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Cognitive & Behavioral Assessment

Assessing risk for preclinical β-amyloid pathology with *APOE*, cognitive, and demographic information

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Abstract

Introduction: Clinical trials in Alzheimer's disease are aimed at early stages of disease, including preclinical Alzheimer's disease. The high cost and time required to screen large numbers of participants for Aβ pathology impede the development of novel drugs. This study's objective was to evaluate the extent to which inexpensive and easily obtainable information can reduce the number of screen failures by increasing the proportion of Aβ+ participants identified for screening.

Methods: We used random forest models to evaluate the positive predictive value of demographics, *APOE*, and longitudinal cognitive rates in the prediction of amyloid pathology, measured by florbetapir PET or cerebrospinal fluid.

Results: Predicting Aβ positivity with demographic, *APOE*, and cognitive information yielded a positive predictive value estimate of 0.65 (95% CI, 0.50–0.96), nearly a 60% increase over the reference Aβ+ prevalence in the cohort of 0.41.

Conclusions: By incorporating this procedure, clinical trial screening costs may be substantially reduced.

Keywords: Preclinical Alzheimer's; Amyloid; Clinical trials; Cognition; APOE

1. Introduction

Dementia is one of the most debilitating consequences of aging, affecting not only patients but also families and caregivers. In 2010, 35.6 million people worldwide were estimated to have dementia, with care costing an estimated U.S. $604 billion [1]. Alzheimer's disease (AD) is the most common cause of dementia, contributing to potentially 60%–70% of these cases. There are currently no approved treatments that slow the progression of AD, despite numerous clinical trials investigating potential disease-modifying therapies. A major obstacle for AD clinical trials is the high cost and time required to screen large numbers of candidate participants to meet specific trial inclusion criteria.

Because the accumulation of evidence suggesting the pathophysiological process of AD begins with β-amyloid (Aβ) deposition, many clinical trials have begun to require

Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf.

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a substantial level of Aβ pathology for inclusion, with Aβ pathology measured by cerebrospinal fluid (CSF) biomarkers or positron emission tomography (PET) imaging [2]. However, measuring Aβ pathology with these technologies is expensive and invasive. This is especially an issue in trials using antiamyloid drugs directed against preclinical or prodromal AD, where evidence of Aβ pathology is essential to avoid diluting the drug effect by inclusion of individuals with normal Aβ levels (Aβ−). Clinical trials attempting to recruit cognitively healthy Aβ positive (Aβ+) elderly may expect large numbers of screen failures, given that the prevalence of Aβ positivity in cognitively healthy people aged 60–90 years is around 31%, as shown in a recent meta-analysis [3]. The overall goal of this study was therefore to provide tools to increase the proportion of Aβ+ participants identified for screening for trials of preclinical AD.

A global effort from organizations like the Brain Health Registry (www.brainhealthregistry.org), the Global Alzheimer's Platform (globalalzplatform.org), and the European Prevention of Alzheimer's Dementia Consortium (ep-ad.org) is underway to establish well-characterized trial-ready cohorts to expedite the screening process for AD clinical trials. Demographic, cognitive, and genetic information will be acquired both online and in clinics over time on large numbers of potential trial participants. Clinical trial recruiters will then be able to evaluate which participants may be likely to meet specific inclusion criteria before screening for specific trials. Recruiters may be able to exploit the associations between brain amyloid pathology and demographic [3–5], genetic [6–8], and cognitive [9–13] factors to improve the prediction of Aβ positivity. However, the degree to which these associations can improve the positive predictive value (PPV) in the forecasting of Aβ pathology in cognitively normal elderly is unknown. Therefore, the goal of this study was to quantify the effect of using demographic, cognitive, and genetic information in cognitively normal elderly to predict Aβ pathology, to reduce the number of screen failures and costs of clinical trials.

2. Methods

2.1. Participants

Data were obtained from the ADNI database (adni.loni.usc.edu). ADNI is the result of efforts of many co-investigators, and participants have been recruited from over 50 sites across the United States and Canada (see www.adni-info.org). The population in this study included ADNI-1 and ADNI-2 participants enrolled into the cognitively normal or subjective memory complaint cohorts. The key inclusion criteria that distinguish the subjective memory complaint cohort are a self-reported significant memory concern from the participant, quantified by using the Cognitive Change Index [14] and the Clinical Dementia Rating of zero. Participants had MMSE scores ≥24, were aged 55–90 years, were tested for CSF biomarkers or ^{18}F-florbetapir PET, and were followed longitudinally for neuropsychological testing for at least 24 months.

2.2. CSF biomarker concentrations

Each CSF sample was collected by lumbar puncture and shipped on dry ice to the ADNI Biomarker Core laboratory at the University of Pennsylvania Medical Center for long-term storage at −80°C. Aβ positivity in CSF was determined by quantifying the 42-amino-acid isoform of $A\beta_{1-42}$ (Aβ42) using the multiplex xMAP Luminex platform (Luminex Corp, Austin, TX) with the Research Use Only INNOBIA AlzBio3 kit (Fujirebio/Innogenetics, Ghent, Belgium) [15,16].

2.3. Florbetapir PET

Brain Aβ deposition was measured with PET using the ligand ^{18}F-florbetapir. Methods to acquire and process ADNI florbetapir PET image data were described previously [10]. Mean florbetapir uptake from gray matter within lateral and medial frontal, anterior, and posterior cingulate, lateral parietal, and lateral temporal regions relative to uptake in the whole cerebellum (white and gray matter) was used as the florbetapir cortical mean for each participant. This measure was used to classify participants as Aβ+ or Aβ− as described below. Full details of acquisition and analysis can be found at http://adni.loni.usc.edu/methods/.

2.4. Cognitive outcomes

Cognitive measures assessed were the mini-mental state examination (MMSE), Alzheimer's Disease Assessment Scale-cognitive subscale, 13-item version (ADAS13), immediate and delayed memory recall from the Wechsler Memory Scale-Revised (iMemory, dMemory), immediate and delayed Rey Auditory Verbal Learning Test (iAVLT, dAVLT), trail making test parts A and B (trails A & B), and category fluency [17–20].

2.5. Statistical analysis

The main analysis of this study was an evaluation of baseline demographics (age, gender, and education), *APOE* ε4 status (presence of at least one ε4 allele), baseline cognitive scores, and rates of change of cognitive scores over 24 months, for their ability to enrich a subsample for Aβ positivity. The main outcome was PPV, that is, the proportion of individuals predicted to be Aβ+ that were also observed to be Aβ+, for predictors assessed both individually and collectively. Aβ+ was defined as florbetapir PET SUVR >1.10 [10] or CSF $A\beta_{42}$ < 192 ng/L [15] in participants without florbetapir PET (n = 54). We classified subjects as Aβ+ if they became positive at any point during follow-up. This approach is based on evidence that if a subject is approaching amyloid positivity in the near term, that is, has emerging amyloid pathology, they are likely to have

increased atrophy rates [21], lower FDG PET, and subtle cognitive dysfunction and should not be included in the reference group [22]. Based on this evidence, several recent publications have suggested that current amyloid-positivity thresholds are likely too conservative [23,24]. Baseline characteristics of the Aβ groups were assessed using Wilcoxon rank-sum test for continuous variables and Fisher exact test for categorical variables.

In the assessment of individual predictors, continuous variables were iteratively thresholded, moving across the spectrum of the predictor, with the proportion of Aβ+ calculated at each threshold. The PPV estimates were then regressed on the range of thresholds using natural splines to produce PPV curves [25]. For the PPV curves of each predictor, 95% confidence intervals were estimated using the margins (2.5 and 97.5 percentiles) from 500 bootstrap samples.

The collective ability for the predictors to increase PPV was estimated using cross-validated random forests [26]. In each of 10 cross-validation folds, the probability of being Aβ+ was estimated for each participant by averaging over the votes from all decision trees. The probability threshold used to classify participants as Aβ+ was selected via cross-validation. For each candidate threshold, models were fit on the training sets (9 of the 10 folds) to get an estimate of mean PPV for 10 test sets. The threshold that maximized mean test set PPV was selected. For example, if the probability threshold $P = .70$ maximized the cross-validated estimate of PPV, then only participants whose estimated probability of being Aβ+ exceeded 0.70 were classified as Aβ+. The resulting 10 estimates from all folds were used to get a mean and 95% confidence interval for PPV using the 2.5th and 97.5th percentiles.

Cognitive tests were administered at baseline, month 6 (except logical memory), month 12, and month 24. Cognitive measures over 24 months were regressed on time from the baseline visit to estimate subject-specific cognitive rates of change using mixed-effects regression with a random intercept and slope and an unstructured covariance matrix for the random effects. By month 24, all cognitive tests had been assessed at 3 or more follow-up visits, allowing participant-specific rates to be estimated. *P* values were all two sided and considered significant at the 0.05 level. All analyses were done in R v3.1.1 (www.r-project.org).

3. Results

There were 353 participants with complete data, including demographic, *APOE*, Aβ information, and 24-month follow-up. One-hundred forty-four participants (40.8%) were Aβ+ (119 measured by PET, 25 by CSF), and 209 (59.2%) were Aβ− (180 by PET, 29 by CSF). Aβ+ participants were older, less educated, and had a higher proportion of females and *APOE* ε4 positivity, compared with Aβ− participants (Table 1). PPV curves for age and education are shown in Fig. 1.

Table 1
Baseline characteristics

Variable	Aβ− (N = 209), mean (SD)	Aβ+ (N = 144), mean (SD)	*P* value
Age	73.8 (6.02)	75.4 (5.34)	<.001
Gender, female, *n* (%)	93 (44.5)	80 (55.6)	.051
Education	16.7 (2.61)	16.1 (2.77)	.033
APOE ε4, *n* (%)	40 (19.1)	55 (38.2)	<.001
Subjective memory complaint, *n* (%)	37 (17.7)	24 (16.7)	.886

Aβ+ participants had lower baseline cognitive scores compared to Aβ− participants on eight of the nine outcomes, five of which were significantly or marginally significantly lower. Cognitive differences are summarized in Table 2. PPV curves for individual baseline cognitive scores and 24-month rates are shown in Fig. 2.

Results of combinations of predictors are shown in Fig. 3. The best performing model included all variables: demographic, *APOE*, baseline cognition, and 24-month rates, yielding a PPV estimate of 0.65, nearly a 60% increase beyond the reference Aβ+ prevalence in the cohort of 0.41. Sixty participants were predicted to be Aβ+, of which 39 were actually positive. Participants predicted to be Aβ+ had a mean age of 78.1 years (range, 65–90 years), an

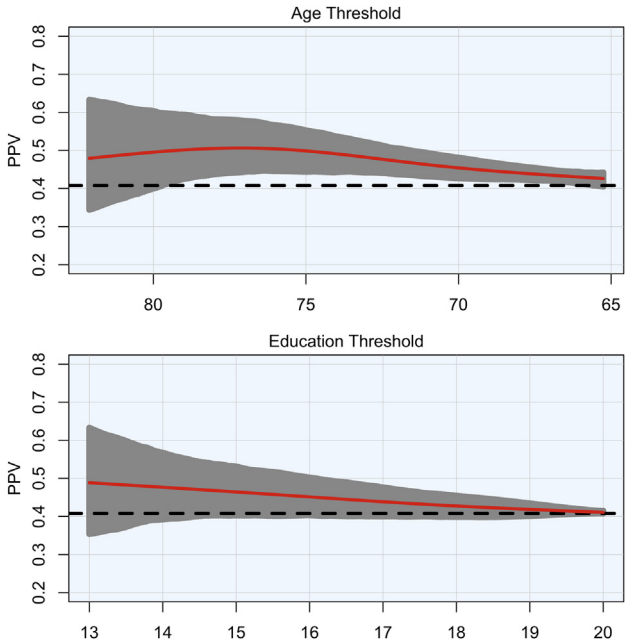

Fig. 1. Positive predictive value (PPV) plots: age and education. Estimates of PPV (proportion of Aβ+) are plotted against continuous predictors, age and education. For age, the thresholds on the x-axis are more exclusive, with fewer participants included moving from right to left, that is, at age = 70 years, the estimate of the proportion of Aβ+'s is shown for individuals ≥70 years. For education, the thresholds are also more exclusive from right to left, that is, at education = 17 years, the estimate of the proportion of Aβ+'s is shown in individuals with ≤17 years of education. The gray shaded areas are 95% confidence intervals for the PPV estimates. The dashed black line is the reference PPV for the full cohort.

Table 2
Baseline cognition

Variable	Aβ− (N = 206), mean (SD)	Aβ+ (N = 125), mean (SD)	*P* value
MMSE	29.1 (1.18)	29.1 (1.11)	.595
ADAS13	8.9 (4.00)	9.7 (4.36)	.063
dMemory	13.5 (3.12)	12.8 (3.53)	.034
iMemory	14.3 (3.04)	13.7 (3.49)	.052
dAVLT	7.7 (4.04)	7.2 (3.77)	.193
iAVLT	54.2 (13.34)	52.4 (11.59)	.255
Trails A	32.5 (9.99)	36.0 (11.96)	.008
Trails B	78.1 (35.70)	90.5 (43.31)	.004
Category fluency	20.8 (5.53)	20.2 (5.40)	.526

average of 15.3 years of education (6–20 years) and were 51.7% female and 41.7% *APOE* ε4+. They had lower baseline cognitive scores and performed worse over time compared with the remainder of the cohort, which were not identified for increased risk of Aβ positivity. Cognitive scores and rates are summarized in Table 3.

4. Discussion

The main finding of this study is that prediction of β-amyloid pathology can be improved in a cognitively normal population without expensive and invasive procedures. Enriching recruitment of cognitively normal Aβ+ subjects is feasible through the use of demographic, cognitive, and genetic predictors, both individually (Figs. 1 and 2) and collectively (Fig. 3). A 0.65 proportion of Aβ-positivity, nearly 60% above the reference proportion of 0.41, was found when all predictors, including longitudinal cognitive rates, were modeled. If used for pre-screening in a clinical trial aimed at recruiting 1000 Aβ+ participants, this information could reduce the number of people undergoing biomarker screening from 2451 to 1539 participants. By

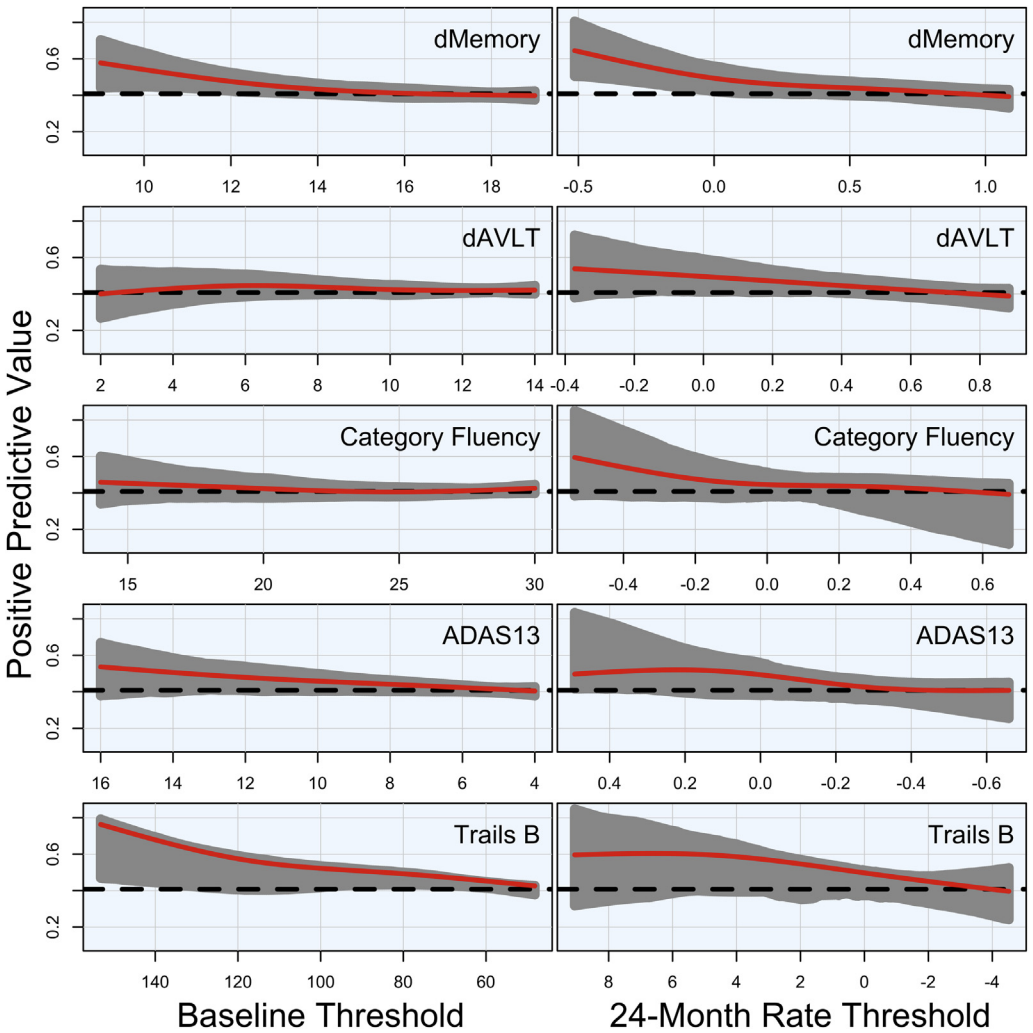

Fig. 2. Individual predictor positive predicted value (PPV) curves: baseline cognition and 24-month rates. PPV curves are plotted against baseline cognitive thresholds in the left column and 24-month rate thresholds in the right column. Thresholds become more exclusive moving from the right to left, i.e. PPV estimates are shown for individuals with worse scores than the threshold given on the x-axis. The gray shaded areas are 95% confidence intervals for the PPV estimates. The dashed black line is the reference PPV for the full cohort. Abbreviations: dMemory, delayed memory recall; dAVLT, delayed AVLT.

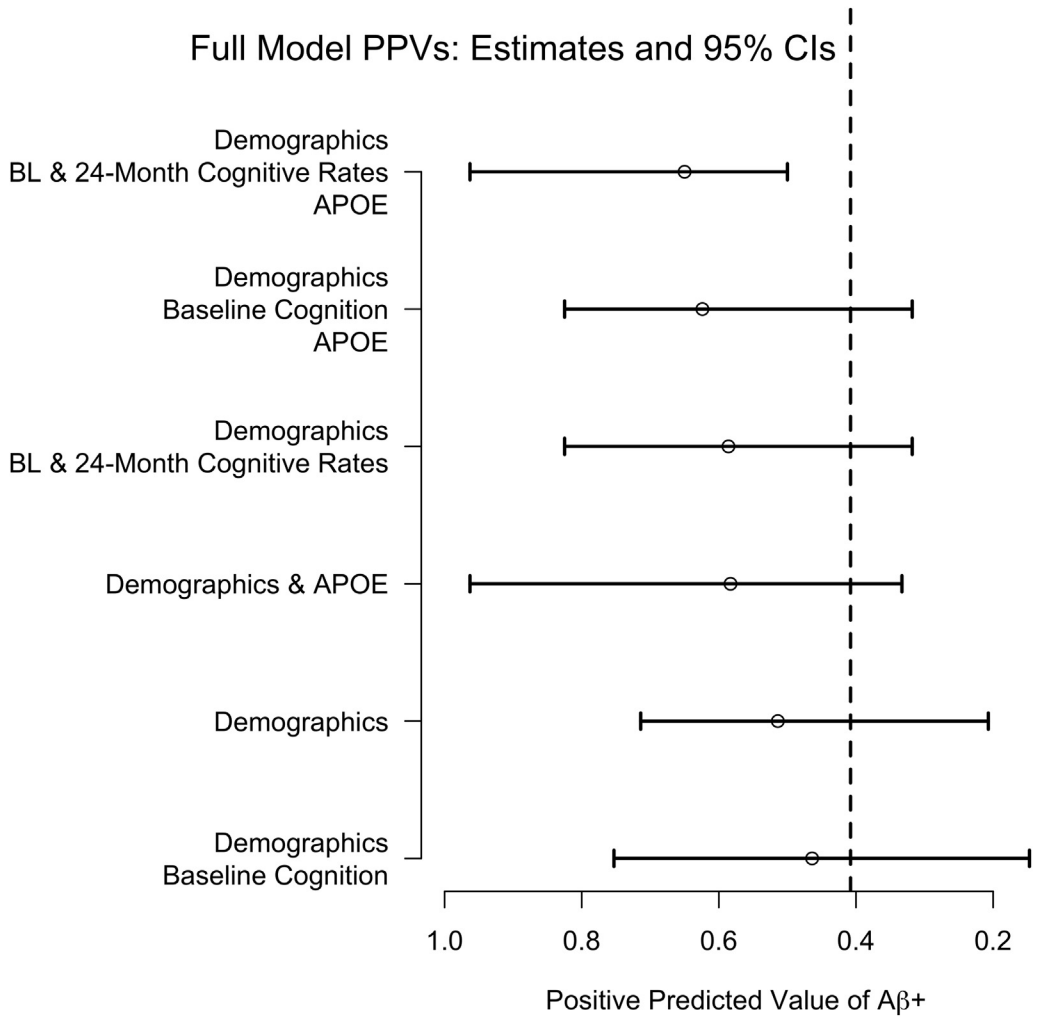

Fig. 3. Full model PPV estimates and 95% confidence intervals. PPV estimates and 95% confidence intervals are shown for seven different groups of predictors. When the 24-month rates are included, baseline (BL) cognition is also included. The vertical dashed black line in the reference PPV for the full cohort.

incorporating this procedure and using online cognitive testing, clinical trial screening costs of approximately 7500 USD per participant ($5000 for an Aβ PET scan and $2500 for an MRI, clinical/cognitive testing, EKG, and other laboratory measures; per written communication, Reisa Sperling, MD, 2016) may be reduced by nearly 7 million USD total, while decreasing the number of people undergoing invasive and time-consuming procedures by almost 40%. PET scan costs vary by country and are considerably greater in the United States compared with Europe [27]. Alternatively, measuring Aβ pathology by lumbar puncture would be markedly less expensive with screening costs around 1400 USD per participant in the United States and again considerably less in Europe (per personal written communication, Niklas Mattsson, MD, PhD, 2016).

The increase in the prevalence of Aβ positivity with age is well established [3–5]. In a large meta-analysis of cognitively normal participants, the prevalence of Aβ positivity increased from about 17% at age 60 years to 33% at age 80 years and up to 50% at age 95 years [3]. In our analysis, the proportion of Aβ+'s steadily increases with age until a plateau in the late 70s. However, the confidence intervals are wide at this end of the age range, and it is unlikely that the rate of Aβ positivity does not continue to increase. Age continues to be one of the strongest predictors of Aβ positivity.

The robust association between *APOE* ε4 genotype and β-amyloid pathology is also well established [6–8]. In this study, 58% of *APOE* ε4 carriers were Aβ+ compared to 34% of noncarriers. This risk increase is similar to the increase of 51% versus 23% shown in the AIBL cohort [3]. Just under 42% of the model-predicted Aβ+ participants in our study were *APOE* ε4+, resulting in a lower rate of *APOE* ε4 positivity compared with the full Aβ+ cohort. This low rate of *APOE* ε4 positivity among those predicted to be Aβ+ highlights the importance of the combination of predictors and not just a dependence on *APOE* genotype to enrich Aβ positivity. From a clinical trial

Table 3
Enriched Aβ groups: baseline cognition and 24-month rates

	Nonenriched (N = 293)		Aβ+ enriched (N = 60)	
Variable	Mean (SD)	Range	Mean (SD)	Range
Baseline cognition				
MMSE	29.1 (1.11)	24–30	28.9 (1.34)	24–30
ADAS13	8.6 (3.96)	0–20	12.2 (3.89)	1–24
dMemory	13.7 (3.13)	6–23	11.1 (3.32)	5–19
iMemory	14.5 (3.03)	5–23	11.9 (3.34)	3–21
dAVLT	7.9 (3.88)	0–15	5.6 (3.61)	0–15
iAVLT	55.1 (12.57)	21–86	45.6 (9.97)	23–74
Trails A	32.5 (9.72)	14–77	41.0 (13.68)	22–90
Trails B	76.9 (34.47)	32–300	113.6 (47.36)	51–251
Category fluency	21.0 (5.50)	6–38	18.8 (5.01)	7–28
24-month rates				
MMSE	−0.05 (0.09)	−0.54 to 0.05	−0.12 (0.11)	−0.40 to 0.03
ADAS13	−0.27 (0.34)	−0.94 to 1.19	0.13 (0.46)	−0.81 to 1.33
dMemory	0.32 (0.49)	−1.15 to 1.58	−0.29 (0.61)	−1.32 to 1.49
iMemory	0.49 (0.23)	−0.21 to 1.10	0.24 (0.26)	−0.25 to 1.07
dAVLT	0.30 (0.42)	−1.37 to 1.50	−0.04 (0.43)	−1.00 to 1.17
iAVLT	1.16 (0.92)	−1.55 to 4.20	0.33 (0.95)	−1.99 to 3.06
Trails A	−0.89 (1.75)	−5.01 to 14.26	0.24 (2.98)	−6.85 to 16.37
Trails B	−0.84 (4.02)	−23.22 to 17.36	3.62 (8.77)	−16.24 to 33.90
Category fluency	0.05 (0.42)	−1.08 to 1.86	−0.16 (0.47)	−1.21 to 1.28

standpoint, refraining from strict inclusion criteria such as *APOE* ε4 positivity will be important to avoid restrictive drug labeling.

The associations of gender and education with Aβ pathology observed in this study are less clear. Although there is a higher rate of AD in females [28,29], the slight increased prevalence of Aβ positivity in females observed in this study was not seen in other large cohort studies [3,8]. However, once age, *APOE*, and cognitive measures were included in the model, gender did not predict Aβ positivity. The ADNI cohort is also more educated than other cohorts, including population-based cohorts, which may contribute to the high overall rate of Aβ positivity in this sample, following from the cognitive reserve hypothesis and similar associations observed in other studies [30,31]. The additional slight increase of Aβ-positivity in individuals with fewer years of education is likely due to the small sample size of less educated individuals in ADNI.

Subtle cognitive dysfunction and increased rates of decline associated with Aβ-positivity in cognitively normal elderly have been replicated in many independent cohorts [9–13]. A meta-analysis comprising 34 independent studies of cognitively normal participants found overall significant associations between amyloid burden and poorer performance on measures of memory, executive function, and global cognition [13]. Given these associations, the increase in the proportion of Aβ+'s at the lower end of the spectrum of cognitive scores and rates observed in this analysis was expected. Increases in PPV are seen with a decrease in the cognitive scores and faster rates of decline in multiple domains (Fig. 2) not only delayed memory recall. It is possible that cognitive measures only marginally associated with Aβ positivity across the entire spectrum of scores in small samples may still be useful for increasing PPV if the concentration of Aβ+'s increases toward the bottom 20%–30% of scores. This is especially true if the rate of Aβ positivity accelerates at the low end of the spectrum, as it appears to do in several cognitive measures in Fig. 2. In large cohorts of thousands of participants, the bottom quartile of scores may represent a large pool from which to recruit into clinical trials. Cognitive measures provide important complementary information to demographics and *APOE* and greatly improve the precision of the prediction of Aβ pathology (Fig. 3).

A study of cognitively normal elderly from the Mayo Clinic Study of Aging [32] found the strongest predictors of Aβ pathology to be age, *APOE* status, family history of dementia, and/or AD, but not cross-sectional cognition and did not evaluate longitudinal cognitive change. Unfortunately, family history of AD was not assessed in our analysis because of the large proportion of missing data for family history, although it is possible or likely that family history information could further improve Aβ enrichment. In summary, the relationships reported in previous studies of Aβ, demographics, *APOE*, and cognitive data support the results of our model to predict Aβ pathology.

In Fig. 3, PPV estimates and confidence intervals are improved but not maximized when only subsets of the available predictors are modeled. It is not until all categories of predictors—demographic, genetic, and cognitive scores and rates—are included that PPV estimates reach 65% and confidence intervals narrow. This suggests that the prediction of Aβ pathology in cognitively normal

participants cannot be optimally done with simple independent thresholds for each predictor, but rather that risk must be evaluated with all predictors in concert. This can be seen by considering the range of characteristics of the predicted Aβ+ group from the best model, where less than half of these participants are *APOE* ε4+, many are aged <75 years, and some have memory or global cognitive scores above the median (Supplementary Table). Thus, whereas rates of Aβ positivity increase with age, declining cognitive scores and *APOE* ε4-positivity, the ability and precision to predict Aβ pathology increases substantially when these risk factors are assessed collectively. As such, clinical trials may benefit from using a set of interdependent inclusion criteria based on multiple factors.

This study has several limitations. The cognitive tests described here were administered in clinic. Whether online cognitive testing will predict Aβ positivity with the same PPV is unknown. The confidence intervals for the models shown in Fig. 3 overlap substantially. However, the best performing model has a lower confidence limit well above the reference PPV. A much larger cohort will be required to provide the power to test for model differences. The prevalence of Aβ positivity in the ADNI cohort of cognitively normal controls is also on the high end of the spectrum of previously reported estimates, calling into question how the methods developed here would perform in other cohorts [33]. This cohort is not population based and is more educated on average, making the relationships among predictors and amyloid pathology observed here potentially less generalizable to other cohorts due to cognitive reserve. The enrichment of Aβ pathology in this analysis relied on subtle cognitive dysfunction within the range considered to be cognitively normal. Identifying Aβ pathology in participants with high cognitive scores remains a challenge and will likely require the identification of further biomarkers associated with Aβ or downstream effects of Aβ pathology. Additionally, the random forest model known for its flexibility in terms of modeling nonlinearity and the interactions among predictors comes at the cost of the ability to report simple estimates of the relationship between the predictors and the response [26]. The effects of predictors in random forest models vary over hundreds of bootstrap resamples, precluding the report of a simple closed form solution to predict amyloid pathology. For this reason, results are summarized by PPV estimates and confidence intervals of subsets of predictors and also the range of characteristics of the predicted Aβ-pathology group. Nevertheless, even without specifying effects of individual predictors, a random forest model such as the one presented here is conceivable as a well-defined statistical working tool for pre-screening participants in clinical trials.

Finally, considerable improvements to the recruitment of cognitively normal elderly with Aβ pathology can be done without expensive or invasive procedures. By implementing a pre-screening procedure to participants enrolled in large online cohorts, the likelihood of Aβ pathology can be assessed and the number of screen failures due to biomarker inclusion criteria and associated costs reduced. When effective treatments for AD become available, a similar approach could be used to identify individuals likely to harbor Aβ pathology to inform decisions concerning treatment.

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Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.dadm.2016.07.002.

RESEARCH IN CONTEXT

1. Systematic review: Clinical trials in Alzheimer's disease are aimed at early stages of disease, including preclinical AD. The high cost and time required to screen large numbers of participants for Aβ pathology impedes the development of novel drugs. This study's objective was to evaluate the extent to which inexpensive and easily obtainable information can reduce the number of screen failures by increasing the proportion of Aβ+ participants identified for screening.
2. Interpretation: In a cohort study of 353 subjects, predicting Aβ-positivity with demographic, *APOE*, baseline cognition and 24-month rates of cognitive change yielded a positive predicted value (PPV) estimate of 0.65 (95% CI, 0.50–0.96), nearly a 60% increase over the reference Aβ+ prevalence in the cohort of 0.41.
3. Future directions: By incorporating a β-amyloid prediction algorithm, clinical trial screening costs, recruitment time and the use of expensive, invasive procedures in trials of preclinical AD may be substantially reduced, thus accelerating the development of novel treatments for AD.

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