



Biomarker-based prognosis for people with mild cognitive impairment (ABIDE): a modelling study

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Summary

Background Biomarker-based risk predictions of dementia in people with mild cognitive impairment are highly relevant for care planning and to select patients for treatment when disease-modifying drugs become available. We aimed to establish robust prediction models of disease progression in people at risk of dementia.

Methods In this modelling study, we included people with mild cognitive impairment (MCI) from single-centre and multicentre cohorts in Europe and North America: the European Medical Information Framework for Alzheimer's Disease (EMIF-AD; n=883), Alzheimer's Disease Neuroimaging Initiative (ADNI; n=829), Amsterdam Dementia Cohort (ADC; n=666), and the Swedish BioFINDER study (n=233). Inclusion criteria were a baseline diagnosis of MCI, at least 6 months of follow-up, and availability of a baseline Mini-Mental State Examination (MMSE) and MRI or CSF biomarker assessment. The primary endpoint was clinical progression to any type of dementia. We evaluated performance of previously developed risk prediction models—a demographics model, a hippocampal volume model, and a CSF biomarkers model—by evaluating them across cohorts, incorporating different biomarker measurement methods, and determining prognostic performance with Harrell's C statistic. We then updated the models by re-estimating parameters with and without centre-specific effects and evaluated model calibration by comparing observed and expected survival. Finally, we constructed a model combining markers for amyloid deposition, tauopathy, and neurodegeneration (ATN), in accordance with the National Institute on Aging and Alzheimer's Association research framework.

Findings We included all 2611 individuals with MCI in the four cohorts, 1007 (39%) of whom progressed to dementia. The validated demographics model (Harrell's C 0.62, 95% CI 0.59–0.65), validated hippocampal volume model (0.67, 0.62–0.72), and updated CSF biomarkers model (0.72, 0.68–0.74) had adequate prognostic performance across cohorts and were well calibrated. The newly constructed ATN model had the highest performance (0.74, 0.71–0.76).

Interpretation We generated risk models that are robust across cohorts, which adds to their potential clinical applicability. The models could aid clinicians in the interpretation of CSF biomarker and hippocampal volume results in individuals with MCI, and help research and clinical settings to prepare for a future of precision medicine in Alzheimer's disease. Future research should focus on the clinical utility of the models, particularly if their use affects participants' understanding, emotional wellbeing, and behaviour.

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Introduction

People with mild cognitive impairment (MCI) have an increased risk of progressing to dementia, most often due to Alzheimer's disease.¹ Roughly half of individuals with MCI develop dementia in the course of 3 years.² The other half remain stable or revert to normal levels of cognition. As a result, these individuals live with uncertainty for a long time. In a former study on the communication of diagnosis, people with MCI indicated they preferred more information on the future course of their disease.³ Diagnostic tests, such as MRI measures or

biomarkers in CSF, could help to establish a more accurate prognosis.^{4–7}

Practice guidelines for MCI from the American Academy of Neurology acknowledge that biomarker research in Alzheimer's disease is a rapidly moving field and that biomarker evidence in MCI might be particularly important for prognosis.⁸ At the same time, these guidelines state that biomarkers are not yet ready for clinical implementation. This was also confirmed by the Geneva Roadmap.⁹ Although there is a wealth of literature showing the prognostic value of CSF and MRI biomarkers

Research in context

Evidence before this study

We searched PubMed, without language restriction, for articles published up to Nov 1, 2018, on prognosis in people with mild cognitive impairment (MCI), at an individual level, on the basis of biomarker evidence, using the terms “([mild cognitive impairment] AND [prognosis] OR [prognostic factor] OR [prediction model])”. Specifically, we focused on prognosis in MCI based on biomarker evidence—ie, atrophy on MRI and amyloid β , total tau, and phosphorylated tau in CSF. A wealth of literature was available on the prognostic performance of these (combinations of) biomarkers in individuals with MCI. However, these studies reported findings at the group level, which do not directly translate to the individual. Our previous study was the only study that allowed the interpretation of biomarkers on an individual level in people with MCI. For this validation study, we took our previously constructed biomarker-based prognostic models that allow risk prediction on the individual level as a starting point for our analysis. However, our proof-of-principle models were based on a homogeneous, single-centre cohort and did not accommodate different cohorts and biomarker measurement methods. Moreover, prediction beyond 3 years was not reliable.

Added value of this study

In the current study of 2611 individuals with MCI from single-centre and multicentre cohorts in Europe and North

America, we validated and updated, according to the TRIPOD guidelines, multivariable, biomarker-based models for the prediction of dementia. We showed that the models had good generalisability and were well calibrated up to more than 5 years of follow-up. Moreover, the models accommodate different biomarker measurement methods. Additionally, we constructed a model combining measures of amyloid, tau, and neurodegeneration to provide predictions in accordance with the most recent research guidelines for Alzheimer's disease.

Implications of all the available evidence

We have shown the generalisability and robustness of the predictions. Our models are freely available for academic use upon request. The models allow clinical researchers to estimate—for any given combination of biomarker results—the probability of progression to dementia within a given period of time. Our models could facilitate a more timely and accurate diagnosis and prognosis of MCI, which is of high importance at the individual level even in the absence of specific therapies, as this is the starting point to plan and organise care.

on a group level,^{5–7} these studies do not allow direct translation to the individual. For example, the prognostic value of biomarkers might be influenced by characteristics such as age, sex, and cognitive status. To extract maximal information from each biomarker, the results should be interpreted in the context of these characteristics. However, these characteristics are often omitted in prognostic research. Furthermore, recommendations on how to handle conflicting and borderline results are lacking.⁹ In this context, the novel National Institute on Aging and Alzheimer's Association (NIA-AA) research framework that defines Alzheimer's disease as a biological construct is of great interest. The research framework proposes to use biomarkers for amyloid, tau, and neurodegeneration (ATN) to classify patients. For MCI, it is unknown how the use of this framework informs predictions.¹⁰

In a previous study,⁴ we constructed proof-of-principle biomarker-based prognostic models that allow risk prediction on the individual level. These models, which were based on a homogeneous, single-centre cohort and we internally and externally validated, provide probabilities of progression to Alzheimer's disease dementia in the course of 1 year or 3 years of follow-up for any given value of each biomarker. To successfully enter clinical practice, however, generalisability has to be shown by extensive external validation.¹¹ A prerequisite for generalisability is that the models are able to accommodate different biomarker

measurement methods and have value for different cohorts, beyond the ones they were initially developed in.⁹ Taking our previous risk prediction models as a starting point, the aim of this study was to establish robust, generalisable prediction models. Additionally, we aimed to construct an ATN-model that would allow the use of this framework to inform predictions.

Methods

Study design and participants

We included individuals with MCI from one single-centre and three multicentre cohorts in Europe and America: the Amsterdam Dementia Cohort¹² (ADC; 666 participants), the Alzheimer's Disease Neuroimaging Initiative¹³ (ADNI; 829 participants), the Biomarkers For Identifying Neurodegenerative Disorders Early and Reliably Study¹⁴ (BioFINDER; 233 participants) and the collaborative cohorts of the European Medical Information Framework for Alzheimer's disease (EMIF-AD; 883 participants) composed of the following studies: DESCRIPA,¹⁵ AddNeuroMed,¹⁶ German Dementia Competence Network (DCN),¹⁷ IMAP,¹⁸ European Alzheimer's Disease Consortium (EADC)-PET,¹⁹ Brescia,²⁰ Coimbra,²¹ Kuopio,²² and Lisbon.²³ Cohort characteristics are summarised in table 1, with characteristics of the separate EMIF cohorts given in the appendix (pp 2–3). ADC and BioFINDER are memory clinic-based cohorts and participants were re-evaluated on a yearly basis. ADNI is a research cohort and diagnosis is evaluated

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	ADC (n=666)	ADNI (n=829)	EMIF-AD (n=883)	BioFINDER (n=233)
Baseline data collection period	1995–2014	2004–14	Varied per substudy*	2010–15
Study design	Single-centre longitudinal cohort study	Multicentre longitudinal cohort study	Multicentre longitudinal cohort study	Multicentre longitudinal cohort study
Setting	Tertiary memory clinic	Research	Memory clinics	Memory clinics
Inclusion criteria	Referred to memory clinic, does not fulfil criteria for dementia	Memory complaints verified by study partner, abnormal memory functioning, MMSE of 24–30, clinical dementia rating scale of 0–5, does not fulfil criteria for dementia	Varied per substudy*	Referred to memory clinic, age 60–80 years, baseline MMSE of 24–30, does not fulfil criteria for dementia
Participants who developed dementia	288 (43%)	319 (38%)	272 (31%)	128 (55%)
Follow-up	Clinical follow-up every 12 months	3–12-month interval	Varied per substudy*	Every 12 months for at least 6 years
MRI available	539 (81%)	705 (85%)	727 (82%)	233 (100%)
MRI quantification method	FSL-FIRST, Freesurfer version 5.3	Freesurfer version 5.3	Varied per substudy*	Freesurfer version 5.3
CSF biomarkers available	485 (73%)	558 (67%)	366 (41%)	221 (95%)
CSF platform	Innotest	Luminex and Elecsys	Innotest	Innotest

ADC=Amsterdam Dementia Cohort. ADNI=Alzheimer's Disease Neuroimaging Initiative. EMIF-AD=European Medical Information Framework for Alzheimer's Disease. MMSE=Mini-Mental State Examination. *For substudy details, see appendix pp 2–3.

Table 1: Characteristics of the cohorts included in validation analyses

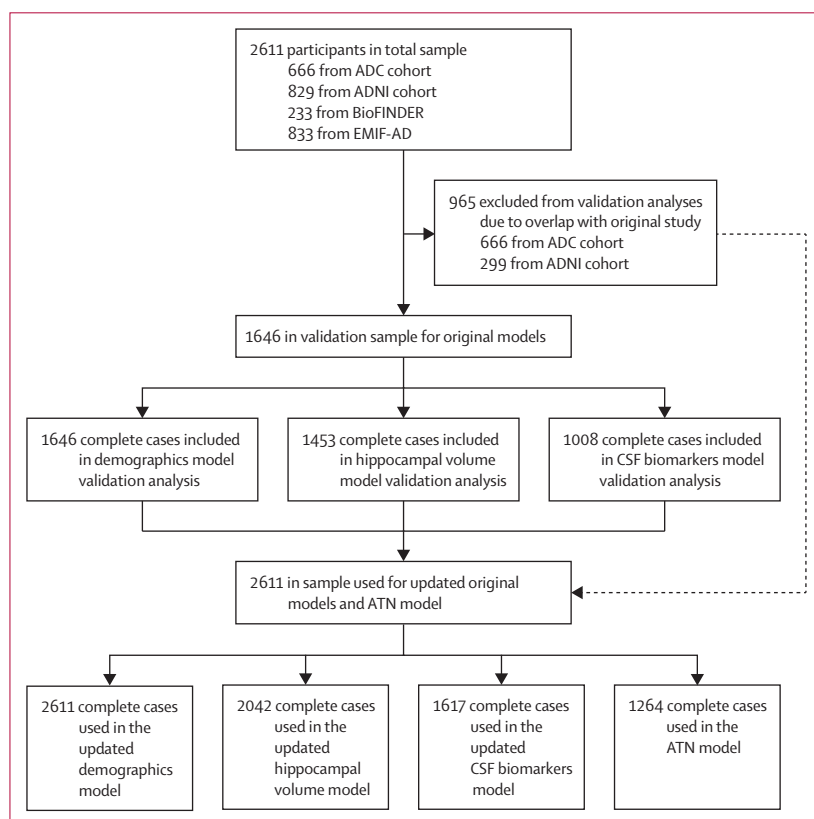


Figure 1: Flow diagram of participants included in validation analyses and model updates
ADC=Amsterdam Dementia Cohort. ADNI=Alzheimer's Disease Neuroimaging Initiative. CSF=cerebrospinal fluid. EMIF-AD=European Medical Information Framework.

at 3–12-month intervals. EMIF-AD substudy follow-up is reported in the appendix (pp 2–3).

For this study, inclusion criteria were a baseline diagnosis of MCI, at least 6 months of follow-up, and availability of a Mini-Mental State Examination (MMSE) and MRI or CSF biomarker assessments at baseline. All participants gave written informed consent for participation in the original studies and for reuse of the data, and institutional review boards approved the study. This study is reported in accordance with the Transparent Reporting of a multi-variable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) guideline.²⁴

Original prediction models

The original prediction models were constructed using Cox proportional hazards modelling in the ADC.⁴ In the current study, we validated the following previously published models: a demographics model, a hippocampal volume model, and a CSF biomarkers model.⁴ Variables included in the models and corresponding estimates are shown in the appendix (p 4). In short, the demographics model included age, sex, and MMSE; the hippocampal volume model included hippocampal volume (cm³), age, and MMSE; and the CSF biomarkers model included amyloid β (1–42), total tau, MMSE, and an interaction term between amyloid β and total tau. As whole brain volume was not available in one cohort (EMIF), we were unable to assess the performance of a model combining CSF and MRI features (ie, a combined model). In the original study, the prognostic models showed moderate to good discrimination as shown with Harrell's C statistic, a

	Original sample		New validation sample		
	ADC, Netherlands (n=485)	ADNI-2, USA (n=299)	ADNI, USA (n=530)	EMIF-AD, Europe (n=883)	BioFINDER, Sweden (n=233)
Follow-up time, years	2.4 (1.6)	2.6 (1.4)	3.3 (2.4)	2.2 (1.1)	2.3 (1.3)
Number of participants progressing to dementia	243 (50%)	88 (29%)	231 (44%)	272 (31%)	128 (55%)
Alzheimer's disease dementia	195 (40%)	85 (28%)	223 (42%)	218 (25%)	87 (37%)
Other types of dementia	48 (10%)	3 (1%)	8 (2%)	54 (6%)	41 (18%)
Age, years	67 (8)	71 (7)	73 (8)	69 (8)	71 (5)
Sex					
Female	192 (40%)	132 (44%)	204 (38%)	461 (52%)	97 (42%)
Male	293 (60%)	167 (56%)	326 (62%)	422 (48%)	136 (58%)
MMSE	27 (2)	28 (2)	27 (2)	27 (2)	27 (2)
Hippocampal volume, cm ³	6.9 (1.1)*	6.9 (1.1)	6.6 (1.1)	0.02 (0.99)†	6.7 (1.2)
CSF biomarkers, pg/ML					
Amyloid β	876 (547)*	872 (322)*	990 (571)	913 (603)	635 (407)
Total tau	256 (141)*	280 (131)*	293 (126)	230 (111)	222 (80)
Phosphorylated tau	27 (16)	27 (15)	29 (15)	25 (16)	25 (14)

Data are n (%) or mean (SD). Note that, for the ADC cohort, we present the characteristics of the original sample. For the current study, 181 new participants, of whom (25%) progressed, were included, making the total sample size 666 participants. ADC=Amsterdam Dementia Cohort. ADNI=Alzheimer's Disease Neuroimaging Initiative. EMIF-AD=European Medical Information Framework for Alzheimer's disease. MMSE=Mini-Mental State Examination. *Values are bridged and therefore do not correspond with the values from the original paper. †Hippocampal volume in the EMIF cohort was measured with different techniques than FSL-FIRST or Freesurfer; therefore, the values were not bridged but converted to Z scores.

Table 2: Demographic and clinical characteristics of participants in the cohorts included in validation analyses

rank concordance statistic that measures the proportion of participant pairs in which predictions and outcomes are concordant (demographics model 0.59 [95% CI 0.54–0.64], hippocampal volume model 0.73 [0.66–0.80], and CSF biomarkers model 0.67 [0.67–0.81]).⁴ External validation in ADNI-2,²⁵ the third wave of the ADNI project with the primary goal to develop biomarkers as predictors of cognitive decline, showed robustness of all models (Harrell's C for the demographics model 0.67 [0.60–0.74], hippocampal volume model 0.73 [0.66–0.80], and CSF biomarkers model 0.74 [0.67–0.81]).⁴

Part of the ADNI sample was used in the original study; we therefore excluded these participants from the validation analyses but included them in the model update.

Predictors

The following baseline predictors were available in all cohorts: demographic characteristics (age and sex), MMSE score, CSF biomarkers (amyloid β , total tau, and phosphorylated tau), and hippocampal volume. The distributions of these predictors are shown across the different cohorts in the appendix (p 5).

Different methods were used across cohorts to analyse CSF and quantify hippocampal volume (platforms are listed in table 1). Because absolute values of both CSF concentrations and volumetric MRI measures varied across methods, we bridged CSF and volumetric MRI data when possible. A detailed description of this bridging analysis is provided in the appendix (pp 6–7).

Outcomes

The primary outcome was clinical progression to any type of dementia at any time. In a secondary analysis, we validated all models with Alzheimer's disease dementia as the outcome.

Statistical analysis

We validated and updated our biomarker-based prediction models in four steps. First, model performances of the originally developed models were assessed in all cohorts with Harrell's C statistic, with 95% CIs calculated with the somersd package in STATA. Model performances were pooled. Second, we updated the models by re-estimating parameters with and without centre-specific effects to evaluate whether we could safely omit the adjustment for centre, which would increase generalisability. In an additional set of analyses, we tested whether centre-specific effects were confounded by measurement methods for MRI and CSF (appendix pp 10–11). Moreover, we replaced total tau by phosphorylated tau in the CSF biomarkers model according to NIA-AA criteria. We chose the original models as final models if they performed similarly (ie, had overlapping 95% CIs) to the updated models. In the CSF biomarkers model, our baseline choice was the updated model with phosphorylated tau to align with NIA-AA criteria. If the performance of re-estimated models with and without centre-effects performed similarly, then we favoured models without centre-specific effects to increase generalisability. Third, we estimated a model including

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See Online for appendix

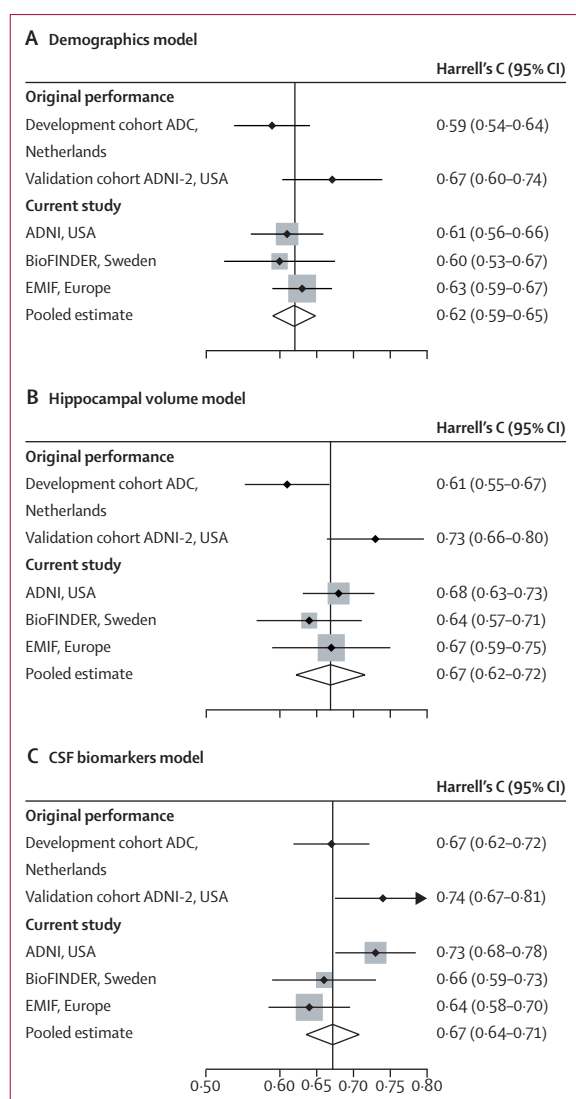


Figure 2: Performance of previous models

As a reference, the model performance of the original development and validation cohort are shown in grey. Pooled estimates of model performance for Alzheimer's disease dementia as a clinical endpoint are shown in the appendix (p 8). ADC=Amsterdam Dementia Cohort. ADNI=Alzheimer's Disease Neuroimaging Initiative. CSF=cerebrospinal fluid. EMIF-AD=European Medical Information Framework for Alzheimer's disease.

amyloid β , phosphorylated tau, and hippocampal volume in accordance with the ATN framework¹⁰ using data from all four cohorts. We subdivided the dataset such that model development was done with three of the included cohorts and model validation was carried out in the remaining cohort. We did this procedure four times, using a different cohort for validation each time (ie, four-fold external cross validation). Candidate variables for the ATN model included demographics (age, sex, and MMSE), amyloid β , phosphorylated tau, hippocampal volume, and interactions between biomarkers and demographic variables. The ATN model was constructed with

Cox proportional hazards analysis via a backwards-selection procedure. Effects with $p < 0.10$ were included in the model. Last, we assessed the calibration (ie, concordance of predicted with observed outcome) of the models by superimposing observed and expected survival predicted by the models. To this end, we defined four risk groups on the basis of the prognostic index of the final models: good prognosis (>84th percentile), fairly good prognosis (50–84th percentile), fairly poor prognosis (16–50th percentile), and poor prognosis (<16th percentile). Observed progression was calculated by Kaplan-Meier. A detailed description of these steps can be found in the appendix (pp 10–12). Analyses were done in STATA SE 14 and were based on complete cases; therefore, the number of patients varies across models.

The final models were used to create a simple spreadsheet calculator. In this calculator, we used the baseline survival functions that were derived from the final models to estimate probabilities of progression within 1, 3, and 5 years. The spreadsheet calculator can be provided by the authors on request, with its clinical research use illustrated by two case studies.

Role of the funding source

The funders of this study had no involvement in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

We included all 2611 participants in the four cohorts (figure 1), with mean age 70 years (SD 8), mean MMSE of 27 (SD 2), and of whom 1153 (44%) were female (table 2). During a mean of 3 years (SD 2) of follow-up, 1007 (39%) of the participants progressed to dementia. We found no heterogeneity between the cohorts in the baseline hazard and baseline survivor function (data not shown).

The pooled Harrell's C statistics for the demographics model (0.62, 95% CI 0.59–0.65), hippocampal volume model (0.67, 0.62–0.72), and the CSF biomarkers model (0.67, 0.64–0.71) were similar to those found in the development cohort of the original study (figure 2). For Alzheimer's disease dementia as the outcome of interest, the pooled Harrell's C statistic of the CSF biomarkers model is lower than in the original study, indicating possible misfit (0.69, 0.65–0.72; appendix p 8).

Re-estimating the parameters did not increase model fit for the models with dementia as the outcome, both with and without centre-specific effects (table 3). For the CSF biomarkers model with Alzheimer's disease dementia as the outcome, re-estimating the parameters did increase model fit (appendix p 9). Inclusion of centre-specific effects did not improve any of the models relative to those without centre-specific effects (table 3). Notably, inclusion of centre-specific effects did not result in a difference in progression probabilities on an individual

level (data not shown). Additional analyses further supported this finding, as we found that centre-specific effects were not confounded by measurement methods for MRI and CSF (appendix pp 10–12). Therefore, we favoured models without centre-specific effects to increase generalisability. Replacing total tau with phosphorylated tau in the CSF biomarkers model did not affect model performance (table 3).

The validation procedure for our ATN model is shown in the appendix (p 13). The main effects of amyloid β , phosphorylated tau, hippocampal volume, age, and MMSE were retained in our ATN model ($p < 0.10$). Moreover, interaction effects between amyloid β and phosphorylated tau, amyloid β and age, and phosphorylated tau and MMSE were included ($p < 0.10$). The interaction between amyloid β and age indicates that the prognostic value of amyloid β was stronger in younger individuals (table 4). The prognostic value of phosphorylated tau was most pronounced in participants with higher (normal) amyloid β values and lower (abnormal) MMSE values. Harrell's C-statistic for the ATN model was 0.74 (0.71–0.76). Results for Alzheimer's disease dementia as a clinical endpoint are shown in the appendix (p 14).

In general, for all models, observed and expected survival according to risk groups appear to be similar, indicating good calibration (figure 3). For the hippocampal volume model, visual inspection suggests a degree of misfit for long-term predictions (>5 years), as the model tends to overestimate survival in the good prognosis group and underestimate survival in the poor prognosis group. Of note, all models are well calibrated up to 5 years of follow-up.

As all models are well calibrated up to 5 years of follow-up, we updated the models to provide 5-year risk estimates in addition to the 1-year and 3-year risk estimates calculated in the original study.⁴ A spreadsheet calculator can be provided by the authors on request (appendix p 16).

Discussion

We have constructed and validated biomarker-based models, including an ATN model, to provide predictions for dementia in individuals with MCI. We have shown that the models have strong external validity across continents and memory clinic cohorts. Moreover, the models accommodate different assays, which further increases their generalisability. The models can be used to extract individually tailored prognostic information from the tests done in the diagnostic setup. We have created a spreadsheet calculator to this effect, illustrated by two case studies (panel). This individually tailored prognostic information sets up the first crucial steps on the road towards a precision medicine approach.

Our study has important clinical implications. Patients and caregivers have become increasingly assertive in their need for prognostic information. In clinical practice,

	Pooled estimates of original parameters	Refitted parameters without centre-specific effects	Refitted parameters with centre-specific effects
Demographics model	0.62 (0.59–0.65)	0.63 (0.61–0.65)	0.65 (0.64–0.68)
Hippocampal volume model	0.67 (0.62–0.72)	0.69 (0.67–0.71)	0.69 (0.67–0.72)
CSF biomarkers model	0.67 (0.64–0.71)	0.72 (0.68–0.74)	0.72 (0.70–0.74)
CSF biomarkers model with phosphorylated tau	NA	0.72 (0.70–0.74)	0.72 (0.69–0.74)

Data are Harrell's C statistic (95% CI). Outcome was progression to any type of dementia. Model performances of the models for Alzheimer's disease dementia as the clinical endpoint are shown in the appendix (p 9). NA=not applicable.

Table 3: Harrell's C statistic of previous models

	Partial regression coefficients (95% CI)
Amyloid β	–0.5187 (–0.633 to –0.405)
Phosphorylated tau	0.6207 (0.439 to 0.802)
Hippocampal volume	–0.4164 (–0.516 to –0.317)
Age	–0.0065 (–0.020 to 0.007)
MMSE	–0.1107 (–0.151 to –0.070)
Amyloid β *phosphorylated tau	0.1772 (–0.024 to 0.378)
Amyloid β *age	0.0166 (–0.002 to 0.035)
Phosphorylated*MMSE	0.0928 (0.019 to 0.167)

Harrell's C of the ATN model is 0.74 (95% CI 0.71–0.76). Model is based on cross-validated estimates from all cohorts. ATN model for Alzheimer's disease dementia as a clinical endpoint is shown in the appendix (p 14). ATN=amyloid, tau, and neurodegeneration. MMSE=Mini-Mental State Examination. *denotes interaction term.

Table 4: Partial regression coefficients of the ATN model

however, risk communication for individuals with MCI is only sparsely observed and, if communicated, is provided mostly as group averages: ie, that being an individual with MCI means that the risk of progression to dementia is 50% risk. With biomarker results available, this 50–50 situation for most individuals is not true. With abnormal biomarkers, the risk of progression might be higher than 50%, whereas with normal biomarkers, this risk can be far lower than 50%, which could provide reassurance to individuals with normal biomarkers. With our validated, biomarker-based prediction models, a prognosis for an individual can be estimated in the context of their own characteristics, showing that precision medicine for Alzheimer's disease might be on the horizon. The models are easy to use and a calculator (simple Microsoft Excel sheet) for academic use can be provided by the authors upon request. To further facilitate its use, we have incorporated the models in an easy-to-use online tool, ADappt.²⁶

However, there are also arguments against the disclosure of risk in clinical practice. A review²⁷ on the disclosure of amyloid PET results in pre-dementia showed that these arguments are to a large extent theoretical in nature and relate mostly to the principle of

For more on ADappt see
<https://www.alzheimercentrum.nl/professionals/adappt-contact>

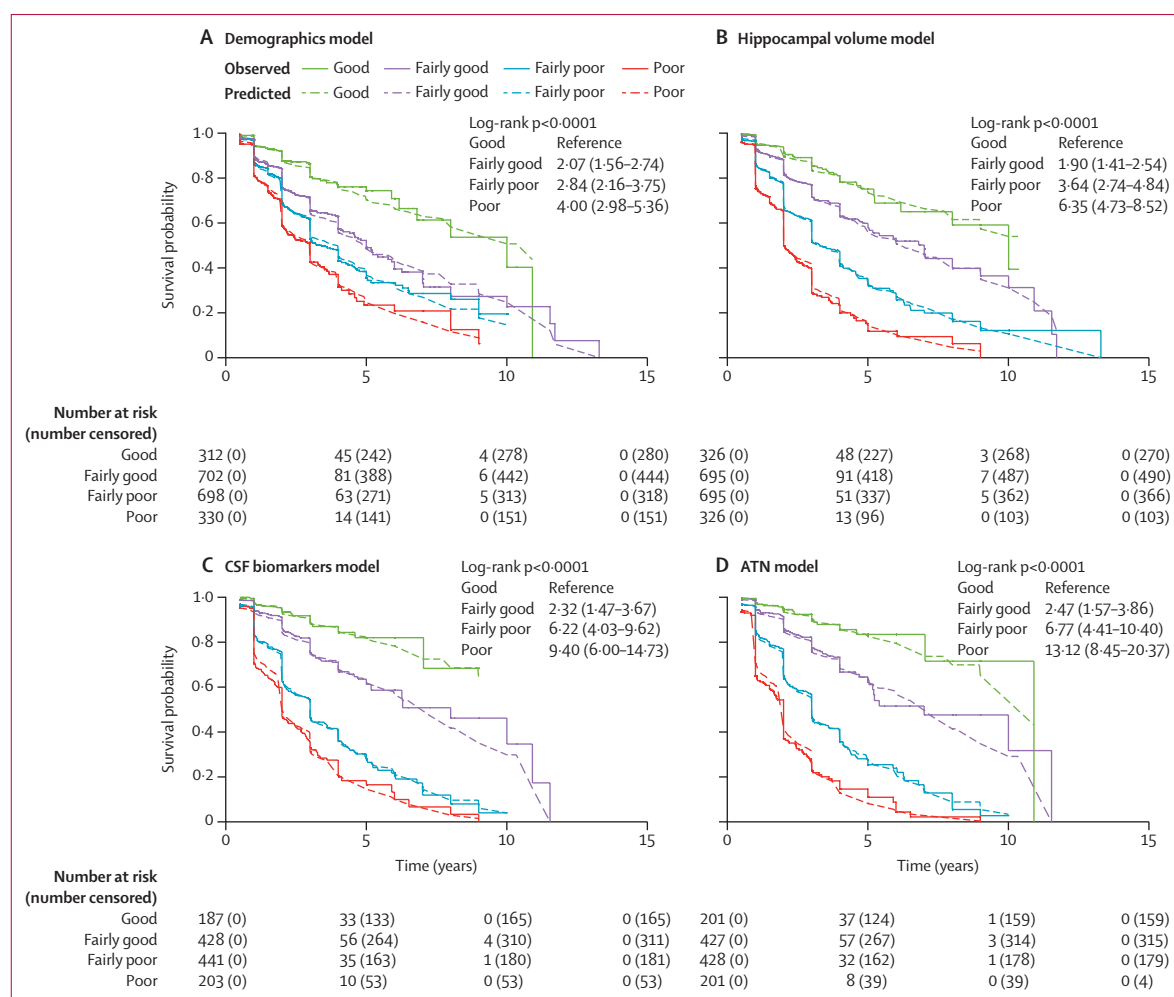


Figure 3: Calibration of biomarker-based models

Observed progression is analysed by Kaplan-Meier whereas predicted progression is analysed with Cox models. Findings are based on data from all four cohorts. Calibration of model performance for Alzheimer's disease dementia as a clinical endpoint is shown in the appendix (p 15). ATN=amyloid, tauopathy, and neurodegeneration.

non-maleficence (ie, do no harm). Empirical evidence is largely lacking and the effect on psychological harm is not known. In a previous ABIDE study, patients and caregivers expressed their need for risk communication in early phases of Alzheimer's disease and anxiety or uncertainty did not increase after disclosure of amyloid PET.^{3,28} These findings suggest that models such as those developed in our study could conceivably be used in clinical practice. Nonetheless, before this type of model could be implemented in clinical practice, there are some important next steps to take, particularly to determine clinical utility. In the current study, we used retrospective data to construct the models. As a first next step, the models should be evaluated prospectively, ideally in a phase 3 randomised controlled trial. This trial should provide answers on the clinical utility of the models, particularly if their use affects participants' understanding, emotional wellbeing, and behaviour (eg, lifestyle changes).

In parallel, studies should focus on the optimal way to disclose risks to individuals without dementia, and it is conceivable that clinicians should receive training on how best to disclose this type of probabilistic information. Moreover, before initiating biomarker testing, it is of utmost importance that realistic expectations are set regarding what kind of results can be anticipated. Another option would be for the risk prediction models to be used before initiating biomarker testing. By filling in hypothetical biomarker results and comparing these to the results of the demographics model, the clinician can evaluate whether these results would add prognostic value. The clinician could also engage the patient and caregiver in this discussion on different biomarker scenarios and potential outcomes. In this light, the models could serve as a decision support tool and could even enhance shared decision making.

We included data from multiple single-centre and multicentre cohorts, both from Europe and the USA.

Although we did not find heterogeneity in the baseline hazard and baseline survivor function, differences inevitably exist between cohorts. For that reason, we thoroughly tested for centre-specific effects. We found that adding centre-specific effects did not improve the performance of the models, nor did it result in a difference in progression probabilities on an individual level. According to the principle of parsimony, a model without centre-specific effects is preferable, as this allows the clinician to use the model without further adjusting it to their own memory clinic. Moreover, this indicates that our models are also applicable for people with MCI in memory clinics that were not included in the development or validation phase of our study. Our results suggested that in the original CSF biomarkers model, the parameters of amyloid β and total tau were overestimated, leading to less optimal model performance in other cohorts. Re-estimating the parameters resulted in an increase in model performance. As a measure of amyloid, we used CSF concentrations rather than amyloid PET. Although of interest, amyloid PET is currently less often used in clinical practice and is usually evaluated in a dichotomous fashion, whereas in the current models we include all biomarkers as continuous measures, with the objective to make it readily available for clinicians. We developed amyloid PET-based models in an earlier study,²⁹ however, and are therefore confident that results would generalise to amyloid PET as well. In our updated models, we replaced total tau by phosphorylated tau to improve alignment with the latest NIA-AA criteria.¹⁰ Because CSF total tau and phosphorylated tau are very highly correlated, this replacement did not influence the model performance. It could be debated whether APOE would have been a helpful addition to the models. Although APOE $\epsilon 4$ is the strongest genetic risk factor for Alzheimer's disease, we decided not to include this genetic characteristic because it is currently not used in clinical practice and, likewise, is not mentioned in any of the diagnostic guidelines. Of note, we have previously found that including APOE $\epsilon 4$ status as an additional variable in biomarker-based models to predict dementia in MCI did not increase prognostic performance or alter the predictions on an individual level.²⁹

The recently launched NIA-AA research framework states that, by coding research participants according to the ATN system, the field moves in the direction of precision medicine.¹⁰ This coding system highly depends on cutoff values because a patient is coded as either positive or negative for a specific biomarker. As a consequence of this dichotomy, the ATN system comprises eight categories. For clinical practice, the use of eight categories might be complex. Simultaneously, reality might be even more complicated than these eight categories as the dichotomisation does not include information on extent of abnormality. In this study, we present a model in which ATN biomarkers are simultaneously considered, yet can be entered into the model as

Panel: Spreadsheet calculator

The spreadsheet calculator allows the user to select which platform was used for CSF analysis (Innotest, Luminex, or Elecsys) and which method was used to calculate hippocampal volume (FSL FIRST or Freesurfer). After selecting the appropriate methods for CSF and MRI, clinicians can easily fill in patient-specific values.

For example, for a 62-year-old woman with MCI and an MMSE of 26, without knowledge of biomarker results, the progression probabilities to dementia are 11% (95% CI 10–12) in 1 year, 39% (36–42) in 3 years, and 57% (52–61) in 5 years. When both MRI and CSF data are available and with abnormal levels (amyloid β = 225, phosphorylated tau = 90 [CSF measured with Innotest], and hippocampal volume = 6.2 [calculated with Freesurfer software]), the progression probabilities change to 40% (33–48) in 1 year, 88% (82–94) in 3 years, and 97% (94–99) in 5 years.

By contrast, a 62-year-old man with MCI and an MMSE of 29, without knowledge of biomarker results, has progression probabilities to dementia of 7% (95% CI 6–8) in 1 year, 26% (23–29) in 3 years, and 40% (44–35) in 5 years. With normal biomarkers (amyloid β = 1264, phosphorylated tau = 12 [measured with Elecsys], and hippocampal volume = 9.8 [calculated with Freesurfer]), he would have progression probabilities of 1% [1–2] in 1 year, 5% (4–7) in 3 years, and 8% (6–11) in 5 years.

MCI=mild cognitive impairment. MMSE=Mini-Mental State Examination

continuous variables, to yield risk estimation of disease progression to dementia in individuals with MCI. By doing so, every combination is possible and maximum information from each biomarker is exploited. To further foster clinical usefulness, our models provide probabilities of progression within a specific time frame, while taking patient characteristics into account. The NIA-AA coding scheme does not provide this type of information yet. From risk communication literature, we know that a numerical format of risk communication is preferred above verbal formats (high, intermediate, low), because verbal formats are sensitive to a high degree of variability in interpretation.³⁰ Accompanying the risk estimate with a time frame is considered best practice, ideally with a visual representation.³⁰

Our current models have been updated to allow the use of raw values of different platforms for CSF biomarkers and two widely used methods of hippocampal volume calculation, further promoting generalisability. With regards to CSF, the field is currently shifting away from manual assays such as Luminex xMAP and Innotest ELISA towards automated platforms such as Elecsys and Lumipulse. In the current study, we bridged Innotest values to Elecsys values.³¹ We used the same method to bridge Luminex to Elecsys values. For the calculation of brain volumes, there is more variation in software. We were able to bridge FSL FIRST data to Freesurfer. These two software packages are widely used, easily available, and have a clear pipeline.

A potential limitation of bridging different types of data is that it might cause additional noise on the risk prediction. However, this did not negatively affect the prognostic performance. Another limitation is that we used complete cases only in the analyses, resulting in

sample size variations, and that might introduce a degree of bias.²⁴ Lastly, the cohorts used in this study inevitably differed not only in the definition of the predictors but also in the outcome of Alzheimer's disease dementia. In validating prediction models, such differences might be intentional for two reasons.²⁴ First, for our models to have clinical usability, they should be aligned with clinical practice. And in clinical practice, differences in the definition of Alzheimer's disease dementia are inevitable. Second, using different definitions in the outcome measure of our analysis will provide information on whether the models can be extrapolated to different populations.

Among the strengths of our study are the size and heterogeneity of the cohorts used. Moreover, prediction models, especially when constructed with Cox proportional hazards analysis, are often not validated to the extent that we did.¹¹ We thoroughly tested for centre-specific effects and concluded that adjustment for centre could safely be omitted. This finding greatly enhances the generalisability and therefore the clinical applicability of our models. Of note, the models are of relevance for memory clinics and, perhaps, in a trial setting, and thus cannot be extrapolated to other settings, such as, for example, general practitioners. For risk stratification purposes, discrimination between those who will and those who will not progress to dementia is clearly the key indicator of model success or failure. But for a model to be used in clinical practice and to provide probabilistic information, calibration (ie, concordance between predicted and observed outcome) is very important. In the evaluation of prediction models, this aspect is often neglected. Specifically for Cox models, studies rarely report on the baseline survival function, which is required for calibration. We do report on the baseline survival function (appendix p 16), which we used to create the spreadsheet calculator. Because we ultimately want our study to support clinical practice, we did a strict type of calibration assessment, leading us to conclude that the models are well calibrated for predictions well beyond 5 years.¹¹

In conclusion, we have constructed and validated biomarker-based models for prediction of progression to dementia in individuals with MCI. We have shown the generalisability and robustness of the predictions and the models are freely available upon request. The models in this study could facilitate a more timely and accurate diagnosis, which is of high importance at the individual level even in the absence of specific therapies, as this is the starting point to plan and organise care. Prospective validation will be needed, preferably in a phase 3 randomised controlled trial.

Contributors

ISvM, JB and WMvF contributed to the study design. ISvM did the literature search, analysed the data, and created the figures. All authors contributed to the data collection and interpretation of results, reviewed and critically revised the manuscript, and approved the final version for submission.

Declaration of interests

All declared interests are outside of the submitted work. CET has functioned in advisory boards of Fujirebio and Roche, received non-financial support in the form of research consumables from ADxNeurosciences and Euroimmun, and performed contract research or received grants from Probiobdrug, Janssen Prevention Center, Boehringer, Brains Online, Axon Neurosciences, EIP Pharma, and Roche. PS has acquired grant support (for the institution) from GE Healthcare, Danone Research, Piramal, and MERCK. In the past 2 years, he has received consultancy or speaker fees (paid to the institution) from Lilly, GE Healthcare, Novartis, Sanofi, Nutricia, Probiobdrug, Biogen, Roche, Avraham, and EIP Pharma. FB is a board member for *Brain*, *Eur Radiology*, *Neurology*, *Multiple Sclerosis Journal*, and *Radiology*; and reports personal fees from Bayer-Schering, Biogen-Idec, TEVA, Merck-Serono, Novartis, Roche, Jansen Research, Genzyme-Sanofi, IXICO, GeNeuro, and Apitope; and grants from AMYPAD (IMI), EuroPOND (H2020), UK MS Society, Dutch MS Society, PICTURE (IMDI-NWO), National Institute for Health Research UCLH Biomedical Research Center, and ECTRIMS-MAGNIMS. LF has received research funding, consultancy fees, or speech honoraria from Allergan, Avid-Eli Lilly, Avanir, Avraham Pharmaceuticals, Axon Neuroscience, Axovant, Biogen, Boehringer Ingelheim, Eisai, Functional Neuromodulation, GE Healthcare, Lundbeck, Merck Sharpe & Dohme, Novartis, Pfizer, Piramal Imaging, Roche, and Schwabe Pharma. JW has acquired research support (for the institution) from Immunogenetics and TECAN-IBL; consultancy fees from Lilly, Roche Pharma, Merck Sharp & Dohme, Boehringer-Ingelheim, and Abbot EPD; speech honoraria from Roche Pharma, Helios Klinikum Wuppertal, Vitos Kurhessen-Bad Emstal, Pfizer, Janssen, AGNP, and Actelion; and has two patents (PCT/EP 2011 001724: new formulations for diagnosis of Alzheimer's disease and PCT/EP 2015 052945: biosensor for conformation and secondary structure analysis). OP reports grants and personal fees from Roche and Biogen and grants from Novartis, Eisai, Lilly, and Pharmatrophix. HH is an employee of Eisai and serves as Senior Associate Editor for the *Journal Alzheimer's & Dementia*; he has received lecture fees from Biogen, Roche, and Eisai; research grants from Pfizer, Avid, and MSD Avenir (paid to the institution); travel funding from Functional Neuromodulation, Axovant, Eli Lilly, Takeda and Zinfandel, GE Healthcare, and Oryzon Genomics, consultancy fees from Qynapse, Jung Diagnostics, Cytox, Axovant, Anavex, Takeda and Zinfandel, GE Healthcare and Oryzon Genomics, and Functional Neuromodulation; and has participated in scientific advisory boards for Functional Neuromodulation, Axovant, Eli Lilly, Cytox, GE Healthcare, Takeda and Zinfandel, Oryzon Genomics, and Roche Diagnostics. HH is co-inventor in the following patents as a scientific expert and has received no royalties: in vitro multiparameter determination method for the diagnosis and early diagnosis of neurodegenerative disorders patent number: 8916388; in vitro procedure for diagnosis and early diagnosis of neurodegenerative diseases patent number: 8298784; neurodegenerative markers for psychiatric conditions publication number: 20120196300; in vitro multiparameter determination method for the diagnosis and early diagnosis of neurodegenerative disorders publication number: 20100062463; in vitro method for the diagnosis and early diagnosis of neurodegenerative disorders publication number: 20100035286; in vitro procedure for diagnosis and early diagnosis of neurodegenerative diseases publication number: 20090263822; in vitro method for the diagnosis of neurodegenerative diseases patent number: 7547553; CSF diagnostic in vitro method for diagnosis of dementias and neuroinflammatory diseases publication number: 20080206797; in vitro method for the diagnosis of neurodegenerative diseases publication number: 20080199966; and neurodegenerative markers for psychiatric conditions publication number: 20080131921. BV reports grants and personal fees from Biogen, MSD, Lilly, and Roche. SL has, within the past 5 years, held research grants with funding from multiple industry partners through the IMI funding scheme and with AstraZeneca. He is currently an employee of Janssen R&D. GC reports grants from Institut National de la Santé et de la Recherche Médicale (Inserm); Fondation Plan Alzheimer (Alzheimer Plan 2008-2012); Programme Hospitalier de Recherche Clinique (PHRCN 2011-A01493-38 and PHRCN 2012 12-006-0347); Agence Nationale de la Recherche (LONGVIE 2007); Région Basse-Normandie; Association France Alzheimer et maladies apparentées; Fondation Vaincre Alzheimer;

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Data sharing

The corresponding author can provide the dataset used or documentation on the analysis performed upon reasonable request.

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For the ADNI database see <http://adni.loni.usc.edu>

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