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Development and assessment of algorithms for predicting brain amyloid positivity in a population without dementia

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Abstract

Background The accumulation of amyloid-β (Aβ) peptide in the brain is a hallmark of Alzheimer's disease (AD), occurring years before symptom onset. Current methods for quantifying in vivo amyloid load involve invasive or costly procedures, limiting accessibility. Early detection of amyloid positivity in non-demented individuals is crucial for aiding early AD diagnosis and for initiating anti-amyloid immunotherapies at early stages. This study aimed to develop and validate predictive models to identify brain amyloid positivity in non-demented patients, using routinely collected clinical data.

Methods Predictive models for amyloid positivity were developed using data from 853 non-demented participants in the MEMENTO cohort. Amyloid levels were measured potentially repeatedly during study course through Positron Emision Tomography or CerebroSpinal Fluid analysis.

The probability of amyloid positivity was modelled using mixed-effects logistic regression. Predictors included demographic information, cognitive assessments, visual brain MRI evaluations of hippocampal atrophy and lobar microbleeds, AD-related blood biomarkers (Aβ42/40 and P-tau181), and ApoE4 status. Models were subjected to internal cross-validation and external validation using data from the Amsterdam Dementia Cohort. Performance also was evaluated in a subsample that met the main criteria of the Appropriate Use Recommendations (AUR) for lecanemab.

Results The most effective model incorporated demographic data, cognitive assessments, ApoE status, and AD-related blood biomarkers, achieving AUCs of 0.82 [95%CI 0.81-0.82] in MEMENTO sample and 0.90 [95%CI 0.86-0.94] in the external validation sample. This model significantly outperformed a reference model based solely on demographic and cognitive data, with an AUC difference in MEMENTO of 0.10 [95%CI 0.10-0.11]. A similar model without ApoE genotype achieved comparable discriminatory performance. MRI markers did not improve model performance. Performances in AUR of lecanemab subsample were comparable.

Conclusion A predictive model integrating demographic, cognitive, and blood biomarker data offers a promising method to help identify amyloid status in non-demented patients. ApoE genotype and brain MRI data were not necessary for strong discriminatory ability, suggesting that ApoE genotyping may be deferred when assessing the risk-benefit ratio of immunotherapies in amyloid-positive patients who desire treatment. The integration of this model into clinical practice could reduce the need for lumbar puncture or PET examinations to confirm amyloid status.

Keywords Prediction, Amyloid, Biomarker, Alzheimer's disease, Immunotherapy

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Background

The accumulation of brain amyloid-β (Aβ) plaques is a key pathological feature of Alzheimer's disease (AD), which can occur several years before the onset of objective cognitive impairment [1, 2]. Aβ plaque targeting is a potential approach to modifying disease progression. Recent clinical trials have shown that high-clearance anti-amyloid immunotherapies (gantenerumab, aducanumab, lecanemab, and donanemab) effectively remove amyloid plaques, as measured by amyloid-PET [3–6]. Beyond biological efficacy, lecanemab and donanemab exhibit modest clinical effects on cognitive and functional decline in early AD. Aducanumab, lecanemab, and more recently, donanemab, have been approved by the United States Food and Drug Administration (FDA).

Anti-amyloid immunotherapies are only approved for amyloid-positive patients in the early stages of AD. Early intervention aimed at reducing Aβ accumulation in cognitively normal amyloid-positive individuals is under investigation as a potential strategy to alter disease progression [7].

Anti-Amyloid clinical trials consistently reported that the risk of amyloid-related imaging abnormalities (ARIA) is higher in patients receiving active anti-amyloid immunotherapies. Although most ARIA cases are asymptomatic, some patients experience headaches, confusion, visual disturbances, and, in rare instances, life-threatening complications [8]. A higher risk of ARIA is associated with apolipoprotein E (ApoE) homozygous ε4 allele carriage, higher treatment doses, the presence of baseline cerebral microhaemorrhages or cortical superficial siderosis, and the use of antithrombotics [9]. Although anticoagulant treatments and significant vascular lesions on magnetic resonance imaging (MRI) are contraindications for lecanemab treatment, ApoE4 status (even homozygous ε4 allele carriage) is not a formal contraindication according to the U.S. Appropriate Use Recommendations (AUR) for lecanemab [10]. However, it is recommended to determine ApoE4 status and discuss the risk-benefit ratio before starting treatment [10].

In this new era of anti-amyloid treatments, only two methods are available in clinical practice to detect cerebral amyloid: lumbar puncture (LP) for cerebrospinal fluid (CSF) collection and amyloid positron emission tomography (PET) neuroimaging. These procedures are either invasive or expensive, and only available in specialised clinical centres. Such limitations create practical, economic, and accessibility challenges in identifying eligible candidates for these treatments, emphasising the need for accurate and accessible tools to determine amyloid status.

In this context, we aimed to develop predictive models for amyloid positivity in individuals with subjective cognitive complaints or mild cognitive impairment, using measures routinely collected in clinical practice, and to evaluate their performance in a population that met the main criteria of the AUR for lecanemab.

Methods

Participants and data collection

The MEMENTO cohort, a French prospective clinical study, consecutively recruited 2,323 participants from 26 memory clinics between April 2011 and June 2014. Eligible participants had either subjective cognitive complaints (SCC) or mild cognitive impairment (MCI) with a Clinical Dementia Rating (CDR) score ≤ 0.5 (no dementia). Exclusion criteria were a history of head trauma resulting in persistent neurological deficits, recent stroke with ongoing neurological impairments during the preceding 3 months, brain tumour, epilepsy, schizophrenia, a known gene mutation for autosomal dominant AD, and illiteracy. Participants attended follow-up every six to twelve months for five years. A comprehensive clinical examination was conducted at each visit, and participants underwent an annual neuropsychological assessment. Brain MRI was conducted at baseline and every two years, along with blood sampling for biobank storage. According to the protocol, both examinations were mandatory at baseline. Lumbar puncture and amyloid PET imaging were optional. The study procedures have been previously published [11].

In this project, the study population was restricted to participants aged ≥ 60 years with known amyloid status and without dementia at the time of amyloid status determination (see the flowchart in Fig. 1A).

Determination of amyloid status

Amyloid status was assessed using amyloid PET and CSF analysis. A lumbar puncture was repeatedly offered during on-site visits, with a maximum of three procedures per participant. The levels of amyloid-β 42 (Aβ42) and amyloid-β 40 (Aβ40) peptides in CSF from the centralised biobank were analysed using the standardised sandwich immunoassay method with the commercial INNOTEST Kit (Fujirebio, Belgium). Participants were classified as CSF-amyloid positive if their Aβ42 level was < 750 pg/mL.

Two optional ancillary studies, Insight-PreAD (at inclusion) and MEMENTO-AmyGing (initiated on average 2 years after baseline), provided amyloid PET images for a subsample of MEMENTO participants [12, 13]. In these ancillary studies, a second examination was offered 2 years later. The Center for Image Acquisition and Processing (CATI; http://cati-neuroimaging.com/) ensured the standardisation of amyloid PET imaging acquisition and performed quality control checks and post-processing of the PET images.

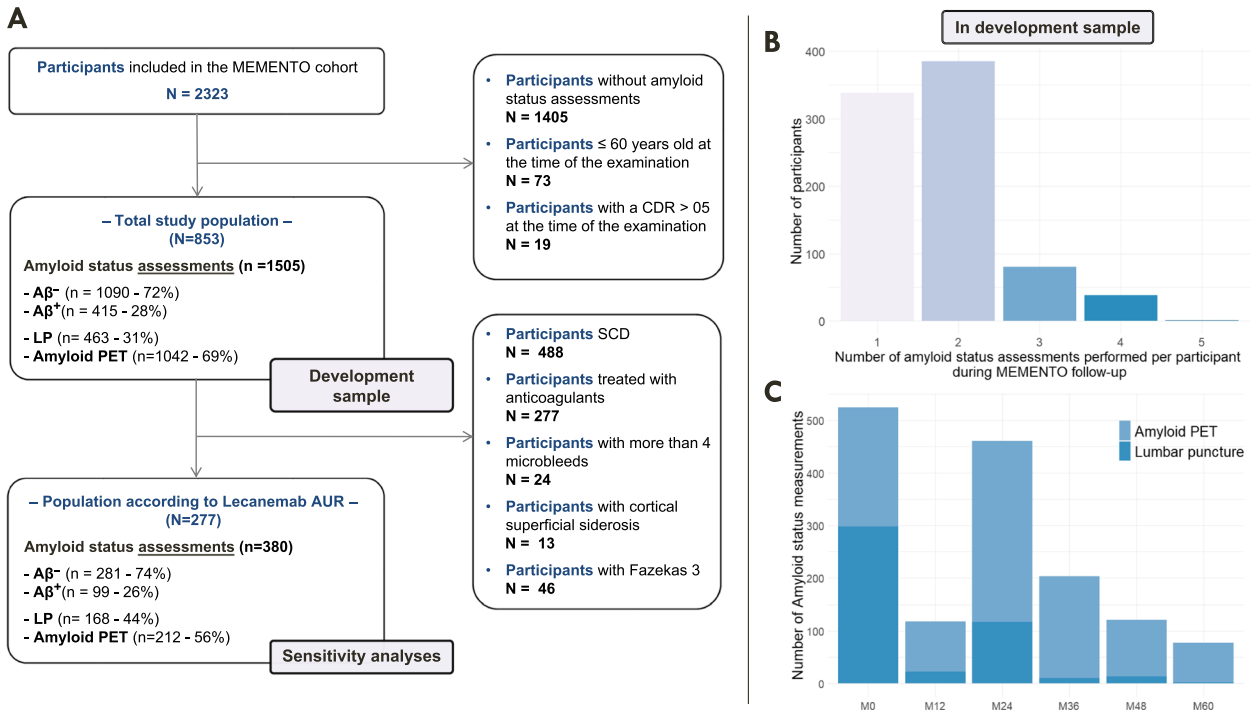

Fig. 1 Selection and distribution of amyloid assessments. The MEMENTO cohort, France, 2011–2014. **A** Flowchart of the study. **B** Number of amyloid assessments available per participant. **C** Amyloid assessments at each annual follow-up visit. CDR: Clinical Dementia Rating scale, ApoE: apolipoprotein E, Aβ: amyloid beta, amyloid PET: amyloid positron emission tomography, LP: lumbar puncture, SCD: subjective cognitive decline. An individual could meet more than one exclusion criterion

Depending on the centre, PET imaging was performed using either 18 F-Florbetapir (18 F-AV45, Amyvid) or 18 F-Flutemetamol (Vizamyl). Amyloid positivity was defined as a standard uptake value ratio (SUVr) of >0.88 for Florbetapir and >1.063 for Flutemetamol [14].

In total, 1505 amyloid assessments (CSF or PET) were available; 59% of the participants ($n=504$) had more than one amyloid measurement available (Fig. 1C). The analyses were conducted using amyloid status as the statistical unit.

The high concordance between Aβ42 concentrations in CSF and amyloid PET results (with Florbetapir or Flutemetamol) in patients with mild cognitive impairment justified considering these three methods to be interchangeable for amyloid status determination [15, 16].

Predictors of amyloid positivity

Candidate predictors were selected based on a literature review and their availability. For predictors collected or measured repeatedly over time, the measurement closest to the amyloid assessment (CSF or PET) was used. Predictors were categorised into demographic and health factors, cognition factors, blood and genetic factors, and brain-imaging factors, as described below.

Demographic and health factors

During face-to-face interviews, information was collected regarding age, sex, level of education, body mass index (BMI), and family history of dementia. The French baccalaureate was considered a high educational level; a family history of dementia was recorded if at least one grandparent, parent, aunt, uncle, first cousin, or sibling had been affected.

Cognition factors

At each annual on-site visit, a comprehensive neuropsychological test battery was administered to assess memory, executive functions, language, and attention. Levels of performance on the following four cognitive tests were considered potential predictor variables: (i) the Mini-Mental Score Examination (MMSE) as a global measure of cognitive performance, (ii) the sum of the three free recalls from the Free and Cued Selective Reminding Test (FCSRT) as a measure of memory performances [17], (iii) semantic verbal fluency (number of animals named in 120 s) [18], and (iv) the Trail-Making Test B (TMTB) for executive functions measured by the time required to complete the task [19]. Investigators and neuropsychologists received training to ensure standardised scoring while administering the neuropsychological test

battery. FCRST and semantic verbal fluency scores were standardised.

Blood and genetic factors

Baseline blood samples were centrally stored at -80 °C in the Genomic Analysis Laboratory-Biological Resource Centre (LAG-CRB) at the Pasteur Institute, Lille (BB-0033-00071). The ratio between blood levels of Aβ42 and Aβ40 (Aβ42/40) and the phosphorylated tau (P-tau181) concentration were measured in plasma and serum samples using Simoa technology and commercial kits on a Quanterix HD-X Analyzer. Specifically, the Neurology 3-Plex A Advantage Kit (item no. 101995) was used for Aβ42 and Aβ40, and the P-tau181 Advantage V2 Kit (item no. 103714) was used for P-tau181. These analyses were performed at the research platform of Bordeaux University Hospital (Bordeaux Biothèques Santé, Center for Biological Resources). The Aβ42/40 ratio and P-tau181 concentration were measured in all baseline blood samples, then used in the models as continuous standardised log-transformed variables.

The apolipoprotein E (ApoE) genotype (0, 1, or 2 alleles) was determined by KBiosciences (UK) [11]. The number of ε4 alleles was included as a categorical predictor variable in the models.

Brain-imaging factors

Brain MRI was performed on 1.5- or 3-Tesla MRI scanners at all centres, at inclusion and at the 2- and 4-year follow-ups. Similar to the amyloid PET acquisitions, MRI scans were centralised, quality-controlled, and post-processed by CATI.

We considered two MRI markers visually assessed: hippocampal atrophy and the number of lobar cerebral microbleeds (CMBs). The Scheltens scale for hippocampal atrophy scoring was used, and the highest atrophy score (from 0 to 4) between the right and left hippocampus was considered [20]. CMBs were visually evaluated by a team at the Toulouse Department of Neurology (Hôpital Pierre-Paul Riquet) from T2*-GRE MRI sequences using the Microbleed Anatomical Rating Scale (MARS) to assess the presence, quantity, and distribution of CMBs [21]. Microbleeds were categorised as lobar (in cortical and cortico-subcortical areas) or deep (in the basal ganglia, thalamus, or brainstem). The number of lobar CMBs was used as a continuous variable in the models.

The Amsterdam dementia cohort (ADC)

The ADC cohort, established at the Alzheimer Center Amsterdam within the Amsterdam University Medical Center since 2000, aims to support patients while advancing disease research [22]. Participants were included for external validation using the same inclusion criteria as the development sample (age ≥ 60 years, CDR ≤ 0.5, with CSF or PET amyloid measurement within 1 year of plasma biomarker measurement). Variables differing between the development and validation studies are presented in Table S1.

Statistical analysis

Participant characteristics were described both globally and according to amyloid positivity status, with frequencies and percentages for qualitative variables and with medians and first and third quartiles (Q1-Q3) for quantitative variables in both the development and external validation samples. The development of the prediction models followed the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis (TRIPOD) recommendations [23].

The baseline model (Model 1) was computed using only cognitive, demographic, and health variables (Fig. 2). Subsequently, combinations of other predictors (ApoE4 status, AD-related blood biomarkers, and brain imaging) were incorporated (Models 2–6; Fig. 2). These nested models reflect the range of daily routine clinical data available to memory clinic physicians.

Because a participant's amyloid status could be measured at multiple time points during follow-up using two techniques (CSF and amyloid PET), we utilised mixed-effect logistic regression models to predict amyloid status, with a random effect on the intercept to adjust for the non-independence of the measurements. Model performance was assessed using the following metrics:

1. Brier score (BS) for prediction errors, ranging from 0 to 1, with a lower score indicating better model performance.
2. Area Under Curve (AUC) and Receiving Operator Characteristic (ROC) curve for discrimination, ranging from 0 to 1, with 1 indicating perfect discrimination ability.
3. Calibration curves for agreement between predicted and observed probabilities of amyloid positivity, where a smaller gap between the bisector of the graph and the model's prediction curve indicates better calibration.
4. Global accuracy evaluated using the Youden Index, which maximises both sensitivity (true positive rate) and specificity (true negative rate). The specificity of each model was determined at a fixed sensitivity of 0.9, adapting the recommendations of the Global CEO Initiative on Alzheimer's Disease for the acceptable performance of blood biomarker tests for amyloid pathology [24].

		Model 1	Model 2	Model 3	Model 4	Model 5	Model 6
Demographic and health predictors	Age	x	x	x	x	x	x
	Sex	x	x	x	x	x	x
	Level of education	x	x	x	x	x	x
	Family history of AD	x	x	x	x	x	x
	BMI	x	x	x	x	x	x
Cognitive predictors	MMSE	x	x	x	x	x	x
	Memory test	x	x	x	x	x	x
	Verbal fluency (animals)	x	x	x	x	x	x
	TMT B	x	x	x	x	x	x
Genetic predictors	ApoE4 allele		x			x	x
Blood predictors	Aβ42/40			x		x	x
	Ptau181			x		x	x
MRI predictors	Hippocampal atrophy				x		x
	Lobar microbleeds				x		x

Fig. 2 Distribution of predictors according to the six amyloid-status prediction models. The MEMENTO cohort, France, 2011–2014. Aβ: amyloid beta, BMI: body mass index, memory test: Free and Cued Selective Reminding Test (FCSRT) used in the MEMENTO cohort and the Rey Auditory Verbal Learning Test (RAVLT) in the external validation cohort ADC, TMT B: Trail-Making Test B, MMSE: Mini-Mental State Examination, CDR: Clinical Dementia Rating scale, ApoE: apolipoprotein E, MRI: magnetic resonance imaging

The added value of Models 2 to 6 relative to the baseline model (Model 1) was estimated and referred to as AUC Delta and Brier score Delta, respectively.

Missing data for predictors (Table S2) were imputed using the multivariate imputation by chained equations (MICE) method (MICE package in R software). Twenty imputed datasets were generated, considering sets of measures in clusters for the same participant. For each imputed dataset, fivefold repeated cross-validation (50 iterations) was implemented to calculate Brier scores and AUCs (BS_{cv} and AUC_{cv}), along with their corresponding variances. The final equation for each prediction model, as well as the associated performance indicators, was obtained by pooling the results of the twenty imputed datasets in accordance with Rubin's rule [25].

The linearity assumptions of quantitative variables were checked using Fractional Polynomials (mfp package in R software) of order 2, and variables were transformed if necessary [26]. Both AD-related blood biomarker variables were log-transformed, and the lobar microbleeds variable was square-root transformed.

External validation : the Amsterdam dementia cohort (ADC)

The equations of the six prediction models were applied to the ADC sample for external validation, and their discriminatory power was evaluated by calculating the AUC. The difference in amyloid positivity prevalence between the development and validation samples was addressed by adjusting the intercept of each model, using the ratio of prevalence in the validation sample to prevalence in the development sample [27].

Sensitivity analyses

We tested the models' abilities to predict amyloid positivity in a subsample of participants who met the main exclusion criteria of the AUR for lecanemab. This subsample excluded participants who had subjective cognitive decline, were receiving anticoagulant therapy, had

more than four cerebral microbleeds, presented with cortical superficial siderosis, or had severe white matter hyperintensities (Fazekas 3).

Cortical superficial siderosis was investigated by a team at the Toulouse Department of Neurology, and white matter hyperintensity volumetry was determined using the automated WHASA software, complemented by a visual assessment performed centrally at CATI by two trained physicians using the Fazekas scale [28, 29].

Due to the significantly increased risk of ARIA in individuals homozygous for ApoE ε4, the prescription of anti-amyloid drugs for these patients remains an open question. For this reason, the models also were tested on the AUR population for lecanemab, excluding ApoE ε4 homozygous individuals.

A second sensitivity analysis aimed to assess the impact of the delay between baseline measurements of AD-related blood biomarkers and the determination of amyloid status on model performance. The elapsed time between these measurements was included as a covariate in the models. By testing the statistical significance of this delay variable, we sought to determine whether time-related changes in biomarker levels could affect prediction accuracy.

Analyses were conducted using R (version 4.1.3) and SAS 9.4.

Results

Among the 2323 individuals enrolled in MEMENTO, 853 were included in the models development population (development sample) (Fig. 1A), comprising 1505 amyloid evaluations (504 individuals with at least two measurements, Fig. 1B). Among these 504 individuals, 92% maintained a stable amyloid status throughout the follow-up period, while 8% experienced a change in amyloid status. Most amyloid examinations in MEMENTO participants were performed at baseline and after 2 years of follow-up (Fig. 1C). Of these examinations, 31% were LPs and 69% were amyloid PET scans (48% Florbetapir amyloid PET, 21% Flutemetamol amyloid PET).

Characteristics of development and validation samples

Table 1 describes participant characteristics at the time of amyloid status determination in the development and external validation samples. In the MEMENTO analytical sample, a participant could undergo multiple amyloid status assessments during the course of the study. Amyloid status was positive in 28.0% of examinations in the development sample and in almost half (49.2%) of those in the validation sample.

Compared to the development sample, participants in the ADC sample were younger (68 vs. 74 years), had a higher frequency of a family history of AD (54% vs. 38%), included a larger proportion of men (62% vs. 43%), had a higher rate of MCI (CDR = 0.5; 57% vs. 42%), and had a higher rate of ApoE ε4 allele homozygosity (13.8% vs. 3.1%).

In both the development and external validation samples, Aβ positivity was associated with older age, worse cognitive performance, higher ApoE ε4 carriage, and more severe hippocampal atrophy. Additionally, the blood Aβ42/40 ratio was lower, and the level of P-tau181 was nearly two-fold higher in Aβ + participants than in Aβ- participants.

Predictive performance and accuracy of the models

The performances of the six prediction models in the development sample are shown in Fig. 3, with the associated odds ratios displayed in Table S3. Model 1, which included only demographic and cognitive predictors, demonstrated moderate predictive performance with an AUC_{cv} of 0.72 [95% CI 0.71–0.72] and a BS_{cv} of 0.17 [95% CI 0.17–0.17] (Fig. 3A).

Compared with the reference Model 1, predictive performance improved with the inclusion of ApoE status (Model 2, AUC_{cv} = 0.76 [95% CI 0.75–0.76], BS_{cv} = 0.16 [95% CI 0.16–0.16]), as well as AD-related blood biomarkers (Model 3, AUC_{cv} = 0.80 [95% CI 0.79–0.80], BS_{cv} = 0.15 [95% CI 0.15–0.15]). Conversely, the addition of hippocampal atrophy and lobar microbleeds to Model 1 did not enhance predictive performance (Model 4, AUC_{cv} = 0.71 [95% CI 0.70–0.72], BS_{cv} = 0.17 [95% CI 0.17–0.18]). The best performance was obtained when demographic, cognitive, ApoEε4, and AD-related blood variables were included in the same model (Model 5, AUC_{cv} = 0.82 [95% CI 0.81–0.82], BS_{cv} = 0.14 [95% CI 0.14–0.15]). The addition of MRI variables to Model 5 did not further enhance predictive performance (Model 6, AUC_{cv} = 0.81 [95% CI 0.80–0.82], BS_{cv} = 0.14 [95% CI 0.14–0.16]). Thus, although its performance was similar to that of Model 6, Model 5 was more parsimonious. Excluding Model 6, the best balances of sensitivity and specificity according to Youden's index were observed for Models 5 and 3 (Model 5: Se = 0.64/Sp = 0.84, Model 3: Se = 0.77/Sp = 0.69). When sensitivity was fixed at 0.9, Models 5 and 3 demonstrated the highest specificities of 0.48 and 0.39, respectively. All calibration curves in the training set showed that the predictions had high accuracy and reliability compared with actual observations (Fig. 3B).

The models were also tested by adding all significant interactions between the different variables of the six models. No improvement in performance was observed (results not shown). For the sake of parsimony and to ensure the simplicity and interpretability of the models, we therefore chose to retain the version without interactions.

To explore the impact of reducing the number of variables, we assessed three simplified models, each retaining

Table 1 Distribution of characteristics according to amyloid status in the development (*N* = 1505) and external validation (*N* = 260) samples

	Development set: MEMENTO			Validation set: ADC		
	Aβ $^-$	Aβ $^+$	Total	Aβ $^-$	Aβ $^+$	Total
N (%)	1090 (72.4)	415 (27.6)	1505	132 (50.8)	128 (49.2)	260
Characteristics at amyloid assessment:						
Demographics						
Sex female - n (%)	629 (57.7)	230 (55.4)	859 (57.1)	37 (28.0)	61 (47.7)	98 (37.7)
Age (years) - median [Q1-Q3]	73.3 [67.9–77.6]	76,5 [72,1–80,1]	74,3 [68,8–78,3]	66.5 [63.2–70.0]	68.7 [65.5–71.4]	67.6 [63.9–71.2]
High educational level* - n (%)	520 (47.8)	172 (41.4)	692 (46.0)	35 (26.5)	31 (24.2)	66 (25.4)
Family history of AD - n (%)	346 (31.9)	143 (34.6)	489 (32.7)	58 (43.9)	83 (64.8)	141 (54.2)
BMI < 25 kg/m^2- n (%)	517 (47.4)	220 (53.0)	737 (49.0)	50 (37.9)	72 (56.2)	122 (46.9)
Cognition						
Memory test[a] (number of words) - median [Q1-Q3]:						
FCSRT – Free recall	31 [26–35]	26 [17–32]	30 [24–34]	-	-	-
RAVLT – Free recall	-	-	-	20 [15–25]	20 [15–25]	20 [15–25]
TMT B (time in seconds) - median [Q1-Q3]	84 [65–110]	105 [79–152]	89 [67–117]	90.0 [71.8-123.2]	104.0 [78.8-138.8]	95.5 [75-131.2]
Verbal fluency (animals)[b] (number of words) - median [Q1-Q3]:						
Conducted in 2 min	30 [24–36]	28 [21–34]	29 [23–35]	-	-	-
Conducted in 1 min	-	-	-	20 [17-24.2]	19 [16–23]	12 [16–24]
MMSE (total score) - median [Q1-Q3]	29 [28–30]	28 [26–29]	29 [27–30]	28 [27–29]	27 [26–29]	28 [26–29]
CDR = 0 - n (%)	660 (61.7)	194 (48.1)	854 (58.0)	73 (55.3)	39 (30.5)	112 (43.1)
CDR = 0.5 - n (%)	409 (38.3)	209 (51.9)	618 (42.0)	59 (44.7)	89 (69.5)	148 (56.9)
Genetic						
Presence of ApoE ε4 alleles - n (%)						
No ε4 allele	799 (76.6)	189 (47.1)	988 (68.4)	105 (79.5)	28 (21.9)	133 (51.2)
1 ε4 allele	229 (22.0)	182 (45.4)	411 (28.5)	26 (19.7)	65 (50.8)	91 (35.0)
2 ε4 alleles	15 (1.4)	30 (7.5)	45 (3.1)	1 (0.8)	35 (27.3)	36 (13.8)
Blood						
AB42/40 ratio - median [Q1-Q3]	0.06 [0.05–0.07]	0.05 [0.04–0.06]	0.06 [0.05–0.06]	0.06 [0.05–0.06]	0.05 [0.05–0.06]	0.05 [0.05–0.06]
Ptau181 - median [Q1-Q3]	0.70 [0.48–0.98]	1.20 [0.82–1.75]	0.79 [0.51–1.21]	1.4 [1.1–1.7]	2.1 [1.7–2.6]	1.7 [1.3–2.3]
MRI						
Hippocampal atrophy						
No atrophy - n (%)	106 (9.8)	21 (5.1)	127 (8.5)	44 (33.3)	39 (30.5)	83 (31.9)
Possible atrophy - n (%)	729 (67.6)	208 (50.5)	937 (62.9)	64 (48.5)	56 (43.8)	120 (46.2)
Discrete atrophy - n (%)	175 (16.2)	109 (26.5)	284 (19.1)	22 (16.7)	28 (21.9)	50 (19.2)
Moderate atrophy - n (%)	55 (5.1)	62 (15.0)	117 (7.9)	2 (1.5)	5 (3.9)	7 (2.7)
Severe atrophy- n (%)	13 (1.2)	12 (2.9)	25 (1.7)	0 (0.0)	0 (0.0)	0 (0.0)
Lobar microbleeds[c] - median [min - max]	0 [0–50]	0 [0–25]	0 [0–50]	0 [0–20]	0 [0-100]	0 [0-100]

Note Sample characteristics according to amyloid status were evaluated at the time of the examination in the MEMENTO population; the same participant might have contributed multiple times

Aβ Amyloid beta, *BMI* Body mass index, *ADC* Alzheimer Disease Cohort, *FCSRT* Free and Cued Selective Reminding Test, *TMT B* Trail-Making Test B, *MMSE* Mini-Mental State Examination, *CDR* Clinical Dementia Rating scale, *ApoE* apolipoprotein E

* High educational level: above the baccalaureate, [a]The recall memory test used in the MEMENTO cohort was the Free and Cued Selective Reminding Test (FCSRT) and the Rey Auditory Verbal Learning Test (RAVLT) was used in the external validation cohort ADC, [b]The verbal fluency test (animals) was conducted for 2 min in MEMENTO and for 1 min in ADC, [c]in ADC, all cerebral microbleeds were used

A

	Training set: MEMENTO						Validation set: ADC
	AUC [IC95%]	AUC Delta [IC95%]	BS [IC95%]	BS Delta [IC95%]	Se/Sp (YI)	Specificity (Se = 09)	AUC [IC95%]
Model 1 *Demographic and cognitive predictors*	0.72 [0.71; 0.72]	--	0.17 [0.17; 0.17]	--	054 / 080	026	0.63 [0.57; 0.70]
Model 2 *Model 1 and ApoE4*	0.76 [0.75; 0.76]	0.041 [0.034; 0.045]	0.16 [0.16; 0.16]	-0.011 [-0.012; -0.009]	049 / 087	034	0.83 [0.78; 0.88]
Model 3 *Model 1 and blood biomarkers*	0.80 [0.79; 0.80]	0.080 [0.075; 0.085]	0.15 [0.15; 0.15]	-0.020 [-0.021; -0.018]	077 / 069	039	0.83 [0.78; 0.88]
Model 4 *Model 1 and MRI*	0.71 [0.70; 0.72]	-0.002 [-0.008; 0.005]	0.17 [0.17; 0.18]	0.001 [-0.001; 0.003]	060 / 074	025	0.65 [0.58; 0.71]
Model 5 *Model 1. ApoE4. and blood biomarkers*	0.82 [0.81; 0.82]	0.102 [0.096; 0.108]	0.14 [0.14; 0.15]	-0.029 [-0.030; -0.027]	064 / 084	048	0.90 [0.86; 0.94]
Model 6 *Model 1. ApoE4. blood biomarkers. and MRI*	0.81 [0.80; 0.82]	0.096 [0.089; 0.103]	0.14 [0.14; 0.15]	-0.027 [-0.029; -0.025]	061 / 086	044	0.90 [0.86; 0.94]

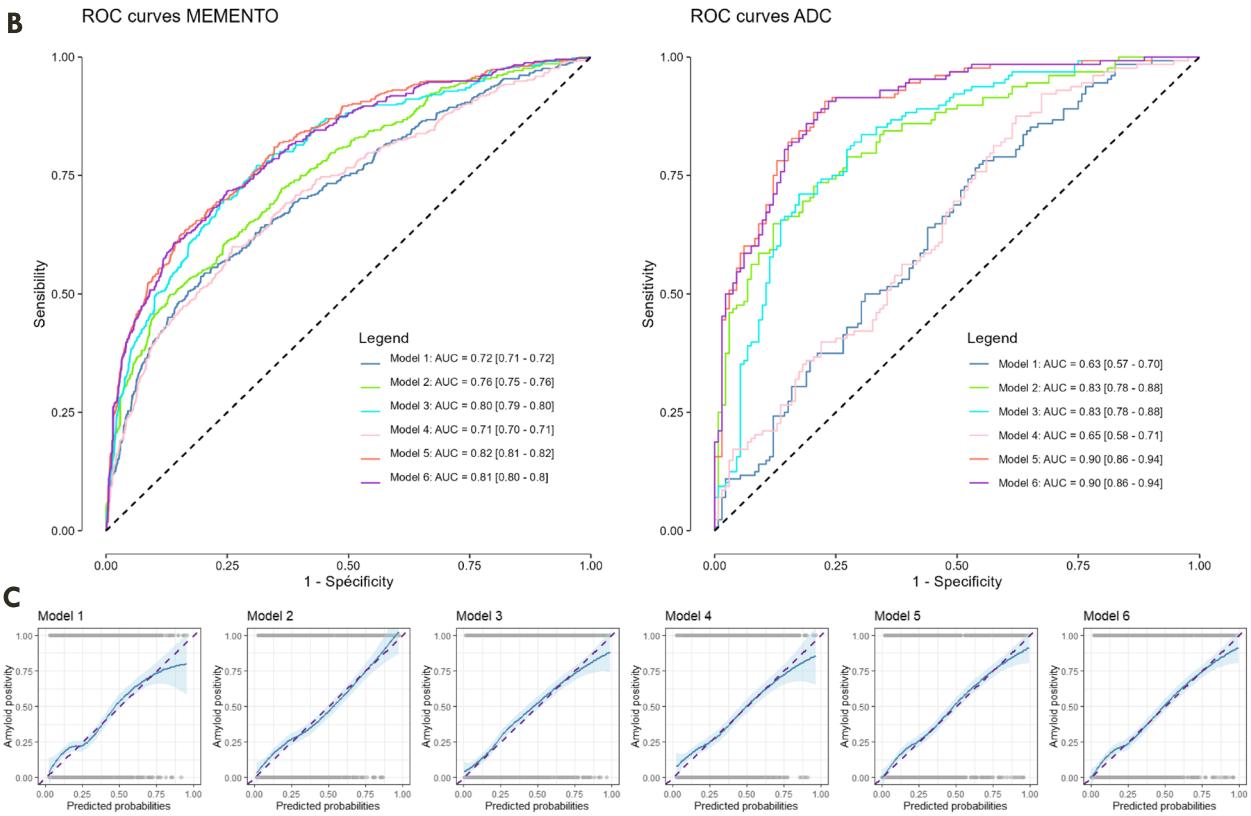

Fig. 3 Development and validation of six Aβ-positivity prediction models. The MEMENTO and ADC studies. **A** Discrimination, error predictions, and performance. **B** ROC curves in a development (MEMENTO) and training set (ADC). **C** Calibration plots in the training set. BS: Brier score, AUC: area under the curve, Se/Sp: sensitivity/specificity, ApoE: apolipoprotein E, YI: Youden Index

only the significant predictive variables (refer to table S3): (Model 2') age, memory test, and ApoE4 status, (Model 3') age, memory test, and AD-related blood biomarkers, and (Model 5') age, memory test, ApoE4 status, and AD-related blood biomarkers. Interestingly, simplifying the models in this way did not result in any meaningful changes in predictive performance (results not shown). Despite this, we opted to retain the broader set of variables to ensure that the models capture all potentially relevant factors influencing amyloid positivity, particularly considering the heterogeneity across different clinical populations.

In the external validation sample, results were consistent, the predictive performance of Model 1 improved with the addition of ApoE and/or AD-related blood biomarkers (Model 1, AUC = 0.63 [95%

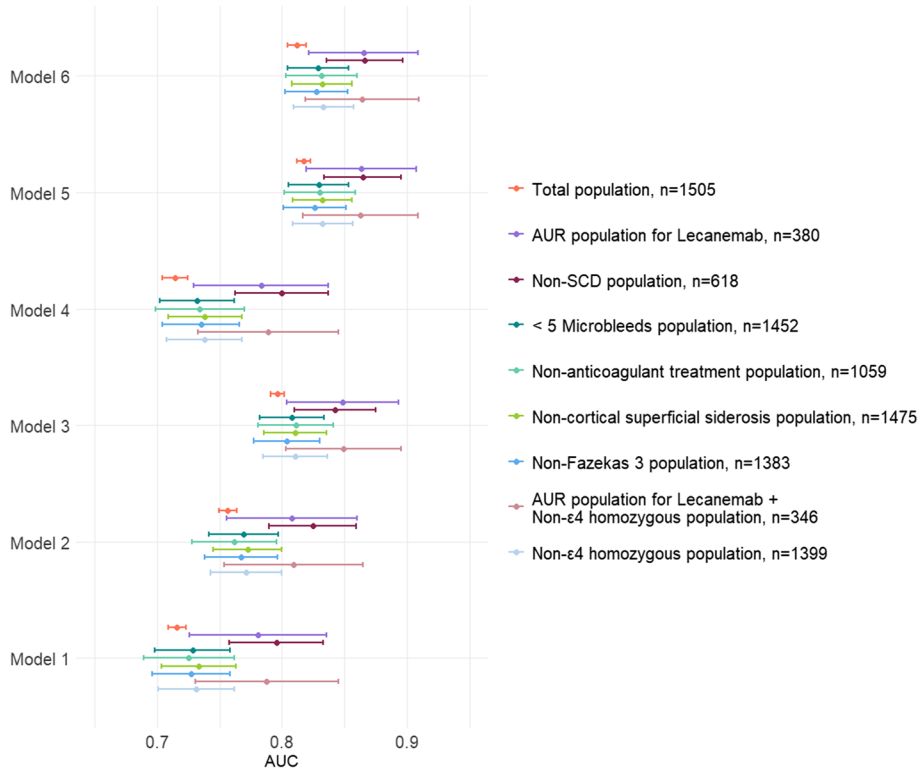

Fig. 4 Discrimination performance of six Aβ prediction models overall and in subsamples following the AUR criteria. The MEMENTO Cohort, France, 2011–2014. Model 1: demographic and cognitive predictors, Model 2: Model 1 and ApoE4 status, Model 3: Model 1 and blood biomarkers, Model 4: Model 1 and MRI, Model 5: Model 1, ApoE4 status, and blood biomarkers, Model 6: Model 1, ApoE4 status, blood biomarkers, and MRI. AUC: area under the curve, AUR: Appropriate Use Recommendations, SCD: subjective cognitive decline, ε4 homozygous: homozygous for ApoE ε4. AUR population for lecanemab: population without SCD participants, without anticoagulant treatment, without siderosis, without severe subcortical hyperintensities consistent with a Fazekas score of 3, and with fewer than five cerebral microbleeds. Total population: population used to develop the predictive algorithm

CI 0.57–0.70], Models 2 and 3, AUC = 0.83 [95% CI 0.78–0.88]), but not with the addition of MRI variables (Model 4, AUC = 0.65 [95% CI 0.58–0.71, Model 6, AUC = 0.90 [95% CI 0.86–0.94]). Model 5 showed the best performance in this population, with an AUC of 0.90 [95% CI 0.86–0.94].

Sensitivity analyses

Model performances in the MEMENTO AUR subsample are shown in Fig. 4. The estimated AUCs were slightly higher than in the initial analytic sample; a significant increase was only observed for Models 1 and 4. The exclusion of participants with SCD alone led to a significant improvement in AUC for all six models; use of the other four exclusion criteria did not result in significant changes. Models 3 and 5 were the most effective, with respective AUCs of 0.85 [0.80; 0.89] and 0.86 [0.82; 0.91] (Fig. 4).

The exclusion of ApoE ε4 homozygous participants did not significantly alter the AUCs of the models. Thus, model performances in the population following AUR, which also considers this criterion, were comparable to performances observed in the initial AUR population.

The delay between the AD blood biomarker assessment and the amyloid burden examination ranged from 0 to 2593 days, with a majority falling between 51 days (Q1) and 957 days (Q3), and a median of 740 days (2 years). Inclusion of this delay as a covariate in the models did not change their predictive performances in the development sample.

Discussion

We developed six incremental models to predict brain amyloid positivity and validated them in an independent sample. The models included data typically collected in clinical practice prior to the administration of anti-amyloid immunotherapy, such as neuropsychological assessments, AD-related blood biomarkers, ApoE genotype, hippocampal atrophy, and lobar microbleed ratings by brain MRI. Models that incorporated demographic data, cognitive scores, and either ApoE4 status or AD-related blood biomarkers demonstrated better discriminatory

power than those that included only demographic and cognitive variables. The addition of imaging data did not improve performance in either the development or validation sample.

Performance was not affected when the best prediction model was restricted to the subsample that met the main exclusion criteria of the AUR for lecanemab or the subsample that excluded homozygous ε4 carriers.

Our model performances were comparable to findings in previous studies that included individuals with subjective cognitive complaints or mild cognitive impairment, where demographic, cognitive variables, and ApoE4 status were used as predictors of amyloid positivity (AUCs ranged from 0.73 to 0.75) [30–32]. The addition of AD-related blood biomarkers also resulted in AUCs between 0.83 and 0.85 [33, 34]. Thus, consistent with the literature, the best model for predicting amyloid status in our study utilised demographic data, cognitive measurements, ApoE status, and AD-related blood biomarkers. Notably, the same model without ApoE (Model 3) also exhibited good discriminatory ability ($AUC_{cv} = 0.80$ [95% CI 0.79–0.80]).

Model high performances were externally validated in a subsample of the ADC cohort, which comprised individuals without dementia. The model incorporating demographic data, cognitive measurements, ApoE status, and AD-related blood biomarkers was confirmed to the greatest discriminatory power for amyloid positivity (AUC = 0.90 [95% CI 0.86–0.94]). The improved predictive performance in the external validation sample could be explained by the higher proportion of MCI in the ADC sample compared with the MEMENTO cohort. Indeed, predictive performance also improved when the model was applied to the development subsample restricted to the AUR recommendations, which excluded non-MCI participants.

As in MEMENTO, the same model without ApoE4 demonstrated strong discriminatory power, with an AUC of 0.83 [95% CI 0.78–0.88]. The impact of ApoE4 on model performance differed between the MEMENTO and ADC cohorts, which may be attributed to the varying proportions of ApoE4 carriers. In subpopulations with a high prevalence of ApoE4, such as ADC, ApoE4 could plays a more significant role in predicting amyloid positivity. However, in more diverse populations like MEMENTO, the added value of ApoE4 may be less critical.

To our knowledge, no study has assessed the impact of incorporating ApoE4 status into a predictive model of amyloid positivity that includes multiple cognition-related variables. An analysis using the Alzheimer's Disease Neuroimaging Initiative (ADNI) database suggested that adding ApoE4 status to a model that included age and only the Rey Auditory Verbal Learning Test immediate recall test as a cognitive variable led to a 0.09-point increase in AUC, which is twice the improvement observed in our development model [35]. However, consistent with our results, several studies indicate that the inclusion of ApoE4 status does not notably enhance the performance of models that include already AD-related blood biomarkers such as Aβ42/40, P-tau181, or P-tau217 [36, 37]. There is currently no recommendation for ApoE disclosure in routine clinical practice, except for discussing the individual risk-benefit ratio of anti-amyloid immunotherapies. Indeed, ApoE genotype disclosure raises ethical concerns and might affect patients and their relatives [38]. ApoE4 status can be determined later if deemed necessary by the clinician to establish the best clinical care pathway, such as when discussing therapeutic options [38, 39]. In this context, Model 3, which excludes ApoE, may be the most suitable for clinical implementation in populations where the prevalence of ApoE carriers is not high, at least before discussing the risk-benefit ratio of anti-amyloid immunotherapies.

Recently, there has been extensive research into the use of blood biomarkers such as Aβ42/40 and phosphorylated Tau (p181, p217, p231) to predict amyloid status [40]. While these biomarkers significantly contribute to improving predictive models, our current and previous studies demonstrate that integrating cognitive and demographic variables substantially improves model performance [41].

The contribution of MRI to amyloid positivity prediction is debated in the literature and highly dependent on the MRI marker used. Consistent with our findings, several studies have demonstrated that measures such as hippocampal atrophy and cortical thickness do not add predictive power in individuals without dementia when cognitive variables are included in the model [42, 43]. However, contrasting findings have been reported by two studies showed that the integration of data requiring complex MRI analysis resulted in a substantial improvement in AUC. The generation of such data requires dedicated teams and infrastructure. These studies used the probabilistic MRI score to assess the presence of Aβ or incorporated structural indicators of Aβ neuropathology, encompassing macrostructural and microstructural features across the entire cerebral cortex [34, 44]. Although patients attending memory clinics are very likely to undergo brain MRI as part of their care, such complex MRI-extracted data are unlikely to be readily available to physicians.

Importantly, the performance of prediction models (and thus their effectiveness) should be evaluated based on predefined clinical or research questions. In the context of screening patients for eligibility for anti-amyloid immunotherapy, the Youden index, which maximises sensitivity and specificity, demonstrated that based on its performance, Model 3 (Se = 0.77, Sp = 0.69) could not

serve as a substitute for LP or PET. Nevertheless, because these procedures are invasive and costly, setting a high sensitivity (Se = 0.9) for the model could reduce the number of confirmatory LPs or PETs. For example, in a population of 400 people with an amyloid positivity prevalence of 25%, Model 3 (Se = 0.9, Sp = 0.4) has a negative predictive value (NPV) of 0.92. This model would identify 130 people at low risk of being amyloid positive (120 true negatives and 10 false negatives), for whom confirmatory testing could be avoided.

The main strength of this study lies in its use of the MEMENTO cohort, which enabled the collection of diverse, high-quality, and standardised data representing real-world information from multiple memory clinics. The large sample size of the MEMENTO cohort makes this project one of the largest studies on this topic. In addition, we leveraged the availability of repeated amyloid measurements in Memento participants, which provides better model specification and more precise risk estimates compared to using a single measurement per participant. Indeed, we also tested the predictive models using only the baseline amyloid data ($N = 853$). The AUCs and their confidence intervals remained similar to those obtained using longitudinal data, however, the calibration curves were less accurate (results not shown). Another strength is the external validation of the models in an independent sample, which confirmed the robustness and generalisability of the models. These strength is partly due to our method of selecting predictive variables. Unlike other studies, which predicted Aβ positivity using data-driven approaches to identify predictors (such as random forest, LASSO-regularised linear regression, machine learning, or eXtreme Gradient Boosting (XGBoost)), which can handle a large number of predictors and often derive them directly from the dataset, our models were based solely on predictors identified in the literature and available in routine clinical care [34, 35, 45, 46]. This approach prevents overfitting to the development data, ensures transparency regarding the variables used, and enhances clinicians' understanding of the prediction tool.

This study also had some limitations. First, while our study primarily focused on early AD-related blood biomarkers for which plasma Aβ42/40 and pTau181 measurements were available, plasma pTau217 has recently emerged as a highly effective biomarker, with some studies reporting AUCs exceeding 0.90 for predicting amyloid pathology [47, 48]. Assessing the impact of pTau217 on the performance of our prediction models using the same analytical strategy would provide valuable insights and surely further improve model accuracy.

Second, investigations of blood biomarkers have revealed significant variability in their concentrations, depending on the assay used. Compared to immunoassays, such as those employed in the MEMENTO cohort, mass spectrometry could provide more precise and reliable measurements of these analytes as biomarkers for cerebral Aβ [49–51]. However, this technique is more challenging to implement at a large scale, such as in memory clinics, compared with the commercial kits used in MEMENTO.

Third, this study is unique because we constructed a prediction model using interchangeably the three primary methods commonly used for assessing amyloid status: CSF analysis and two amyloid PET tracers (Florbetapir and Flutemetamol). Consideration of the amyloid status determined using these methods enabled the model to adjust for the range of examinations conducted in routine clinical practice.

Finally, the variables used to construct the prediction models were based on measurements taken closest to the determination of amyloid status, except for plasma biomarkers (only from baseline blood samples). Thus, amyloid status could have been determined several months after baseline. We assumed minimal variation in these biomarkers over time and found no association when this delay was included in the models. However, any changes in these factors, particularly an increase in cerebral amyloid burden, could lead to underestimation of the performances of prediction models incorporating these variables.

Conclusions

The models developed in this study offer a promising method to help identify non-demented patients likely to exhibit cerebral amyloid positivity, which would facilitate early diagnosis of AD or early intervention with anti-amyloid immunotherapies. Their integration into clinical practice could streamline treatment decision-making processes, reducing the need for reference examinations such as PET or CSF analysis.

Abbreviations

Aβ	Amyloid-β
AD	Alzheimer's disease
ADC	Amsterdam Dementia Cohort
ApoE4	ε4 allele of the apolipoprotein
ARIA	Amyloid-Related Imaging Abnormalities
AUC	Area Under Curve
AUR	Appropriate Use Recommendations
CDR	Clinical Dementia Rating
CMBs	Cerebral microbleeds
CSF	Cerebrospinal fluid
FCSRT	Free and Cued Selective Reminding Test
FDA	Food and Drug Administration
LP	Lumbar puncture
MCI	Mild cognitive impairment
MICE	Multivariate Imputation by Chained Equations
MMSE	Mini-Mental Score Examination
MRI	Magnetic Resonance Imaging
PET	Positron emission tomography

P-tau181	Phosphorylated tau
ROC	Receiving Operator Characteristic
SCC	Subjective cognitive complaints
TMTB	Trail Making Test B
TRIPOD	Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13195-024-01595-5.

Supplementary Material 1.

Supplementary Material 2.

Supplementary Material 3.

Supplementary Material 4.

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Consortia
for the MEMENTO Cohort Study Group.

Authors' contributions
LLS: study design, statistical analysis, results interpretation, and manuscript drafting. VB: statistical analysis, results interpretation, and manuscript revision. PJV: statistical analysis (external validation) , and manuscript revision. WMF: major role in the acquisition of ADC data, and manuscript revision.CET: manuscript revision. IMWV: manuscript revision. VP: results interpretation, and manuscript revision. GC: creation and direction of the MEMENTO study, and manuscript revision. CD: creation and direction of the MEMENTO study, study supervision, results interpretation, and manuscript revision. All authors read and approved the final version of the manuscript.

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Availability of data and materials
MEMENTO data access request is available via the Dementia Platform UK Data Access appliance form (https:// portal. demen tiasp latfo rm. uk/ Apply) or via the MEMENTO Secretariat (sophie.lamarque@u-bordeaux.fr).

Declarations

Ethics approval and consent to participate
This study was performed in accordance with the Declaration of Helsinki. All participants provided written informed consent. The MEMENTO cohort protocol was approved by the local ethics committee ("Comité de Protection des Personnes Sud-Ouest et Outre Mer III"; approval number 2010-A01394-35) and was registered on 16 August 2013 in ClinicalTrials.gov (Identifier: NCT01926249).

Consent for publication
Not applicable.

Competing interests
During the past three years, VP was a local unpaid investigator or sub-investigator for clinical trials granted by NovoNordisk, Biogen, TauRx Pharmaceuticals, Janssen and Alector. He received consultant fees for animal studies from Motac Neuroscience Ltd.All other authors declare no competing interests.All other authors declare no competing interests.

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