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RESEARCH ARTICLE

Contribution of Global Amyloid-PET Imaging for Predicting Future Cognition in the MEMENTO Cohort

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Abstract

Background and Objectives

Global amyloid-PET is associated with cognition and cognitive decline, but most research on this association does not account for past cognitive information. We assessed the prognostic benefit of amyloid-PET measures for future cognition when prior cognitive assessments are available, evaluating the added value of amyloid measures beyond information on multiple past cognitive assessments.

Methods

The French MEMENTO cohort (a cohort of outpatients from French research memory centers to improve knowledge on Alzheimer disease and related disorders) includes older outpatients with incipient cognitive changes, but no dementia diagnosis at inclusion. Global amyloid burden was assessed using positron emission tomography (amyloid-PET) for a subset of participants; semiannual cognitive testing was subsequently performed. We predicted mini-mental state examination (MMSE) scores using demographic characteristics (age, sex, marital status, and education) alone or in combination with information on prior cognitive measures. The added value of amyloid burden as a predictor in these models was evaluated with percent reduction of the mean squared error (MSE). All models were conducted separately for evaluating the added value of dichotomous amyloid positivity status compared with a continuous amyloid-standardized uptake-value ratio.

Results

Our analytic sample comprised 510 individuals who underwent amyloid-PET scans with at least 4 MMSE assessments. The mean age at the PET scan was 71.6 (standard deviation 7.4) years; 60.7% were female. The median follow-up was 4.6 years (interquartile range: 0.9 years). Adding amyloid burden when adjusting for only demographic characteristics reduced the MSE of predictions by 5.08% (95% CI 0.97%–10.86%) and 12.64% (95% CI 3.35%–25.28%) for binary and continuous amyloid, respectively. If the model included 1 past MMSE measure, the MSE improvement was 3.51% (95% CI 1.01%–7.28%) when adding binary amyloid and 8.83% (95% CI 2.63%–16.37%) when adding continuous amyloid. Improvements in model fit were smaller with the addition of amyloid burden when more than 1 past cognitive assessment was included. For all models incorporating past cognitive assessments, differences in predictions amounted to a fraction of 1 MMSE point on average.

Discussion

In a clinical setting, global amyloid burden did not appreciably improve cognitive predictions when past cognitive assessments were available.

Trial Registration Information

ClinicalTrials.gov Identifier: NCT02164643.

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Go to Neurology.org/N for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

MEMENTO Cohort Study Group and DPUK coinvestigators are listed in Appendix 2 at links.lww.com/WNL/D395.

Glossary

AD = Alzheimer disease; **CDR** = Clinical Dementia Rating; **DPUK** = Dementias Platform UK; **IDEAS** = Imaging Dementia—Evidence for Amyloid Scanning; **MAE** = mean absolute error; **MCI** = mild cognitive impairment; **MMSE** = mini-mental state examination; **MSE** = mean squared error; **SUVr** = standardized uptake value ratio.

Introduction

Positron emission tomography with amyloid ligands (amyloid-PET) allows for in vivo assessment of brain amyloid burden.[1,2] Previous studies found an association between amyloid burden and global cognitive measures,[3-5] amyloid burden and cognitive decline,[3,6-10] as well as future mild cognitive impairment and Alzheimer disease diagnoses.[11] Although amyloid burden is considered an essential biomarker for assessing Alzheimer disease (AD), some individuals with substantial brain amyloid burden never develop AD or dementia.[12] Amyloid-PET is therefore not currently the standard of care for older adults experiencing cognitive complaints. However, questions remain regarding whether amyloid imaging provides useful prognostic information and alters clinical management in ways that are beneficial to patients. The Imaging Dementia—Evidence for Amyloid Scanning (IDEAS and New IDEAS) cohort study is underway to evaluate whether amyloid imaging is a useful clinical tool and alters clinical management of mild cognitive impairment (MCI) and dementia.[13,14] Although amyloid imaging is not considered appropriate to evaluate dementia severity, its use and predictive ability in patients with MCI are less clear.[15] It has been suggested that in certain settings, amyloid imaging may provide utility in clinical practice settings.[16-18]

For routine use of amyloid-PET to provide benefit to patients, it must result in detectable, clinically significant improvements in predictions of future cognitive outcomes. Previous results from a small, California-based community sample indicated that in a context with numerous past cognitive assessments before neuroimaging, the added value of amyloid-PET measures was limited.[19] It is unknown whether amyloid-PET imaging may be more informative in other settings. It is also unclear whether even a single cognitive assessment would be sufficient to eliminate the prognostic benefit of an amyloid-PET scan, or if multiple, repeated cognitive measures are needed to render additional prognostic value of the amyloid-PET superfluous. Many new AD-related biomarkers are under development and may enter clinical practice.[20,21] Developing and implementing methods to evaluate whether biomarkers aid in evaluating prognosis compared with less invasive and less costly measures is essential for determining how to prioritize data collection in patients. The current work represents an effort to assess the added value of amyloid-PET under conditions similar to those in a clinical setting. The methods developed and employed here can be used to rigorously evaluate new biomarkers or compare the prognostic ability of 2 different biomarkers.

Methods

Analysis Overview

Using data from the MEMENTO cohort (formally, the cohort of outpatients from French research memory centers to improve knowledge on Alzheimer disease and related disorders), we examined whether amyloid positivity or total amyloid uptake as measured with the standardized uptake value ratio (SUVr) improved predictions of the trajectory of global cognition compared with simpler models based on commonly available clinical data.

We use a subsample of the MEMENTO cohort that includes individuals with amyloid-PET scans, combined with semi-annual cognitive assessments after the PET scan, recruited from French memory clinics, but without a dementia diagnosis at the PET scan. This provides an opportunity to evaluate amyloid's prognostic ability in a comparatively large cohort.

Since amyloid-PET is costly compared with routine cognitive testing, improved understanding of the settings in which amyloid predicts cognitive decline can help guide its use in clinical settings.

MEMENTO Cohort

MEMENTO is a multicenter national prospective cohort study of more than 2,323 individuals consecutively recruited from 26 participating French memory clinics between April 2011 and June 2014. The study, its procedures, and baseline characteristics of participants are described in detail elsewhere.[22] At enrollment, participants presented either with mild cognitive impairment (MCI) or with isolated cognitive complaints (if 60 years or older), with a Clinical Dementia Rating scale score less than 1 (≤0.5). As described elsewhere,[22] MCI was defined as (1) performing 1 standard deviation worse than the participant's own age, sex, and education-level group mean in 1 or more cognitive domains, this deviation being identified for the first time through cognitive tests performed recently (less than 6 months preceding screening phase), and (2) having a Clinical Dementia Rating (CDR) ≤ 0.5 and not having dementia. A participant was eligible for inclusion in the isolated subjective cognitive complaint stratum if the participant had subjective cognitive complaints (assessed through visual analog scales) without any of objective cognitive deficit as defined above and was aged 60 years or older. Exclusion criteria are also detailed in reference 22. Inclusion criteria included agreement to undergo brain

MRI and have blood samples collected, as well as healthcare coverage.

Standard Protocol Approvals, Registrations, and Patient Consents

This study was performed in accordance with the guidelines of the Declaration of Helsinki. The MEMENTO study protocol has been approved by the local ethics committee ("Comité de Protection des Personnes Sud-Ouest et Outre Mer III"; approval number 2010-A01394-35, ClinicalTrials.gov Identifier: NCT02164643). All participants provided informed consent.[22] This study was secondary data analysis of deidentified data. Data were accessed through an approved project with the Dementias Platform UK (DPUK) secure data portal.

Cognitive Data and Demographic Covariates

Neuropsychological assessments were performed for all participants at baseline. Global cognition was assessed using the mini-mental state examination (MMSE) at baseline and semiannually thereafter for up to 5 years. We used MMSE in our analyses because it is commonly available in routine clinical settings and is more likely to guide clinical management. Demographic variables were obtained at enrollment and include age, sex, education categorized as highest degree obtained (primary school; secondary school, first cycle; upper secondary school; or third-level/higher level studies), and marital status (married, single, divorced, or widowed).

Amyloid-PET Data

Amyloid-PET imaging procedures are described in detail elsewhere.[23,24] Briefly, amyloid-PET imaging was offered to all participants without dementia but was not mandatory. Amyloid-PET imaging was performed on 661 individuals using either ^{18}F-florbetapir (Amyvid, Eli Lilly) or ^{18}F-flutemetamol (Vizamyl, GE Healthcare) radioligands. PET images were coregistered onto the corresponding MRI and corrected for partial volume effects using the RBV-sGTM method. All amyloid-PET scans were acquired in a single session on a Philips Gemini GXL CT-PET scanner. For both tracers, standardized uptake value ratios were calculated about a combination of the whole cerebellum and pons using the RACHEL method.[23] The mean brain amyloid standardized uptake value ratio, referred to as global amyloid burden henceforth, was used for this study.[24] Amyloid positivity was determined based on the following cutoffs: 0.88 for florbetapir and 1.0629 for flutemetamol.

Analysis

eFigure 1 (links.lww.com/WNL/D394) in the supplement gives a schematic of the analysis. Half of participants were randomly assigned to a training set and half to a testing set. The following steps were then performed to evaluate the added value of amyloid in the context of past cognitive assessments. Previous work has noted the limitations of MMSE about floor and ceiling effects and sensitivity to cognitive change that differs across the cognitive range. We adopted a normalization procedure developed to address these limitations.[25] The transformation presented in this article was developed by fitting latent variable models of cognition to MMSE data to determine a scale over which a given percent change was constant across the cognitive range. In essence, this transformation puts MMSE scores on a scale such that a given percent change in transformed MMSE indicates the same change in cognition, regardless of the starting point in cognition. Before analysis, cognition was transformed using the associated R package NormPsy.[26] For interpretability, cognitive predictions were subsequently detransformed to present final results on the native-MMSE scale.

Developing an Optimized Measure of Amyloid Burden

Previous research has evaluated both binary and continuous amyloid as predictors of cognition and cognitive decline. Although amyloid burden is often dichotomized, substantial evidence indicates that amyloid burden above or below the positivity threshold may be related to cognition.[27,28] The relationship between amyloid burden and cognitive outcomes may also be nonlinear and vary by the radiotracer used for the scan. Therefore, we considered it important to include linear and nonlinear terms for amyloid and interactions of amyloid with radiotracer and time in an optimized measure of amyloid burden.

Ridge regression with 10-fold cross-validation was used to create the optimized measure of amyloid burden using data from the training set. Ridge regression results in improved model predictions by shrinking regression coefficients toward the null.[29] We estimated separate ridge regressions for dichotomous amyloid and for continuous amyloid, each trained on half of the sample (training set) to predict transformed cognition.

For the model with dichotomous amyloid, predictors included amyloid positivity and amyloid positivity times time since PET scan. For the model using continuous amyloid, predictors included all main effects and interactions for continuous amyloid burden, continuous amyloid burden squared, the natural logarithm of amyloid burden, an indicator variable for radiotracer, and time since PET scan (with the exception of time since amyloid-PET scan and the interaction of radiotracer by time since amyloid-PET scan because these terms do not include amyloid burden).

Determining the Added Value of Amyloid

In the testing data, we predicted transformed cognition without amyloid using each of the prespecified time-series models listed in Table 1. The demographic model included no past cognitive data, predicting only cognitive data from the covariates baseline age (linear and squared terms as orthogonal polynomials), time since amyloid-PET scan, sex, marital status, and categorical education. The 1, 2, and 3 past cognitive assessment models represent simple ways of incorporating past cognitive assessments as independent

Table 1 Model Predictors in Compact Symbolic Form

Model name	Predictors of current cognition
Demographic model	Demographics
One past cognitive assessment	c_{n-1} + demographics
Two past cognitive assessments	$c_{n-1} + c_{n-2}$ + demographics
Three past cognitive assessments	$c_{n-1} + c_{n-2} + c_{n-3}$ + demographics
Two past cognitive assessments, trajectory model	$\overline{k_2}+v_{n-1}\left(t_n-\frac{(t_{n-1}+t_{n-2})}{2}\right)$ + demographics
Three past cognitive assessments, trajectory model	$\overline{k_3}+\bar{v}\left(t_n-\frac{(t_{n-1}+t_{n-2}+t_{n-3})}{3}\right)$ + demographics

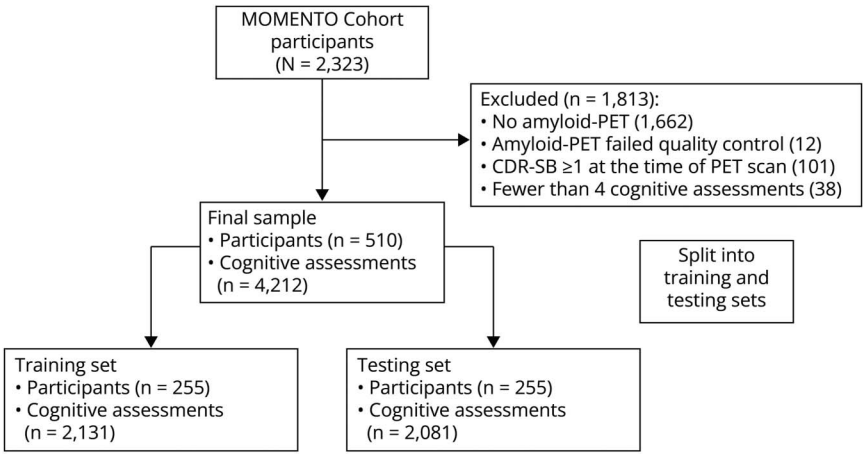
c_n represents cognition at assessment n and is the dependent variable, t_n is the time at cognitive assessment n, $v_{n-1}=\frac{c_{n-2}-c_{n-1}}{t_{n-2}-t_{n-1}}$, $v_{n-2}=\frac{c_{n-3}-c_{n-2}}{t_{n-3}-t_{n-2}}$, $\bar{v}=\frac{v_{n-2}+v_{n-1}}{2}$, and $\overline{k_i}$ refers to the mean of the last i cognitive assessments. Demographics refers to the following set of prespecified predictors: sex, age and age squared as orthogonal polynomials, categorical education, and marital status.

predictors of current cognition. The trajectory models for 2 and 3 past cognitive assessments encode information on the trajectory to date. Specifically, trajectory models have 2 predictors (in addition to demographics): average cognition and expected change cognition based on the previous 2 or 3 cognitive assessments.

Using coefficients obtained from the ridge regression, we calculated the optimized measure of amyloid burden by applying the ridge regression coefficients to the testing data set. That is, we used coefficients obtained from the ridge regression estimated in the training data to calculate predicted cognitive scores for each person at each cognitive assessment in the testing data. We then assessed whether optimized amyloid burden improved predictions of the subsequent cognitive measures post-PET for each of the models in Table 1. This was performed by evaluating whether the addition of optimized amyloid burden to these models improved cognitive predictions. We then assessed the mean squared error (MSE) of each of the models in Table 1, with and without optimized amyloid burden. MSE is defined as the mean squared difference between each observed MMSE and the predicted MMSE from the model being evaluated. MSE is a standard approach to evaluating prediction improvements.[30] The predictive added value was evaluated by using the percent reduction of MSE of a model including optimized amyloid burden comparing with a model without as a reference. Confidence intervals of reduction in mean squared error were obtained by bootstrap resampling individuals (2,000 replicates). Reductions in mean absolute error, and associated confidence intervals, were also calculated.

Multiple sensitivity analyses were performed. First, the analysis was repeated without transforming MMSE scores. Second, to evaluate whether improvements in predictions changed for later cognitive assessments, the analysis was repeated with only cognitive assessments at least 2.5 years after PET scan. Third, a sensitivity analysis was performed to determine the improvement in predictions with a single past cognitive assessment with variability in the timing of the past cognitive assessment. That is, the 1 past cognitive assessment

Figure 1 Flowchart of Inclusions and Exclusions and Sample Splitting Into Training and Testing Sets



To avoid predicting from approximately contemporaneous amyloid burden, we predict only cognitive tests at least quarter of a year after PET scan.

Table 2 Characteristics of the Analytic Sample

	Overall
Number of individuals (n)	510
Age at PET (mean (SD))	72.9 (7.0)
Women (n (%))	306 (60.0)
Marital status (n (%))	
Divorced/separated	85 (16.7)
Married/cohabiting partner	317 (62.2)
Single	33 (6.5)
Widow(er)/death of spouse	75 (14.7)
Education (n (%))	
Primary school	33 (6.5)
Secondary level first cycle	81 (15.9)
Third-level/higher level studies	268 (52.5)
Upper secondary school	128 (25.1)
Flutemetamol (vs. florbetapir) (%)	138 (27.1)
Number of assessments post-PET (median [IQR])	9.0 [6.0, 10.0]
MMSE (mean (SD))	28.6 (1.2)
CDR = 0.5 vs 0 (n %)	173 (33.9)

Abbreviation: MMSE = mini-mental state examination.

model was repeated with assessments 1 and 1.5 years prior. Fourth, sensitivity analysis with CDR-SB as the outcome was performed using past MMSE scores as the predictor. Fifth, the analysis was repeated with only individuals stratified by CDR-SB at baseline. Finally, we repeated the analysis using alternative cognitive outcomes both as a predictor and outcome: the Trail-Making Test A and Letter P Fluency.

Data Availability

This work was undertaken using resources made available by the DPUK Data Portal. Data are available to qualified researchers on application.

Results

Figure 1 shows how the analytic sample was obtained. Of 2,323 participants, 1,662 had no amyloid-PET scan. Of the 661 individuals with a PET scan, 12 additional participants failed quality control. Of 649 remaining participants, 101 had a CDR-SB greater than or equal to 1 at baseline. Of the remaining individuals, 38 had fewer than 4 cognitive assessments. The analytic sample consisted of 510 participants for whom at least 4 cognitive assessments were available and who did not have dementia at the first study visit. Within this sample, individuals completed a median of 8 semiannual assessments (interquartile range: 6 to 9) following the amyloid-PET scan.

The mean age of study participants at the PET scan was 71.6 (standard deviation 7.4) years, and 60.7% were female. The median time between baseline and last cognitive assessment was 4.6 years, with an interquartile range of 0.9 years. The median number of cognitive assessments at least 3 months post-PET was 8, with an interquartile range of 3. Table 2 gives additional summary information on participants. Table 3 reports the ridge regression coefficients. A total of 1,825 cognitive predictions were made for the demographic model, 1,824 for the 1 past cognitive assessment models, 1,580 for the 2 past cognitive assessment models, and 1,336 for 3 past cognitive assessment models in the testing set. The models without the added burden of amyloid explain the following percent variances (R-squared): 7.3% (demographic model), 22.7% (1 past cognitive assessment), 29.4% (2 past cognitive assessments), 29.4% (2 past cognitive assessments–trajectory model), 32.7% (3 past cognitive assessments), and 32.6% (3 past cognitive assessments–trajectory model).

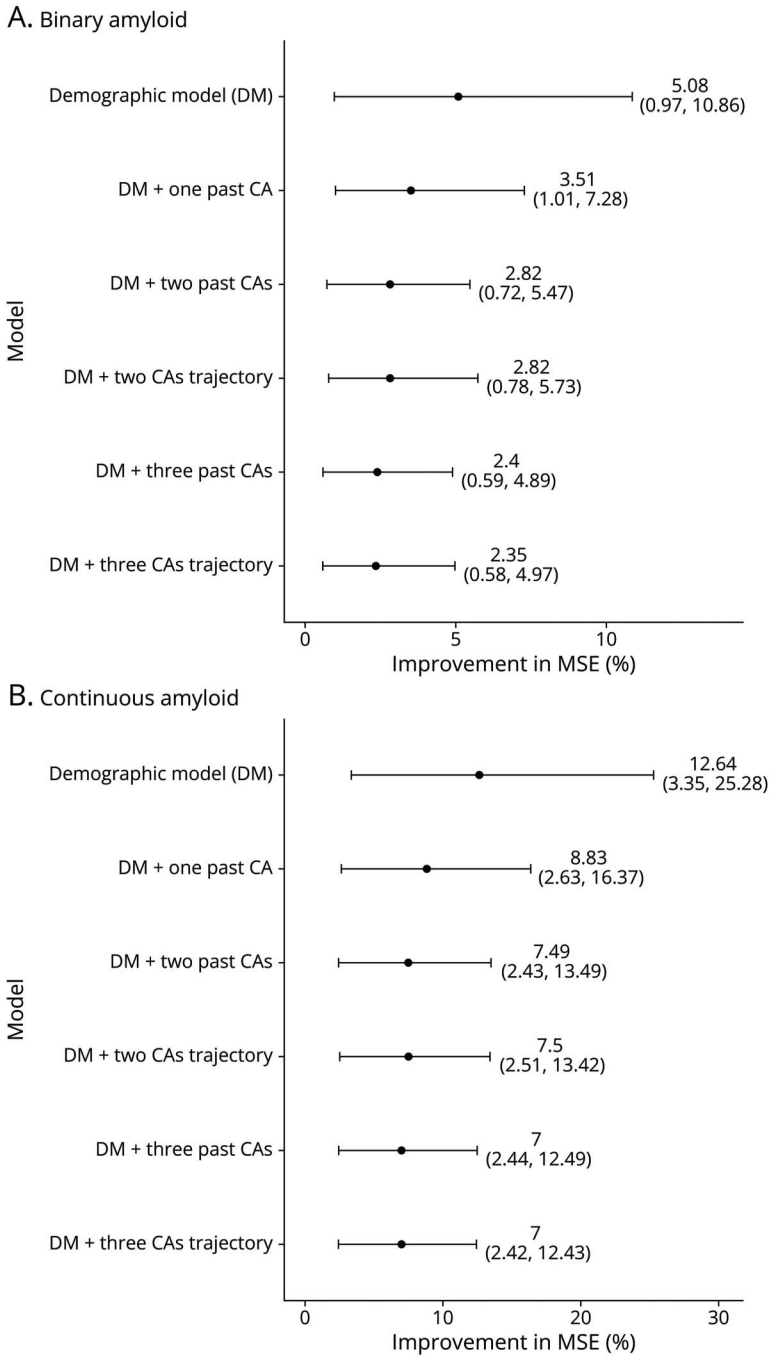
The plots in Figure 2 show improvements in the MSE of 5.08% (95% CI 0.97%–10.86%) when adding the optimized transform of binary amyloid and 12.64% (95% CI 3.35%–25.28%) when adding optimized transform of continuous amyloid to models adjusting only for demographic covariates. For the models that incorporate past cognitive assessments, smaller but

Table 3 Ridge Regression Coefficients for Amyloid Variables Predicting Transformed MMSE Scores, Estimated in the Training Data in the MEMENTO Sample

	Coefficient
Binary amyloid	
Amyloid$^+$ vs amyloid$^-$	−2.6
Amyloid$^+$ × time	−0.9
Continuous amyloid	
log(SUVr)	−1.9
log(SUVr)× time	−0.9
log(SUVr)× flutemetamol	9.1
log(SUVr)× time × flutemetamol	3.8
SUVr	−33.9
SUVr^2	−3.9
SUVr × time	−22.9
SUVr^2× time	−8.6
SUVr × flutemetamol	−151.1
SUVr^2× flutemetamol	137.2
SUVr × time × flutemetamol	−52.0
SUVr^2× time × flutemetamol	15.0

Abbreviation: MMSE = mini-mental state examination.

Figure 2 Reduction in Mean Squared Error



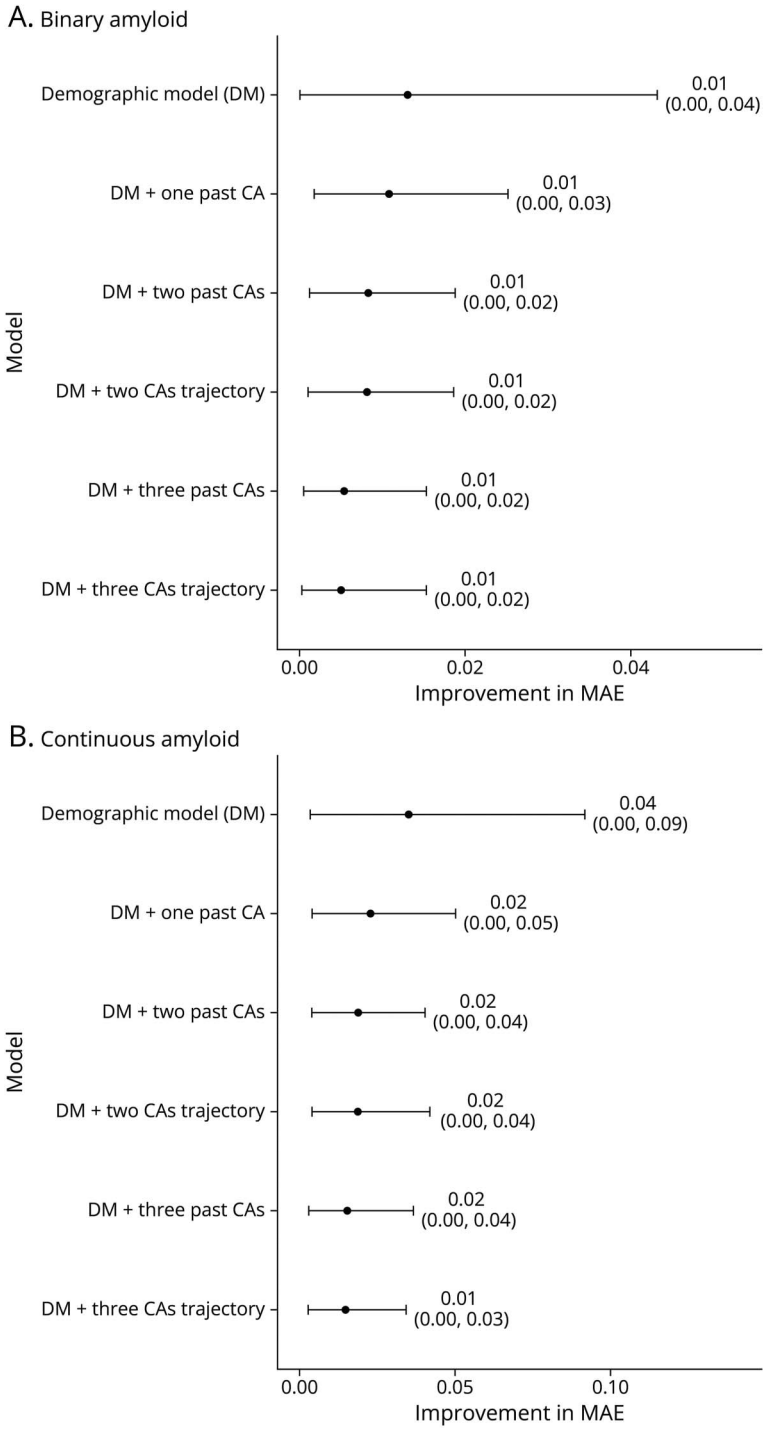
Percent reduction (95% CI) in the mean squared error with the addition of optimized binary amyloid (A) or continuous amyloid (B) to models including demographic covariates, including demographics plus 1 or 2 past cognitive assessments (CAs), or including demographics, average of past CAs, and slope of change in past CAs (trajectories).

statistically significant improvements in prediction were achieved. For the optimized binary transform of amyloid, percent improvements in the MSE over models that incorporated past cognitive assessments ranged from 2.35% to 3.51%. For the optimized transform of continuous amyloid, percent improvements in the MSE over models that incorporated past cognitive assessments ranged from 7.00% to 8.83%.

Improvements in predictions achievable by adding amyloid were slightly larger when using continuous instead of binary amyloid. In addition, across both sets of models, results did not appreciably differ between trajectory models and their counterparts incorporating the same number of past cognitive assessments.

To facilitate clinical interpretability, the plots in Figure 3 show the improvements in the mean absolute error (MAE). The MAE gives the average amount by which cognitive predictions would differ with and without information on amyloid burden. For the demographic model, the addition of optimized amyloid burden improves the MAE by 0.01 (95% CI

Figure 3 Reduction in Mean Absolute Error

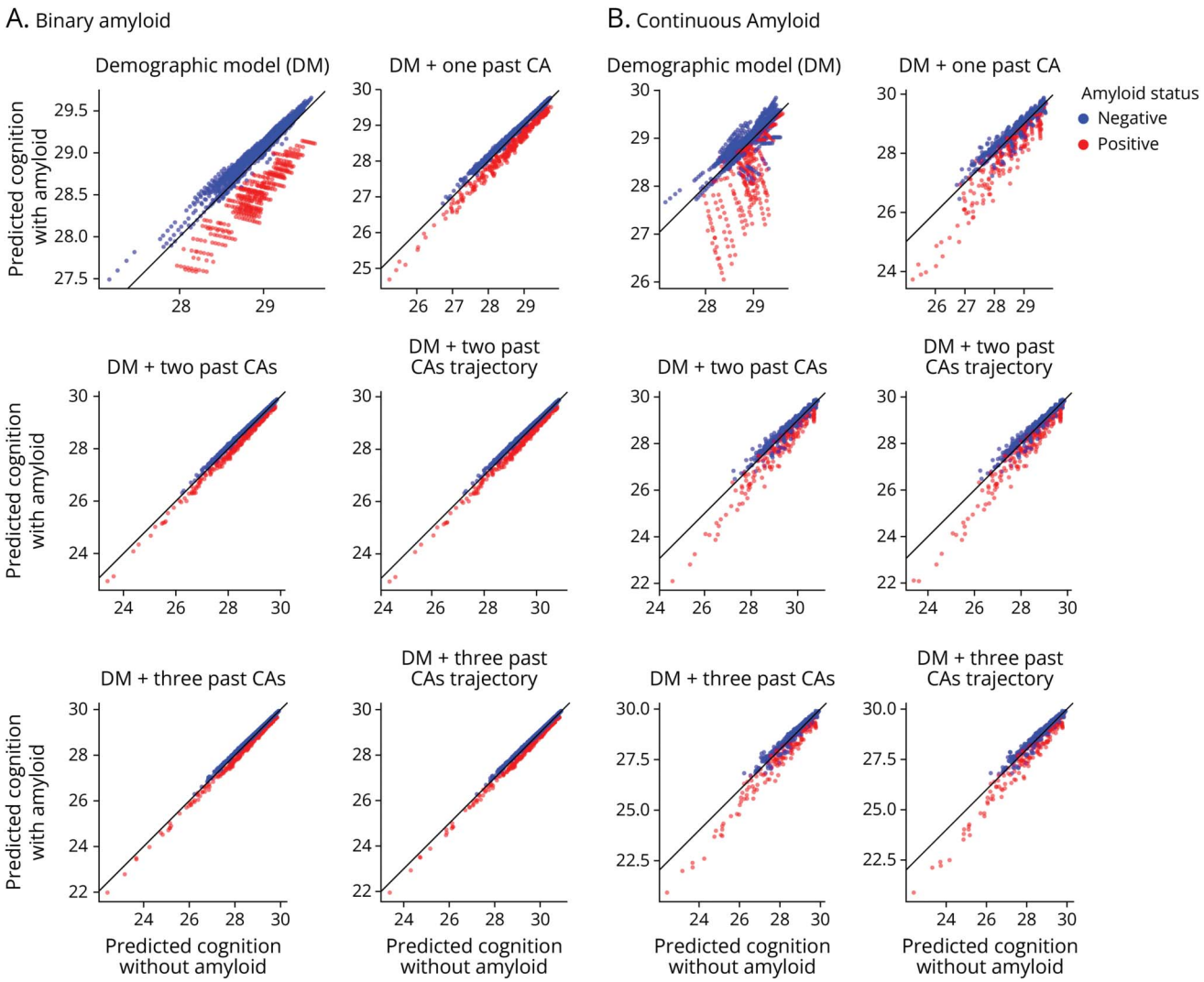


Absolute reduction (95% CI) in the mean absolute error with the addition of optimized binary amyloid (A) and continuous amyloid (B) to models including demographic covariates, including demographics plus 1 or 2 past cognitive assessments (CAs), or including demographics, average of past CAs, and slope of change in past CAs (trajectories). Values are on the original MMSE scale, so an improvement of 0.02 implies that the addition of amyloid data would bring the average prediction 0.02 units closer to the true MMSE score. MMSE = mini-mental state examination.

0.00–0.04) MMSE points for the optimized transform of binary amyloid and 0.04 (95% CI 0.00–0.09) MMSE points for the optimized transform of continuous amyloid. Improvements in the MAE were smaller with the incorporation of past cognitive assessments.

For binary amyloid and the demographic model, 36.0% and 37.8% of the time cognitive predictions differ from the true value by more than 1 MMSE point without and with the addition of optimized amyloid burden, respectively. For continuous amyloid and the demographic model, we find that 36.0% and 37.0% of the time cognitive predictions differ from the true value by more than 1 MMSE point without and with the addition of optimized amyloid burden, respectively. Results were similar for models including additional past cognitive assessments: adding amyloid did little to reduce the

Figure 4 Predicted Cognitive Scores With and Without Amyloid



Cognitive scores predicted from models with amyloid plotted against cognitive scores predicted from models without amyloid, using (A) binary amyloid or (B) continuous amyloid to improve predictions, by amyloid positivity status. Amyloid-negative individuals are shown in blue and amyloid-positive individuals are shown in red. As expected, incorporating amyloid information into the models leads to slightly lower average predicted scores for amyloid-positive individuals (red dots) and slightly higher average predicted scores for amyloid-negative individuals (blue dots). The visible substructure in the demographic model figure is due to repeated assessments on individuals.

chance of a prediction error greater than or equal to 1 MMSE point. eTable 2 (links.lww.com/WNL/D394) gives these results for each model without and with the addition of optimized amyloid burden.

Figure 4 shows the relationship between predictions with and without optimized binary amyloid and optimized continuous amyloid. Predictions that lie along the diagonal line $y = x$ correspond to no difference in predictions with and without amyloid. Predictions for each of every individual's cognitive tests are shown by amyloid positivity status.

Compared with a model using only demographic predictors, adding amyloid to the prediction model decreased predicted cognition by 1–2 MMSE points for a small number of amyloid-positive individuals. For all models that incorporate past cognitive assessments, all predictions lie close to the diagonal line $y = x$.

Results from additional and sensitivity analyses are given in the supplement and did not appreciably differ from those given here (eTables 1–2 and eFigures 2–24, links.lww.com/WNL/D394). When restricting to cognitive tests at least 2.5 years after the PET scan, improvements in predictions with the addition of amyloid burden were similar. Improvements in model fit for the demographic models were quite similar but slightly larger than improvements seen when incorporating earlier cognitive assessments (7.67% vs 6.35% for binary amyloid and 13.45% vs 12.04% for continuous amyloid), although confidence intervals overlap considerably. When

adjusting for past cognitive assessments, results were also comparable and did not have a consistent pattern of larger percent improvements for later cognitive assessments. In sensitivity analyses stratified by CDR-SB at baseline, larger improvements in predicted cognition associated with the addition of amyloid burden for individuals CDR-SB of 0.5 at baseline, although improvements were nonetheless small. Improvements in predictions with the additional cognitive tests were smaller than improvements seen with the MMSE.

Discussion

In a longitudinal cohort of older individuals without diagnosed dementia presenting at memory clinics across France, we showed that amyloid burden contributes to improved prediction of future cognition. Compared with models with only demographic covariates, incorporating amyloid status can lead to nontrivial differences in predictions, particularly among amyloid-positive individuals. However, the added value of amyloid information becomes smaller if even 1 recent cognitive assessment is available: in models adjusting for past cognitive assessments, predictions with and without amyloid differ by a fraction of 1 MMSE point and lead to substantial improvements in prediction for almost no participants. Our results were robust to different specifications of past cognition, including using each of 2 or 3 past cognitive assessments and using a mean cognition and a trajectory in lieu of treating past cognitive assessments independently. That is, for these trajectory models, predictions did not appreciably differ from models adjusting for past cognitive assessments as independent linear predictors. Finally, the optimized transformation of continuous amyloid improved predictions more than the optimized transformation of binary amyloid.

Results from analyses that only adjust for demographic characteristics are consistent with previous studies that show an association between amyloid and cognition and amyloid and cognitive decline (e.g., reference 3). These results also confirm the results of prior work in a single California-based sample showing that amyloid adds little to prediction when past cognitive information is available.[19] These results were in a sample of individuals who were cognitively normal at baseline, but with varying numbers of cognitive assessments. With the even spacing of cognitive assessments post-PET scan and a large sample of individuals with at least 4 cognitive assessments in MEMENTO, it was possible to extend prior work and ascertain how the prognostic benefit of amyloid changes with an increasing number of past cognitive assessments. Given that dichotomizing a measure results in information loss and previous work has shown that amyloid burden below the positivity threshold is associated with cognition,[27] it is not surprising that the optimized transform of continuous amyloid typically improved predictions more than the optimized transform of binary amyloid. However, this work should be replicated with other cognitive tests and in other cohorts.

Although amyloid imaging is currently primarily used in research settings,[31,32] there is interest in determining the extent to which it has significant clinical utility, particularly to identify patients who will develop dementia in a short term.[13] Across all individuals in the testing sample, differences in predicted cognition with and without amyloid burden were small for all (1, 2, or 3 past cognitive assessment models) or nearly all (demographic model) individuals. Compared with using only demographic information, additionally incorporating amyloid improved predictions for a subset of individual, moving predicted scores down for amyloid-positive individuals. When past cognitive scores were available, prediction improvements were too small to be detectable for an individual: MMSE differences less than a point would not measurable in an individual, so clinically relevant prediction improvements would need to be at least 1 MMSE point. Furthermore, the addition of amyloid burden did not appreciably reduce the fraction of predictions that are incorrect by more than 1 point. We note that a 1-point improvement would represent a lower bound because, due to additional factors that result in variability in cognitive test performance (medication usage, time of day, who is administering the test), clinically detectable differences in cognition might be expected to exceed a single MMSE point. Finally, we note that the contribution of amyloid-PET to the prediction is limited even for the demographic model.

This study has several strengths. First, we used several methods to avoid over fitting. Since the addition of parameters, such as amyloid burden, will always increase the variance explained by a model, it is important to use methods that accurately assess whether the added value is significant. We used out-of-sample testing and resampling to accurately ascertain the added value of amyloid. Second, we used an optimized measure of amyloid burden, developed using ridge regression in the training sample with independent coefficients for each tracer. Previous studies use amyloid positivity or continuous SUVr, neither of which may be appropriately scaled to optimally predict cognition. In doing so, we gave amyloid its "best shot" at improving predictions. Third, MEMENTO has a relatively large PET subsample, with repeated, regularly spaced cognitive measures. Our results are consistent with and extend past work in a smaller, but more diverse US-based sample.[19]

This study has several limitations. First, these results do not preclude that global amyloid burden is a more useful predictor of cognition on timescales beyond the 5 years of follow-up available in MEMENTO. Since amyloid is believed to be a potentiating first step in Alzheimer pathogenesis,[33-36] prognostic ability may be better when considering longer time frames. However, we note that results from our sensitivity analysis restricting to only later cognitive test scores did not appreciably differ from results that also included earlier cognitive assessments. Conversely, if all of the effect of amyloid on cognition takes place within a short time frame, we would not expect to see a benefit of amyloid in prediction cognition

conditional on an intermediate cognitive measure. We also note that our results do not preclude amyloid being a useful predictor of cognition assessed contemporaneously with the PET scan because models adjusting for past cognitive assessments could only be used to evaluate improvements in predictions for later cognitive measures. However, given amyloid's potentiating role, this possibility seems less likely.

Second, results may differ depending on timing of past cognitive assessments. A sensitivity analysis predicting cognition using 1 past cognitive assessment across variable time delays is provided in the supplement (eFigures 8 and 9, links.lww.com/WNL/D394). The added value of amyloid burden does not appreciably increase when compared with models with only more distant cognitive assessments. The improvement potentially achievable by adding amyloid to any such model could not be larger than the improvement achieved by adding amyloid to the demographic-only model.

Third, the MMSE, a measure of global cognition was selected because it is comparable with cognitive tests feasibly used in clinical settings to assess for dementia, as opposed to more time-intensive neuropsychological assessments. However, we obtain similar results in a sensitivity analysis with CDR-SB as the outcome for both binary and continuous amyloid using past MMSE scores as the predictor. Results of sensitivity analyses using alternative cognitive outcomes are qualitatively similar, with attenuated improvements with the inclusion of amyloid relative to the MMSE.

Fourth, this work does not preclude that for certain cognitive domains,[19,37] amyloid's prognostic ability may differ. However, we note that although MMSE may not be as sensitive to incipient Alzheimer disease-related cognitive changes as other cognitive measures, adjustment for even 1 past values of MMSE mitigated much of amyloid's prognostic ability. A sensitivity analyses using only individuals with a CDR-SB of 0.5 at baseline produced larger improvements in predicted cognition with the addition of amyloid burden, indicating the potential for difference in the prognostic ability of amyloid across the disease process. However, differences in absolute predictions were nonetheless also small.

Fifth, not accounting for determinants of cognitive test scores (practice effects, sleep quantity and quality, medication use) could make it appear that amyloid is a more significant predictor than it is when accounting for such effects. However, we find that the predictive ability of amyloid is significantly attenuated with the inclusion of even just 1 previous test score, and so accounting for such factors would only further attenuate the predictive ability of amyloid burden.

Finally, our analysis addresses only the question of whether amyloid-PET is a valuable adjunct when the goal is anticipating future cognitive trajectory. This fills an important gap in understanding of the clinical relevance of amyloid-PET, particularly for those with subjective memory complaints or MCI, but does not evaluate other reasons it may be adopted in clinical settings, e.g., diagnostic classification based on the amyloid-tau-neurodegeneration framework. Furthermore, although we would argue that this analysis with observational data closely approximates the corresponding clinical situation in which a clinician has past cognitive assessments and must determine whether an amyloid-PET is warranted, it does not exactly replicate such a scenario. However, similar results were obtained from an analysis in a previous publication that included cognitive assessments before a PET scan because PET technology was not available when the study began.[19] Furthermore, our results indicate that repeated cognitive testing is not required to attenuate the added value of amyloid-PET because this is accomplished with even a single past cognitive test. Sensitivity analyses indicate that the timing of this single test can be flexible.

In the broader context of biomarkers in Alzheimer disease and dementia research, it is now possible to measure an increasing number of biomarkers, including inflammatory measures (e.g., reference 20 and plasma measures of amyloid and tau[21,38]). As new biomarkers are developed and existing measures enter clinical practice, methods to evaluate whether these biomarkers add to what is already known based on existing and potentially less expensive measures are essential for determining how to best prioritize data collection in patients. Differences in dynamic range, increased noise, and variability in blood-based measures with body mass index and comorbidities (especially kidney disease) are likely to confound their interpretations and may limit their predictive ability of individuals.[39] Our approach offers a valuable template to evaluate newer, potentially expensive technologies in the context of existing metrics.

In conclusion, in the MEMENTO cohort, the addition of amyloid significantly improved predictions of cognition compared with models that included only demographic characteristics. When even a single, recent cognitive assessment is available, the additional clinical utility of amyloid-PET in predicting future cognitive outcomes may be limited.

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Appendix 2 Coinvestigators

Coinvestigators are listed at links.lww.com/WNL/D395.

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