Received: 9 November 2022 | Revised: 6 April 2023 | Accepted: 28 April 2023

DOI: 10.1002/alz.13161

Alzheimer's & Dementia®
THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION

RESEARCH ARTICLE

Predicting amyloid-beta pathology in the general population

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Funding information
Alzheimer's Association Research, Grant/Award Number: AARG-22-972229; ZonMw Memorabel, Grant/Award Number: 733050817; European Union's Horizon 2020 research and innovation programme, Grant/Award Number: 101032288; ZonMW, Grant/Award Numbers: #73305095007, #10510032120003; Health Holland, Topsector Life Sciences & Health (PPP-allowance), Grant/Award Number: #LSHM20106

Abstract

INTRODUCTION: Reliable models to predict amyloid beta (Aβ) positivity in the general aging population are lacking but could become cost-efficient tools to identify individuals at risk of developing Alzheimer's disease.

METHODS: We developed Aβ prediction models in the clinical Anti-Amyloid Treatment in Asymptomatic Alzheimer's (A4) Study (n = 4,119) including a broad range of easily ascertainable predictors (demographics, cognition and daily functioning, health and lifestyle factors). Importantly, we determined the generalizability of our models in the population-based Rotterdam Study (n = 500).

RESULTS: The best performing model in the A4 Study (area under the curve [AUC] = 0.73 [0.69–0.76]), including age, apolipoprotein E (*APOE*) ε4 genotype, family history of dementia, and subjective and objective measures of cognition, walking duration and sleep behavior, was validated in the independent Rotterdam Study with higher accuracy (AUC = 0.85 [0.81–0.89]). Yet, the improvement relative to a model including only age and *APOE* ε4 was marginal.

DISCUSSION: Aβ prediction models including inexpensive and non-invasive measures were successfully applied to a general population–derived sample more representative of typical older non-demented adults.

KEYWORDS
Alzheimer's disease, amyloid-beta pathology, dementia, machine learning, prediction models

1 | BACKGROUND

In 2021, the World Alzheimer Report estimated there were > 55 million cases of dementia worldwide and forecasted that this number would increase up to 42% within the next 10 years.[1] Alzheimer's disease (AD) is the leading cause of dementia, defined by neurotoxic plaques forming amyloid beta (Aβ) peptides in the brain.[2,3] Aβ can trigger the aggregation of neurofibrillary tangles and subsequently neurodegeneration resulting in progressive and irreversible cognitive decline. It was estimated that Aβ accumulation starts 15 to 20 years before the onset of clinical symptoms.[4]

Given the key role of Aβ accumulation in the pathophysiology of AD, enormous efforts are being undertaken to develop anti-amyloid drug treatments that remove Aβ plaques at the preclinical stage, before dementia symptoms manifest.[5,6] A crucial step in study enrolment, as well as in translating treatment into clinical practice, is to identify patients at an early stage of AD when irreversible brain damage is still minimal. The only two clinically approved methods to confirm an

elevated Aβ burden are a positive amyloid positron emission tomography (PET) scan or positive cerebrospinal fluid (CSF) markers, both of which are costly and invasive procedures with limited availability and restricted to hospitals. Identifying at-risk individuals via an algorithm predicting Aβ positivity is a cost-efficient, non-invasive method that could help screening patients in clinical trials and eventually in primary care before more elaborate confirmatory testing.

Ashford et al. provided a review of previously developed Aβ prediction models.[7] They found that prior work mostly restricted to patients from highly specialized memory clinics, for example, 31.5% of studies included the Alzheimer's Disease Neuroimaging Initiative (ADNI) cohort.[7–12] Due to recruitment mechanisms (e.g., self-selection in response to advertisement) and strict inclusion criteria (e.g., no vascular disease), clinical studies like ADNI tend to include highly educated individuals who are more likely to report a family history of dementia and show fewer comorbidities as well as higher prevalence of Aβ pathology than observed in the general population.[13–16] Aβ prediction models derived from clinical samples may not translate well to broader applications. Of particular concern is the lack of internal and external validation found in 41% and 71%, respectively, of previous studies.[7] In contrast to clinical samples, epidemiological population-based studies invite all residents of a well-defined area to participate with less stringent inclusion criteria, and by design, are more representative of the general population.[17] Of the 21 studies which performed external validation in Ashford et al.,[7] only one study validated Aβ prediction models in a population-based sample. This study demonstrated good generalizability, but the validated model contained only three predictors (age, apolipoprotein E [*APOE*] ε4, memory performance) achieving moderately high performance (area under the curve [AUC] = 0.71).[18] To extend previous work, we examined the generalizability of more complex Aβ prediction models in the current study.

Our goal was to determine how accurately prediction models, developed in a large convenience (clinical) sample with a wide range of easily ascertainable predictors, could identify amyloid-positive individuals from a population-based sample of older nondemented adults. To this end, we developed two Aβ prediction models (with and without *APOE* ε4 genotype) in cognitively unimpaired participants of the cross-sectional Anti-Amyloid Treatment in Asymptomatic Alzheimer's (A4) Study (n = 4,119), considering 19 predictors. It should be noted that other authors had already developed Aβ prediction models in the A4 Study.[19–21] Yet, new model development was necessary to include the largest possible set of predictors that was available in both the development and validation sample. Second, we internally validated our models by estimating how accurately they identified Aβ status in A4 Study participants not included in the model development, as well as how much prediction improved compared to "basic models" (age and *APOE* ε4), the two strongest known Aβ predictors.[7] Third and critically, we assessed external validity and temporal stability in the prospective population-based Rotterdam Study (n = 500), which was recently enriched by amyloid PET (2018–2021), using predictors collected at three different timepoints (on average 12 years before, 7 years before, and 2 years after PET acquisition).

RESEARCH IN CONTEXT

- **Systematic Review**: We reviewed the literature on amyloid beta (Aβ) prediction via PubMed and found that most prediction models were derived from clinical studies without external validation. The generalizability to a broader population that Aβ prediction models intend to assist, for example, during primary care workup of prodromal Alzheimer's disease, remains unclear.
- **Interpretation**: Our study developed and internally validated models that identified the presence of Aβ pathology in a large cohort of nondemented adults with moderate accuracy (area under the curve [AUC] = 0.73 [0.69–0.76], n = 4,119). Importantly, we externally validated our models in a population-based cohort with higher accuracy (AUC = 0.85 [0.81–0.89], n = 500). Age and apolipoprotein E (*APOE*) ε4 genotype are the strongest predictors, while other easily ascertainable predictors, such as family history of dementia and subjective memory complaints, seem to improve prediction mainly when *APOE* ε4 status is not available.
- **Future Directions**: While our Aβ prediction model generalized well to a geographically diverse but predominantly White and highly educated cohort, further validation in other ethnocultural groups and more diverse educational backgrounds is urgently needed.

2 | METHODS

2.1 | Participants

2.1.1 | A4 Study

The A4 Study was a randomized clinical trial that tested whether solanezumab, an anti-amyloid antibody, slowed down cognitive decline at the preclinical stage.[14] The study consisted of 67 sites across four countries (United States, Canada, Australia, and Japan) and collected data from 2014 to 2017.[22] Inclusion criteria were age 65 to 85 years, living independently, normal cognition (Mini-Mental State Examination [MMSE] between 25 and 30, Clinical Dementia Rating [CDR] = 0, Logical Memory II between 6 and 18 depending on educational level) and having a study partner. Exclusion criteria were use of AD medication, significant depression or anxiety, and unstable medical condition. For the current study we used the screening data that was collected before the start of the clinical trial and included 4,486 participants who all underwent amyloid PET examination. We excluded participants without information on *APOE* ε4 genotype (n = 45). We further excluded participants with missing data regarding any of the 19 predictors (n = 322). The final sample contained 4,119 participants,

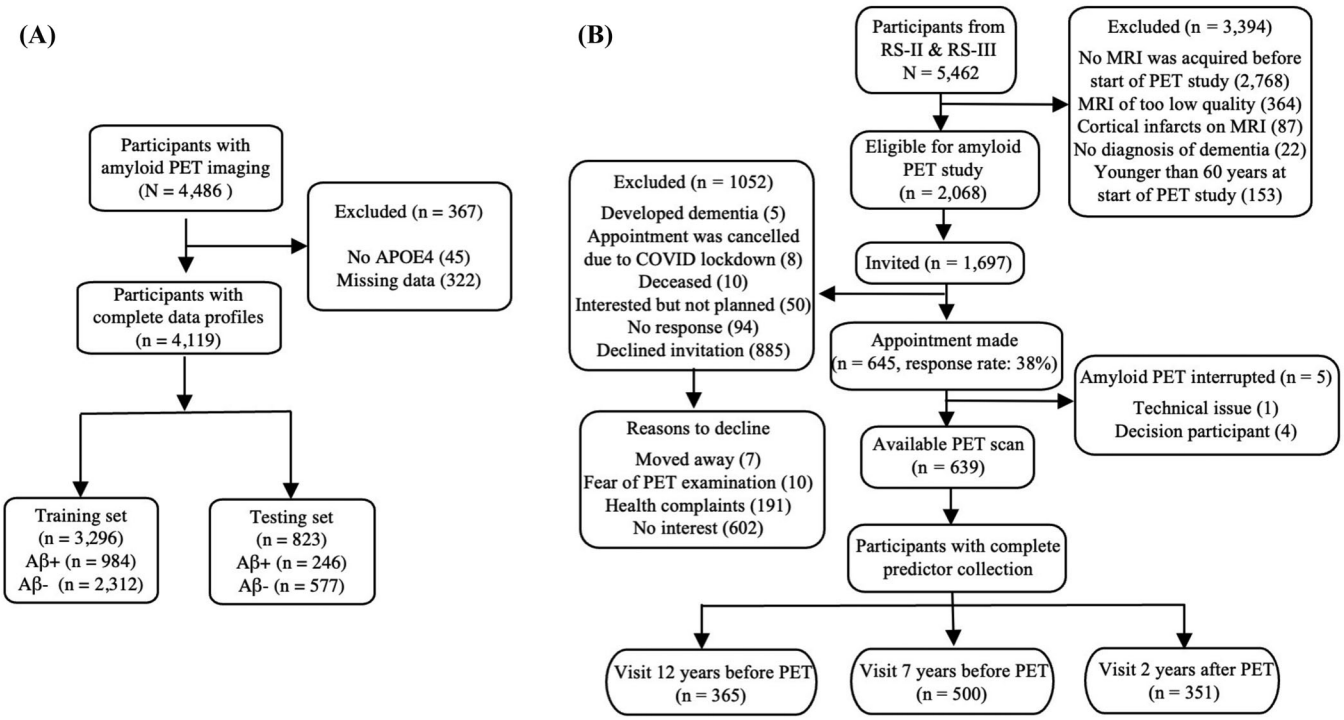

FIGURE 1 Flow chart illustrating the study design of (A) the A4 Study and (B) the Rotterdam Study. Aβ, amyloid beta; *APOE*, apolipoprotein E; MRI, magnetic resonance imaging; PET, positron emission tomography; RS, Rotterdam Study

which served as our training and test dataset. A flowchart of the participant inclusion is shown in Figure 1A.

2.1.2 | Rotterdam Study

The Rotterdam Study is an ongoing longitudinal population-based cohort study in the well-defined Ommoord district in the city of Rotterdam in the Netherlands.[23] The Rotterdam Study started with 7,983 participants (RS-I) in 1990, extended with 3,011 participants (RS-II) in 2000, and 3,932 participants (RS-III) in 2006 (response rates were 78%, 68%, and 65%, respectively). Participants were re-examined every 3 to 4 years. Between 2018 and 2021, a subsample of RS-II and RS-III participants, who were ≥60 years, had a good-quality brain magnetic resonance imaging [MRI], no PET-related contraindications, no large cortical infarcts, or a clinical diagnosis of dementia were invited for PET examination. Out of 1,697 invited participants, 645 made an appointment (response rate 38%) and 639 PET scans were acquired (more details in Method S1 in supporting information and in van Arendonk et al.[24]). Figure 1B and Figure S1 in supporting information illustrate participant inclusion and study design of the Rotterdam Study. For the current study, we excluded participants with missing data for any predictor that was chosen in our models. Overall, 365, 500, and 351 participants had all predictors collected on average 12 years before (2006-2011), 7 years before (2010–2015), and 2 years (2021–2022) after PET, respectively. We used the largest dataset ($n = 500$) to investigate the external validity of our prediction models. Because only a subsample of the Rotterdam Study could receive a PET examination, we evaluated possible selection bias with respect to all individuals who were eligible for the PET study but did not participate (Table S1 in supporting information). PET participants were on average younger (69.0 vs. 71.7 years), more highly educated (34.0% vs. 24.7%), had slightly higher MMSE scores (28.6 vs. 28.3), and better Digit Symbol Substitution Test performance (32.3 vs. 30.9 pairs) than non-participants. All other variables, for example, *APOE* ε4 or family history of dementia, showed no significant group differences.

2.2 | Study outcome

^{18}F-florbetapir and ^{18}F-florbetaben amyloid PET imaging was, respectively, performed in the A4 Study[22] and the Rotterdam Study[24] and further processed according to an established pipeline in which average cortical standardized uptake value ratio (SUVR) was calculated within FreeSurfer-defined frontal, cingulate, lateral parietal, and lateral temporal regions and using the cerebellum as a reference (more details in Method S2 in supporting information). Aβ status was determined by an algorithm combining both quantitative SUVR and qualitative visual reads in both studies.[25] Two tracer-specific SUVR thresholds were used to mark early and established Aβ accumulation, for example, 1.10 to 1.15 in the A4 Study[26] and 1.10 to 1.24 in the Rotterdam Study.[24,27] An SUVR > 1.15/1.24 was deemed positive while an SUVR < 1.10 was deemed negative independent of the visual rating. An SUVR between both thresholds was deemed positive only when the visual read was considered positive by two independent raters.

2.3 | Study predictors

We included all possible predictors that were collected identically or comparably and had no more than 30% missing values in both cohorts (for details regarding predictor inclusion/exclusion see Table S2 in supporting information).

2.3.1 | Demographics

The demographic predictors included age, sex (female, male), education (lower [< 10 years of education], further [10–12 years], higher [> 12 years]), marital status (married/not married), and family history (0, 1, or 2 parents diagnosed with dementia).

2.3.2 | Genetic measures

We included the number of *APOE* ε4 risk alleles (0, 1, 2) in our model, as it is a strong genetic predictor of late-onset AD.[7] *APOE* genotyping (rs7412 and rs429358) was performed on the Illumina Global Screening Array in the A4 Study or on a biallelic Taqman assay in the Rotterdam Study.[24,28]

2.3.3 | Objective measures of cognitive performance

We included a screening test for dementia (MMSE), a test for executive functions (Digit- or Letter-Symbol Substitution), and for memory performance (total free recall score from the Free and Cued Selective Reminding Test of the A4 Study[29] and the 15-words learning test of the Rotterdam Study[30]). Both memory tests measured delayed word recall under controlled learning conditions.

2.3.4 | Subjective measures of daily functioning

We also considered self-reports on cognitive complaints and daily activities. To this end, two independent evaluators (PTNH and JN) matched the content of different questionnaires across the two studies. They consistently identified four questions with comparable content reflecting "subjective memory difficulties" and "subjective word-finding difficulties" as well as the "need for assistance with finances or medication" (more details in Table S3 in supporting information).

2.3.5 | Health and lifestyle measures

The seven health and lifestyle predictors we included were body mass index (BMI, kg/m^2), current smoking (yes/no), alcohol consumption (number of glasses per day), sleep duration (number of hours per night), napping during the day (yes/no), and physical activity (time spent doing aerobics exercise and walking). In the A4 Study, physical activity was assessed using the two questions: "average number of minutes of walking per day" and "average number of hours of aerobic exercise per week." In the Rotterdam Study, physical activity was assessed using the LASA Physical Activity Questionnaire.[31]

2.4 | Data analysis

Data analysis was performed in R statistical software (v4.1.3). To develop our Aβ prediction models, we split the A4 dataset into two parts, with 80% serving as the training set and 20% as the test set. The test set was not seen during model training. To select only the most informative predictors, we applied the least absolute shrinkage and selection operator (LASSO) technique (caret package, v6.0-92). Compared to standard logistic regression, LASSO constrains the sum of the regression coefficients to minimize overfitting and model misspecification, which are known problems for predicting rare events such as Aβ positivity.[32] Specifically, LASSO can discard predictors from the final model (by shrinking their coefficients), thus reducing variance that is specific to the training data but would otherwise compromise generalizability. The strength of the coefficient shrinkage is determined by the lambda parameter. To choose the optimal values for lambda, we ran 10-fold cross-validation during which we oversampled amyloid-positive cases using the Synthetic Minority Oversampling Technique[33] to prevent the algorithm from learning mainly to predict amyloid negativity. Because the coefficient shrinkage is sensitive to the variables' unit, all predictors were centered and scaled.

For our second aim, evaluating internal validity, we determined the models' calibration (by calibration slope and intercept [rms package v6.2.0]) and classification performance in the A4 test set. Classification performance was assessed by the area under the curve (AUC; pROC package v1.18.0). We calculated the 95% confidence intervals (CI) of the AUC values based on 1000 bootstrap samples. In addition to AUC, we also reported sensitivity, specificity, and positive and negative predictive value. We further estimated whether our models (hereafter referred to as "extended model") added predictive performance beyond a "basic model" containing age and *APOE* ε4.

For our third aim, validating our models in an independent population-based sample, we compared the AUCs in the A4 test set to those in the Rotterdam Study. To estimate the models' temporal stability, we compared the AUCs with predictors collected at the three different Rotterdam Study visits. In a supplementary analysis, we contrasted model performance across datasets that contained only those participants that had all predictors available at all three visits ($n = 178$). Finally, based on our models' performance in the Rotterdam Study validation dataset, we estimated how many PET scans would need to be performed to find one amyloid-positive scan when using our models with and without *APOE* ε4 compared to a situation in which no prediction model is used.

3 | RESULTS

3.1 | Sample characteristics

Table 1 summarizes the sample characteristics. The average age at PET acquisition was 71.3 (standard deviation [SD] = 4.7), 71.0 (SD = 4.8),

TABLE 1 Sample characteristics.

		A4 Study		Rotterdam Study		
		Training set	Test set	12 years before PET	7 years before PET	2 years after PET
n		3296	823	365	500	351
Age at PET, mean (SD)		71.30 (4.66)	70.98 (4.75)	69.51 (5.33)	68.99 (5.10)	68.64 (5.04)
Years between predictors and PET, mean (SD)		0 (0)	0 (0)	−12.32 (0.96)	−7.03 (0.86)	1.86 (0.71)
Amyloid PET status (%)	Negative	2312 (70.1)	577 (70.1)	302 (82.7)	422 (84.4)	306 (87.2)
	Positive	984 (29.9)	246 (29.9)	63 (17.3)	78 (15.6)	45 (12.8)
Demographic information						
Sex (%)	Female	1970 (59.8)	491 (59.7)	199 (54.5)	262 (52.4)	179 (51.0)
	Male	1326 (40.2)	332 (40.3)	166 (45.5)	238 (47.6)	172 (49.0)
Race (%)	White	3064 (93.0)	770 (93.6)	337 (92.3)	450 (90.0)	319 (90.9)
	Asian	68 (2.1)	15 (1.8)	5 (1.4)	6 (1.2)	3 (0.9)
	Black or African American	118 (3.6)	28 (3.4)	3 (0.8)	3 (0.6)	2 (0.6)
	American Indian or Alaskan Native	6 (0.2)	3 (0.4)	0 (0)	0 (0.0)	0 (0.0)
	Native Hawaiian or other Pacific Islander	2 (0.1)	0 (0)	0 (0)	0 (0.0)	0 (0.0)
	Mixed	0 (0)	0 (0)	1 (0.3)	1 (0.2)	0 (0.0)
	Not available	38 (1.2)	7 (0.9)	19 (5.2)	40 (8.0)	27 (7.7)
Education (%)	Lower	13 (0.4)	4 (0.5)	66 (18.1)	91 (18.2)	55 (15.7)
	Intermediate	311 (9.4)	73 (8.9)	166 (45.5)	239 (47.8)	162 (46.2)
	Higher	2972 (90.2)	746 (90.6)	133 (36.4)	170 (34.0)	134 (38.2)
Married (%)	No	999 (30.3)	232 (28.2)	57 (15.6)	101 (20.2)	95 (27.1)
	Yes	2297 (69.7)	591 (71.8)	308 (84.4)	399 (79.8)	256 (72.9)
Family history (%)	No parent had dementia	1166 (35.4)	280 (34.0)	347 (95.1)	475 (95.0)	332 (94.6)
	One parent had dementia	1788 (54.2)	460 (55.9)	17 (4.7)	24 (4.8)	18 (5.1)
	Both parents had dementia	342 (10.4)	83 (10.1)	1 (0.3)	1 (0.2)	1 (0.3)
Genetic measures						
APOE ε4 allele count (%)	0	2153 (65.3)	523 (63.5)	259 (71.0)	342 (68.4)	253 (72.1)
	1	1038 (31.5)	273 (33.2)	92 (25.2)	141 (28.2)	87 (24.8)
	2	105 (3.2)	27 (3.3)	14 (3.8)	17 (3.4)	11 (3.1)
Objective measures of cognitive performance						
MMSE, mean (SD)		28.81 (1.21)	28.86 (1.17)	28.48 (1.47)	28.57 (1.29)	27.53 (5.58)
Delayed word-learning test, mean (SD)		28.91 (5.55)	29.23 (5.77)	8.18 (2.75)	8.65 (2.77)	7.25 (2.85)
Digit Symbol Substitution Test, mean (SD)		43.65 (8.91)	44.21 (9.09)	33.52 (5.79)	32.34 (5.90)	30.68 (6.27)
Subjective measures of daily functioning						
Subjective memory difficulty (%)	No	2547 (77.3)	633 (76.9)	199 (54.5)	281 (56.2)	162 (46.2)
	Yes	749 (22.7)	190 (23.1)	166 (45.5)	219 (43.8)	189 (53.8)
Subjective word-finding difficulty (%)	No	1236 (37.5)	324 (39.4)	273 (74.8)	381 (76.2)	240 (68.4)
	Yes	2060 (62.5)	499 (60.6)	92 (25.2)	119 (23.8)	111 (31.6)

(Continues)

TABLE 1 (Continued)

		A4 Study		Rotterdam Study		
		Training set	Test set	12 years before PET	7 years before PET	2 years after PET
Need for assistance with finances or medication (%)	No	3076 (93.3)	770 (93.6)	340 (93.2)	437 (87.4)	319 (90.9)
	Yes	220 (6.7)	53 (6.4)	25 (6.8)	63 (12.6)	32 (9.1)
Lifestyle measures						
BMI, mean (SD)		27.59 (5.18)	27.44 (4.78)	27.04 (4.13)	27.36 (4.14)	27.15 (3.96)
Aerobic exercise, hours/week, mean (SD)		2.87 (3.79)	3.03 (3.89)	2.98 (3.62)	3.14 (4.72)	2.76 (5.19)
Walking, minutes/day, mean (SD)		58.75 (60.47)	60.90 (66.40)	28.02 (36.06)	31.93 (40.10)	26.93 (25.91)
Sleep duration, hours/night, mean (SD)		7.12 (1.06)	7.09 (1.06)	6.71 (1.06)	6.75 (1.21)	6.64 (1.41)
Napping during the day (%)	No	2062 (62.6)	504 (61.2)	321 (87.9)	433 (86.6)	298 (84.9)
	Yes	1234 (37.4)	319 (38.8)	44 (12.1)	67 (13.4)	53 (15.1)
Current smoking (%)	No	3245 (98.5)	812 (98.7)	300 (82.2)	411 (82.2)	328 (93.4)
	Yes	51 (1.5)	11 (1.3)	65 (17.8)	89 (17.8)	23 (6.6)
Alcohol, glasses/day, mean (SD)		0.77 (1.12)	0.73 (1.19)	0.77 (0.93)	0.71 (0.91)	0.54 (0.80)

Abbreviations: A4, Anti-Amyloid Treatment in Asymptomatic Alzheimer's; *APOE*, apolipoprotein E; BMI, body mass index; MMSE, Mini-Mental State Examination; PET, positron emission tomography; SD, standard deviation; y, years.

and 69.0 years (SD = 5.10) in the A4 training set, A4 test set, and the Rotterdam Study validation set, respectively. All three datasets included slightly more women (59.8%, 59.7%, and 52.4%, respectively) than men and the majority of participants were White (93%, 93.6%, and 90%, respectively). In the A4 training and test sets, 34.7% and 36.5%, respectively, carried at least one *APOE* ε4 risk allele, which was not significantly different from the 31.6% in the Rotterdam Study. More than half of the A4 Study participants, 64.6% in the training set and 66% in the test set, had at least one parent diagnosed with dementia, in contrast to only 5.0% in the Rotterdam Study. Aβ positivity was more frequent in the A4 Study (29.9%) than in the Rotterdam Study (15.6%).

3.2 | Model development and predictor selection

The extended model included most predictors, except higher education, BMI, and alcohol consumption. The strongest predictors of Aβ positivity were age (β = 0.20), family history with both parents diagnosed with dementia (β = 0.18), and subjective memory (β = 0.14) and word-finding (β = 0.12) difficulties (Table 2). When *APOE* ε4 was included, carrying one (β = 0.59) or two (β = 0.44) *APOE* ε4 risk allele(s) became the strongest predictors, followed by age (β = 0.27), family history (β = 0.12), and subjective memory (β = 0.13) and word-finding (β = 0.08) difficulties. The predictor selection was consistent with the results of multivariate logistic regressions (Table S4 in supporting information) showing that all predictors with small (β > 0.05) to medium (β > 0.10) LASSO weights were significantly related to Aβ status.

3.3 | Internal validity and added classification performance of the Aβ prediction models

Calibration plots are presented in Figure S2 in supporting information. The calibration slopes of the extended models were close to the target value of one in both the A4 training and test sets (range: 0.89–1.06) suggesting that the predicted risks were not extreme (e.g., not too high for participants at high risk or not too low for participants at low risk). The calibration intercepts were all slightly negative (−0.82 to −0.85) implying that both models had a small tendency to overestimate the risk of Aβ positivity in all participants. Classification performance is shown in Table 3. The extended model showed moderate predictive performance with an AUC of 0.62 [95% CIs: 0.60–0.64] in the A4 training set and 0.61 [0.57–0.65]) in the A4 test set, which was higher relative to the performance of a basic model including only age (A4 training set: AUC = 0.56 [0.54–0.58]; A4 test set: AUC = 0.58 [0.54–0.63]). The extended model with *APOE* ε4 reached an AUC equal to 0.73 [0.71–0.75] in the A4 training set and to 0.73 [0.69–0.76] in the A4 test set. The improvement relative to the basic model with *APOE* ε4 was marginal (A4 training set: AUC = 0.71 [0.69–0.73]; A4 test set: AUC = 0.72 [0.68–0.76]).

TABLE 2 Standardized LASSO weights for Aβ prediction models.

	Basic model	Extended model	Basic model with *APOE* ε4	Extended model with *APOE* ε4
Age	0.22	0.20	0.32	0.27
APOE, one ε4 allele	–	–	0.62	0.59
APOE, two ε4 alleles	–	–	0.46	0.44
Female	–	0.03	–	Not selected
Education, intermediate	–	−0.04	–	Not selected
Education, higher	–	Not selected	–	Not selected
Married	–	0.05	–	Not selected
Family history, one parent had dementia	–	0.04	–	−0.02
Family history, both parents had dementia	–	0.18	–	0.12
MMSE	–	−0.03	–	−0.02
Delayed word-learning test	–	−0.09	–	−0.05
Digit Symbol Substitution Test	–	−0.08	–	−0.05
Subjective memory difficulty	–	0.14	–	0.13
Subjective word-finding difficulty	–	0.12	–	0.08
Need for assistance with finances or medication	–	0.01	–	Not selected
BMI	–	Not selected	–	Not selected
Aerobic exercise, hours/week	–	0.02	–	Not selected
Walking, minutes/day	–	−0.03	–	−0.02
Sleep duration, hours/night	–	−0.06	–	−0.04
Napping during the day	–	−0.09	–	−0.06
Current smoking	–	0.03	–	Not selected
Alcohol, glasses/day	–	Not selected	–	Not selected

Abbreviations: Aβ, amyloid beta; *APOE*, apolipoprotein E; BMI, body mass index; LASSO, least absolute shrinkage and selection operator; MMSE, Mini-Mental State Examination.

3.4 | External validity and temporal stability of the Aβ prediction models

External validity of the Aβ prediction models was tested in the Rotterdam Study using predictors collected 7 years before PET (Table 3). While the relative predictive accuracy across the different models was similar to that in the A4 Study, the absolute accuracy was higher in the Rotterdam Study indicating high external validity. For the extended model, AUC increased from 0.61 [0.57–0.65] in the A4 test set to 0.63 [0.56–0.70] in the Rotterdam Study. For the extended model with *APOE* ε4, performance improved considerably from an AUC of 0.73 [0.69–0.76] in the A4 test set to 0.85 [0.81–0.89] in the Rotterdam Study. Table S5 in supporting information shows the performance at different probability thresholds. ROC curves are plotted in Figure 2. The models performed robustly across the three Rotterdam Study visits including predictors that were collected at three different timepoints (Figure S3 in supporting information). AUC values ranged from 0.61 to 0.63 for the extended model and from 0.82 to 0.85 for the extended model with *APOE* ε4 (Table 3). A supplementary analysis, in which we only included participants with complete data across the three visits (n = 178), yielded identical AUCs for the visits 12 and 7 years before PET, but a slightly higher AUC for the visit 2 years after PET (Table S6 in supporting information).

Finally, as a proof of concept, we estimated how many individuals from the general population (age range 60–90 years) would need to undergo PET imaging to find one amyloid-positive case (Table 4). When no prediction model is used, 8.1 PET scans would have to be acquired. This number was calculated as the inverse Aβ prevalence, which was estimated to be 18.9% in non-demented individuals similar to the whole Rotterdam Study cohort.[24] By applying our extended model with *APOE* ε4 before PET, this number could be reduced to 6.5 PET scans (at a probability threshold set to achieve 90% sensitivity) or 4.1 PET scans (at a probability threshold set to achieve 90% specificity). For our extended model without *APOE* ε4, we estimated that 8.0 PET scans (at 90% sensitivity) or 6.7 PET scans (at 90% specificity) would be necessary. The numbers for the prediction models were calculated as the inverse positive predictive values which the models achieved in the Rotterdam Study validation dataset, assuming again an Aβ prevalence of 18.9%.

TABLE 3 Performance of the Aβ prediction models in the training, test, and external validation datasets.

Model	*n*	Prevalence	Sensitivity	Specificity	PPV	NPV	Accuracy	AUC [95% CI]
A4 training set								
Basic model	3296	0.30	0.48	0.61	0.34	0.73	0.54	0.56 [0.54–0.58]
Extended model	3296	0.30	0.57	0.60	0.38	0.77	0.59	0.62 [0.60–0.64]
Basic model with *APOE ε4*	3296	0.30	0.63	0.70	0.47	0.82	0.66	0.71 [0.69–0.73]
Extended model with *APOE ε4*	3296	0.30	0.64	0.71	0.48	0.82	0.67	0.73 [0.71–0.75]
A4 test set								
Basic model	823	0.30	0.48	0.67	0.38	0.75	0.57	0.58 [0.54–0.63]
Extended model	823	0.30	0.55	0.62	0.38	0.76	0.58	0.61 [0.57–0.65]
Basic model with *APOE ε4*	823	0.30	0.66	0.68	0.47	0.82	0.67	0.72 [0.68–0.76]
Extended model with *APOE ε4*	823	0.30	0.63	0.70	0.47	0.82	0.67	0.73 [0.69–0.76]
Rotterdam Study, 2 years after PET								
Basic model	351	0.13	0.62	0.57	0.18	0.91	0.60	0.60 [0.50–0.69]
Extended model	351	0.13	0.60	0.59	0.18	0.91	0.60	0.63 [0.54–0.71]
Basic model with *APOE ε4*	351	0.13	0.78	0.75	0.32	0.96	0.77	0.82 [0.75–0.88]
Extended model with *APOE ε4*	351	0.13	0.78	0.73	0.30	0.96	0.75	0.82 [0.76–0.88]
Rotterdam Study, 7 years before PET								
Basic model	500	0.16	0.64	0.59	0.23	0.90	0.62	0.63 [0.56–0.69]
Extended model	500	0.16	0.56	0.61	0.21	0.88	0.59	0.63 [0.56–0.70]
Basic model with *APOE ε4*	500	0.16	0.82	0.72	0.35	0.96	0.77	0.84 [0.79–0.88]
Extended model with *APOE ε4*	500	0.16	0.82	0.72	0.35	0.96	0.77	0.85 [0.81–0.89]
Rotterdam Study, 12 years before PET								
Basic model	365	0.17	0.63	0.61	0.25	0.89	0.62	0.64 [0.56–0.71]
Extended model	365	0.17	0.60	0.62	0.25	0.88	0.61	0.61 [0.53–0.69]
Basic model with *APOE ε4*	365	0.17	0.78	0.73	0.38	0.94	0.75	0.82 [0.76–0.87]
Extended model with *APOE ε4*	365	0.17	0.75	0.74	0.37	0.93	0.74	0.82 [0.76–0.87]

Abbreviations: A4, Anti-Amyloid Treatment in Asymptomatic Alzheimer's; Aβ, amyloid beta; *APOE*, apolipoprotein E; AUC, area under the curve; CI, 95% confidence intervals; NPV, negative predictive value; PET, positron emission tomography; PPV, positive predictive value.

TABLE 4 Number of cognitively unimpaired participants necessary to undergo PET imaging to find one amyloid-positive case.

	No prediction model[a]	Prediction model[b] with *APOE ε4*			Prediction model[b] without *APOE ε4*		
Probability threshold[c]	–	≥0.42	≥0.5	≥0.68	≥0.38	≥0.5	≥0.62
Number needed to scan	8.1	6.5	5.9	4.1	8.0	7.5	6.7

[a]When no prediction model is applied the number to be scanned for identifying one amyloid-positive case was calculated as the inverse of the estimated Aβ prevalence. We assumed an average Aβ prevalence of 18.9% in cognitively unimpaired individuals aged between 60 and 90 years (this is an adjusted prevalence estimate we previously computed using an inverse probability weighting approach to adjust the proportion of amyloid-positive participants to the characteristics (age, sex, education, and *APOE ε4* allele count) of all Rotterdam Study participants alive at the start of the PET study; see van Arendonk et al.,[24] and Table S2 in supporting information).

[b]When our extended models with and without *APOE ε4* are applied the number to be scanned was calculated as the inverse of the positive prediction value (i.e., the likelihood to be truly amyloid-positive after a positive screen) derived for three different probability thresholds and assuming again a prevalence of 18.9%.

[c]The probability thresholds were chosen to achieve at least 90% sensitivity (at ≈ 40% probability), balanced sensitivity and specificity (at 50% probability), or 90% specificity (at 60%–70% probability).

Abbreviations: Aβ, amyloid beta; *APOE*, apolipoprotein E; PET, positron emission tomography.

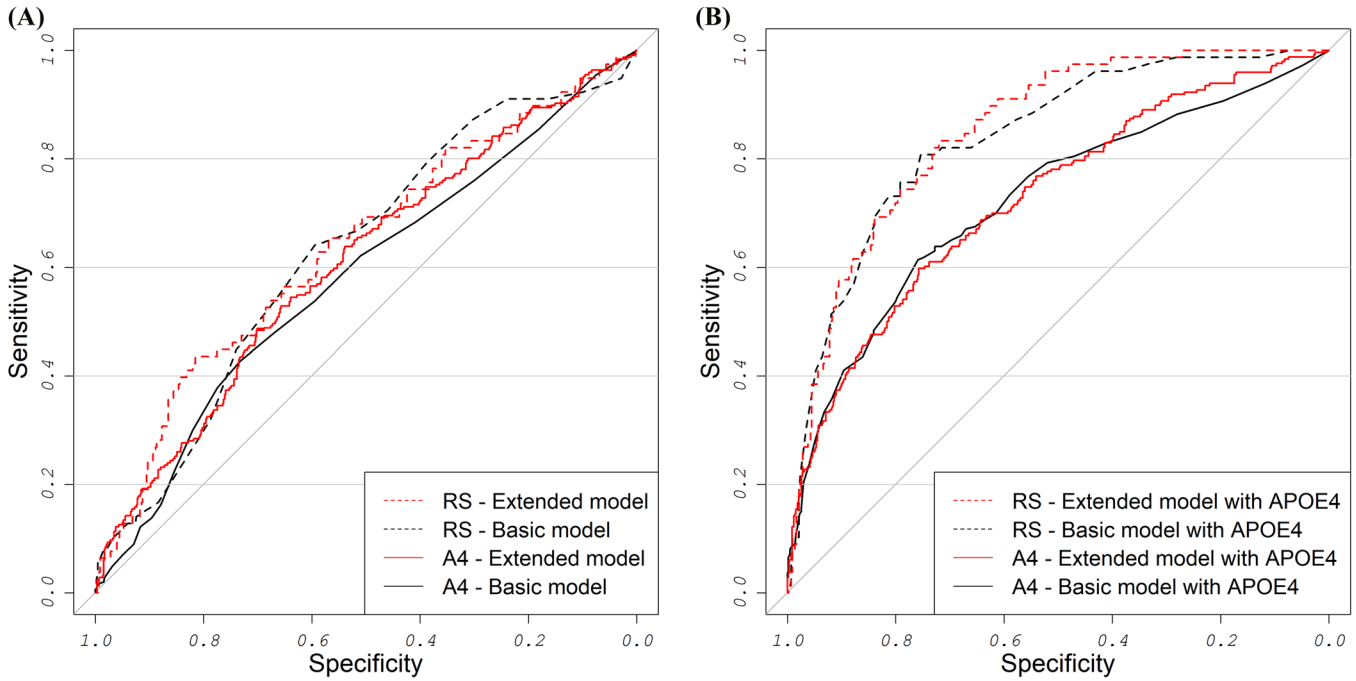

FIGURE 2 Receiver operating characteristic (ROC) curves display the performance of the (A) models without *APOE* ε4 and (B) models with *APOE* ε4 in the A4 Study test dataset and in the Rotterdam Study dataset used for external validation. A4, Anti-Amyloid Treatment in Asymptomatic Alzheimer's Study; *APOE*, apolipoprotein E; RS, Rotterdam Study

4 | DISCUSSION

In the current study, we developed two Aβ prediction models, one without and one with *APOE* ε4, based on the A4 Study, the largest amyloid PET study conducted to date ($n = 4{,}119$). When *APOE* ε4 was not considered, easily ascertainable predictors, such as family history of dementia or subjective cognitive complaints, improved predictive accuracy (AUC = 0.61) compared to a basic model including only age (AUC = 0.58). When *APOE* ε4 status was included, these predictors did not considerably increase predictive accuracy compared to using age and *APOE* ε4 only (AUC of 0.73 vs. 0.72). Importantly, these findings were validated in the prospective population-based Rotterdam Study ($n = 500$) with higher accuracy (e.g., AUC increased from 0.73 to 0.85).

Economic models only including predictors that are readily available in the clinical routine (without *APOE* ε4) have not achieved AUCs above 0.70.[8,9,34–36] Two studies that also developed prediction models in the A4 Study classified amyloid-positive cases with an AUC of 0.61 (based on age, family history, BMI, free recall)[19] or of 0.62 (based on age, education, sex, family history, activity of daily living, cognitive status [Cogstate, Cognitive Function Index, Preclinical Alzheimer Cognitive Composite]).[20] Because our extended model's performance (AUC of 0.61) was highly consistent with these reports, the inclusion of novel predictors, such as sleep duration,[37] did not appear to aid predictive performance. Including *APOE* ε4 genotype improved prediction performance above AUCs of 0.7 in most prior work including the current and other A4-based studies (AUC = 0.73 in Petersen et al.[19] and in current study or AUC = 0.74 in Langford et al.[20]). Our results further suggest that other readily ascertainable predictors did not increase predictive accuracy significantly beyond the strong effect of *APOE* ε4. Likewise, no considerable improvement above *APOE* ε4 was found for MMSE and objective memory performance in the Amyloid Biomarker Study ($n = 2{,}908$)[38] or for subjective cognitive decline in the Harvard Aging Brain Study, ADNI, and Australian Imaging Biomarker and Lifestyle (AIBL) study ($n = 890$).[35]

To more accurately predict Aβ status, more sophisticated predictors are probably necessary. Structural MRI and blood-based markers (Aβ42/40, phosphorylated tau181), for example, helped to reach AUCs above 0.8 in multiple,[9–11,39,40] but not all, previous studies.[41,42] Because these models were developed in relatively small and highly selected patient samples and often lacked external validation, their performance in the wider population has yet to be determined (for first population-based data see Mielke et al.[43]). Although available, we decided not to include MRI in our models, because imaging is burdensome and expensive and therefore of limited use for screening purposes. Plasma biomarkers, on the other hand, were not available in the current cohorts, but seem to be promising minimally invasive predictors of Aβ positivity if inconsistencies in sample handling and untransparent usage of in-house assays are overcome.[44] We are planning to enrich the Rotterdam Study with plasma biomarkers soon to then validate corresponding Aβ prediction models.

The key strength of this study was that we externally validated our developed models in an independent sample. The differences in sample characteristics between the A4 Study and the Rotterdam Study (multi-centric cross-sectional assessment of a convenience sample from North America, Australia, Japan versus mono-centric prospective assessment of a population-based sample from Northern

Europe) allowed us to thoroughly determine the models' performance across different populations. Somewhat unexpectedly, predictive performance was similar (model without *APOE* ε4) or higher (model with *APOE* ε4) in the population-based validation dataset indicating that Aβ prediction models can be applied to a broader population than the one in which they were developed. We can only speculate about what might have caused this performance boost. One explanation is that an accumulation of various genetic factors (other than *APOE* ε4) and/or environmental factors related to the high prevalence of family history of dementia in the A4 Study may have underestimated the predictive power of *APOE* ε4, while *APOE* ε4 is the main driver of Aβ in an unselected sample like the Rotterdam Study. One previous study that tested external validity in a population-based sample also found robust performance. The best-performing model (including age, *APOE* ε4, memory performance) reached an AUC of 0.75 and 0.72 in the clinical training cohorts (ADNI, AIBL) and 0.71 in the Mayo Clinic Study of Aging (MCSA) validation cohort.[18] This result was similar to the performance of the best model developed directly in the MCSA cohort (AUC = 0.70; based on age, *APOE* ε4, family history, and subjective cognitive difficulties[45]), but lower than the performance observed in the current validation dataset (AUC = 0.85).

To our best knowledge the current study is one of the first to estimate the stability of Aβ prediction models over time. We found robust performance using predictors collected at three different timepoints before and after PET acquisition. This was not surprising for the models including static *APOE* ε4 status. However, even the model without *APOE* ε4, which contained comparably strong static (family history) and dynamic predictors (subjective memory difficulty), showed high temporal stability with a slight superiority for the timepoint closest to PET. Future studies should confirm whether Aβ positivity can be predicted with a time difference of up to 12 years as suggested by the current results.[42]

We suggest two scenarios in which Aβ prediction models may be useful in a general population setting: screening for clinical AD trials and in primary care. Clinical trials increasingly move toward the inclusion of asymptomatic subjects, because treatment may be more effective before notable cognitive impairment and brain damage have occurred. In trials which aim to include only amyloid-positive individuals (and thus would require a high specificity), prediction models could reduce the number of unnecessary (negative) PET scans. We calculated that half the number of PET scans (4.1 instead of 8.1) would be necessary for identifying one amyloid-positive individual, when applying our best performing model (extended model with *APOE* ε4) in individuals similar to the Rotterdam Study. In contrast, in a future scenario in which primary care would like to identify individuals for early disease management, this would require high sensitivity to miss as few amyloid-positive individuals as possible. Here, a prediction model could increase confidence of primary health-care providers to refer a patient to a specialized clinic. Such selective referrals may become even more critical in the future considering an increasing number of older adults and likely more approved treatments against AD that require confirmatory testing of underlying AD pathology as a first step.[46]

The current study has several limitations. First, not all predictors were measured in identical ways across the two cohorts, with the largest mismatch occurring between the different delayed recall tests. Misestimation of Aβ risk could be a possible consequence but should be marginal given the relatively small contribution of memory performance to Aβ prediction. Second, the Rotterdam Study validation sample was not free of selection or nonparticipation bias, which should be considered when interpreting the results. Third, although our models performed comparably well relative to previous models, the absolute performance was still insufficient for clinical use. Fourth, it is likely that blood-based biomarkers could have improved prediction, but they were not available in the two cohorts. Finally, although we involved two independent studies in geographically diverse populations, most participants were non-Latinx White and highly educated, and it therefore remains crucial to further validate the resulting models in other ethnocultural groups and more diverse educational backgrounds.

In conclusion, we confirmed that Aβ prediction models can be generalized to a population with very different characteristics than the convenience sample in which they were developed and which, importantly, was more representative of typical older non-demented adults.

AUTHOR CONTRIBUTIONS

Julia Neitzel and Phuong Thuy Nguyen Ho developed the study design. Joyce van Arendonk, Rebecca Steketee, and Frank van Rooij led data acquisition and management. Phuong Thuy Nguyen Ho and Julia Neitzel performed the statistical analysis and drafted the manuscript. All authors contributed to the interpretation of the results, critically revised the manuscript, and approved the final draft of this report.

ACKNOWLEDGMENTS

The A4 Study is a secondary prevention trial in preclinical Alzheimer's disease, aiming to slow cognitive decline associated with brain amyloid accumulation in clinically normal older individuals. The A4 Study is funded by a public–private–philanthropic partnership, including funding from the National Institutes of Health–National Institute on Aging, Eli Lilly and Company, Alzheimer's Association, Accelerating Medicines Partnership, GHR Foundation, an anonymous foundation and additional private donors, with in-kind support from Avid and Cogstate. The companion observational Longitudinal Evaluation of Amyloid Risk and Neurodegeneration (LEARN) Study is funded by the Alzheimer's Association and GHR Foundation. The A4 and LEARN Studies are led by Dr. Reisa Sperling at Brigham and Women's Hospital, Harvard Medical School and Dr. Paul Aisen at the Alzheimer's Therapeutic Research Institute (ATRI), University of Southern California. The A4 and LEARN Studies are coordinated by ATRI at the University of Southern California, and the data are made available through the Laboratory for Neuro Imaging at the University of Southern California. The participants screening for the A4 Study provided permission to share their de-identified data to advance the quest to find a successful treatment for Alzheimer's disease. We would like to acknowledge the dedication of all the participants, the site personnel, and all of the partnership team members who continue to make the A4 and LEARN Studies possible. The complete A4 Study Team list is available at: a4study.org/a4-study-team. We would like to thank the entire staff

of the Nuclear Medicine department of Erasmus Medical Center, for their help in acquiring the amyloid PET data in the Rotterdam Study, including but not limited to Dennis Kuijper, Annelies Schipper, Pieter Meppelink, and Jean-Baptiste Aarssen for their coordinating roles. We would also like to acknowledge the immense contribution of the data management team of the Rotterdam Study, with Jolande Verkroost-van Heemst in particular, and of the Imaging Trialbureau. Last, we would like to thank our Rotterdam Study participants for their contribution. This project has received funding from the European Union's Horizon 2020 research and innovation programme (MSCA-IF-GF no. 101032288 to J.N.), ZonMW Memorabel grant 733050817 (to M.W.V.), Alzheimer's Association Research Grant (AARG-22-972229 to M.W.V. and J.N.), ABOARD, which is a public-private partnership receiving funding from ZonMW (no. 73305095007) and Health Holland, Top-sector Life Sciences & Health (PPPPriceallowance; no. LSHM20106 to M.W.V.) as well as TAPPricedementia, a ZonMw funded project (no. 10510032120003 to M.W.V.) in the context of the Dutch National Dementia Strategy. PET tracer supply was supported by Life Molecular Imaging GmbH, Berlin (Germany). The Rotterdam Study is funded by Erasmus Medical Center and Erasmus University, Rotterdam, the Netherlands; Organization for the Health Research and Development (ZonMw); the Research Institute for Diseases in the Elderly (RIDE); the Ministry of Education, Culture and Science; the Ministry for Health, Welfare and Sports; and the European Commission.

CONFLICT OF INTEREST STATEMENT

The authors report no competing interests. Author disclosures are available in the supporting information.

DATA AVAILABILITY STATEMENT

A4 data used in this article are available for download from the Laboratory of NeuroImaging (LONI; loni.usc.edu). Rotterdam Study data can be obtained upon request. Requests should be directed toward the management team of the Rotterdam Study (secretariat.epi@erasmusmc.nl), which has a protocol for approving data requests. Because of restrictions based on privacy regulations and informed consent of the participants, data cannot be made freely available in a public repository. The Rotterdam Study has been entered into the Netherlands National Trial Register (NTR; www.trialregister.nl) and into the WHO International Clinical Trials Registry Platform (ICTRP; www.who.int/ictrp/network/primary/en/) under shared catalogue number NTR6831.

STANDARD PROTOCOL APPROVALS, REGISTRATIONS, AND PATIENT CONSENTS

The A4 Study was approved by the institutional review boards of all participating institutions (NCT02008357). The Rotterdam Study has been approved by the Medical Ethics Committee of the Erasmus MC (MEC-2018-085) and by the Dutch Ministry of Health, Welfare and Sport (Population Screening Act WBO, license number 1071272-159521-PG). Written informed consent was obtained from all participants. This study followed the TRIPOD guidelines for reporting prognostic models.[47]

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SUPPORTING INFORMATION

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

How to cite this article: Nguyen Ho PT, van Arendonk J, Steketee RME, et al. Predicting amyloid-beta pathology in the general population. *Alzheimer's Dement*. 2023;1-12. https://doi.org/10.1002/alz.13161