events–domains used to characterized disease progression, method used to combine assessed domains, instruments used to measure disease severity, health states in model, method used to connect pre-dementia and dementia (if applicable), dementia risk factors (if applicable), mortality.
4. Post-diagnosis treatment characteristics–whether and what post-diagnosis treatment was modeled, how the treatment effect was modeled, length of treatment, what happens once treatment stops.
5. Evaluation results–the main results, including key results from sensitivity analyses, were summarized with all prices converted to 2024£GBP using a Web-based cost converter.[53]

2.4.2 | Quality assessment of included study

The Philips checklist[54] designed for the assessment of conduct and reporting qualities of health economic models was completed by two reviewers; any disagreements were resolved by a third reviewer. Whether an item was reported in the review was recorded as yes ("+"), no ("-"), partial ("P", for items that had multiple elements and were not fully satisfied by the study), and not applicable (".", for items that were not relevant to the study). The review also noted key assumptions of each model and its strengths and limitations as reported by the study authors or perceived by the review authors.

2.4.3 | Narrative synthesis, critical appraisal, and recommendations for decision-making

This review narratively synthesized the extracted features of included studies. The synthesis summarized the main methodological characteristics of the existing models and critically appraised the current

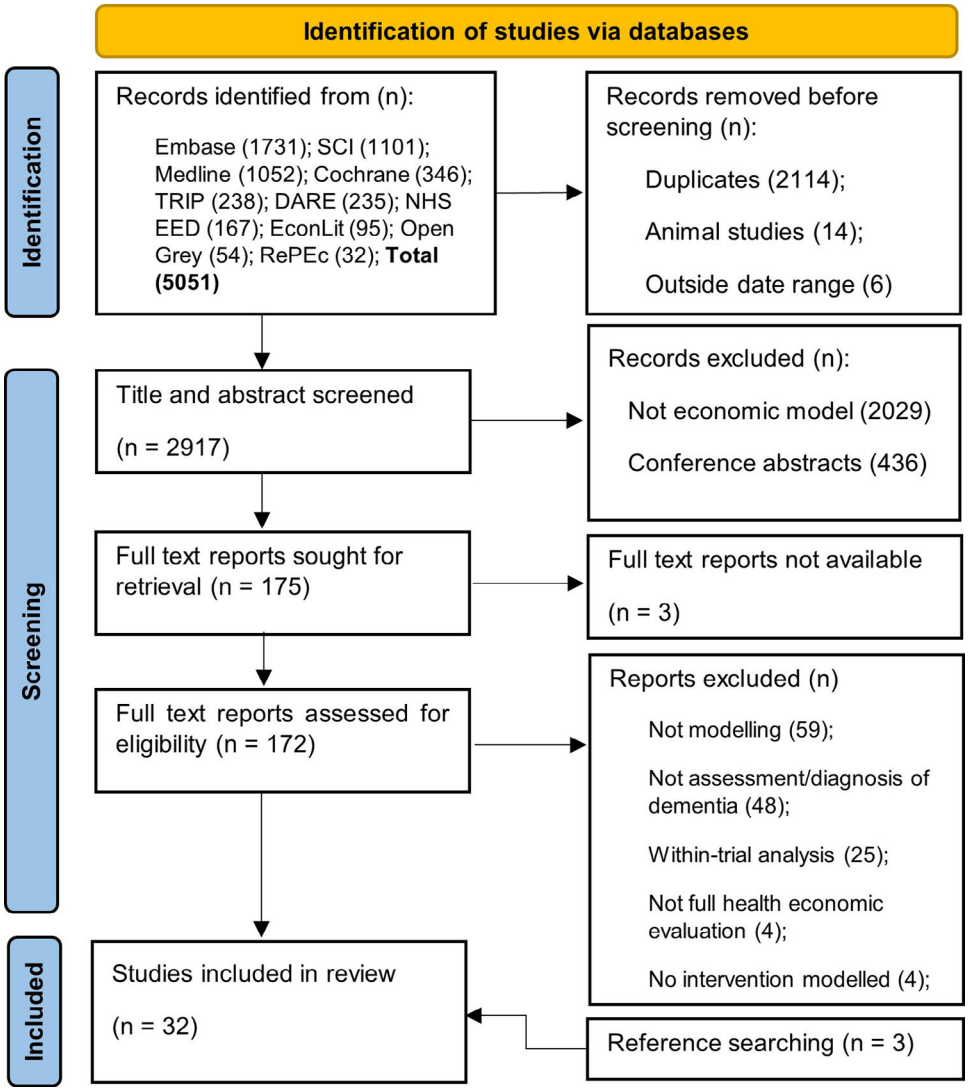

FIGURE 1 Preferred reporting items for systematic reviews and meta-analyses flow diagram.

practices and limitations with respect to addressing the key methodological challenges for model-based health economic evaluation of initial assessment and diagnosis of dementia. Here, several criteria established by expert consensus for decision modeling in general[55] and for AD models in particular[31] guided the synthesis and appraisal.

Recommendations for decision-making on dementia diagnostic investments were made based on the CUA evaluation results and methodological features of included studies. Incremental cost-effectiveness ratio (ICER)–calculated from costs converted to 2024£GBP prices–of less than £30,000 per quality-adjusted life year (QALY) gained was deemed cost-effective.[56] Likewise, positive incremental net health/monetary benefit calculated using the cost-effectiveness threshold of £30,000 per QALY gained was deemed cost-effective. For probabilistic sensitivity analysis (PSA) results, if the probability of an intervention being cost-effective relative to comparator(s) was higher than 50% at a threshold adjacent to £30,000 per QALY gained, this was deemed cost-effective.

3 | RESULTS

3.1 | Search results

Figure 1 presents the PRISMA flow diagram, which combines the flows under the original and updated reviews. The database searches identified 5051 articles, of which 29 were included; further inclusion of three from reference searching resulted in 32 studies being included for data extraction and synthesis. The aforementioned study[52] that evaluated a dementia diagnostic strategy but was published in 1985 was excluded; see previous reviews[29,41] for appraisal of this study.

3.2 | Characteristics of included studies

Table 1 shows the main characteristics of the included studies. All studies were set in high- or upper-middle income countries: 15 in the United

TABLE 1 Summary of main study characteristics

Reference	Country	Study aim	Dementia type	Target population	Assessment/ diagnostic strategy	Comparator strategy
CSF biomarkers (*n* = 6 studies)						
Handels et al. (2015)[57]	Netherlands	To conduct an early health technology assessment to estimate the headroom value of development and application of CSF biomarker test strategies for MCI subjects assuming the availability of a hypothetical disease-modifying AD treatment	AD and non-AD	People with MCI	CSF biomarker test strategies: (1) perfect CSF test for subjects who received either AD positive or negative clinical diagnosis; (2) "verify AD"—CSF add-on for subjects who received AD positive diagnosis by current practice; (3) "rule-out AD"—CSF add-on for subjects who received AD negative diagnosis by current practice	Current diagnostic practice alone: physical, clinical & NP examination; patient and informal caregiver history; MRI
Handels et al. (2017)[58]	Netherlands	To conduct an early health technology assessment to estimate the cost-effectiveness of adding CSF biomarker testing to the standard diagnostic workup to establish prognosis from MCI to dementia	All types	People with MCI	CSF biomarker testing in addition to the usual care diagnostic workup	Usual care diagnostic workup
Lee et al. (2017)[59]	USA	To evaluate the cost-effectiveness of performing CSF biomarker analysis in patients with suspected dementia without definitive diagnosis after MRI	AD and non-AD	People with suspected AD without MRI diagnosis	CSF biomarker testing after usual diagnostic practice and MRI	Usual diagnostic practice and MRI
Michaud et al. (2018)[60]	USA	To determine the value of CSF biomarker testing in MCI patients by comparing various test-and-treat strategies, including strategies without testing	AD	People with MCI aged 65 years	CSF biomarkers to categorise MCI patients into three different risk levels of AD progression. Six different test-and-treat: (1) no test, no MCI treatment; (2) test, treat high risk; (3) test, treat high or intermediate risk; (4) test, treat low risk; (5) test, treat low or intermediate risk; (6) no test, treat all	Comparison between six test-and-treat strategies
Önen Dumlu et al. (2023)[61]	USA	To determine optimal screening programs for AD using a partially observable Markov decision process model, focusing on the preclinical phase of AD and biomarker-based screening	AD	People aged 50 without symptoms of MCI or clinical AD	CSF biomarker screening with Aβ1–42 level	No CSF biomarker screening

(Continues)

TABLE 1 (Continued)

Reference	Country	Study aim	Dementia type	Target population	Assessment/ diagnostic strategy	Comparator strategy
Valcarcel-Nazco et al. (2014)[62]	Spain	To determine the cost-effectiveness of the use of Aβ42, total tau, and p-tau proteins in CSF to diagnose AD in MCI and dementia patients	AD	People with (1) MCI; (2) symptoms of dementia	Combined determination of Aβ42, total tau, and p-tau proteins in CSF as biomarkers of AD	Standard clinical diagnosis based on the NINDS-ADRDA criteria
Neuroimaging biomarkers ($n = 11$ studies)						
Bermingham (2014)[63]	Canada	To assess which clinical guideline for structural imaging is most cost-effective for differential diagnosis of mild-moderate dementia; where structural imaging is indicated, which modality (CT or MRI) is most cost-effective	AD, VaD, mixed (AD/VaD), SOLs (NPH, SDH, BT)	People with diagnosis of mild-moderate dementia	Strategies: (1) image all with CT then MRI for SOL; (2) image all with MRI; (3) CT for those meeting CCC criteria then MRI for SOL; (4) MRI for those meeting CCC criteria	Comparison between four strategies
Biasuitti et al. (2012)[64]	France	(1) To evaluate the cost-effectiveness of MRI plus new contrast agent CLP detecting Aβ (MRI+CLP) relative to standard diagnostic strategy for patients with MCI symptoms. (2) To evaluate MRI+CLP as part of national screening (general or targeted at APOE4 carriers) relative to standard strategy. Evaluate new AD treatment with significant efficacy at early AD stage	AD	(1) Patients consulting for MCI aged 70; (2) general population/ APOE4 carriers aged 60	Imaging strategies: (a) Standard diagnostic strategy followed by MRI+CLP; (b) Standard diagnostic strategy plus non-enhanced MRI	Standard diagnostic strategy: interview with AD specialist; cognition tests such as MMSE; laboratory tests
Contador et al. (2023)[65]	Spain	To determine the cost-effectiveness of Aβ-PET relative to CSF biomarkers (Aβ42, total tau, and p-tau) for the diagnosis of AD in patients with early-onset cognitive impairment	AD	People with early-onset (< 65 years) cognitive impairment	Diagnosis using Aβ-PET	Diagnosis using CSF biomarkers
Guo et al. (2012)[66]	US	To develop an exploratory economic model assessing the clinical and economic value of florbetaben PET for AD diagnosis and to identify key value drivers and data gaps, which will direct future economic assessment of this technology	AD and non-AD	People presenting to doctor with MCI or dementia symptoms	Clinical guidelines plus florbetaben-PET	Usual diagnostics: mix of clinical guideline alone and clinical guideline plus MRI or CT of MTA

(Continues)

TABLE 1 (Continued)

Reference	Country	Study aim	Dementia type	Target population	Assessment/ diagnostic strategy	Comparator strategy
Hornberger et al. (2015)[67]	Spain	To evaluate long-term health economic outcomes of: (1) florbetapir-PET plus standard evaluation versus standard evaluation alone for AD diagnosis in cognitively impaired patients; (2) florbetapir-PET plus standard evaluation versus FDG-PET plus standard evaluation	AD	People with mild to moderate cognitive impairment	Florbetapir-PET plus standard clinical evaluation	(1) Standard clinical evaluation alone; (2) FDG-PET plus standard clinical evaluation
Hornberger et al. (2017)[68]	France	To evaluate cost-effectiveness of: (1) Aβ-PET plus standard evaluation versus standard evaluation alone for AD diagnosis; (2) Aβ-PET plus standard evaluation versus CSF plus standard evaluation	AD	People with mild to moderate cognitive impairment	Florbetapir -PET plus standard diagnostic evaluation	(1) Standard diagnostic evaluation; (2) CSF plus standard diagnostic evaluation
Lee et al. (2021)[69]	South Korea	To evaluate the cost-effectiveness of including Aβ-PET for assessing individuals with MCI	AD	People aged 60 diagnosed with MCI	Aβ-PET	Current practice (not described)
McMahon et al. (2000)[70]	USA	To evaluate the cost-effectiveness of functional neuroimaging in the workup of patients at specialized AD clinics	AD	Patients referred to AD clinics	Functional neuroimaging strategies: (a) standard examination including CT; (b) MRI plus DSC-MRI for all; (c) visual SPECT for patients with possible AD after standard exam; (d) computed SPECT for possible AD	Comparison between four intervention strategies
McMahon et al. (2003)[71]	USA	To evaluate the cost-effectiveness of FDG-PET in the diagnosis of AD in community-dwelling patients with mild-to-moderate dementia who present to specialised AD clinics	AD and non-AD	Patients referred to AD clinics	Strategies: (a) standard examination including CT; (b) MRI plus DSC-MRI for all; (c) FDG-PET for patients with possible AD after standard exam; (d) computed SPECT for possible AD	Comparison between four intervention strategies
Moulin-Romsee et al. (2005)[72]	Belgium[a]	To estimate the economic effects of incorporating FDG-PET in the diagnostic workup of AD in Belgian and European setting	AD	People with cognitive symptoms & suspected AD	FDG-PET to detect abnormal metabolism	Conventional approach: clinical criteria to detect dementia and exclude non-AD etiologies

(Continues)

TABLE 1 (Continued)

Reference	Country	Study aim	Dementia type	Target population	Assessment/ diagnostic strategy	Comparator strategy
Silverman et al. (2002)[73]	USA	To evaluate two strategies to detect cognitive symptoms due to early AD: (a) conventional clinical criteria; (b) FDG-PET to detect abnormal metabolism	AD	People with cognitive symptoms & suspected AD	FDG-PET to detect abnormal metabolism	Conventional approach: clinical criteria to detect dementia and exclude non-AD etiologies
Blood-based biomarkers ($n = 3$ studies)						
Mattke et al. (2020)[74]	USA	To predict the impact of different triaging strategies involving blood-based biomarker and brief cognitive test at primary care on the cost and wait times of diagnosing those with MCI due to AD who are eligible for DMT	AD and non-AD	People aged 50+	Strategies for primary care-based triage: (1) BBBM alone; (2) MMSE followed if positive by BBBM; (3) BBBM followed by MMSE	Primary care-based triage using MMSE alone (most closely reflects current practice)
Mattke et al. (2024)[75]	USA	To estimate the cost-effectiveness of a hypothetical screening and prevention program for cognitively unimpaired persons with blood biomarker evidence of Aβ plaques	AD	People aged 50-79 without cognitive impairment	Blood test for AD pathology in primary care followed by: (1) hypothetical continuous DMT until progression to MCI; (2) one-year DMT, monitoring with blood test and one-dose re-treatment at amyloid re-accumulation	No blood test and no DMT
Noda et al. (2024)[76]	USA	To examine the cost-effectiveness of blood biomarker test as a diagnostic method relative to amyloid PET and CSF tests	AD	Unclear	Blood biomarker test to detect amyloid pathology	(1) Aβ-PET; (2) CSF
Genetic testing ($n = 2$ studies)						
Djalalov et al. (2012)[77]	Canada	To assess the cost-effectiveness of genetic testing for APOE4 allele in combination with preventive donepezil treatment relative to the standard of care for AMCI	AD	Patients with AMCI aged 70	APOE4 genetic test during a visit to a memory clinic or a neurologist followed by targeted therapy for carriers of one or more APOE4 allele	Standard of care: routine monitoring until progression to AD
Iragorri et al. (2023)[78]	Canada	To estimate the cost and health benefits of implementing ONDRISeq in Ontario to identify genetically indicated AD relative to the status quo of out-of-country testing	AD	People aged 65	ONDRISeq: next-generation sequencing-based panel targeting 80 genes, including 21 AD-specific genes	(1) Out-of-country genetic testing using LifeLabs for 7 genes. (2) No genetic testing

(Continues)

TABLE 1 (Continued)

Reference	Country	Study aim	Dementia type	Target population	Assessment/ diagnostic strategy	Comparator strategy
Initial assessment and early diagnosis ($n = 10$ studies)						
Banerjee & Wittenberg (2009)[79]	UK	To analyze the costs and benefits of commissioning memory services for early diagnosis and intervention for dementia	All types	People aged 65+ and caregivers	Multidisciplinary and interagency service to generate early diagnosis and provide psychosocial intervention to patients and caregivers, based on the Croydon Memory Service Model	No access to Memory Service Model
Barnett et al. (2014)[80]	UK	To explore how early assessment and treatment (symptomatic or disease modifying) affects cost-effectiveness of AD intervention	AD	People aged 75, 9 years before standard AD diagnosis	Hypothetical early assessment and diagnosis involving GP visit, CT/MRI scan and specialist consultation followed by symptomatic or DMT	No early diagnosis under standard practice
Dixon et al. (2015)[81]	England & Wales	To examine the number of people with dementia who could be diagnosed and the likely cost-effectiveness of a one-off screen for dementia for people aged 75 years in England & Wales	All types	People aged 75	One-off screen for dementia using MMSE applied by nurses and GPs during a standard 15-min primary care appointment or other secondary care appointment	No screening
Getsios et al. (2012)[82]	UK	To evaluate the cost-effectiveness of early assessment of individuals presenting with memory complaints and treating those with mild-moderate AD with donepezil	AD	Undiagnosed AD patients reporting memory complaints	Annual early assessment consisted of initial visit to GP, two specialist visits, laboratory tests, and MRI/CT scan for 5% of cases	(i) No early assessment and no treatment; (ii) Treatment without early assessment
Ren et al. (2022)[83]	China	To evaluate the effectiveness and cost-effectiveness of screening for AD in mainland China among individuals aged 60	AD	People aged 60	Screening using MMSE, followed by diagnosis using clinical exam, laboratory test and neuroimaging	No screening
Saito et al. (2014)[84]	USA	To assess the economic benefit of community-based dementia assessment and diagnosis	All types	People aged 18+	Community based dementia diagnosis: conducted by neurologist located in local community; program advertised locally; diagnostic workup—MMSE, history, physical and neurological examinations, comorbidities	No community-based dementia diagnosis

(Continues)

TABLE 1 (Continued)

Reference	Country	Study aim	Dementia type	Target population	Assessment/ diagnostic strategy	Comparator strategy
Shore et al. (2023)[85]	UK	(1) To conduct an economic evaluation of the Integrated Cognitive Assessment (ICA) tool compared with standard cognitive tests when used for dementia assessment in primary care. (2) To evaluate the ICA tool when used for initial triage in memory clinics	All types	People with suspected dementia	ICA is a brief, language independent, self-administered, computerized cognitive test which uses an explainable artificial intelligence model to improvement the accuracy of cognitive impairment diagnosis	(1) Standard cognitive testing in primary care: MMSE; GPCOG; 6CIT; AMTS; MoCA (2) Standard triage process in memory clinic: MoCA; ACE-III
Tong et al. (2017)[86]	England	To investigate the cost-effectiveness of three cognitive tests (MMSE, GPCOG, 6CIT) for use by GPs to detect cognitive impairment in primary care setting	AD	People aged 65+	Assessment strategies: (i) MMSE; (ii) GPCOG; (iii) 6CIT; followed by referral to memory clinic	Unassisted GP judgment of MCI/AD
Weimer & Sager (2009)[87]	USA	To evaluate the social and fiscal costs and benefits of the early identification and treatment of AD patients	AD	Undiagnosed AD patients aged 65	Early diagnosis of AD by screening program	No screening
Yu et al. (2015)[88]	South Korea	To investigate the cost-effectiveness of the NDEDP in Korea as a national screening program for dementia.	All types	People aged 65+	NDEDP one-off screening program: MMSE-DS followed by CERAD-K, laboratory test and neuroimaging as diagnostic procedure	No NDEDP screening

Abbreviations: 6CIT, six-item cognitive impairment test; AAN, American Academy of Neurology; ACE-III, Addenbrooke's cognitive examination III; AD, Alzheimer's disease; Aged 50+, aged 50 years and over; AMCI, amnestic mild cognitive impairment; AMTS, abbreviated mental test score; APOE4, apolipoprotein E ε4 allele; Aβ, beta-amyloid; BBBM, blood-based biomarker; BT, brain tumor; CCC, Canadian Consensus Conference on the Diagnosis and Treatment of Dementia; CERAD-K, Consortium to Establish a Registry for Alzheimer's Disease Korean version; CLP, contrastophore-linker-pharmacophore; CSF, cerebrospinal fluid; CT, computerized tomography; DMT, disease-modifying therapy; DSC, dynamic susceptibility contrast-enhanced; FDG, fluorodeoxyglucose; GP, general practitioner; GPCOG, general practitioner assessment of cognition; ICER, incremental cost-effectiveness ratio; MCI, mild cognitive impairment; MMSE(-DS), Mini Mental State Examination (for dementia screening); MoCA, Montreal cognitive assessment; MRI, magnetic resonance imaging; MTA, medial temporal lobe atrophy; N/A, not applicable; NDEDP, National Dementia Early Detection Program; NINDS-ADRDA, National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association; NP, neuropsychological; NPH, normal-pressure hydrocephalus; ONDRISeq, Ontario Neurodegenerative Disease Research Initiative gene sequencing; PET, positron emission tomography; p-tau, phosphorylated tau; SDH, subdural hematoma; SOL, space-occupying lesion; SPECT, single photon emission computed tomography; VaD, vascular dementia.
[a]Conducts sensitivity analyses using cost data from Finland, Greece, Spain, Ireland, the Netherlands, France, Germany, and England.

States and Canada, 14 in Europe, two in South Korea, and one in China. Twenty studies (63%) focused only on AD as a dementia type. Six studies evaluated the use of CSF biomarkers[57–62]; 11 neuroimaging[63–73]; three blood-based biomarkers[74–76]; two genetic testing[77,78]; and 10 strategies for initial assessment and early diagnosis of dementia that did not involve the use of fluid or imaging biomarkers.[79–88]

Four CSF biomarker studies targeted people with MCI (before the onset of dementia), either to achieve differential diagnosis of prodromal AD[57,62] or to estimate the risk of progression to dementia.[58,60] Others targeted asymptomatic subjects to diagnose preclinical AD[61] and symptomatic subjects with undiagnosed dementia to confirm AD diagnosis.[59] Michaud et al.[60] compared six strategies with different test-and-treat combinations; the rest evaluated the use of CSF biomarkers relative to standard diagnostic practice.

The neuroimaging studies targeted people with cognitive symptoms prior to dementia diagnosis, except Bermingham[63] which evaluated the provision of CT and MRI to people with diagnosed mild to moderate dementia to identify the underlying cause, and Biasutti et al.[64] which evaluated the application of enhanced MRI on the general population aged 60 years old. PET scans for amyloid (Aβ-PET), including those using tracers florbetaben and florbetapir, for the diagnosis of prodromal AD or AD dementia were evaluated by five recently published studies against the following comparators: CSF[65,66,68]; fluorodeoxyglucose (FDG) PET[66,67]; single-photon emission computerized

TABLE 2 Summary of model and evaluation characteristics

Reference	Type of analysis	Outcome metric	Perspective	Model type		Model starting point	Model end point	Cycle length	Time horizon
				Diagnosis	Treatment/ disease progression				
CSF biomarkers ($n = 6$ studies)									
Handels et al. (2015)[57]	CUA	Cost, QALY, INMB, average age at dementia onset, average potential beneficial treatment years	Societal	Decision tree	DES	MCI	Death or 30 years in dementia stage	N/A	Lifetime
Handels et al. (2017)[58]	CUA	Cost, QALY, ICER, INMB, prognostic accuracy	Healthcare	Decision tree	DES	MCI	Death or simulation end	N/A	5 years
Lee et al. (2017)[59]	CUA	Cost, QALY, ICER	Societal	Decision tree	Markov	Suspected dementia without diagnosis after MRI	Death	1 month	Lifetime
Michaud et al. (2018)[60]	CUA	Cost, QALY, ICER	Societal	Markov		MCI	Death	1 year	Lifetime
Önen Dumlu et al. (2023)[61]	CUA	Cost, QALY, ICER	Healthcare	Decision tree	Partially observable Markov	No symptom of MCI or AD aged 50	Death or simulation end	1 year	50 years
Valcarcel-Nazco et al. (2014)[62]	CEA	Cost, probability of correct diagnosis, ICER[a]	Healthcare	Decision tree		(1) MCI; (2) dementia symptoms	Death	N/A	Lifetime
Neuroimaging biomarkers ($n = 11$ studies)									
Bermingham (2014)[63]	CUA	Cost, QALY, ICER	Healthcare	Decision tree	Markov	Mild-moderate dementia, diagnosed clinically	Death	6 weeks	Lifetime
Biasuitti et al. (2012)[64]	CUA	Cost, QALY, ICER	Societal	Decision tree	Markov	(1) MCI symptoms aged 70; (2) general population/APOE4 carriers aged 60	Death	6 months	(1) 3 years; (2) 15 years
Contador et al. (2023)[65]	CEA	Cost, percentage of AD cases correctly diagnosed, ICER[a]	Healthcare	Decision tree		Early-onset MCI	Simulation end	N/A	3 months
Guo et al. (2012)[66]	CUA	Cost, QALY, carer cost and QALY, ICER, survival, time to diagnosis, time in—pre-dementia, each disease stage, institutional care	Societal	DES		Symptoms of MCI or dementia at initial doctor visit	Death	N/A	Lifetime
Hornberger et al. (2015)[67]	CUA	Cost, QALY, ICER, survival, time in community/NH	Societal	Decision tree	Linear progression in MMSE score	Mild to moderate cognitive impairment	Death or simulation end	N/A	10 years
Hornberger et al. (2017)[68]	CUA	Cost, QALY, ICER, survival, time in community/NH	Societal	Decision tree	Linear progression in MMSE score	Mild to moderate cognitive impairment	Death or simulation end	N/A	10 years
Lee et al. (2021)[69]	CUA	Cost, QALY, ICER	Healthcare	Markov		Diagnosed MCI	Death	3 months	Lifetime

(Continues)

TABLE 2 (Continued)

Reference	Type of analysis	Outcome metric	Perspective	Model type		Model starting point	Model end point	Cycle length	Time horizon
				Diagnosis	Treatment/ disease progression				
McMahon et al. (2000)[70]	CUA	Cost, QALY, ICER	Societal	Decision tree	Markov	Referral to AD clinic	Death or simulation end	6 weeks	18 months
McMahon et al. (2003)[71]	CUA	Cost, QALY, ICER	Societal	Decision tree	Markov	Referral to AD clinic	Death or simulation end	6 weeks	18 months
Moulin-Romsee et al. (2005)[72]	CEA	Cost, number of correct diagnosis, ICER[a]	Societal	Decision tree		Suspected AD with cognitive symptom	AD diagnosis	N/A	1 year
Silverman et al. (2002)[73]	CEA	Cost, number of correct diagnosis, ICER[a]	US payer	Decision tree		Early cognitive symptoms	AD diagnosis	N/A	1 year
Blood-based biomarkers ($n = 3$ studies)									
Mattke et al. (2020)[74]	CEA	Cost of diagnosis, wait time for diagnosis, ICER[a]	Medicare & Medicaid	Markov and systems dynamics		Aged 50+	Death or simulation end	1 year	30 years
Mattke et al. (2024)[75]	CUA	Cost, INMB	Medicare & Medicaid; Societal	Markov		Aged 50–79 without cognitive impairment	Death or simulation end	1 year	30 years
Noda et al. (2024)[76]	CEA	Incremental accuracy, cost, ICER[a]	Healthcare: diagnostic costs only	Unclear, likely decision tree		Unclear, cites ADNI cohort	Simulation end	N/A	N/A
Genetic testing ($n = 2$ studies)									
Djalalov et al. (2012)[77]	CUA	Cost, QALY, ICER	Societal	Markov		AMCI aged 70	Death	1 year	Lifetime (30 years)
Iragorri et al. (2023)[78]	CUA	Cost, QALY, ICER, INMB	Public healthcare	Decision tree	Markov	Aged 65	Death or simulation end	1 year	25 years
Initial assessment and early diagnosis ($n = 10$ studies)									
Banerjee & Wittenberg (2009)[79]	CUA	Cost, QALY, ICER	Societal[b]	Binary decision model[c]		Aged 65+	Simulation end	N/A	10 years
Barnett et al. (2014)[80]	CUA	Cost, QALY, INMB	Healthcare	Cohort epidemiological model		Aged 75 with mean MMSE of 26	Standard AD diagnosis	Unclear	10 years
Dixon et al. (2015)[81]	Net cost-savings[d]	Net cost saving	Societal	Binary decision model[c]		Aged 75	Death	N/A	Lifetime
Getsios et al. (2012)[82]	CUA	Cost, QALY, ICER, years in community	Healthcare; Societal	DES		Undiagnosed AD	Death or simulation end	N/A	10 years
Ren et al. (2022)[83]	CUA	Cost, QALY, ICER, INMB, death and untreated severe AD avoided	Societal	Markov		Aged 60	Death or simulation end	1 year	20 years
Saito et al. (2014)[84]	CEA	Cost per person assessed, time spent in disease states	Unclear	Markov		Aged 18+ presenting to dementia assessment	Death or simulation end	1 year	10 years
Shore et al. (2023)[85]	CUA	Cost, QALY, ICER, INMB, INHB, number of referrals, unnecessary referrals and diagnoses	NHS & PSS	Decision tree	Markov	(1) General older population attending GP; (2) Subjects referred to memory clinic	Death	1 year	Lifetime

(Continues)

TABLE 2 (Continued)

Reference	Type of analysis	Outcome metric	Perspective	Model type: Diagnosis	Model type: Treatment/ disease progression	Model starting point	Model end point	Cycle length	Time horizon
Tong et al. (2017)[86]	CUA	Cost, QALY, INMB	NHS & PSS; Societal	DIS		Aged 65+	Death	1 year	Lifetime
Weimer & Sager (2009)[87]	CBA	Net monetary benefit	Societal; state; federal	Monte Carlo model with two equations for MMSE progression		Undiagnosed AD aged 65	Death	1 year	Lifetime
Yu et al. (2015)[88]	CUA	Cost, QALY, ICER	Societal	Decision tree	Markov	Aged 65+	Death or simulation end	1 year	10 years

Abbreviations: AD, Alzheimer's disease; ADNI, Alzheimer's Disease Neuroimaging Initiative; Aged 50+, aged 50 years and over; AMCI, amnestic mild cognitive impairment; APOE4, apolipoprotein E ε4 allele; CBA, cost-benefit analysis; CEA, cost-effectiveness analysis; CSF, cerebrospinal fluid; CUA, cost-utility analysis; DES, discrete event simulation; DIS, discrete individual simulation; ICER, incremental cost-effectiveness ratio; INMB, incremental net monetary benefit; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; MRI, magnetic resonance imaging; N/A, not applicable; NH, nursing home; PSS, Personal Social Services; QALY, quality-adjusted life year.

[a]Incremental cost per correctly diagnosed case.

[b]Costs included memory service costs incurred by NHS and public and private costs of care home admissions.

[c]Model compared scenarios with and without the evaluated intervention; it did not contain any event probabilities, health states, or time cycles.

[d]The study considered financial costs incurred and savings generated by the intervention.

tomography (SPECT)[66]; MRI[66]; and standard clinical evaluation.[67–69] Earlier studies evaluated the use of FDG-PET,[71–73] SPECT,[70,71] and MRI (enhanced to detect amyloid or standard)[64,70,71] in AD diagnosis. Bermingham[63] evaluated alternative options for the use of CT and MRI for identifying potentially reversible causes of cognitive impairment.

Two studies of blood test for AD pathology targeted the general older adult population[74] and those specifically without cognitive impairment[75] and situated the test in non-specialist setting as a population-level screening tool in the United States with high uptake rates (50%[74] and 100%[75]). They evaluated scenarios of different sequences of blood test and cognitive test using the Mini-Mental State Examination (MMSE) as initial assessment strategies[74] and a scenario of the blood test being used to monitor the effects of a hypothetical DMT to inform treatment dosage.[75] The third blood biomarker study by Noda et al.[76] had an unclear target population and directly compared the blood test with Aβ-PET and CSF for AD diagnosis.

There were two studies of tests for AD-related genotypes, the apolipoprotein E4 (APOE4) allele[77] and a panel of 21 AD-specific genes.[78] Djalalov et al.[77] evaluated APOE4 testing against usual care for those with amnestic MCI visiting a specialist setting, while Iragorri et al.[78] evaluated domestic gene panel testing against foreign testing and no testing for the general older population. In both studies, those tested to be at high genetic risk were prescribed preventive pharmacological treatments.

Of 10 studies evaluating strategies for initial assessment and early diagnosis that did not involve the use of fluid or imaging biomarkers, seven targeted the general older population,[79–81,83,84,86,88] while the rest targeted suspected or yet undiagnosed dementia patients.[82,85,87] Two studies[81,86] focused on initial assessment in non-specialist setting using paper-based cognitive tests, followed by referral to specialist setting. Shore et al.[85] evaluated the use of computerized cognitive tests for initial assessment at primary care or as a triage tool in memory clinic. Four studies[80,82,83,88] evaluated programs that combined initial assessment and specialist diagnosis. Two studies[79,84] evaluated schemes that made specialist diagnostic service more accessible in the community. Weimer and Sager[87] did not clearly specify the diagnostic strategy. Three studies evaluated population-level screening policies in England and Wales,[81] China,[83] and South Korea[88] with uptake rates above 80%. By contrast, Tong et al.[86] specified that initial assessment of dementia in England would remain opportunistic, with the uptake rate below 20% for persons without MCI or dementia.

Table 2 summarizes the model and evaluation characteristics of the included studies. Most studies (23 of 32; 72%) conducted CUA with incremental cost per QALY gained as the evaluation outcome; seven conducted CEA with incremental cost per correctly diagnosed case[62,65,72–74,76] or per person assessed[84] as outcome; Weimer and Sager[87] conducted CBA with net monetary cost (monetary value of QALY was used) as outcome; and Dixon et al.[81] compared the financial costs and savings from intervention. Most studies (19 of 32; 59%) conducted the evaluation from the societal perspective. The cohort-level Markov model was the most frequently used model type, used by 16 studies (50%), nine[59,61,63,64,70,71,78,85,88] with an appended decision tree to characterize the intervention strategies. Mattke et al. (2020)[74] combined the Markov model with systems dynamic model to capture capacity constraints in specialist diagnosis and Aβ-PET utilization. Five studies used discrete event[57,58,66,82] or individual[86] simulation, two[57,58] with appended decision tree. Four studies[62,65,72,73] used decision tree alone, while three[67,68,87] used equations for dynamic trajectory of MMSE-defined dementia severity. The model time horizon ranged from three months to lifetime.

Table SA.1 in the Appendix details the disease characteristics and health events modeled by the included studies. Half of the studies (16 of 32) did not clearly state the domains for disease progression or track the progression after dementia diagnosis. There was a wide variation in

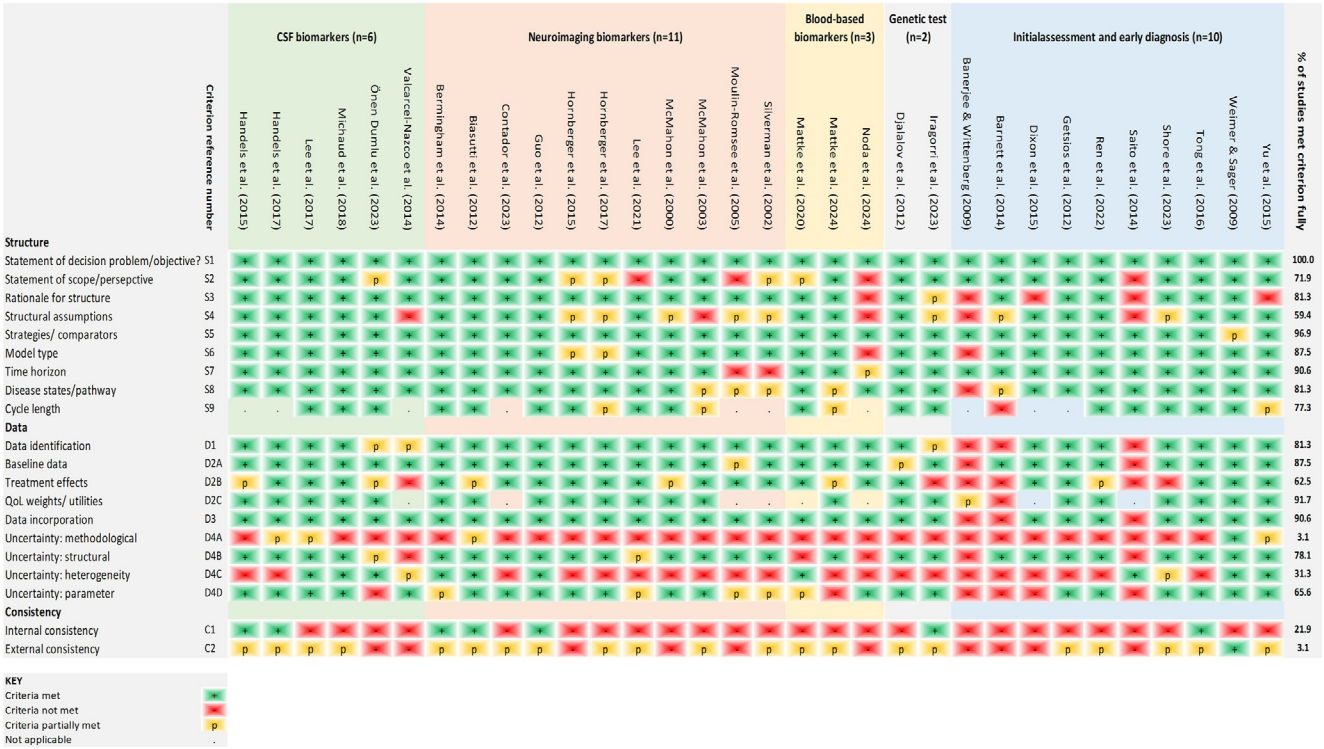

FIGURE 2 Philips checklist quality assessment results. CSF: cerebrospinal fluid.

the range of health states modeled, depending on the model type and target population. Eighteen studies (56%) targeted pre-dementia populations and depicted the progression from pre-dementia to dementia. The risk factors incorporated by the studies concerning dementia progression were limited, being restricted to age and/or sex[64,83,85,86] or to specific biomarker or genotype being investigated as diagnostic tool,[60,61,69,74,75,77,78] or not being stated or considered at all.[62,66–68,84] Only two studies conducted primary analyses to justify the risk factors modeled.[57,58]

Table SA.2 in the Appendix summarizes the characteristics of treatments received post-diagnosis. Five studies[57,61,64,75,80] evaluated hypothetical DMTs with differing assumptions on efficacy, while four[58,65,74,76] considered no intervention. Mattke et al. (2024)[75] considered a scenario of interaction between post-diagnostic treatment and continued biomarker assessment: the hypothetical DMT was stopped after a year then recommenced at re-accumulation of the Aβ biomarker detected through the use of blood biomarker of AD pathology. Table A.3 in the Appendix summarizes the main evaluation results of the included studies.

3.3 | Quality assessment

3.3.1 | Philips checklist

Figure 2 shows the results of the quality appraisal of included studies using the Philips checklist. Assessments of methodological uncertainty and external consistency were the least fully addressed and/or reported model quality items, with only Weimer and Sager[87] (3.1%) fully addressing the two items. Specifically, the study[87] was deemed to have addressed methodological uncertainty by considering two alternative trajectories of MMSE to characterize the disease severity progression, and to have addressed external consistency by comparing the MMSE trajectories to external data from literature. That said, 21 of 32 studies (65.6%) compared their outcomes to those of previous models (i.e., cross-validation) to partially meet the criterion of external consistency. Internal consistency was likewise poorly addressed, with only 21.9% of studies reporting how model performance was verified (e.g., testing outcomes under extreme input values). Credibility of results was compromised for the 24 studies (75.0%) that performed and reported neither internal nor external validation.

3.3.2 | Key assumptions, strengths, and limitations

Table SA.4 in the Appendix summarizes the key assumptions made in each study. Several assumptions were made specifically regarding the initial assessment and/or diagnosis aspects of models. Many studies made assumptions on the accuracy of the assessment and/or diagnostic intervention, or on how external accuracy data are applied.[63,64,72,73,75,77,78,80,81,83,85,86,88] Eight[66–69,72,73,83,88] made assumptions on how the assessment and/or diagnostic intervention promotes early diagnosis by shortening the time to diagnosis or reducing the severity of dementia at the point of diagnosis. Other assumptions concerned frequency and uptake of assessment and/or

diagnosis.[66,74,75,78,80,81,83,88] Mattke et al. (2020)[74] considered capacity constraints for diagnostic work-up involving specialists and Aβ-PET but not CSF, while Contador et al.[65] considered the risk of technical difficulties in performing CSF. Only Handels et al. (2017)[58] considered the HRQoL impact of stigmatization following from true or false diagnosis of dementia.

Table SA.5 in the Appendix highlights key strengths and limitations noted for each study. Some noted strengths included: conducting primary analyses of individual-level data to obtain model inputs[57,58,60,66,69,88]; characterizing the pre-symptomatic stages before dementia incidence[61,74,75,86]; incorporating multiple dimensions of dementia severity[82,86]; directly comparing biomarker or neuroimaging diagnostic techniques against each other[65,67,68,76,78]; evaluating diagnostic strategies for non-AD dementia[63]; evaluating caregiver support interventions[81,87]; and conducting extensive scenario analyses.[57,58,60,70,71,75]

As for limitations specifically regarding the initial assessment and/or diagnosis aspects of models, these included: unrealistic uptake rates of assessment and/or diagnosis[64,74,75]; lack of repeat testing to confirm diagnosis[61,70]; non-consideration of patient preferences over diagnostic modality[65]; non-consideration of implementation challenges that may result in constraints and delays in diagnosis (e.g., insufficient specialist resources to handle increased number of referrals from more sensitive initial assessment)[57,73,85,86]; non-consideration of the harms of false diagnosis (e.g., anxiety, relationship disruptions, premature adaptations)[57,65,81,86]; and non-consideration of the broader benefits of true diagnosis (e.g., reduced anxiety from more certain diagnosis).[63,68,70] Moreover, studies often faced issues with the quality of diagnostic accuracy data,[59,62,64,65,70–72,74] particularly concerning sequential diagnostic tests wherein the test accuracies are correlated rather than independent.[71,72]

3.4 | Recommendations for decision-making

Evidence from CUA evaluation results to inform the recommendations for decision-making on dementia diagnostic investments were as follows (see Table SA.6 in the Appendix for further details on how the CUA evaluation results were interpreted):

1. CSF test to achieve AD diagnosis for those who remain undiagnosed after undergoing standard clinical evaluation and MRI is cost-effective versus no addition of CSF.
2. There is mixed cost-effectiveness evidence for CSF testing versus no testing to achieve AD prognosis.
3. Aβ-PET supplementing standard clinical evaluation is cost-effective versus no supplementation for individuals presenting with symptoms of dementia (more severe than MCI), but the initial investment costs of increasing access to Aβ-PET have not been thoroughly incorporated in evaluations.
4. FDG-PET, enhanced MRI techniques, and SPECT are not cost-effective versus standard MRI or CT when supplementing standard clinical evaluation.
5. There is a lack of reliable CUA evidence for the cost-effectiveness of blood-based biomarkers versus no biomarker use.
6. CUA results for the cost-effectiveness of genetic testing (APOE4, multi-gene panel) versus no testing have used less than reliable effectiveness estimates such that no firm conclusion can be drawn.
7. Early assessment and diagnosis using multidisciplinary services (e.g., combination of GP visit, specialist visit, and neuroimaging) is cost-effective versus no early assessment for undiagnosed dementia patients reporting cognitive symptoms, while the evidence is mixed when conducted on general older populations.
8. Cognitive testing in non-specialized settings (e.g., primary care) is cost-effective versus no testing, with more accurate tests (e.g., computerized test) increasing the health economic benefits.

Based on these results, for decision-makers who are willing to pay £30,000 per QALY gained, there are evidence-based cases to invest in:

1. Cognitive tests, particularly computerized tests with greater accuracy than standard paper-based tools, in non-specialized settings for general older population, if no such testing is included in current practice.
2. Multidisciplinary diagnostic service, including specialist and neuroimaging (e.g., MRI, CT) inputs, for undiagnosed patients reporting dementia-related cognitive symptoms, if no such testing is included in current practice.
3. CSF test to achieve AD diagnosis for those who remain undiagnosed after undergoing standard clinical evaluation and MRI–that is, the multidisciplinary diagnostic service in (b)–if no such testing is included in current practice.
4. Decision-makers may consider supplementing standard clinical evaluation with Aβ-PET, provided that Aβ-PET capacity is already available or its investment cost is reasonable.

Decision-makers should nevertheless conduct a more thorough transferability assessment[89] to verify that the evidence informing these recommendations are suited to their local contexts.

4 | DISCUSSION

This study presents an up-to-date and comprehensive systematic review of health economic models of initial assessment and diagnostic strategies for dementia. The 32 included studies evaluated strategies that used biomarkers obtained from CSF, neuroimaging, and blood and genetic tests, as well as strategies for initial assessment and early diagnosis that did not involve the use of fluid or imaging biomarkers. The modeling methods and assumptions were highly heterogeneous. The review was nevertheless able to identify some frequent methodological limitations of models such as the non-consideration of all relevant costs and benefits of false and true diagnoses (which are poorly captured by common health economic outcomes such as QALY gain and healthcare cost) and to issue recommendations for decision-making.

These findings should identify evidence gaps (e.g., a lack of CUA evidence on cost-effectiveness of blood-based biomarkers) and improve the methodological quality of future dementia economic models of dementia assessment and diagnosis.

The contributions of the current review can be put in context. As noted, only one review by Handels et al.[41] had previously evaluated models of diagnostic strategies for AD, identifying eight models published before March 2011. Other reviews provided overviews of the existing models regardless of their clinical pathway component of interest[29,34,39,43,45] or focused on models of components other than diagnosis, including AD treatments,[36–38,40,42] non-pharmacological interventions[44,48] and primary prevention.[46,47] The current study thus meets the need for an up-to-date systematic review of models of initial assessment and diagnosis of dementia which accounts for the recent technological advances such as the use of blood-based AD biomarkers.

Most studies in the review solely focused on the AD subtype of dementia, which means that the following expert recommendations on health economic modeling of AD interventions are relevant[31]: (i) incorporating the pre-dementia stages of AD; (ii) modeling effectiveness of DMTs in terms of change in AD biomarker levels; (iii) characterizing disease progression using cognition, behavior, and function; (iv) adopting the societal perspective to cover informal caregiving cost and health burden in particular; and (v) conducting external validation. However, these recommendations were generally unmet. Only three studies[61,64,75] modeled the preclinical stage of AD when subjects have AD pathology but no symptoms, though five further studies[57,60,66,69,74] modeled MCI due to AD. No study modeled the effectiveness of DMT in terms of AD biomarker changes. Only three studies[66,82,86] tracked all three domains of cognition, behavior, and function. Although most studies (19 of 32; 59.4%) adopted the societal perspective, several[58,63,67,68,78,79,81,85,88] noted the narrow range of outcomes as a study limitation. Finally, only Weimer and Sager[87] conducted external validation. Overall, further research is warranted on operationalizing these recommendations.

The ability of health economic models to inform dementia diagnostic policies is reduced by two further factors: (1) the non-consideration of broader benefits and costs of true and false diagnoses; and (2) the non-consideration of capacity constraints in the diagnostic pathway. Concerning (1), access to an effective treatment is not the only potential benefit from accurate and timely diagnosis. Other possible benefits include decreased anxiety where the cause of cognitive symptoms is found not to be irreversible neurodegenerative disease, proactive management of cognitive symptoms to reduce burden, and planning for future care and personal adjustments to prevent crisis situations.[58] These benefits should be balanced by costs, including side-effects from diagnostic procedures (e.g., headache after lumbar puncture), harms from false diagnosis (e.g., premature adaptations) and anxiety and stigmatization that can follow both true and false diagnoses of both dementia and pre-dementia stages.[58,81,90–93] Yet there exists no consensus on how these non-medical effects can be incorporated, and only Handels et al. (2017)[58] quantified them as HRQoL decrements using expert elicitation.

Concerning (2), only Mattke et al. (2020)[74] estimated the capacity implications of a population-level screening and diagnostic strategy, with supply bottlenecks being placed on dementia specialists and Aβ-PET scan. It then demonstrated that the blood test for AD pathology ought to be combined with a cognitive test to avoid excess demand and long wait times for AD diagnosis.[74] The non-consideration of capacity constraints by models of Aβ-PET led to the recommendation by the current review that healthcare decision-makers should consider the initial investment cost of Aβ-PET. That said, two further models[66,82] attempted to capture the implementation constraints by parameterizing the time to diagnosis which the evaluated diagnostic strategies reduced. Moreover, Iragorri et al.[78] noted that the feasibility and overall impact of polygenic testing for AD risk would depend on the province-wide testing capacity despite the test being cost-saving. Overall, there is a need for further modeling work that uses capacity simulation techniques[94–98] within health economic evaluations of population-level dementia interventions.

Indeed, the ability to evaluate population-level (national or local) interventions is a key strength of decision modeling relative to health economic evaluations alongside single clinical studies.[30,51] In the case of AD dementia subtype, population-wide assessment and diagnosis have been motivated by the recent advances in blood-based biomarkers and ATTs with potential population-level coverage.[14,25,99] Accordingly, five models[74,75,81,83,88] in this review evaluated population-level *screening* programs, including two[74,75] that evaluated blood tests assumed to achieve uptake rates similar to cancer screening. Nevertheless, unlike for cancer, concerns remain over the appropriateness of population screening for dementia, the chief one being the lack of effective and cost-effective treatments to prevent or slow the disease.[100–104] Evidence from the above screening models can contribute to this debate, but their assumptions on post-diagnostic treatments reduces their credibility. Specifically, one of the two models of blood-based biomarkers evaluated a hypothetical DMT,[75] while the other was conducted absent any treatment.[74] Another screening model by Ren et al.[83] assumed that AChEI is indicated for MCI patients (as did three further studies in the review[60,66,77]), despite there being no robust evidence for AChEI effectiveness on MCI patients.[105] The final two screening models[81,88] evaluated treatments for dementia rather than pre-dementia stages. Overall, until a health economic model jointly evaluates an actual DMT that follows screening and diagnosis at pre-dementia stages (a recent model of lecanemab only included the costs of Aβ-PET scan and CSF rather than a diagnostic pathway[99]), the debate over the merits of population-wide screening would continue.

The decision-making recommendations can be compared against the clinical guidelines on dementia diagnosis, such as that of National Institute for Health and Care Excellence (NICE)[1] which is broadly representative of the international expert consensus on dementia diagnosis.[106] NICE recommends that initial assessment of dementia be carried out in non-specialist settings using brief cognitive tests such as 6CIT, and this was affirmed by the included models.[85,86] In specialist setting, if diagnosis of AD is still uncertain after clinical evaluation and structural imaging (i.e., MRI/CT), NICE recommends further

tests using CSF or FDG-PET.[1] The current review found health economic evidence to support CSF testing[59] but not FDG-PET.[71] NICE currently does not consider Aβ-PET scan at this point, and the current review evidence found that Aβ-PET scan to confirm AD diagnosis may be cost-effective,[66–68] pending further analyses of capacity investment costs. The recent conceptual pathway for the delivery of ATTs published by NHS England[107] considers the potential contributions of blood-based AD biomarkers and APOE4 genetic testing to efficiently identify patients eligible for ATTs. The current review found that there is yet no reliable health economic evidence to support the implementation of blood-based biomarkers and genetic testing. Overall, the CUA results synthesized by the current review broadly affirmed the recommendations of current clinical guidelines while also highlighting the need for further health economic research on novel diagnostic strategies. Decision-makers should prioritize the sustainable and equitable delivery of current clinical guidelines for dementia diagnosis while facilitating further research where feasible.

This review has several limitations. First, the review excluded several studies[108–111] that were not full health economic evaluations (e.g., included only intervention costs without any outcomes) but nevertheless contained modeling features that would have contributed to the synthesis of modeling methods in this topic area. Second, beyond completing the data-related items on the Philips' checklist, the review did not systematically catalogue and evaluate the data sources used by the models. As noted, lack of high-quality data was one of the most frequent limitations for the models, and a catalogue of previously used data sources (after evaluating their quality and generalizability) could aid the development of future models. Finally, the decision-making recommendations on dementia diagnostic investments were based solely on CUA evaluation results and were not based on full transferability assessment. Decision-making settings that use economic evaluation evidence differ in key factors including preferred type of analysis (e.g., CUA, CEA, CBA), perspective, cost-effectiveness threshold, and methods of QALY derivation, which subsequently affect the relevance of each evaluation result.[89,112] Therefore, the decision-making recommendations made by the current study should be interpreted in a general sense, and specific decisions should be based on individual model(s) that is most transferable to the given setting.

5 | CONCLUSION

This systematic review identified 32 studies that applied modeling for health economic evaluation of initial assessment and diagnostic strategies for dementia, including the use of fluid and imaging biomarkers as well as assessment strategies conducted in non-specialist settings. The modeling methods and quality were highly heterogeneous and several methodological limitations were identified that warrant further research. These include incorporating broader benefits and harms from diagnosis, characterizing capacity constraints in the dementia intervention pathway, characterizing preclinical stages of dementia (particularly of the AD subtype), accounting for correlated test accuracies, modeling effectiveness of ATTs in terms of underlying biomarker changes, and conducting external validation. Addressing these challenges would improve the credibility of dementia economic models for informing decisions that promote timely diagnosis and treatment of dementia. The decision-making recommendations derived from CUA evaluation results generally support the implementation of current clinical guidelines on dementia diagnosis.

AUTHOR CONTRIBUTIONS

All authors declare that they: (1) made substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data; or the creation of new software used in the work; (2) drafted the work or revised it critically for important intellectual content; (3) approved the version to be published; and (4) agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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CONFLICT OF INTEREST STATEMENT

A.Y.C.S. is an employee of F. Hoffmann-La Roche Ltd. RH received outside this study consulting fees in the past 36 months from Lilly Nederland and from the Institute for Medical Technology Assessment (paid to institution). E.R. was employed by GE Healthcare at the time of this study. R.T. was employed by Biogen at the time of this study and is currently employed by Viatris UK and owns stock in Biogen. Novartis Pharma AG, GE Healthcare, Biogen, Eli Lilly and Company Limited, and Roche are industry partners in the ROADMAP Project. All other authors declare no conflicts of interest. Author disclosures are available in the Supporting Information.

ETHICS STATEMENT

No ethical approval was required.

CONSENT FOR PUBLICATION

All the authors have reviewed the final manuscript and consented for publication.

DATA AVAILABILITY STATEMENT

All data used are made available in the manuscript and the Appendix.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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