GeroScience
https://doi.org/10.1007/s11357-025-02032-7

ORIGINAL ARTICLE

Evaluating dementia risk prediction in mild cognitive impairment: an early health technology assessment of the AI-Mind tool

Robin J. Vermeulen · Marcel G. M. Olde Rikkert · Ron Handels · Ira R. J. Hebold Haraldsen · Hanna Renvall · Paolo M. Rossini · Camillo Marra · Fernando Maestú · Maroeska M. Rovers · Tim M. Govers

Received: 15 August 2025 / Accepted: 28 November 2025

Abstract This study aimed to evaluate the potential cost-effectiveness of implementing a prediction tool for estimating mild cognitive impairment (MCI) to dementia conversion risk. A decision-analytic model was developed to compare the costs and effects of current practice for subjects with MCI to a situation in which the risk of dementia is estimated using a prediction tool. Different scenarios in terms of prediction horizons, prediction characteristics (e.g. sensitivity and specificity), and treatment availability were evaluated. The model was applied to the AI-Mind tool, which is currently under development for predicting MCI to dementia risk. In a clinical situation, with no widely applicable and highly effective disease-modifying treatment available, implementing a dementia risk prediction tool leads to lower QALYs and higher costs compared to current practice without such a prediction tool (9.32 vs 9.36 QALYs and €115,837 vs €115,032 for the analyses in this paper). This loss in QALYs was caused by the impact on quality of life associated with predicted dementia conversion risk. Risk prediction followed by efficient treatment strategies based on the predicted risk could lead to a cost-effective alternative in case of specific treatment characteristics. These findings suggest that standalone (i.e. without highly effective treatment

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s11357-025-02032-7.

R. J. Vermeulen (✉) · M. M. Rovers · T. M. Govers
Department of Medical Imaging, Radboud University Medical Centre, Geert Grooteplein 10, 6525 GA Nijmegen (route 767), PO Box 9101, 6500 Nijmegen, The Netherlands
e-mail: robin.vermeulen@radboudumc.nl

M. G. M. O. Rikkert
Radboudumc Alzheimer Centre, Department of Geriatrics, Radboud University Medical Centre, Geert Grooteplein 10, 6525 GA Nijmegen (Route 678), Nijmegen, the Netherlands

R. Handels
Faculty of Health Medicine and Life Sciences, Department of Psychiatry and Neuropsychology, Alzheimer Centre Limburg, Mental Health and Neuroscience Research Institute, Maastricht University, P.O. box 616, 6200MD Maastricht, the Netherlands

R. Handels
Division of Neurogeriatrics, Department of Neurobiology, Care Sciences and Society, Karolinska Institutet., 171 64 Solna, Sweden

I. R. J. H. Haraldsen
Department of Neurology, Division of Clinical Neuroscience, Oslo University Hospital, Oslo, Norway

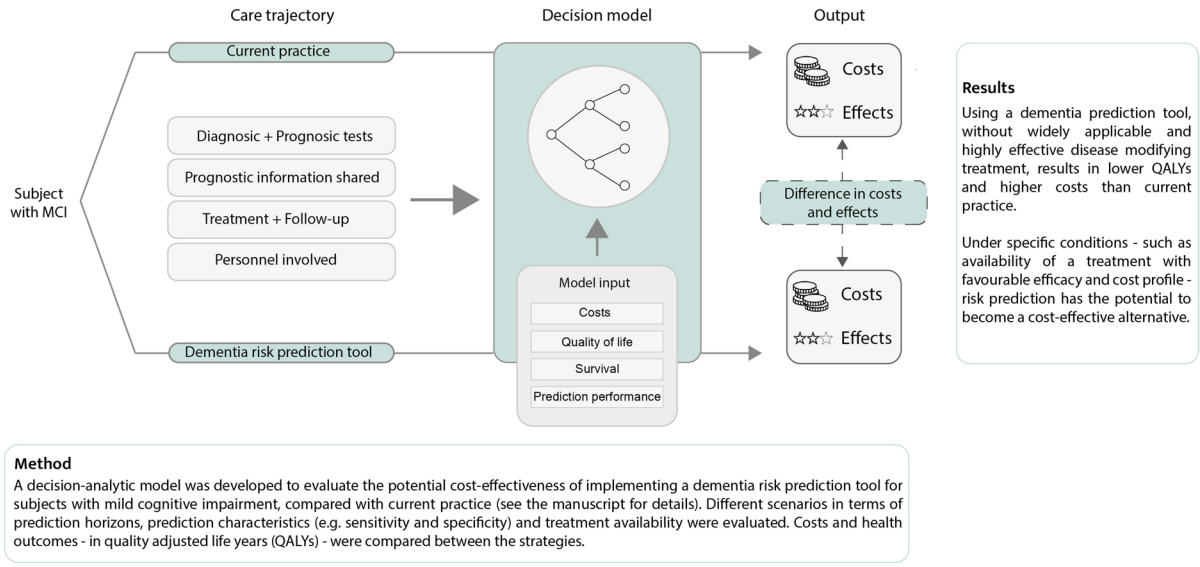
H. Renvall
Department of Neuroscience and Biomedical Engineering, Aalto University, Helsinki, Finland

H. Renvall
BioMag Laboratory, HUS Medical Imaging Centre, Helsinki University Hospital, Helsinki University and Aalto University School of Science, Helsinki, Finland

Published online: 23 February 2026

options) use of a dementia risk prediction tool may not be cost-effective, but it could result in a cost-effective alternative in combination with a treatment with favourable efficacy and cost profile.

Graphical abstract



P. M. Rossini
Department of Neuroscience and Neurorehabilitation, IRCCS San Raffaele, Rome, Italy

C. Marra
Memory Clinic, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy

C. Marra
Department of Psychology, Catholic University of Sacred Heart, Milan, Italy

F. Maestú
Centre for Cognitive and Computational Neuroscience, Universidad Complutense de Madrid, Madrid, Spain

F. Maestú
Department of Experimental Psychology, Cognitive Psychology and Speech and Language Therapy, Universidad Complutense de Madrid, Pozuelo de Alarcón, Spain

F. Maestú
Institute of Sanitary Investigation (IdISSC), San Carlos University Hospital, Madrid, Spain

Keywords Mild cognitive impairment · Dementia · Alzheimer's disease · Risk prediction · Risk assessment · Prognosis · Cost-effectiveness · AI-Mind

Introduction

The ongoing advancement of healthcare technologies in prevention, detection, treatment, and patient care has significantly improved medical outcomes. As these innovations have evolved, healthcare expenditures have increased significantly over time [1]. To ensure sustainable investment in new technologies, it is essential to evaluate their cost-effectiveness before implementation in clinical practice. Ideally, this assessment should begin in the early stages of development, allowing for the identification of promising technologies that have the potential to offer both clinical benefits and cost-effective solutions in healthcare [2, 3].

Dementia is one of the leading causes of disability among the elderly worldwide, affecting not only the individuals diagnosed but also their caregivers and society at large [4]. Annually, dementia costs the global economy over $1.3 trillion [5]. Currently, the management of dementia is based on temporarily relieving symptoms and addressing the known modifiable risk factors, as no treatment to cure the disease is available [6]. With the prevalence of dementia expected to increase drastically in the coming decades, the burden on individuals and caregivers, as well as the pressure on healthcare systems and expenditures will continue to increase [5, 7, 8].

Dementia is often preceded by mild cognitive impairment (MCI) [9]. MCI is characterized by cognitive deterioration that is considerably greater than expected for an individual's age, sex, cultural background and education, but not severe enough to substantially interfere with daily functioning [10]. Reported progression rates from MCI to dementia vary depending on care setting and population. However, up to 40% of the MCI cases will convert to dementia, mostly to Alzheimer's disease, within 5 years [11, 12].

Current practice lacks prediction tools to distinguish the MCI subjects who will progress to dementia from those that remain stable. However, research increasingly focusses on the early identification of individuals at high risk of conversion to dementia, using prediction tools [13, 14]. The AI-Mind project (www.ai-mind.eu) is an ongoing European research project that aims to develop an artificial intelligence-based prediction tool to accurately estimate the individual risk of conversion to dementia among subjects with MCI. By integrating a comprehensive set of biomarkers, including blood based measures, sociodemographic variables, digital cognitive test scores, and electroencephalography (EEG) into AI based algorithms, AI-Mind seeks to create a clinically applicable systems for early risk stratification and personalized intervention [15, 16]. Early identification of MCI subjects at high-risk of conversion could help detect cases that will most likely benefit from treatment and target the administration of present and future drugs to those subjects. Additionally, prediction of conversion risk could reduce uncertainty about the future and facilitate advanced care planning [17]. At the policy level, targeting high-risk populations offers an advantage for cost-effective drug prescription and reimbursement, although this approach is less applicable to primary or universal prevention strategies. Initiatives such as the AI-Mind project aim to enhance subject quality of life by providing more accurate prognostic information, supporting timely decision-making, personalized counselling, and better preparation for potential disease progression. However, given the current absence of widely applicable disease modifying treatment, it remains important to recognize that prognostic information may also result in increased worry for the future and stigma [17].

It is important to evaluate the potential cost-effectiveness of dementia risk prediction tools, such as the AI-Mind tool, compared to current clinical practice. This evaluation should start already in the early development phases. Early Health Technology Assessment (HTA) employs methodologies designed to provide industry and stakeholders with insights into the potential value of medical products during their developmental phases [3]. This approach supports decision-making by offering early evaluations of a product's future impact. One of the frequently used methods in early HTA is health economic modelling, which can be used to estimate the expected cost-effectiveness of emerging innovations. By simulating different scenarios, this modelling approach delivers critical information that can guide further product development and improve its alignment with clinical and economic goals [18].

The aim of this study was to perform an early cost-effectiveness analysis comparing the current practice for people with MCI to a scenario where a dementia risk prediction tool (like the AI-Mind-tool) is implemented.

Methods

Decision analytic model

We developed a decision-analytic model to evaluate the potential cost-effectiveness of implementing a tool for predicting the risk of conversion from MCI to dementia, compared to the standard of care for people with MCI. This model consisted of a decision tree representing the potential options regarding predictive information that is shared with a subject in both strategies (i.e. current practice and risk prediction involving a prediction tool) and a Markov model simulating

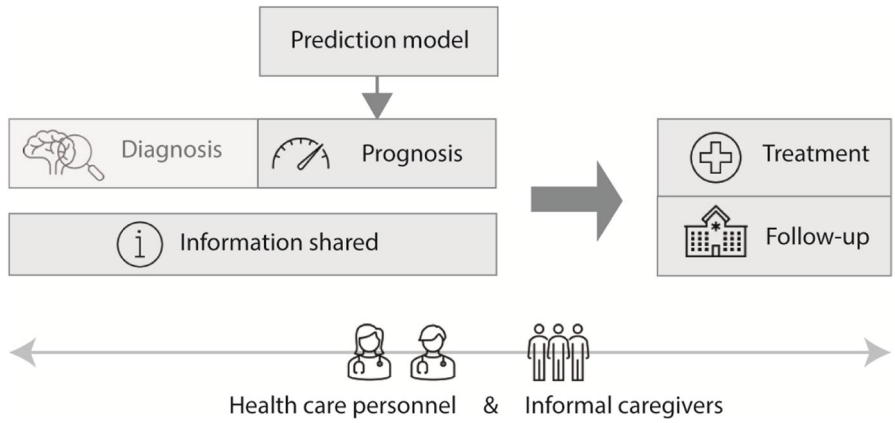


Fig. 1 Components of the subject trajectory that are included in the model

the consequences on long-term disease progression. Strategies were compared in terms of survival, health related quality of life (QoL), and healthcare costs. The study is reported according to the Consolidated Health Economic Evaluation Reporting Standards 2022 (CHEERS 2022) Statement [19], and the model was validated in accordance with the AdViSHE checklist [20].

Model development

The decision-analytic model was developed based on existing literature, guidelines, and consultations with experts in the field. Figure 1 illustrates the components of the subject trajectory, from risk prediction to the end of follow-up, which were included in the model: diagnostic testing, prognostic testing, risk prediction based on test information, information shared with the subject, follow-up, treatment, and the involvement of healthcare personnel and informal caregivers throughout the entire process. Although diagnostic tests are performed with a different aim than prognostic tests, they are closely interconnected in practice, where prognosis often builds upon diagnostic findings. The (costs of) diagnostic tests performed to confirm MCI were therefore also included in the decision model. A survey among European medical specialists [21], an internal questionnaire within the AI-Mind study consortium, and expert consultations revealed that the current practice for managing MCI varies widely between countries and even between different healthcare settings within the same country (e.g. the number and type of diagnostic/prognostic tests that are performed and subject counselling). Additionally, the tests performed often depend not only on the setting but also on characteristics of the subject and their social environment. To be able to account for these variations, we developed an interactive online dashboard (Supplementary Fig. 1), which is available via https://ai-mind.shinyapps.io/earlyHTA/. This interactive online dashboard enables users to adjust specific model characteristics (tests performed, conversion risk information shared, personnel involved, treatment, follow-up, involvement informal caregivers) and input values (probabilities, costs, quality of life), allowing for flexible application across different settings. This adaptability ensures that the analysis can be tailored to various scenarios, making it a useful tool for evaluating and optimizing prediction in various medical contexts.

The different input options are specified in more detail below. Since this was an early health economic evaluation, specifications (e.g. sensitivity/specificity of the risk prediction) and costs of the prediction tool were not known yet. Input estimates for these parameters were therefore varied in the model to study the minimal required predictive performance or maximum costs for the prediction tool to become a cost-effective alternative. Unlike typical cost-effectiveness evaluations where the costs and treatment options of current practice are well-established, evaluating the cost-effectiveness of dementia prediction tools is more complex due to the rapidly evolving treatment landscape. Until recently, no highly effective disease-modifying treatment for (AD type) dementia was available in Europe. However, lecanemab has now been approved by the EMA under strict conditions for subjects with MCI or mild AD dementia with

confirmed amyloid pathology [22–25]. Donanemab has also been approved by the FDA and is currently still under review by the EMA [24, 26]. Although lecanemab has received a positive recommendation, its availability will likely vary across European countries, depending on national health authorities' decisions and reimbursement policies. The same is expected to apply to donanemab, should it receive EMA approval. This regulatory uncertainty and the varying target populations (e.g. definition of high risk for adverse events) add complexity to evaluating the potential cost-effectiveness dementia risk prediction tools. To address this, we incorporated multiple scenarios in the decision model—such as starting treatment based on the predicted risk of conversion—to explore the potential consequences of using a risk prediction tool. This approach helped identify the conditions under which implementing a risk prediction tool is most likely to become a cost-effective alternative.

Target population

The target population of the model consisted of subjects with confirmed MCI. Since the diagnostic process for confirming MCI varies across centres and is based on specific tests and criteria, users can specify the tests performed to diagnose MCI in the interactive online dashboard (see below). In this paper, we considered a target population of MCI subjects that have been confirmed as having MCI by neuropsychological testing, supported by laboratory assessment

Table 1 Input options patient trajectory

	Tests performed	Healthcare personnel involved	Time involvement per person
Diagnosis and prognosis	Short cognitive screening Neuropsychological testing Lab assessment (blood)* Fluid biomarkers (blood)† Fluid biomarkers (CSF)† Genetic testing (APOE4) MRI CT EEG SPECT PET Other	Geriatrician Neurologist (Neuro)psychologist (Neuro)psychiatrist Radiologist Nurse General practitioner Other	Time in minutes
Information	**Prognostic information shared**	**In case of individual information**	
	General Individual	2 prediction categories 3 prediction categories	
Follow-up	**General follow-up frequency**	**Dependent on prediction outcome?**	**If yes: follow-up frequency per risk group**
	Number of visits	Yes No	Number of visits
Treatment	**Disease modifying treatment**	**Dependent on prediction outcome?**	**If yes: which groups receive treatment?**
	Medication Lifestyle intervention Combination None	Yes No	Low risk High risk Intermediate risk
Informal caregivers	**Include informal caregiver costs and effects**		
	Yes No		

*Includes: CRP, Hb, TSH, creatinine, glucose

†Includes: ABeta40, ABeta42, Total Tau, Ptau 181

and magnetic resonance imaging (MRI) to identify or exclude underlying causes. These tests were reported to be used most often as standardized diagnostic workup to determine MCI by European clinicians [21], which was confirmed during conversations with experts in the field.

Input options subject trajectory

All different input options regarding the subject trajectory are specified in Table 1. People entering the decision model were confirmed MCI cases based on diagnostic tests. Although diagnostic tests are performed with a different aim than prognostic test, diagnostic and prognostic testing are interconnected processes as prognostic testing often builds upon diagnostic findings. The diagnostic tests performed to confirm MCI and their associated test costs are therefore also included in the decision model. All inputs of the subject trajectory are associated with specific costs and/or effects. Supplementary Table 1 shows all the input values as used in the analyses in this study. For follow-up, only the number of visits could be specified. Follow-up was assumed to consist of outpatient visits, without extensive imaging or laboratory assessments. Costs per year per disease state were based on a meta-analysis specifying the costs per dementia state and include potential medication use (e.g. acetylcholinesterase inhibitors) or other treatments that are prescribed in current practice [27]. In current practice, lifestyle advice—such as recommendations on physical activity, nutrition, and caregiver support—is often provided. However, this guidance differs from active intervention and is generally broad and given irrespective of an individual's estimated progression risk. The treatment option in our model applied to a situation in which efficient disease modifying treatment with an estimated efficacy would be available (either medication, specific lifestyle intervention program, or both). This offers the possibility to study the potential cost-effectiveness of a dementia risk prediction tool if a treatment could be started

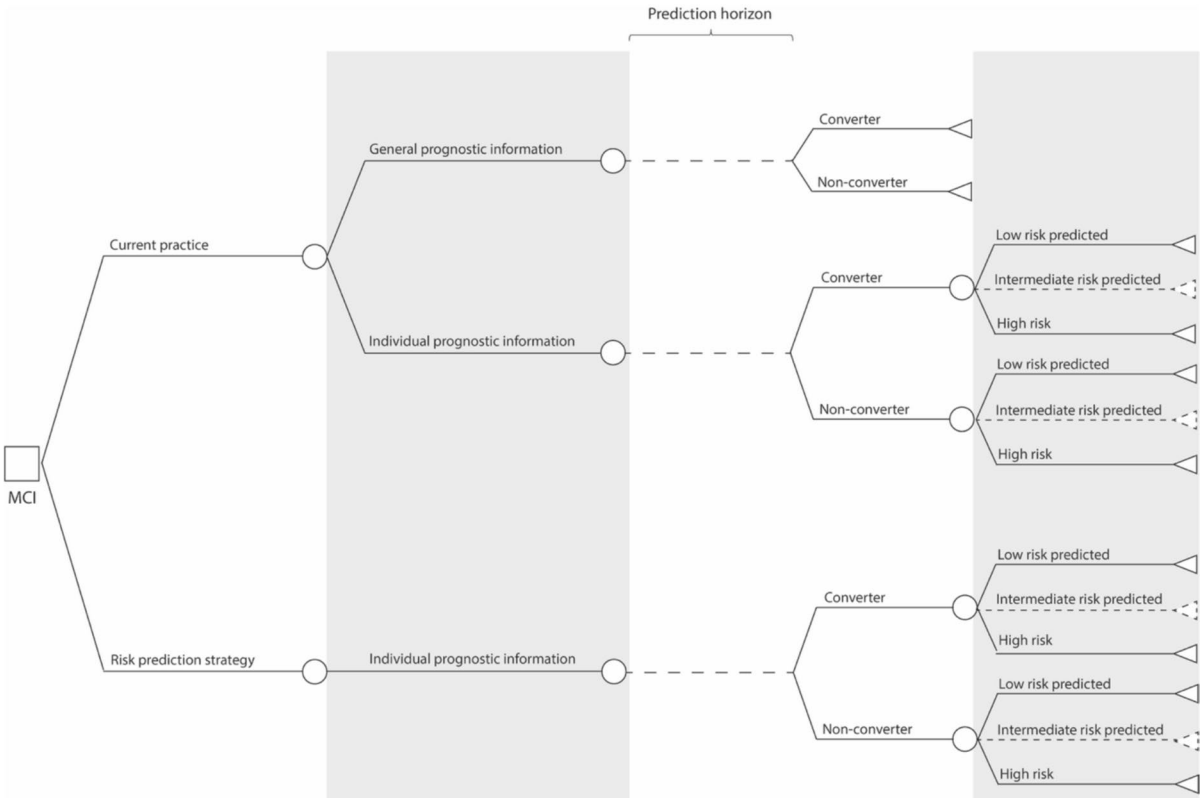


Fig. 2 Decision tree representing short-term clinical pathway of both strategies

based on the predicted outcome. Dementia leads to high caregiver burden, resulting in substantial informal care costs and reduced caregiver QoL [27, 28]. Including caregiver costs and utilities in the valuation can add value, particularly in health care settings that rely heavily on informal caregiving. Accordingly, the model can account for the costs and QoL of informal caregivers per health state to perform the evaluation from a societal perspective.

Decision tree

The decision tree (Fig. 2) represented the two strategies (i.e. current practice and risk prediction involving a prediction tool) and how a risk was communicated with a person with MCI in both strategies (i.e. either general or individualized predictive information). General predictive information consists of the general explanation that approximately half of the people with MCI will convert to dementia within 5 years. In contrast, an individualized risk prediction consists of a risk to convert to dementia based on individual test results. This individualized risk prediction was operationalized as either two categories (low or high risk) or three categories (low, intermediate, or high risk). In the risk prediction strategy, the individualized risk prediction was based on the results of a risk prediction tool—in this study, the AI-Mind tool. In current practice, an individualized risk prediction could be provided based on local guidelines. The prediction horizon, i.e. the time between the risk prediction until the end of follow-up in which conversion from MCI to dementia is predicted and can be clinically observed during follow-up visits, can be 2, 3, or 5 years.

Markov model

A Markov model, with a lifetime horizon, simulated the consequences of the predictive information on the long-term (Fig. 3). Subjects entered one of the MCI health states based on the received prognostic information and the actual disease state at the end of the prediction horizon, as confirmed during clinical follow-up visits (stable MCI or conversion to dementia). From the specific MCI state, subjects could progress to mild dementia and subsequently transition between different dementia states (mild, moderate, or severe). From all health states, subjects could progress to death. After each cycle of 1 year, subjects could move between the disease-severity specific health states in the model. For each year subjects spend in a specific health state, corresponding outcomes in terms of QoL and costs were assigned.

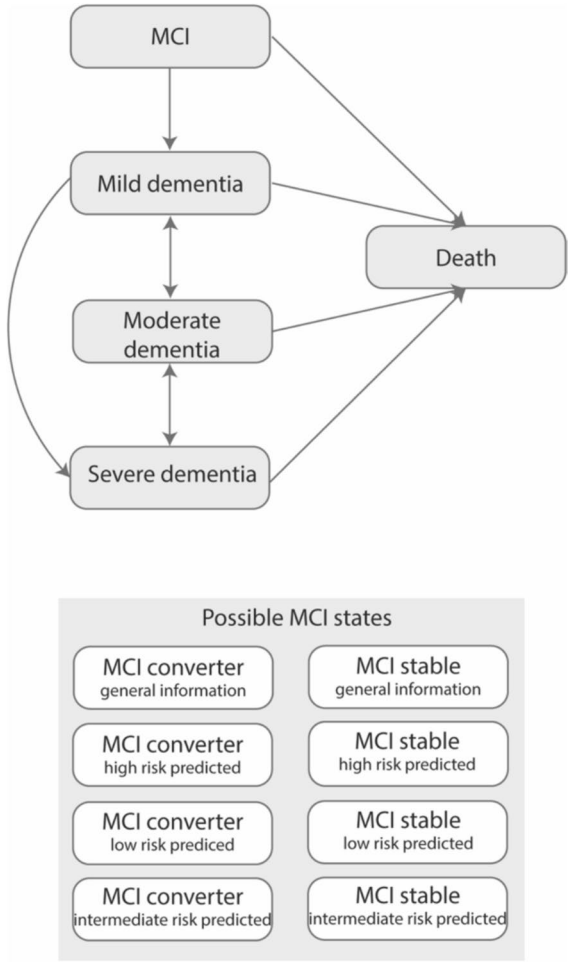


Fig. 3 Markov model simulating long-term follow-up

Input values

Supplementary Table 1 shows the input values of the model as used in this study. Input values can be changed in the interactive online dashboard to make the outcomes of the model applicable to other situations.

Probabilities

Sensitivity and specificity of the risk prediction tool for individual dementia risk prediction were varied in the model, as well as the proportion that gets an intermediate predicted risk in case of three prediction categories (low, intermediate, or high risk). The 5-year conversion rate from MCI to dementia was assumed to be 38.2% based on a meta-analysis including 41 cohort studies [11]. We assumed a linear trend in the conversion rate, resulting in an annual conversion rate of 7.64% from MCI to dementia in the first 5 years. After five cycles, the conversion rate from MCI to dementia was assumed to be 2.3%, based on a study in people with subjective cognitive decline [29]. The probability to progress between the dementia states was based on a study that used the SveDem registry to estimate the natural progression in dementia [30]. Age-related background mortality was based on Dutch statistics on age-related death among the general population (Supplementary Table 2) [31]. The hazard rate (HR) for mortality in the different health states was also based on the SveDem registry [30] and a study by Andersen et al. [32]. In the online interactive dashboard, the prediction horizon of the risk prediction tool can be selected to be 2, 3, or 5 years. The effect of a disease modifying treatment can be specified as a HR on progression from MCI to mild dementia and is applied for 5 years. It is likely that not every person will be eligible for treatment once treatment becomes available. It is therefore possible to specify the proportion of people that is eligible to receive treatment. No standardized guidelines exist for follow-up frequency: in this study, we assumed a general follow-up frequency of one visit per year. The proportion of people living in a nursing home facility per disease state was derived from a study using the National Alzheimer's Coordinating Center Uniform Data Set [33].

Costs

Costs (in Euros) were calculated from the Dutch health care perspective and were adjusted to the price index of 2023. Cost prices for health care personnel and tests were based on the Dutch costing guidelines [34, 35], and if not specified in the costing guidelines, based on hospital specific cost data (Radboud University Medical Centre) or based on data of The Alzheimer's Organization [36]. Medical care costs per health state were based on a meta-analysis by Jönsson et al. [27] in which direct medical, direct non-medical, and informal care costs per dementia severity state were studied for different regions in Europe. Medical care costs included inpatient care, outpatient care and pharmaceuticals, and non-medical care costs included residential care (e.g., nursing home) and community care (e.g., home help or delivered meals) [27]. Informal care costs included both costs related to caregiver productivity loss and costs related to caregiver time [27]. Costs per health state were weighted for the proportion in community or residential care setting per dementia severity state [33]. The ratio of costs for MCI compared to costs for mild dementia was based on the ratio's per cost category found by Robinson et al. [37]. Costs for a (hypothetical) treatment were not known and were therefore varied in the model. Similarly, cost for the prediction tool were varied. Costs were discounted with an annual rate of 3% [35].

Utility values

Effectiveness was measured in quality adjusted life years (QALYs), a measure combining both survival and health state utility. The latter is expressed on a scale where 0 corresponds to death and 1 to perfect health [38]. The impact on health state utility resulting from receiving a dementia risk prediction, both with and without the availability of treatment, was derived from a discrete choice experiment specifically designed to obtain input values for this study [39]. This experiment was developed to capture how risk prediction outcomes influence patient preferences and to quantify the impact on perceived quality of life. (Dis)utility values related to the predicted risk (-0.18 for high predicted risk, -0.05 for intermediate predicted risk, $+0.06$ for low predicted risk) and the availability or absence of intervention options ($+0.13$ for lifestyle intervention, $+0.05$ for medication intervention) were added to the average utility in MCI. We applied these (dis)utilities only during the prediction horizon for which the conversion risk was estimated. For the subsequent cycles, we assumed that the predicted risk did no longer have an impact on QoL anymore. We extracted caregiver rated utility values, corresponding to the different dementia health states in the model, from a meta-analysis by Landeiro et al.

[40]. Health state utility of caregivers for people with mild to severe dementia were based on a study by Reed et al. [28]. The health state utility of those caring for people with MCI was assumed to be the same as for those caring for someone with mild dementia. Treatment might result in side effects that lead to a decrease in health state utility [23, 26], which can be specified in the online tool. Effects were discounted with an annual rate of 3% [35].

AI-Mind

The analyses in this paper were based on the AI-Mind tool, which is currently being developed. AI-Mind is an ongoing EU Horizon 2020 funded project (www.ai-mind.eu) that aims to develop an artificial intelligence (AI)-based prediction tool to accurately estimate the risk of conversion to dementia among people with MCI [15, 16]. The AI-Mind study suggests that currently, a window of opportunity for early intervention to reverse or delay onset of dementia for those at high-risk of conversion is missed and that individuals who are not at risk of conversion to dementia may experience unnecessary anxiety about their future and undergo avoidable clinical procedures. The project aims to develop a risk prediction tool for MCI to dementia conversion by combining a comprehensive set of biomarkers, including blood samples, sociodemographic information, digital cognitive test scores, and electroencephalography (EEG) into AI-based algorithms. With this prediction tool, the project aims to offer a window of opportunity for improved guidance of those identified as high-risk MCI subjects. AI-Mind aims to predict the dementia conversion risk with a high sensitivity and specificity of 95%.

Analyses

Costs and effects of both strategies were compared, and an incremental cost-effectiveness ratio (ICER) was calculated when applicable. The Willingness to Pay (WPT) threshold was set at €20,000 per QALY, based on the estimated burden of disease (Supplementary material 3). Analyses were performed from a healthcare perspective. The interactive online dashboard offers the possibility to perform the analysis from a societal perspective by including caregiver costs and health state utility values.

Base case analysis

In the analyses conducted in this paper, we took one scenario for both current practice and the risk prediction strategy as an example. For the current practice strategy, we assumed that MCI cases had been confirmed by a diagnostic workup consisting of neuropsychological testing, laboratory assessment, and MRI, as these diagnostic tests were shown to be most often performed by a survey among European clinicians [21], which was confirmed during conversations with experts in the field. The risk of dementia was communicated in general terms. Based on expert consultations, we assumed that a geriatrician and neuropsychologist are involved (besides the healthcare personnel involved during MRI and laboratory testing) for 90 and 150 min, respectively. Follow-up frequency in general practice was assumed to be 1 visit per year.

In the risk prediction strategy, the tests performed correspond to the tests used in the AI-Mind tool: neuropsychological testing, laboratory assessment, fluid biomarkers derived from blood, EEG, and APOE4. We assumed that a geriatrician and neuropsychologist are involved for the same duration in time as in the current practice strategy. A prediction in two risk categories was taken as an example for the base case analysis. In alignment with AI-Mind's objectives, the prediction sensitivity and specificity were assumed to reach 95%. The prediction horizon in the base case analysis was 5 years, as this aligns with the observed progression interval of MCI, and it corresponds to the general belief that the initiation of (future) treatment early in the disease trajectory offers the most the significant benefit [41, 42]. Follow-up frequency in the risk prediction strategy was assumed to be one visit per year for people predicted to be at low risk of conversion and two visits per year for people predicted to be at high risk for conversion. In the base case analysis, no costs were calculated for the AI-Mind tool to support a threshold analysis. Table 2 specifies the assumptions made for both strategies. The age of onset of MCI was assumed to be 70 in the base case analysis.

Headroom, scenario, and threshold analyses

Although the difference with the base case analysis is small, we conducted a headroom analysis to evaluate

Table 2 Base case assumptions current practice and risk prediction strategy

Current Practice	Risk prediction
Diagnostic and prognostic tests	
Neuropsychological testingLab assessment (blood)MRI	Neuropsychological testingLab assessment (blood)Fluid biomarkers (blood)EEGAPOE4
Healthcare personnel + time involvement	
Geriatrician: 90 minutesNeuropsychologist: 150 minutes	Geriatrician: 90 minutesNeuropsychologist: 150 minutes
Information shared	
General prognostic information	Individual prognostic information· Costs prediction model = 0 euro2 prediction categories· 95% sensitivity and specificity
Prediction horizon	
n.a.	5 year
Follow-up	
1x per year	Low risk: 1x per yearHigh risk: 2x per year

the maximum potential value of the AI-Mind tool assuming 100% predictive performance.

We conducted several scenario analyses:

1) In the first scenario analysis, the prediction horizon was changed to 2 years. We evaluated the impact of a shorter prediction horizon on potential cost-effectiveness since systematic reviews showed that the follow-up period in prediction model development and/or validation studies is often 2 or 3 years [43]. Clinical follow-up in the AI-Mind study is 2 years as well. We first assumed the 95% sensitivity and specificity in this analysis. Additionally, we evaluated the impact of reaching a lower prediction sensitivity and specificity of 80% over a prediction horizon of 2 years. Based on the systematic review on MCI to dementia prediction models, we considered that a 95% prediction sensitivity and specificity might be challenging to reach and that 80% might be more feasible [43].
2) In the second scenario analysis, we assessed the impact of treatment based on the predicted conversion risk as estimated by the AI-Mind tool.

    a. Treatment scenario a: This scenario was based on the recent EMA approval of lecanemab for MCI subjects and very mild stage AD patients with confirmed amyloid beta plaques and one or no copy of the ApoE4 allele. Based on strict criteria, approximately 8% of the MCI subjects will probably be eligible for treatment with lecanemab [44]. We assumed an HR of 0.7 for disease progression following treatment, as was observed over 18 months in clinical trials [23, 26]. We extrapolated this effect to the 5-year progression rate in this study. The annual treatment cost was set at €24,300 per subject per year [45], reflecting the anticipated market price for lecanemab. Side effects of treatment are assumed to cause a disutility of 0.14 for 12 weeks in 9.9% of the subjects [46]. In the current practice strategy (with no risk prediction), all ApoE4 negative or one single-allele MCI/AD subjects who also fulfil the other in- and exclusion criteria were assumed to receive lecanemab (8% of all MCI subjects). In the risk prediction strategy (both 95% and 80% sensitivity and specificity were evaluated), only subjects identified as high risk by the AI-Mind tool, and fulfilling the biomarker criteria, were assumed to receive treatment. We assume that all individuals (8% of the population) who fulfil the biomarker criteria are included in the high-risk group as identified by the prediction model. The high-risk group may also include additional individuals who are not eligible for treatment. The impact of this treatment scenario was evaluated across different prediction horizons and prediction tool performances.

    b. Treatment scenario b: This scenario was structured similarly to treatment scenario a but differs in two aspects: it assumes univer-

sal eligibility regardless of biomarker status. In the current practice strategy, therefore, all MCI subjects were assumed to receive treatment. In the risk prediction strategy, treatment was limited to those identified as high-risk by the AI-Mind prediction tool. Additionally, this scenario assumes lower treatment costs of €5,100 per subject per year [41], which was identified in a previous cost-effectiveness analysis as the maximum price at which lecanemab could be considered a cost-effective targeted treatment.

3) In the third scenario analysis, as current practice differs considerably between centres, we explored the potential cost-effectiveness of the AI-Mind tool compared to a current practice situation in which a more extensive test battery is performed, including neuropsychological testing, laboratory assessment, MRI, liquor (CSF), and PET. The sensitivity and specificity of the AI-Mind tool were assumed to be 95% in this analysis as well.

When applicable, a threshold analysis was performed to determine the maximum cost at which the AI-Mind tool would be considered a cost-effective alternative.

Sensitivity analysis

We performed a one-way deterministic sensitivity analysis to evaluate the impact of single input value uncertainties on the model outcomes. We varied input values for conversion rate from MCI to mild dementia, sensitivity and specificity of the prediction tool, and (dis) utility values associated with low and high predicted conversion risk over a range of 25%. Other inputs were comparable between the two strategies in the base case analysis, as no consequences other than the impact on quality of life and follow-up frequency based on the risk prediction were applied in this analysis.

Results

Base case analysis

In the base case analysis, assuming a 95% prediction sensitivity and specificity and a 5-year prediction horizon without treatment, current practice remains

Table 3 Model outcomes

	QALYs	Costs (€)	ICER (€/QALY)
Base case analysis			
CP	9.36	115032	Dominant
RP	9.32	115928	-
Headroom analysis			
CP	9.36	115032	Dominant
RP	9.34	115917	-
Scenario analyses			
1) Prediction horizon 2-year			
Sensitivity and specificity 95%			
CP	9.36	115032	-
RP	9.40	115837	20,133
Sensitivity and specificity 80%			
CP	9.36	115032	Dominant
RP	9.35	115900	-
*2a) Treatment scenario 1**			
Prediction horizon 5-year (sensitivity and specificity 95%)			
CP	9.42	122714	Dominant
RP	9.39	127513	-
Prediction horizon 5-year (sensitivity and specificity 80%)			
CP	9.42	122714	Dominant
RP	9.32	130150	-
Prediction horizon 2-year (sensitivity and specificity 95%)			
CP	9.42	122714	-
RP	9.41	119800	291,400
Prediction horizon 2-year (sensitivity and specificity 80%)			
CP	9.42	122714	Dominant
RP	9.36	124964	-
*2b) Treatment scenario 2***			
Prediction horizon 5-year (sensitivity and specificity 95%)			
CP	9.41	135338	-
RP	9.43	121967	Dominant
Prediction horizon 5-year (sensitivity and specificity 80%)			
CP	9.41	135338	-
RP	9.36	123372	239,308
Prediction horizon 2-year (sensitivity and specificity 95%)			
CP	9.41	135338	-
RP	9.42	117903	Dominant
Prediction horizon 2-year (sensitivity and specificity 80%)			
CP	9.41	135338	-
RP	9.38	120644	489,772
*3) Current practice: extensive test battery****			
Prediction horizon 5-year			
CP	9.36	116284	-
RP	9.32	115928	8892
Prediction horizon 2-year			
CP	9.36	116284	-

Table 3 (continued)

	QALYs	Costs (€)	ICER (€/QALY)
RP	9.40	115837	Dominant

CP = current practice strategy; RP = risk prediction strategy

* Medication, HR=0.7, current practice: 8% receives treatment, risk prediction: 8% receives treatment (all high predicted risk), proportion eligible = 8%, price = €24,300/year, side effects = −0.14 (for 12 weeks, in 9.9%)

**Medication, HR=0.7, current practice: all receive treatment, risk prediction: risk groups that receive treatment = high predicted risk, proportion eligible = 100%, price = €5100/year, side effects = −0.14 (for 12 weeks, in 9.9%)

*** Tests current practice: neuropsychological testing, lab assessment, MRI, CSF, PET

the dominant strategy as it results in both lower costs and higher QALYs compared to the AI-Mind strategy at the end of the total model duration (Table 3).

Headroom analysis

The headroom analysis shows that, under the assumption of perfect prediction performance (100% sensitivity and specificity) and a 5-year prediction horizon without treatment, current practice remains the dominant strategy, as it results in both lower costs and higher QALYs at the end of the total model duration (Table 3).

Scenario analyses

1) In the first scenario analysis, evaluating the impact of a shorter prediction horizon of 2 years with a 95% prediction sensitivity and specificity, implementing the AI-Mind tool results in higher QALYs compared to current practice (9.40 vs 9.36). In this scenario, the ICER of 20,133 €/QALY slightly exceeds the WTP threshold of 20,000 €/QALY. In a scenario with a prediction horizon of 2 years and 80% prediction of sensitivity and specificity, current practice appears to be the dominant strategy as this results in higher QALYs (9.36 vs 9.35) and lower costs (€115,032 vs €115,900) compared to implementing the AI-Mind tool.
2) The second scenario analyses, assessing the potential cost-effectiveness of the AI-Mind tool in combination with targeted treatment for people at high risk for conversion, show that
   a. When a small proportion of the MCI subjects would be eligible for treatment (8%), based on the strict eligibility criteria for lecanemab, current practice appeared to be the most cost-effective alternative in all analyses. Regardless of whether the prediction tool results in 95% or 80% prediction sensitivity and specificity, and whether a 5-year or 2-year prediction horizon is applied, current practice yields higher QALYs.
   b. When subjects would be eligible for treatment regardless of biomarker status and at reduced treatment costs, the AI-Mind strategy would be considered the dominant strategy both with a 5-year and 2-year prediction horizon and 95% sensitivity and specificity, as it results in higher QALYs and lower costs compared to current practice. However, treatment regardless of biomarker status with a reduced prediction sensitivity and specificity of 80%, the AI-Mind strategy does not result in a cost-effective alternative compared to current practice.
3) In the third scenario analysis, evaluating the potential cost-effectiveness of the AI-Mind tool compared to a current practice setting involving more extensive diagnostic testing, AI-Mind appears to be considered the dominant strategy in case of a 2-year prediction horizon given 95% sensitivity and specificity. A threshold analysis to assess the maximum costs for AI-Mind per subject to remain the dominant or cost-effective strategy shows that the maximum costs for AI-Mind per subject could be €447 to remain the dominant strategy and €1246 to remain considered the cost-effective alternative. As 80% prediction sensitivity and specificity does result in lower QALYs for the AI-Mind strategy compared to current practice, no threshold analysis for this scenario was performed.

Sensitivity analysis

Figure 4 shows the results of the deterministic sensitivity analysis. Changes in conversion rate from

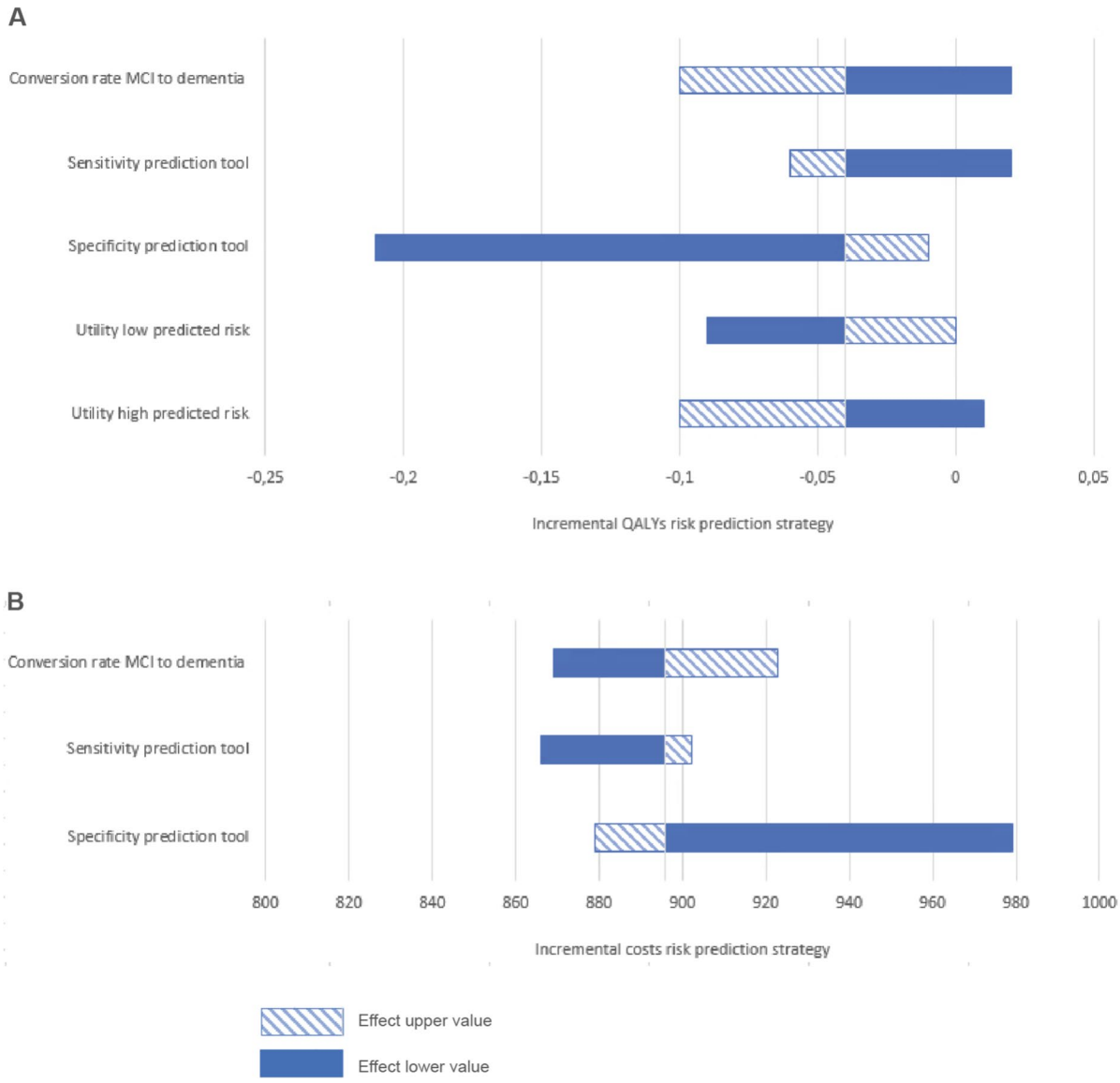


Fig. 4 Tornado plot for deterministic sensitivity analysis. **A** Effects; **B** Costs. This tornado plot illustrates the impact of variations in parameter values on the observed difference in costs and effects between both strategies (current practice value—risk prediction strategy value)

MCI to dementia, sensitivity, and specificity of the prediction tool, and (dis)utility values associated with low and high predicted risk all appear to have a considerable impact on incremental QALYs of the risk prediction strategy compared to current practice. Conversion rate from MCI to dementia and sensitivity and specificity of the prediction tool also have some impact, albeit mostly limited, on incremental costs.

Discussion

The aim of this study was to evaluate the potential cost-effectiveness of implementing a prediction tool for MCI to dementia conversion compared to current clinical practice. We developed a decision model, which we applied to the AI-Mind tool—a tool under development for predicting MCI to dementia conversion based on a comprehensive set of biomarkers—to

demonstrate the potential cost-effectiveness of this specific tool. An interactive online dashboard was developed to enable flexible application of the model across different healthcare settings and prediction tools.

The base case analysis in this study shows that, with a 5-year prediction horizon and 95% sensitivity and specificity of the AI-Mind tool, current practice is the dominant strategy, as current practice results both in lower costs and higher QALYs (€115,032 vs €115,928; 9.36 vs 9.32). The lower QALYs are explained by the negative impact of receiving a high-risk prediction which outweighed the positive impact of receiving a low-risk prediction. Although with a shorter prediction horizon of 2 years, the QALYs for the risk prediction strategy increase to 9.40, with an ICER of 20,133 €/QALY, current practice remains the cost-effective alternative in this scenario. Under specific conditions, however, implementing the AI-Mind tool could become a cost-effective alternative compared to current practice. When introducing a targeted treatment strategy in addition to the risk prediction, the results show that such a prediction tool could result in a cost-effective alternative depending on the treatment characteristics and the prediction sensitivity and specificity reached. Moreover, when comparing the implementation of the risk prediction tool to a situation in which extensive diagnostic testing is performed, it could become a cost-effective alternative.

The results show a difference in total QALYs for the AI-Mind strategy when considering a 2-year or 5-year prediction horizon. This difference can be explained by a difference in impact of the prognostic information. Fewer people suffer from the negative impact of a high predicted risk when a prediction tool estimates conversion risk in a 2-year prediction horizon with 95% sensitivity and specificity. This is because only a small proportion of the cases will be classified as high risk: those who progress within 2 years and are correctly identified (true positives), along with a few false positives (i.e. high predicted risk but stable at 2 years after baseline). This small proportion will experience the negative effect on health state utility (−0.18) during the 2 years following the prediction, whereas the remainder will experience the positive effect on health state utility (+0.06) as the result of a low predicted risk. However, in subsequent years, some cases that were correctly identified as stable at 2 years will progress to dementia. These (high-risk) converter cases will be 'missed' by the initial prediction and will not benefit from counselling and treatment if this becomes available in the future. A 5-year prediction horizon might be more clinically relevant, as it allows for the detection of more cases that could benefit from, e.g. advanced care planning and treatment strategies based on their predicted risk, and as this contributes to treatment initiation earlier in the disease process. However, in this scenario, more people are affected by the negative impact on health state utility (−0.18). The disutility associated with individuals receiving a high predicted risk outweighs the utility gained (+0.06) for those predicted to be at low risk, especially in a scenario where no treatment could be provided or where only a small proportion of the subjects is eligible for treatment. The deterministic sensitivity analysis shows that, in a situation without treatment, a higher prediction specificity leads to a decrease in QALYs, which might seem counterintuitive. However, this can be explained by the larger disutility of receiving a high predicted risk than the increased utility after a low predicted conversion risk.

The observed QALY differences between the modelled strategies are small. The observed QALY differences may partly fall within the expected model noise and, on average, might not be clinically meaningful at the individual level. However, given the current absence of widely applicable and effective disease-modifying treatments, it is important to interpret these results cautiously, as part of the population may experience disutility from prognostic information without experiencing subsequent clinical benefits.

The results show that when disease modifying treatment could be provided regardless of biomarker status, the AI-Mind strategy could result in a cost-effective alternative. This applies for both a 2- and 5-year prediction horizon, if 95% sensitivity and specificity would be reached. However, if only a small proportion of subjects are eligible for treatment, the added value of a risk prediction tool diminishes, and the risk prediction strategy no longer results in a cost-effective alternative compared to current practice. If a reduced prediction sensitivity and specificity of 80% would be reached, treatment initiation based on predicted risk would not lead to a cost-effective alternative with both a 2- and 5-year prediction horizon. This could be explained by a lower number of true positives identified that would benefit from treatment

and a higher number of false positives that receive treatment while they will not benefit from it.

In the scenarios, we based the treatment effect on observations made in of lecanemab and donanemab [23, 26], which also corresponds to assumptions made in other cost-effectiveness models [47]. Although it introduces potential over- or underestimation of the treatment effect, we extrapolated the observed treatment effect beyond the available 18-month follow-up evidence from clinical studies to a 5-year horizon. Due to the limited empirical evidence on sustained treatment effect, persistence of the treatment effect over time was assumed. Since, in this scenario analysis, only people at high risk are treated in the risk prediction strategy, the side effects of treatment remain limited to those most likely benefitting from treatment in the risk prediction strategy. As all cases in the current practice strategy received treatment, this also results in side effects and additional costs for those who will not benefit from treatment. Since lecanemab and donanemab are only considered eligible for individuals who are amyloid positive and have one or no copy of the ApoE4 allele, in practice, a limited number of people would benefit from these treatments, potentially influencing the effect of initiating treatment based on the risk prediction. It is likely that when a risk prediction tool for MCI to dementia prediction is introduced in practice, this should be applied in combination with a test suggesting pathological amyloid load to select those high-risk cases that will benefit from treatment.

Our study adds to previously performed studies in this field. For example, a cost-effectiveness analysis evaluating the potential of adding CSF testing to the diagnostic work-up in people with MCI showed a potential for CSF biomarkers to determine disease prognosis to be cost-effective. This result was, however, marked by a high degree of uncertainty, as the impact of the prediction on quality of life was based on expert opinion rather than based on empirical research. Authors concluded the need for such empirical evidence on the impact of a prognosis on quality of life [48]. Our model included health state (dis) utility values corresponding to predicted conversion risk, which have been extracted from a study specifically designed to obtain this information, and showed a considerable impact of these (dis)utility values on model outcomes. In line with our study, Michaud et al. show that guiding treatment decisions based on predicted risk of progression from MCI to dementia could potentially result in a cost-effective strategy, albeit dependent on the level of treatment effectiveness [49]. We show that, in addition to treatment effectiveness, the proportion of cases that is correctly identified as eligible for treatment is also an important factor. Nguyen et al. performed a modelling study to quantify the cost-effectiveness of lecanemab and to evaluate how the cost-effectiveness varies based on the accuracy of Alzheimer's disease testing and the presence of APOE e4 status, known genetic risk factor of AD. They concluded that targeted lecanemab treatment and treatment unrestricted by ApoE4 genotype do not result in cost-effective strategies, given the current market price for lecanemab. Therefore, the standard of care remains the optimal strategy from a cost-effectiveness perspective [41].

AI-Mind is not the first project aiming to develop an accurate prediction model for the conversion of MCI to dementia. An example of another prediction tool for this purpose is an AI-guided tool, using cognitive tests and structural MRI, to predict whether subjects with MCI will remain stable or progress to dementia within 3 years. This predictive prognostic model demonstrated a sensitivity of 82.4% and a specificity of 80.9% [50]. Furthermore, this tool is capable of predicting whether an individual will demonstrate rapid or slow progression. The predictive performance of this tool is considerably lower than the 95% sensitivity and specificity that AI-Mind aims to reach. A systematic review of prediction models for MCI to dementia conversion suggests that achieving this level of predictive performance may be challenging [43]. Most models in this review were not externally validated and demonstrated predictive performances below the 95% sensitivity and specificity threshold when evaluated internally. Our results show that in scenario's where a prediction sensitivity and specificity of 80% would be reached, even a targeted treatment strategy based on the predicted outcomes would not result in a cost-effective alternative. This could be explained by a higher number of false positive and false negative cases, resulting in an increased impact of disutility as a result of a high predicted risk and a smaller number of converters benefitting from disease progression delaying treatment if applicable.

A strength of this study is that we provide valuable information on the potential cost-effectiveness of using a prediction tool for estimating the risk of

conversion from MCI to dementia. This is in line with developments in the field, where identifying individuals at risk has gained much attention over the last decades. Information from our analysis could guide the further development and pricing of the AI-Mind tool specifically [2, 18]. Our analyses provide information into the conditions under which implementing the AI-Mind tool would be considered a cost-effective alternative to current practice. This includes factors such as the required sensitivity and specificity, associated costs, and other prerequisites like disease-modifying treatment. This information can steer the further development of the tool. In addition, by providing an interactive online dashboard, we enable the exploration of implications across various settings and prediction tools, also beyond AI-Mind. This is crucial, as current practices for managing people with MCI vary significantly between countries and even between settings in the same country, and as a variety of prediction tools for this purpose are developed.

Some limitations of this study also need consideration. First, in our decision model, we do not make a distinction between underlying causes of dementia (e.g. Alzheimer's disease, vascular dementia). In practice, dementia with different underlying causes might result in different survival rates, costs, caregiver burden, and different treatment options. With the interactive online dashboard, however, it is possible to study the potential cost-effectiveness for specific settings and subject groups. Second, in our scenario analyses, we modelled the impact of treatment based on the predicted conversion risk. We did not include treatment duration, waning, and discontinuation (e.g. due to adverse effects). As a result, the effects of treatment are taken into account relatively roughly, whereas in practice, this will be more nuanced. Third, although it could be considered relevant to perform a probabilistic sensitivity analysis (PSA) also in early HTA studies, we did not perform one. In this study, uncertainty extends beyond parameter uncertainty (e.g. disease progression rates), as current clinical practice varies substantially across countries and healthcare settings, and, therefore, a structural level of uncertainty is introduced as well (e.g. tests performed, prediction horizon). Conducting a PSA in this study would have involved comparing one defined current practice scenario to the implementation of a prediction tool. PSA results might be context-specific and not reflect the broader variability in current practice. We believe a PSA would give an invalid reflection of uncertainty, as it is related only to a limited selection of factors for which a quantification of uncertainty was available. We therefore focused on scenario-based analyses to better capture the impact of different clinical contexts and input values. Fourth, cost estimates in the model are based on Dutch healthcare costs, and results of the model using cost prices of other countries could therefore change. The interactive dashboard provides the possibility to study the potential cost-effectiveness with costs that are applicable in other countries or settings as well. Fifth, although advanced care planning is one of the benefits of early identification of subjects at high risk of progression, both for the subjects and informal caregivers, we did not capture this in the model. Research suggests that advanced care planning could have positive effects on various aspects, such as quality of life; however, there is limited direct evidence available specifically for subjects with MCI [51–53].

One of the benefits of estimating the risk of conversion from MCI to dementia is the potential for early intervention attributed to subjects where there is a high risk of conversion. This helps limit the costs associated with administration of present and future drugs and, more important, limit the potential side effects, which can be severe and may not be ethically justifiable for individuals at low risk of conversion. In addition, some studies have shown individuals with MCI express a desire to receive information regarding the expected course of their symptoms [54, 55]. The objective of this study was to evaluate the potential cost-effectiveness of implementing a prediction tool—here, the AI-Mind tool—for the conversion of MCI to dementia. This study demonstrates that the effect of receiving a dementia risk prediction on health-state utility has a significant impact on the potential cost-effectiveness, especially the negative impact of a high predicted conversion risk, regardless of whether that prediction is correct or incorrect, has a significant impact on the outcomes. We show, however, that under very specific conditions, depending on the prediction horizon and treatment options, the AI-Mind tool has the potential to become cost-effective. Our analyses show that the outcome of the model is sensitive to variations in input values for conversion rate from MCI to dementia, sensitivity, and specificity of the prediction tool, and (dis)utility values associated

with the risk prediction. Moreover, the outcome is sensitive to variations in the scenarios that were evaluated. The clinical relevance of scenarios in which the AI-Mind tool or other dementia risk prediction tools appear to result in a cost-effective alternative should be critically evaluated for clinical relevancy. If a prediction tool is considered clinically relevant and is implemented in practice, the demand for health services associated with risk prediction is likely to increase. Our study focuses on participants referred to a memory clinic or similar specialized setting. However, many MCI cases are currently not referred to specialized centres. This might change when risk prediction would become a standard of care. This underscores the importance of evaluating whether implementation in practice would be feasible, in addition to demonstrating the potential cost-effectiveness.

To conclude, under the current clinical conditions, implementing a dementia risk prediction tool similar to AI-Mind is not likely to result in a cost-effective alternative due to an overall decrease in quality of life resulting from information on conversion risk. However, under specific circumstances and assumptions, a risk prediction tool has the potential to become a cost-effective alternative compared to current practice. We recommend to critically evaluate the clinical relevance of cost-effective scenarios with respect to locally available treatment options and costs before considering further development and eventual implementation.

Author contribution Study conception and design: RV, MOR, RH, IHH, HR, PR, CM, FM, MR, and TG; data collection: RV; data analysis: RV and TG; writing the paper: RV; reviewing the paper: MOR, RH, IHH, HR, PR, CM, FM, MR, and TG.

Funding This work has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement 964220.

Declarations

Ethics approval and consent to participate Not applicable.

Interactive dashboard The interactive dashboard is available at https://ai-mind.shinyapps.io/earlyHTA/.

Competing interests The authors declare no competing interests.

References

1. (OECD) OfEC-oaD. Health expenditure and financing 2024 [Available from: https://data-explorer.oecd.org/vis?lc=en&fs[0]=Topic%2C1%7CHealth%23HEA%23%7CHealth%20expenditure%20and%20financing%23HEA_EXP%23&pg=0&fc=Topic&bp=true&snb=4&vw=tl&df[ds]=dsDisseminateFinalDMZ&df[id]=DSD_SHA%40DF_SHA&df[ag]=OECD.ELS.HD&df[vs]=1.0&dq=.A.EXP_HEALTH.PT_B1GQ._T.._T.._T...&pd=1970%2C2023&to[TIME_PERIOD]=false&ly[cl]=TIME_PERIOD&ly[rw]=REF_AREA.Accessed 16 Oct 2024.
2. Grutters JPC, Govers T, Nijboer J, Tummers M, van der Wilt GJ, Rovers MM. Problems and promises of health technologies: the role of early health economic modeling. Int J Health Policy Manag. 2019;8(10):575–82.
3. I MJ, Koffijberg H, Fenwick E, Krahn M. Emerging use of early health technology assessment in medical product development: a scoping review of the literature. Pharmacoeconomics. 2017;35(7):727–40.
4. El-Hayek YH, Wiley RE, Khoury CP, Daya RP, Ballard C, Evans AR, et al. Tip of the iceberg: assessing the global socioeconomic costs of Alzheimer's disease and related dementias and strategic implications for stakeholders. J Alzheimers Dis. 2019;70(2):323–41.
5. World Health Organization. Global status report on the public health response to dementia. Geneva: World Health Organization; 2021. p. 137. available from:https://www.who.int/publications/i/item/9789240033245?utm_source=chatgpt.com
6. Petersen RC, Lopez O, Armstrong MJ, Getchius TSD, Ganguli M, Gloss D, et al. Practice guideline update summary: mild cognitive impairment: report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. Neurology. 2018;90(3):126–35.
7. Nandi A, Counts N, Chen S, Seligman B, Tortorice D, Vigo D, et al. Global and regional projections of the economic burden of Alzheimer's disease and related

dementias from 2019 to 2050: a value of statistical life approach. EClinicalMedicine. 2022;51:101580.
8. Estimation of the global prevalence of dementia in 2019 and forecasted prevalence in 2050: an analysis for the Global Burden of Disease Study 2019. Lancet Public Health. 2022;7(2):e105-e25.
9. Knopman DS, Petersen RC. Mild cognitive impairment and mild dementia: a clinical perspective. Mayo Clin Proc. 2014;89(10):1452–9.
10. Petersen RC. Mild cognitive impairment as a diagnostic entity. J Intern Med. 2004;256(3):183–94.
11. Mitchell AJ, Shiri-Feshki M. Rate of progression of mild cognitive impairment to dementia–meta-analysis of 41 robust inception cohort studies. Acta Psychiatr Scand. 2009;119(4):252–65.
12. Ward A, Tardiff S, Dye C, Arrighi HM. Rate of conversion from prodromal Alzheimer's disease to Alzheimer's dementia: a systematic review of the literature. Dement Geriatr Cogn Disord Extra. 2013;3(1):320–32.
13. Chen Y, Qian X, Zhang Y, Su W, Huang Y, Wang X, et al. Prediction models for conversion from mild cognitive impairment to Alzheimer's disease: a systematic review and meta-analysis. Front Aging Neurosci. 2022;14:840386. https://pubmed.ncbi.nlm.nih.gov/35493941/
14. Hou XH, Feng L, Zhang C, Cao XP, Tan L, Yu JT. Models for predicting risk of dementia: a systematic review. J Neurol Neurosurg Psychiatry. 2019;90(4):373–9.
15. AI-Mind. Artificial intelligence for dementia prevention. [Available from: https://www.ai-mind.eu/. Accessed 14 Aug 2025.
16. Haraldsen IH, Hatlestad-Hall C, Marra C, Renvall H, Maestú F, Acosta-Hernández J, et al. Intelligent digital tools for screening of brain connectivity and dementia risk estimation in people affected by mild cognitive impairment: the AI-Mind clinical study protocol. Front Neurorobot. 2023;17:1289406.
17. Smedinga M, Tromp K, Schermer MHN, Richard E. Ethical arguments concerning the use of Alzheimer's disease biomarkers in individuals with no or mild cognitive impairment: a systematic review and framework for discussion. J Alzheimers Dis. 2018;66(4):1309–22.
18. Grutters JPC, Kluytmans A, van der Wilt GJ, Tummers M. Methods for early assessment of the societal value of health technologies: a scoping review and proposal for classification. Value Health. 2022;25(7):1227–34.
19. Husereau D, Drummond M, Augustovski F, de Bekker-Grob E, Briggs AH, Carswell C, et al. Consolidated health economic evaluation reporting standards 2022 (CHEERS 2022) statement: updated reporting guidance for health economic evaluations. Value Health. 2022;25(1):3–9.
20. Vemer P, Corro Ramos I, van Voorn GA, Al MJ, Feenstra TL. AdViSHE: a validation-assessment tool of health-economic models for decision makers and model users. Pharmacoeconomics. 2016;34(4):349–61.
21. Bertens D, Vos S, Kehoe P, Wolf H, Nobili F, Mendonça A, et al. Use of mild cognitive impairment and prodromal AD/MCI due to AD in clinical care: a European survey. Alzheimers Res Ther. 2019;11(1):74.
22. Hlavka JP, Mattke S, Liu JL. Assessing the preparedness of the health care system infrastructure in six European countries for an Alzheimer's treatment. Rand Health Q. 2019;8(3):2.
23. van Dyck CH, Swanson CJ, Aisen P, Bateman RJ, Chen C, Gee M, et al. Lecanemab in early Alzheimer's disease. N Engl J Med. 2023;388(1):9–21.
24. FDA. Drugs@FDA: FDA-approved drugs [Available from: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=BasicSearch.process. Accessed 24 Dec 2024.
25. Commission E. Commission authorises medicine for treatment of early Alzheimer's disease 2025 [Available from: https://ec.europa.eu/newsroom/sante/items/879055/en. Accessed 25 Apr 2025.
26. Sims JR, Zimmer JA, Evans CD, Lu M, Ardayfio P, Sparks J, et al. Donanemab in early symptomatic Alzheimer disease: the TRAILBLAZER-ALZ 2 randomized clinical trial. JAMA. 2023;330(6):512–27.
27. Jönsson L, Tate A, Frisell O, Wimo A. The costs of dementia in Europe: an updated review and meta-analysis. Pharmacoeconomics. 2023;41(1):59–75.
28. Reed C, Barrett A, Lebrec J, Dodel R, Jones RW, Vellas B, et al. How useful is the EQ-5D in assessing the impact of caring for people with Alzheimer's disease? Health Qual Life Outcomes. 2017;15(1):16.
29. Mitchell AJ, Beaumont H, Ferguson D, Yadegarfar M, Stubbs B. Risk of dementia and mild cognitive impairment in older people with subjective memory complaints: meta-analysis. Acta Psychiatr Scand. 2014;130(6):439–51.
30. Wimo A, Handels R, Winblad B, Black CM, Johansson G, Salomonsson S, et al. Quantifying and describing the natural history and costs of Alzheimer's disease and effects of hypothetical interventions. J Alzheimers Dis. 2020;75(3):891–902.
31. CBS. Levensverwachting; geslacht, leeftijd (per jaar en periode van vijf jaren) [Available from: https://opendata.cbs.nl/statline/#/CBS/nl/dataset/37360ned/table?dl=B2F1C. Accessed 08 Jan 2025.
32. Andersen K, Lolk A, Martinussen T, Kragh-Sørensen P. Very mild to severe dementia and mortality: a 14-year follow-up - the Odense study. Dement Geriatr Cogn Disord. 2010;29(1):61–7.
33. Davis M, T OC, Johnson S, Cline S, Merikle E, Martenyi F, et al. Estimating Alzheimer's disease progression rates from normal cognition through mild cognitive impairment and stages of dementia. Curr Alzheimer Res. 2018;15(8):777–88.
34. Hakkaart - van Roijen L, Peeters S, Kanters T, van Baal P, Brouwer W, Drost R et al. Kostenhandleiding voor economische evaluaties in de gezondheidszorg: Methodologie en Referentieprijzen. Herziene versie 2024 ed. Diemen, 2024. p. 81.
35. Zorginstituut Nederland. Richtlijn voor het uitvoeren van economische evaluaties in de gezondheidszorg: herziene versie 2024. Diemen: Zorginstituut Nederland; 2024. November 16, 2024. (Revision date: 16 januari 2024)
36. The Alzheimer's Organization. Alzheimer's organization: genetic testing. The ApoE genetic test for Alzheimer's risk. [Available from: https://www.alzheimersorganization.org/alzheimers-test. Accessed 08 Jan 2025.
37. Robinson RL, Rentz DM, Andrews JS, Zagar A, Kim Y, Bruemmer V, et al. Costs of early stage Alzheimer's disease in the United States: cross-sectional analysis of

a prospective cohort study (GERAS-US)1. J Alzheimers Dis. 2020;75(2):437–50.
38. Drummond MF, Sculpher MJ, Claxton K, Stoddart GL, Torrance GW. Methods for the economic evaluation of health care programmes. Oxford university press; 2015.
39. Vermeulen RJ, Roudijk B, Govers TM, Rovers MM, Olde Rikkert MGM, Wijnen BFM. Prognostic information on progression to dementia: quantification of the impact on quality of life. J Alzheimers Dis. 2024;97(4):1829–40.
40. Landeiro F, Mughal S, Walsh K, Nye E, Morton J, Williams H, et al. Health-related quality of life in people with predementia Alzheimer's disease, mild cognitive impairment or dementia measured with preference-based instruments: a systematic literature review. Alzheimers Res Ther. 2020;12(1):154.
41. Nguyen HV, Mital S, Knopman DS, Alexander GC. Cost-effectiveness of lecanemab for individuals with early-stage Alzheimer disease. Neurology. 2024;102(7):e209218.
42. Aye S, Handels R, Winblad B, Jönsson L. Optimising Alzheimer's disease diagnosis and treatment: assessing cost-utility of integrating blood biomarkers in clinical practice for disease-modifying treatment. J Prev Alzheimers Dis. 2024;11(4):928–42.
43. Vermeulen RJ, Andersson V, Banken J, Hannink G, Govers TM, Rovers MM, Rikkert MGMO. Limited generalizability and high risk of bias in multivariable models predicting conversion risk from mild cognitive impairment to dementia: a systematic review. Alzheimers Dement. 2025;21(4):e70069. https://doi.org/10.1002/alz.70069.
44. Pittock RR, Aakre JA, Castillo AM, Ramanan VK, Kremers WK, Jack CR Jr., et al. Eligibility for anti-amyloid treatment in a population-based study of cognitive aging. Neurology. 2023;101(19):e1837–49.
45. Zorginstituut Nederland. Lecanemab 2024 [Available from: https://www.horizonscangeneesmiddelen.nl/geneesmiddelen/lecanemab-neurologische-aandoeningen-dementie/versie2. Accessed 09 May 2025.
46. Tahami Monfared AA, Tafazzoli A, Chavan A, Ye W, Zhang Q. The potential economic value of lecanemab in patients with early Alzheimer's disease using simulation modeling. Neurol Ther. 2022;11(3):1285–307.
47. Handels R, Herring WL, Grimm S, Sköldunger A, Winblad B, Wimo A, Jönsson L. New IPECAD open-source model framework for the health technology assessment of early Alzheimer's disease treatment: development and use cases. Value Health. 2025;28(4):511–518. https://doi.org/10.1016/j.jval.2024.07.009.
48. Handels RLH, Wimo A, Dodel R, Kramberger MG, Visser PJ, Molinuevo JL, 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):1477–87.
49. Michaud TL, Kane RL, McCarten JR, Gaugler JE, Nyman JA, Kuntz KM. Using cerebrospinal fluid biomarker testing to target treatment to patients with mild cognitive impairment: a cost-effectiveness analysis. Pharmacoeconomics. 2018;2(3):309–23.
50. Lee LY, Vaghari D, Burkhart MC, Tino P, Montagnese M, Li Z, et al. Robust and interpretable AI-guided marker for early dementia prediction in real-world clinical settings. eClinicalMedicine. 2024. https://doi.org/10.1016/j.eclinm.2024.102725.
51. Abshire Saylor M, Hanna V, Zhang P, Thai GH, Green CM, Cagle JG, et al. Advance care planning in adults ages 80 years and older with impaired cognition: using actual conversations to examine best practices. Alzheimers Dement. 2025;21(1):e14331.
52. Gabbard JL, Carpenter JG, Ernecoff NC, Mournighan K, Cornea I, McKone M, et al. Evaluating the pragmatic characteristics of advance care planning outcome measures in dementia clinical trials: a scoping review. J Am Geriatr Soc. 2023;71(11):3595–608.
53. Robinson L, Dickinson C, Rousseau N, Beyer F, Clark A, Hughes J, et al. A systematic review of the effectiveness of advance care planning interventions for people with cognitive impairment and dementia. Age Ageing. 2012;41(2):263–9.
54. Kunneman M, Smets EMA, Bouwman FH, Schoonenboom NSM, Zwan MD, Pel-Littel R, et al. Clinicians' views on conversations and shared decision making in diagnostic testing for Alzheimer's disease: the ABIDE project. Alzheimers Dement Transl Res Clin Interv. 2017;3(3):305–13.
55. Paulsen JS, Nance M, Kim JI, Carlozzi NE, Panegyres PK, Erwin C, et al. A review of quality of life after predictive testing for and earlier identification of neurodegenerative diseases. Prog Neurobiol. 2013;110:2–28.