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Integrating plasma, MRI, and cognitive biomarkers for personalized prediction of decline across cognitive domains

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ABSTRACT

Plasma biomarkers are associated with cognitive performance and decline in Alzheimer's disease, making them promising for early detection. This study investigates their predictive value, combined with non-invasive measures, in forecasting cognitive decline in individuals without dementia. We developed a multimodal machine-learning approach incorporating plasma biomarkers (Amyloidβ42/40 (Aβ42/40), p-tau181, NfL), MRI, demographics, APOE4, and cognitive assessments to predict the rate of cognitive decline. Various models were designed to predict decline rates across cognitive domains (memory, executive function, language, and visuospatial abilities) and assess their relevance in predicting dementia progression. Cross-validated correlations between predicted and actual cognitive decline rates were 0.50 for memory, 0.49 for language, 0.42 for executive function, and 0.44 for visuospatial ability. MRI showed greater predictive importance than plasma biomarkers. Among plasma biomarkers, NfL and p-tau181 outperformed Aβ42/40. Predicting cognitive decline and progression to MCI/dementia was most accurate in the memory domain, where plasma biomarkers (Aβ42/40, p-tau181, NfL) added significant value to predictive models, likely due to their AD-specific nature. Plasma biomarkers contributed less to predictions in other cognitive domains. The results indicate that plasma biomarkers, particularly when combined with MRI, demographics, APOE4, and cognitive measures, have significant potential for predicting memory decline and assessing the risk of dementia progression, even in cognitively unimpaired individuals.

1. Introduction

Alzheimer's disease (AD) is a common neurodegenerative disease with a complex and unclear pathway and a long prodromal phase. Early detection and accurate prediction of AD are crucial for implementing timely interventions that may slow disease progression and improve patient outcomes. With several promising AD-modifying therapies currently in development (Van Dyck et al., 2023; Mintun et al., 2021), the early identification of individuals at risk for cognitive decline has become increasingly important. As these therapies become available, accurately predicting cognitive decline at the patient level will be crucial for guiding clinical decisions. This ensures that costly treatments with potential side effects are administered only to those likely to benefit, thereby optimizing clinical outcomes and resource allocation.

Current diagnostic guidelines for AD involve detecting markers associated with brain amyloid-β (Aβ) plaques, aggregated tau (T), and neurodegeneration or neuronal injury (N) (Jack et al., 2018), typically measured using cerebrospinal fluid (CSF) (Tarasoff-Conway

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[1] Data used in the 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 the 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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et al., 2015) and positron emission tomography (PET) imaging (McKhann et al., 2011). However, these methods are often impractical for widespread use in community health settings due to their high costs and invasive nature. There is a critical need for more affordable, less resource-intensive, and widely accessible blood-based biomarkers (Wang et al., 2023). Recent advancements in biomarker research have highlighted plasma biomarkers as a promising alternative. These non-invasive indicators of neurodegenerative processes facilitate earlier diagnosis and more effective monitoring of disease progression (West et al., 2021; Mattsson-Carlgren et al., 2023; Moradi et al., 2019; Brand et al., 2022). Key plasma biomarkers, such as Aβ42/40, p-tau 181, and neurofilament light (NfL), offer significant insights into AD pathology, aiding in a better understanding and earlier detection of the disease (Mattsson-Carlgren et al., 2023; Zhang et al., 2024).

While plasma biomarkers offer significant diagnostic accuracy for AD, they have limitations when used alone. The limited exchange of proteins between plasma and brain extracellular fluid can complicate the tracking of longitudinal changes in AD pathology (Blennow and Zetterberg, 2018; Yu et al., 2024). Integrating plasma biomarkers with other non-invasive measures, such as MRI and cognitive test results can enhance the predictive accuracy of AD conversion outcomes. This combination leverages the complementary strengths of various biomarkers, providing a more comprehensive understanding of the disease. Recent studies have underscored the importance of integrating different biomarkers to improve the predictive performance of early AD detection (Moradi et al., 2015; Aberathne et al., 2023; Hl et al., 2024; Moradi et al., 2024). However, most previous research has focused on combining biomarkers such as MRI, cognitive test results, and PET imaging, with less emphasis on the role of plasma biomarkers in predicting cognitive decline across various cognitive domains (Aberathne et al., 2023; Cao et al., 2023). While recent studies have increasingly used plasma biomarkers to predict brain amyloidosis, their utility in predicting cognitive decline remains underexplored (Palmqvist et al., 2019; Brand et al., 2022).

This study aims to explore the role of plasma biomarkers in conjunction with other non-invasive biomarkers, including MRI data, demographic information, APOE4, and cognitive assessments, to predict the rate of cognitive decline in individuals without dementia using machine learning approaches. The specific objectives are to develop an ML-based approach by integrating different non-invasive biomarkers, including three key plasma biomarkers (Aβ42/40, p-tau 181, and NfL) to (a) predict the rate of cognitive decline across different domains, (b) investigate the relevance of various composite cognitive scores in predicting progression to dementia, and (c) predict progression to mild cognitive impairment (MCI) or dementia in cognitively unimpaired (CU) and MCI groups.

2. Materials and methods

2.1. ADNI data

Data used in this work were obtained from the ADNI (http://adni.loni.usc.edu). The ADNI was launched in 2003 as a public–private partnership, led by Principal Investigator Michael W. Weiner, MD. The primary goal has been to test whether serial MRI, PET, other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of MCI and early AD. For up-to-date information, see (www.adni-info.org).

This study included participants with baseline demographics, APOE4, plasma biomarkers (Aβ42/40, p-tau181, NfL), and T1-weighted MRI, who also had available baseline and longitudinal composite cognitive scores. We included individuals who had at least one follow-up visit with available composite cognitive scores occurring two years or more after the baseline assessment. Since not all the selected participants had the plasma Aβ42/40 measure, we created two study cohorts for our analysis. Cohort 1 included participants with plasma biomarkers of NfL and p-tau181, but not Aβ42/40. The Cohort 2 included all three plasma biomarkers: Aβ42/40, p-tau181, and NfL. Cohort 2, which includes Aβ42/40, is a subset of Cohort 1. Having two cohorts is important because it allows us to utilize a larger sample size in Cohort 1, thereby improving the statistical power of our findings when Aβ42/40 is not considered. This approach is critical because NfL and p-tau 181 alone can still provide significant insights into cognitive decline and AD progression, as they are well-established markers of neurodegeneration and tau pathology, respectively (Mendes et al., 2024; Smirnov et al., 2022). Cohort 2 allows us to specifically evaluate the added value of including the Aβ42/40 biomarker, which has been suggested to predict brain amyloidosis (Doecke et al., 2020), a hallmark of AD. By conducting all experiments separately for both cohorts, we can compare the predictive power of models with different biomarker combinations, and assess the importance of Aβ42/40 in conjunction with other biomarkers. The baseline characteristics of study cohorts are presented in Table 1 and participant's RIDs are available as supplementary material.

2.2. Demographics, APOE4, composite cognitive scores

The ADNI baseline demographics (age, gender, years of education), APOE4, and baseline diagnosis were obtained from ADNIMERGE.csv table and the Composite cognitive scores were obtained from "UWNPSYCHSUM.csv", downloaded from the ADNI website (http://adni.loni.usc.edu/).

The ADNI study has developed composite cognitive scores to assess multiple domains, including memory, executive function, language, and visuospatial skills. These scores are derived from a combination of standardized neuropsychological tests, selected to comprehensively evaluate each domain (Crane et al., 2012; Gibbons et al., 2012; Choi et al., 2020). A list of the individual tests contributing to each domain is provided in Supplementary Table 1. Since these measures were derived by the ADNI study, we refer to them as ADNI-MEM (memory), ADNI-EF (executive function), ADNI-LAN (language), and ADNI-VS (visuospatial functioning) throughout this paper. These composite scores provide standardized, robust measures across cognitive domains, aiding in the early detection and monitoring of cognitive decline in dementia.

To calculate the rate of cognitive decline, we measured the change in each cognitive domain and divided it by the time over which the change occurred. This time frame varied for each individual, as we used the last available follow-up as the endpoint. Additionally, we ensured that the final follow-up was no less than 2 years for all participants.

2.3. Plasma biomarkers

In the ADNI study, plasma was collected according to the ADNI procedures manual. Detailed information about the acquisition and analysis methods can be found on the ADNI website available at: https://adni.loni.usc.edu/methods/documents/.

Plasma Aβ42/40 levels were analyzed by liquid chromatography-tandem mass spectrometry (LC-MS/MS) as previously described (Ovod et al., 2017) and we obtained them from the ADNI depository (files: batemanlab_20190621.csv, batemanlab_20221118.csv). The samples with QC Status "Failed" were excluded. Plasma p-tau181 levels were measured using the Single Molecule Array (Simoa) technique (Karikari et al., 2020) and obtained from the ADNI depository (file: UGOTp-tau181_06_18_20.csv). Plasma NfL was analyzed by the Single Molecule array (Simoa) technique by using a combination of monoclonal antibodies and purified bovine NfL as a calibrator. Plasma NfL was obtained from the ADNI_BLENNOWPLASMANFLLONG_10_03_18.csv file.

Table 1
Baseline characteristics of the study cohorts: The reported values for continuous measures are reported as mean(standard deviation). CN: cognitively normal, SMC: subjective memory concern (participants with self-reported significant memory concern), MCI: mild cognitive impairment, EMCI: early MCI, LMCI: late MCI. Classification of EMCI and LMCI is done by ADNI based on the WMS-R Logical Memory II Story A score. The specific cutoff scores were as follows (out of a maximum score of 25): EMCI was assigned for a score of 9–11 for 16 or more years of education, a score of 5–9 for 8–15 years of education, or a score of 3–6 for 0–7 years of education. LMIC was assigned for a score of ≤ 8 for 16 or more years of education, a score of ≤ 4 for 8–15 years of education, or a score of ≤ 2 for 0–7 years of education (Edmonds et al., 2019). The Aβ-positivity is determined based on the global PET SUVR measure; further details are provided in the Supplementary Materials, Section 'PET Measurements'.

Baseline characteristics	Cohort 1 (without Aβ42/40)				Cohort 2 (with Aβ42/40)			
	CN	SMC	EMCI	LMCI	CN	SMC	EMCI	LMCI
Sample size (N)	162	90	244	129	110	50	154	79
ADNIGO/ADNI2	0/162	0/90	105/139	0/129	0/110	0/50	65/89	0/79
Age, years	73.3(6.4)	72.1(5.7)	71.1(7.3)	71.6 (7.7)	73.7(6.6)	71.4(5.6)	70.5(7.6)	70.4(7.6)
Sex, M/F	83/79	35/55	137/107	67/62	59/51	17/33	88/66	39/40
Education, years	16.7 (2.5)	16.8(2.5)	16.1(2.6)	16.6(2.4)	16.7(2.6)	16.3(2.4)	16.1(2.7)	17.0(2.3)
APOE4 (0/1/2)	117/40/5	59/30/1	142/84/18	59/52/18	79/28/3	33/16/1	95/51/11	36/30/13
ADNI-MEM	1.07 (0.6)	1.07(0.57)	0.62(0.57)	−0.04(0.65)	1.08(0.56)	1.05(0.53)	0.61(0.56)	0.02(0.64)
ADNI-EF	0.71 (0.7)	0.61 (0.71)	0.39 (0.70)	0.03(0.83)	0.75(0.73)	0.65(0.69)	0.39(0.67)	0.18(0.80)
ADNI-LAN	0.89 (0.7)	0.76 (0.67)	0.49(0.71)	0.21(0.73)	0.98(0.72)	0.74(0.68)	0.50(0.66)	0.29(0.70)
ADNI-VS	0.24 (0.6)	0.18 (0.59)	0.10(0.68)	−0.13 (0.76)	0.29(0.58)	0.21(0.58)	0.07(0.69)	−0.09 (0.79)
Plasma Aβ42/40	–	–	–	–	0.12(0.01)	0.12(0.01)	0.12(0.01)	0.12 (0.01)
Plasma p-tau181	15.7 (11.0)	16.7(16.5)	16.4(10.2)	20.2(13.4)	15.2(11.0)	15.3(6.7)	16.1(10.1)	18.7(9.1)
Plasma NFL	35.6(23.9)	31.9 (12.6)	36.6(18.0)	39.0 (18.8)	34.8 (14.9)	32.0(11.8)	34.6(15.9)	36.3(15.8)
Aβ-Positivity (PET Global SUVR)	47 Aβ+, 114 Aβ−, 1 Unknown	34 Aβ+, 55 Aβ−, 1 Unknown	117 Aβ+, 126 Aβ−, 1 Unknown	83 Aβ+, 45 Aβ−, 1 Unknown	34 Aβ+, 75 Aβ−, 1 Unknown	22 Aβ+, 28 Aβ−	71 Aβ+, 82 Aβ−, 1 Unknown	51 Aβ+, 28 Aβ−

2.4. MRI measures

We used the volumetric and thickness measures derived from CAT12 toolbox (https://neuro-jena.github.io/cat/ Version 8.1) using the default settings (Gaser et al., 2024): For 136 volume measures, the T1-weighted MRI were segmented into grey matter (GM) and white matter (WM) and non-linearly normalized to a stereotactic space using the shooting approach (Ashburner and Friston, 2011). Based on spatially normalized GM and WM segments, the neuromorphometrics atlas was used to extract the regional volumes. The atlas is derived from the maximum probability tissue labels derived from the "MICCAI 2012 Grand Challenge and Workshop on Multi-Atlas Labeling" http://www.neuromorphometrics.com/2012_MICCAI_Challenge_Data.htm with the MRIs from OASIS project and the labeled data provided by Neuromorphometrics, Inc. (Neuromorphometrics.com) under academic subscription. Following Karaman et al. (2022), we included intra-cranial volume (ICV) as one of the MRI features, rather than serving solely as a normalization factor, alongside regional volumetric measures. The cortical thickness values (Dahnke et al., 2013) were computed and registered to the FSaverage surface template (Yotter et al., 2011), where DK40 atlas (Desikan et al., 2006) was used to define 69 regionally averaged cortical thickness measurements.

2.5. Machine learning framework

We developed a machine learning framework to predict the rate of cognitive decline based on four composite cognitive scores: memory (ADNI-MEM), executive function (ADNI-EF), language (ADNI-LAN), and visuospatial (ADNI-VS) abilities. The framework involves two main stages. In the first stage, ridge linear regression (RLR) was applied to MRI data to calculate an MRI score. In the second stage, the MRI score is combined with other predictors including demographics, APOE4, baseline composite cognitive scores, and plasma measures, using random forest (RF) regression. This two-stage modeling strategy was employed to reduce the dimensionality of the MRI data and to prevent it from dominating the predictive model due to its high feature count. Importantly, each MRI score was specifically trained to reflect its association with the target cognitive outcome. For instance, the MRI score for ADNI-MEM was trained to predict the rate of memory decline, while distinct scores were trained to predict rates of decline in executive function, visuospatial skills, and language. This outcome-specific strategy tailors the MRI representation to each target domain, ensuring the final model captures the most relevant structural information for that specific cognitive outcome.

To ensure robust model performance, we employed nested and stratified cross-validation (CV) with two loops. The inner CV loop was used for calculating MRI score and the outer CV loop was used to split data into main training and test sets. This approach allowed us to build the MRI model while ensuring that the same data was not used for both training and predicting MRI scores in the training set, thus preventing overfitting. This two-stage process is illustrated in Fig. 1. The same framework was used to predict the rate of cognitive decline based on the four composite cognitive scores. The participants in all experiments were the same, and the experiments were conducted in parallel for both Cohort 1 and Cohort 2.

We designed four models with different feature combinations. The first model, the basic model, was trained using only demographic information, APOE4, and the baseline composite cognitive scores. The second model, the plasma model, included plasma biomarkers and predictors used in the basic model. The third model, the MRI model, incorporated MRI data with the predictors of the basic model. Finally, the fourth model, termed the combined model, utilized all available predictors: demographic data, APOE4, composite cognitive scores, plasma biomarkers, and MRI data. Our two-stage framework, illustrated in Fig. 1, was applied to experiments involving MRI measures (i.e., the MRI and combined models). For the basic and plasma models, which did not include MRI data, we used a random forest regression to predict the rate of cognitive decline. The R codes are available at "https://github.com/ElahehMoradi/Cognitive-decline-prediction".

2.6. Implementation and performance evaluation

To divide the data into training and test sets, we used two nested and stratified cross-validation loops, each with 10 folds. In the inner CV loop, the MRI-training set (outer loop) was further divided into MRI-training and test sets (inner CV) to learn the MRI model with the RLR approach and predict MRI scores for the training set (outer loop). We used the inner CV loop to ensure that the same dataset was not used for both learning the MRI model and calculating the MRI score in the training set, thus avoiding overfitting. After calculating the MRI scores for the training data (outer loop), the MRI training set of the outer CV loop was used to predict the MRI score for the MRI test set of the outer CV loop. The MRI scores of the training data were then

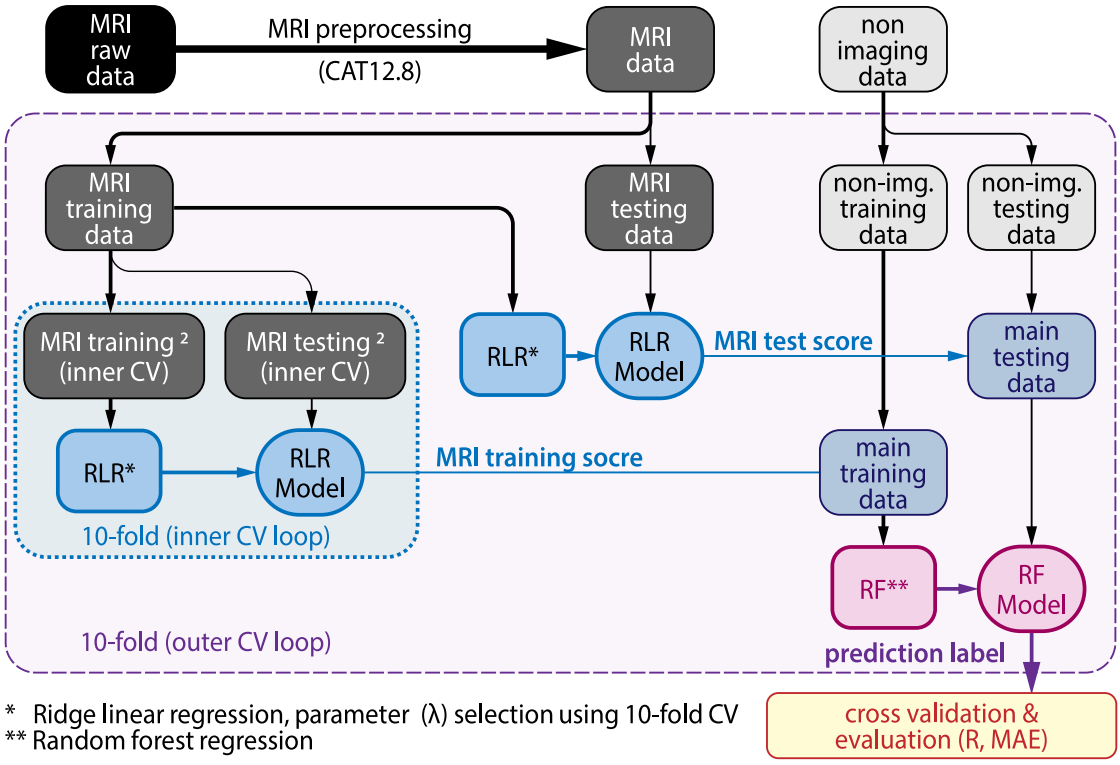

Fig. 1. Schematic representation of the regression framework.

combined with other predictors of the training dataset, and the MRI score of the test set was combined with other predictors of the test set. We then used the new training set with all the predictors, including the MRI score, to design a Random Forest regression model and predict the rate of cognitive decline in the test set. The Random Forest regression parameters were set to their default values, except for the number of trees, which was increased to 1000 to enhance the model's stability and improve the accuracy of feature importance determination. It is important to note that the test set of the outer loop was not used in any learning stages and was used only for evaluating the model. The implementation steps are visualized in Fig. 1.

The performance of the model was evaluated based on the cross-validated Pearson correlation coefficient (R) and the mean absolute error (MAE) between the estimated and true rate of cognitive decline. The reported results are averages over 10 nested 10-fold CV runs to minimize the effect of random variation.

To compare the correlation coefficient we used methods described by Diedenhofen and colleagues (Diedenhofen and Musch, 2015). All the analyses were done using R (version 4.1.1), with the following packages: glmnet (Friedman et al., 2021), caret (Kuhn, 2008), cocor (Diedenhofen and Musch, 2015), pROC (Robin et al., 2011), Daim (Potapov et al., 2009), ggplot2 (Wickham, 2011), and complexheatmap (Gu et al., 2016), survival (Therneau and Lumley, 2015).

3. Results

3.1. Predicting the rates of cognitive decline in individuals without dementia

We predicted the rate of cognitive decline in different cognitive domains based on ADNI-MEM, ADNI-EF, ADNI-LAN, and ADNI-VS composite cognitive scores. As explained in the Methods, we designed four models with different feature combinations for each regression experiment. Fig. 2 shows the results of all these computational analyses. These results are the average over 10 repeated 10-fold cross-validation analyses for each experiment. The p-values for comparing the performance of different models are provided in Supplementary Tables 2&3.

According to Fig. 2 (panel a), the prediction performance in cohorts 1 and 2 was similar, despite the absence of Aβ42/40 in Cohort 1. The following analysis is based on Cohort 1 due to the larger sample size. For predicting the rate of change in the ADNI-MEM measure, the average correlation score across 10 computation runs, derived from the basic model, was 0.38 with a 95% confidence interval (CI) of 0.30 to 0.45. The average MAE was 0.11 (95% CI of 0.10 to 0.12). Adding plasma biomarkers to the basic model (plasma model) significantly improved performance, with an improved correlation score of 0.45 (95% CI of 0.38 to 0.52) and a decreased MAE of 0.10 (95% CI of 0.10 to 0.11). Similarly, adding MRI data to the basic model (MRI model) significantly improved performance to a correlation score of 0.46 (95% CI of 0.39 to 0.54) and an MAE of 0.10 (95% CI of 0.10 to 0.11). Although the correlation score of the MRI model was slightly higher than that of the plasma model, the difference was not statistically significant. Finally, the combined model integrating plasma and MRI measures to the basic model, provided significantly improved prediction performance compared to all other models (basic, plasma, and MRI models), with an average correlation score of 0.50 (95% CI of 0.44 to 0.57) and an MAE of 0.10 (95% CI of 0.09 to 0.11). The improvement in the correlation score of the combined model compared to the plasma and MRI models indicates that plasma and MRI measures provide different information for predicting the rate of cognitive decline based on the ADNI-MEM score, and both data types are important for this prediction task.

Interestingly, within other cognitive domains, the cognitive changes could be predicted as well based on the basic model than based on the model integrating biomarker information (see Fig. 2 a). The only exception to this was ADNI-LAN, where the MRI and combined models offered a significant advantage over the basic model.

Fig. 2 panel b presents a scatter plot of the actual cognitive decline rate versus the predicted rate using the combined model in Cohort 1. Individuals from different diagnostic groups are labeled with different

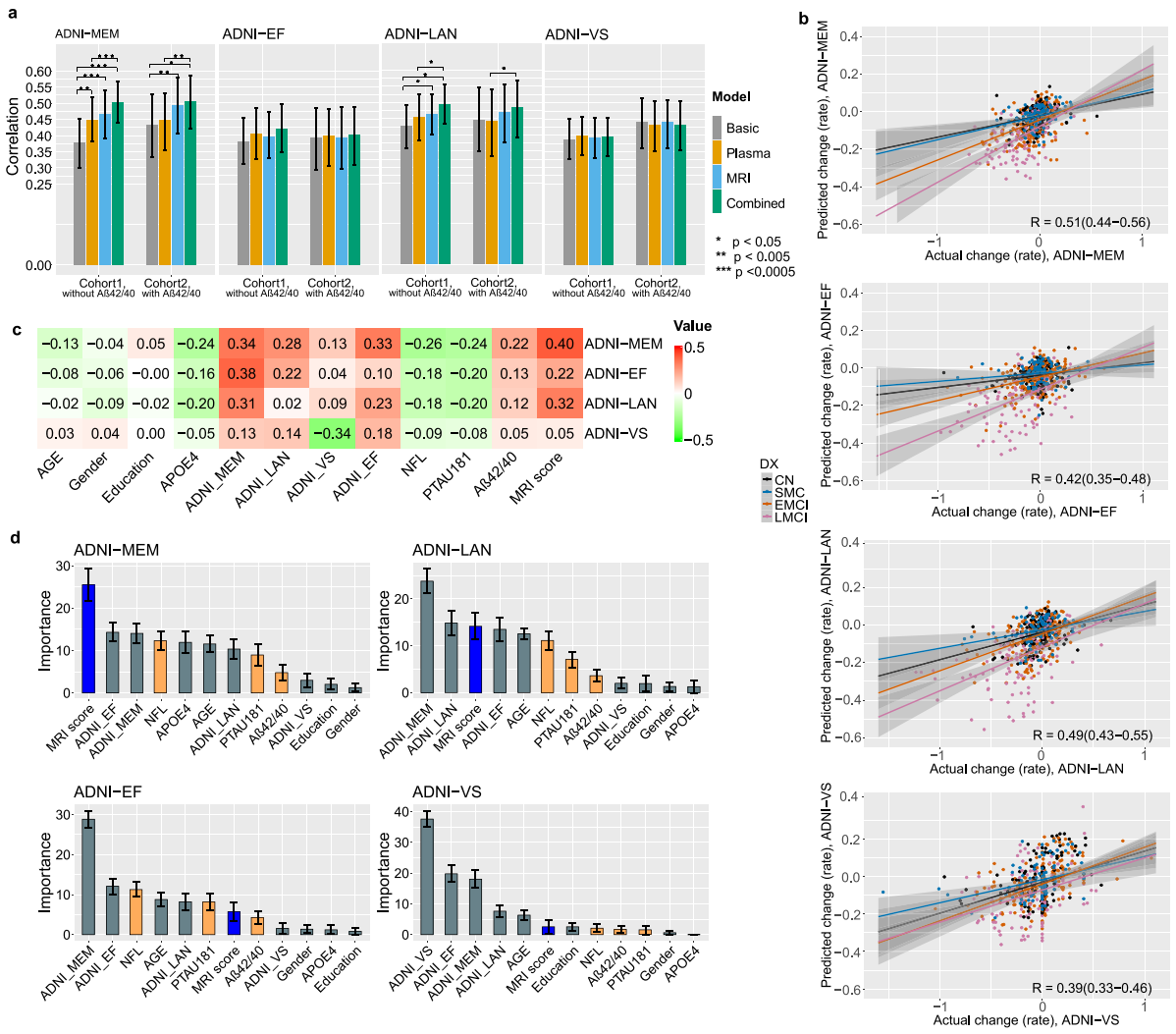

Fig. 2. Predicting the rates of cognitive decline in individuals without dementia: (a) Bar plots with 95% confidence interval error bars show the average correlation score across 10 computation runs for predicting the rate of cognitive decline in both study cohorts. (b) Scatter plot for actual cognitive decline rate vs. predicted rate using the combined model in Cohort 1, with correlation score and 95% CIs. (c) Heatmap of correlation values derived from the univariate analysis of the actual rate of cognitive decline and the predictors based on all four composite cognitive scores in Cohort 2. (d) The importance of different predictors calculated by RF regression models for each experiment using the combined model in Cohort 2, which includes all predictors, including plasma Aβ42/40. (MRI score is the mean value of the cross-validated MRI score derived by applying RLR on MRI data in test subsets).

colors, and a linear fit is plotted for each diagnosis group. In the ADNI-MEM score, a clear relationship between the rate of cognitive decline and the diagnostic groups existed. As expected, there was a higher correlation between the observed and predicted values in the MCI groups (EMCI and LMCI) compared to cognitively unimpaired (CU) individuals (CN and SMC). It is also evident that the rate of cognitive change was markedly smaller in the CU group, catalyzing more challenging prediction task in these individuals. This effect is also visible in the ADNI-EF and, on a smaller scale, in the ADNI-LAN score, but not in the ADNI-VS score.

We investigated the contribution of individual variables in predicting the rate of cognitive decline. Fig. 2, panel d & Supplementary Fig. 1, panel b, show the importance of different variables derived from 100 RF models, based on 10 runs of 10-fold cross-validation. The bar plot displays the mean importance of each variable across 100 computation runs. These results are from the combined model using Cohort 2, which includes the Aβ42/40 measure. The MRI score represents the mean value of the cross-validated MRI score, derived from RLR applied to the MRI data in the test subset, as described in the methods section.

For predicting the rate of cognitive decline based on the ADNI-MEM score, the MRI score emerged as the most important predictor. While it did not hold the highest importance in other cognitive domains, it still played a significant role in predicting ADNI-LAN performance and, to a lesser extent, in the ADNI-EF score. Interestingly, APOE4 was found to be significant only for ADNI-MEM, with no notable importance for other cognitive scores. Furthermore, the baseline ADNI-MEM score was the strongest predictor for cognitive decline rate in the ADNI-EF and ADNI-LAN domains, surpassing the predictive value of the baseline ADNI-EF and ADNI-LAN scores.

Among the plasma biomarkers, Aβ42/40 had the lowest importance in predicting the rate of cognitive decline across different composite cognitive scores. This might explain why the prediction performance in Cohort 1 and Cohort 2 was similar, despite the absence of the Aβ42/40 measure in Cohort 1. In contrast, plasma NfL and p-tau181 were identified as important features for predicting the rate of cognitive decline based on ADNI-MEM, ADNI-EF, and ADNI-LAN scores, but not for ADNI-VS score. In the case of ADNI-VS, all plasma biomarkers and MRI scores had low importance, indicating that baseline composite cognitive scores contributed the most to the model. Univariate analysis of the actual rate of cognitive decline with different predictors revealed that neither plasma biomarkers nor MRI scores showed significant correlations with ADNI-VS (Fig. 2, panel c & Supplementary Fig. 1, panel

Table 2
Correlation-based comparison of cognitive decline prediction using domain-specific MRI scores vs. AD-related MRI measures (hippocampal and ventricular volumes).

Cognitive domain	With MRI score	With AD-related MRI measures	P-value
ADNI-MEM	0.50 (0.44, 0.57)	0.48 (0.41, 0.55)	0.132
ADNI-EF	0.42 (0.35, 0.50)	0.38 (0.30, 0.46)	0.014
ADNI-LAN	0.49 (0.43, 0.56)	0.44 (0.36, 0.51)	0.001
ADNI-VS	0.40 (0.34, 0.45)	0.41 (0.35, 0.47)	0.227

a). This finding aligns with the low contribution of these variables to the ADNI-VS model. In contrast, plasma biomarkers and MRI measures demonstrated stronger correlations with ADNI-MEM and, to a certain degree, with ADNI-EF and ADNI-LAN, which explains their greater contribution to model performance in these cognitive domains.

Previous studies have shown that the plasma p-tau181/Aβ42 ratio is linked to amyloid-β status and future cognitive decline (Fowler et al., 2022). However, because it is highly correlated with the Aβ42/Aβ40 ratio (Campbell et al., 2021), its incremental value over Aβ42/Aβ40 ratio remains uncertain. To address this, we performed an additional analysis in Cohort 2, replacing the separate p-tau181 and Aβ42/40 variables with the single p-tau181/Aβ42 ratio in both our plasma-only and combined models. The change in predictive performance was minimal. In the plasma-only model, the ADNI-MEM correlation increased slightly from 0.45 to 0.46, with comparable small gains for ADNI-EF, ADNI-LAN, and ADNI-VS. In the combined model, ADNI-MEM increased from 0.51 to 0.52, while other domains remained stable or improved marginally. These results suggest that replacing individual biomarkers with the p-tau181/Aβ42 ratio does not substantially affect model performance. Complete results are provided in Supplementary Table 4.

We also evaluated how individual MRI features contribute to domain-specific MRI scores. Supplementary Fig. 2 shows bar plots of the top 20 features with the highest average absolute regression coefficients, based on 100 Ridge Linear Regression models (from 10 repetitions of 10-fold cross-validation). Each bar represents the mean absolute coefficient, with error bars indicating the standard deviation. As shown in Supplementary Fig. 2, the most influential regions align closely with domain-specific expectations. In the ADNI-MEM model, the hippocampus volumes emerged as the most important MRI predictors, consistent with the well-known role of hippocampus in memory processes. Additional influential regions included the middle and inferior temporal gyri, amygdala, and basal forebrain, all regions previously implicated in memory function. For ADNI-EF, cortical thickness measures prominently contributed, particularly from the temporal pole, middle temporal, and inferior parietal cortices. Important volumetric measures included the middle temporal gyrus, basal forebrain, and hippocampus. In the ADNI-LAN model, the basal forebrain was the most influential feature, followed closely by volumetric and cortical thickness measures in the middle temporal gyrus, hippocampus, and inferior temporal cortex. For ADNI-VS, feature importance plots showed considerable variability, reflected in higher standard deviations, indicating instability and less consistent selection of brain regions. The middle occipital gyrus was among the top contributors, aligning with its role in visuospatial processing. Nevertheless, as highlighted in the main results (Fig. 2 a), incorporating MRI data did not enhance predictive performance for visuospatial cognitive decline. This outcome corresponds to the observed feature instability and suggests that MRI-derived features provided more noise than predictive value in the visuospatial domain.

Since our primary focus is on predicting AD dementia, we investigated whether models using domain-specific MRI scores perform better than those using known AD-related MRI measures. We selected two AD-related measures: the volumes of the hippocampus and ventricles. This experiment was conducted using Cohort 1, as it focuses on MRI data (not plasma measures) and includes a larger sample size. Table 2 presents results from combined models predicting the rate of cognitive decline across different cognitive domains, comparing performance when using the MRI score versus when replacing it with hippocampal and ventricular volumes. Our results show that, except for ADNI-VS, using domain-specific MRI scores improved the prediction of cognitive decline in all other domains. The significant improvements were seen for ADNI-EF and ADNI-LAN. As shown in Supplementary Fig. 2, these MRI scores include contributions from multiple brain regions beyond the hippocampus, suggesting that a broader, domain-specific view of brain structure provides more predictive power than traditional AD-related measures.

3.2. Predicting the rates of cognitive decline in cognitively unimpaired and MCI groups separately

We extended our analysis by predicting the rate of cognitive decline in CU and MCI groups separately. Participants in both cohorts were divided into cognitively unimpaired (CN and SMC) and MCI groups (EMCI and LMCI), and the combined method was applied to each group individually. The results are illustrated in Fig. 3. As expected, predicting the rate of cognitive decline was markedly more challenging in the CU individuals than the MCI individuals across all four cognitive domains.

For predicting the rate of cognitive decline in the ADNI-MEM domain, the average correlation score across 10 computation runs in Cohort 1 was 0.17 (95% CI of 0.06 to 0.28) for the CU group and 0.53 (95% CI of 0.45 to 0.61) for the MCI group. For ADNI-EF, the correlation score was 0.19 (95% CI of 0.07 to 0.32) for the CU group and 0.46 (95% CI of 0.37 to 0.54) for the MCI group. The correlation score based on ADNI-LAN was 0.22 (95% CI of 0.11 to 0.32) for the CU group and 0.52 (95% CI of 0.45 to 0.59) for the MCI group. The results for ADNI-VS differed from other cognitive scores, with a smaller difference in correlation scores in CU and MCI groups. For ADNI-VS, the correlation score was 0.33 (95% CI of 0.24 to 0.42) for the CU group and 0.40 (95% CI of 0.32 to 0.47) for the MCI group.

Fig. 3b shows the scatter plot for one computation run with median performance across 10 computation runs for actual versus predicted rates of cognitive decline based on different composite cognitive scores, with a linear fit plotted for each group. A clear difference can be seen for ADNI-MEM, ADNI-EF, and ADNI-LAN scores between the CU and MCI groups, but not for the ADNI-VS score. These results underscore that predictive performance in the visuospatial domain differs from that of memory, executive function, and language in the context of dementia progression. While ADNI-MEM, ADNI-EF, and ADNI-LAN scores showed strong associations with diagnostic group (CU vs. MCI), ADNI-VS did not. This distinction is further supported by Supplementary Tables 5 and Supplementary Fig. 3, which present rates of cognitive decline across domains separately for CU and MCI groups.

3.3. Predicting the rates of cognitive decline in Aβ-positive and Aβ-negative groups separately

We extended our analysis by stratifying participants based on baseline amyloid status, categorizing them into Aβ-positive and Aβ-negative groups. Most participants in both cohorts had Aβ status determined by PET imaging (see section "PET measurements in the supplement).

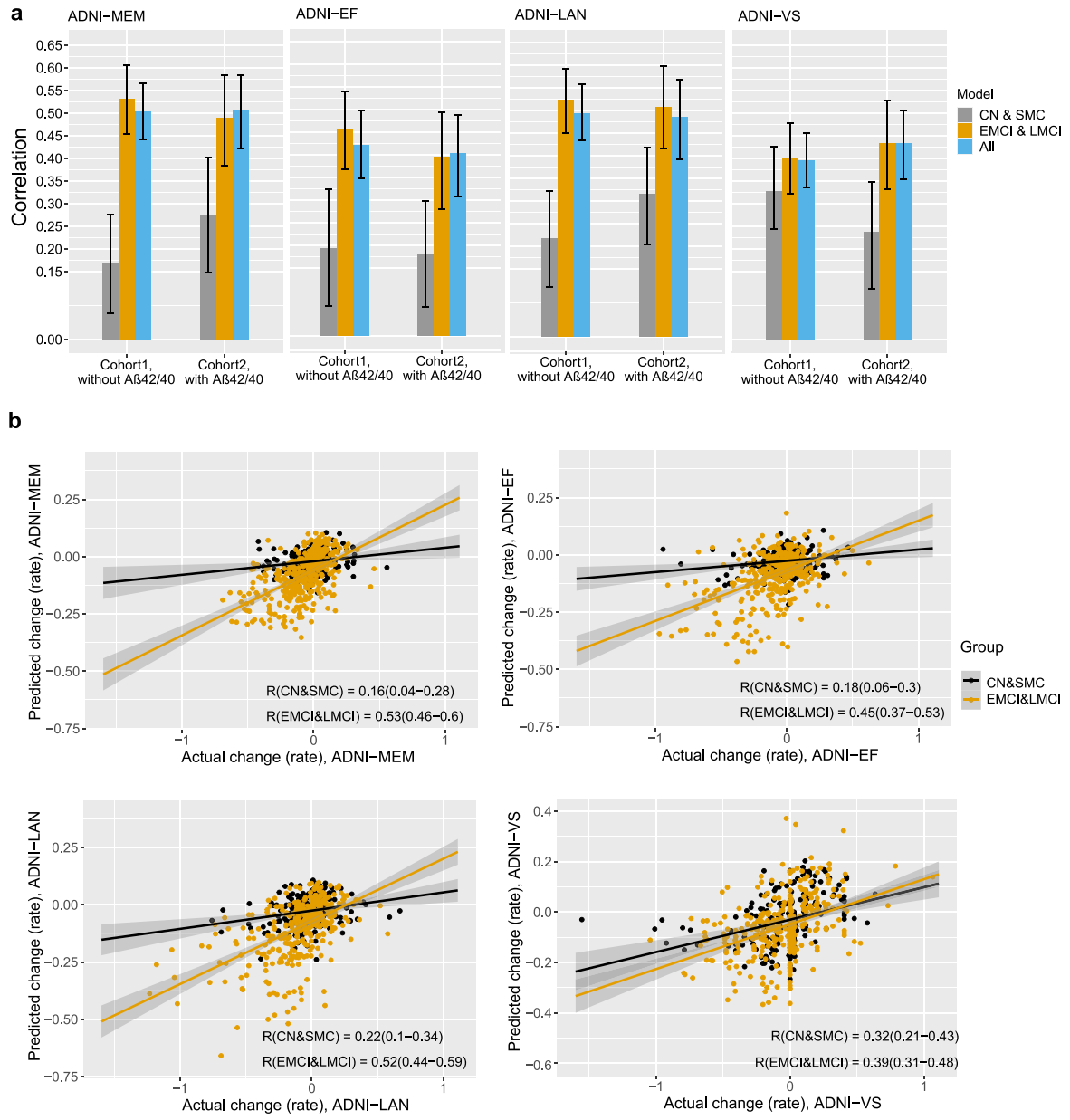

Fig. 3. Predicting the rates of cognitive decline in CU and MCI groups separately. (a) Bar plots with 95% confidence interval error bars show the average correlation score across 10 computation runs for predicting the rate of cognitive decline in CU and MCI groups, both separately and combined, in Cohort 1 and Cohort 2. (b) Scatter plot for actual cognitive decline rate vs. predicted rate using the combined model in Cohort 1 in CU and MCI groups, with correlation score and 95% CIs.

However, data were missing for 4 individuals in Cohort 1 and 2 individuals in Cohort 2; these individuals were excluded from the stratified analyses. The combined model was then applied separately to each group across both cohorts. Results are shown in Fig. 4. Overall, the Aβ-negative group showed lower predictive performance than the Aβ-positive group for ADNI-MEM, ADNI-EF, and ADNI-LAN. In the ADNI-VS domain, the performance was similar in both groups.

In Cohort 1, the average correlation (across 10 runs) for predicting memory decline (ADNI-MEM) was 0.29 (95% CI: 0.20–0.38) in Aβ-negative participants, compared to 0.49 (95% CI: 0.40–0.57) in Aβ-positive participants. For ADNI-EF, the correlations were 0.26 (95% CI: 0.13–0.36) in Aβ-negative participants, and 0.36 (95% CI: 0.25–0.44) in Aβ-positive participants. In the ADNI-LAN, the values were 0.32 (95% CI: 0.23–0.41) for Aβ-negative and 0.47 (95% CI: 0.39–0.55) for Aβ-positive participants. In contrast, ADNI-VS showed similar predictive performance across groups, with correlations of 0.38 (95% CI: 0.30–0.46) in Aβ-negative and 0.37 (95% CI: 0.28–0.47) in Aβ-positive participants. Similar patterns were observed in Cohort 2.

A scatter plot (Fig. 4b) illustrates actual versus predicted decline rates for one run (with median performance across 10 computation runs), showing a clear difference between Aβ-positive and Aβ-negative groups in the ADNI-MEM, ADNI-EF, and ADNI-LAN, but not in the ADNI-VS. Consistent with findings from the CU and MCI group analyses, these results indicate that predictive performance in the visuospatial domain behaves differently from memory, executive function, and language when examined in the context of dementia-related pathology. ADNI-MEM, ADNI-EF, and ADNI-LAN scores were strongly linked to Aβ-positivity, whereas ADNI-VS showed no such association. Supplementary Tables 6 and Supplementary Fig. 3 further support this distinction by detailing domain-specific rates of cognitive decline in Aβ-positive and Aβ-negative groups.

3.4. Prediction of progression to MCI/dementia

To assess the effectiveness of our cognitive decline prediction models in predicting dementia progression, we evaluated the predictive

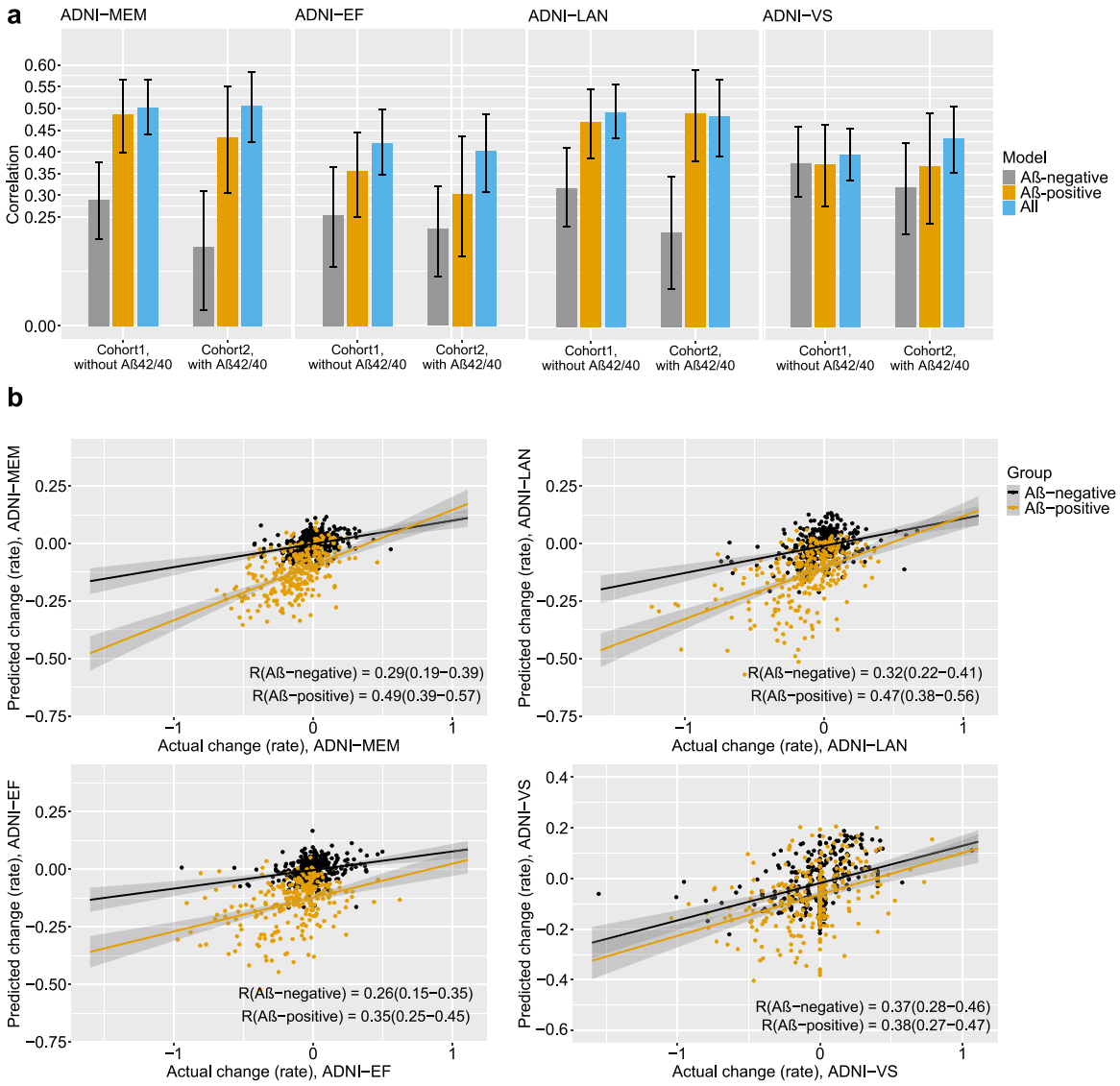

Fig. 4. Predicting the rates of cognitive decline in Aβ-positive and Aβ-negative groups separately. (a) Bar plots with 95% confidence interval error bars show the average correlation score across 10 computation runs for predicting the rate of cognitive decline in Aβ-positive and Aβ-negative groups, both separately and combined, in Cohort 1 and Cohort 2. (b) Scatter plot for actual cognitive decline rate vs. predicted rate using the combined model in Cohort 1 in Aβ-positive and Aβ-negative groups with correlation score and 95% CIs.

power of estimated cognitive decline rates, derived from various composite cognitive scores. This analysis was conducted across both CU individuals and those with MCI.

In Cohort 2, which included 160 cognitively unimpaired individuals (CN and SMC), 30 transitioned to MCI or dementia during the follow-up period, and 96 remained stable with a follow-up duration of at least four years. In the MCI group (EMCI and LMCI), 65 individuals progressed to dementia, and 120 remained with MCI status.

For the analysis, predicted cognitive decline rates were categorized into 3 tertiles. Individuals in the first tertile had the lowest predicted rate of cognitive decline, while those in the last tertile had the highest predicted rate. Fig. 5 shows the Kaplan–Meier survival analysis results and log-rank tests across tertiles, focusing on the predicted rate of the ADNI-MEM cognitive score for Cohort 2. The survival curves reveal significant differences among the tertiles in both CU and MCI individuals, as determined using all four models (log-rank $p < 0.001$). Results for other cognitive scores and experiments with Cohort 1 are provided in the supplementary materials (Supplementary Fig. 4–7)

The predicted ADNI-MEM score rate from the basic model demonstrated a C-index (concordance index) of 0.68 for predicting progression to MCI/dementia in CU individuals. When plasma biomarkers were added (plasma model), the C-index improved to 0.72. The MRI model showed a slightly lower C-index of 0.69. However, the combined model yielded an improvement over the plasma model, achieving a C-index of 0.76, indicating better predictive accuracy. For predicting dementia progression in individuals with MCI, the basic model yielded a C-index of 0.76. Adding plasma biomarkers did not enhance predictive accuracy (C-index of 0.74), but the MRI model offered a slight improvement with a C-index of 0.77. The combined model also achieved the highest performance for the MCI group, with a C-index of 0.79. Although our cognitive decline prediction model based on ADNI-MEM was primarily designed to estimate memory domain decline rates, rather than directly predict progression to dementia, it still showed strong predictive power for early-stage dementia, even in CU individuals.

Table 3 summarizes the hazard ratios (HRs) for the predicted rates of cognitive decline, as measured by the ADNI-MEM score, across tertiles using four models: basic, plasma, MRI, and combined. The first tertile, representing individuals with the lowest predicted rate of decline, served as the reference group. Among CU individuals, the combined model demonstrated that those in the highest tertile (fastest predicted decline) had a risk of progressing to MCI/dementia that was more than 33 times greater than those in the lowest tertile (slowest

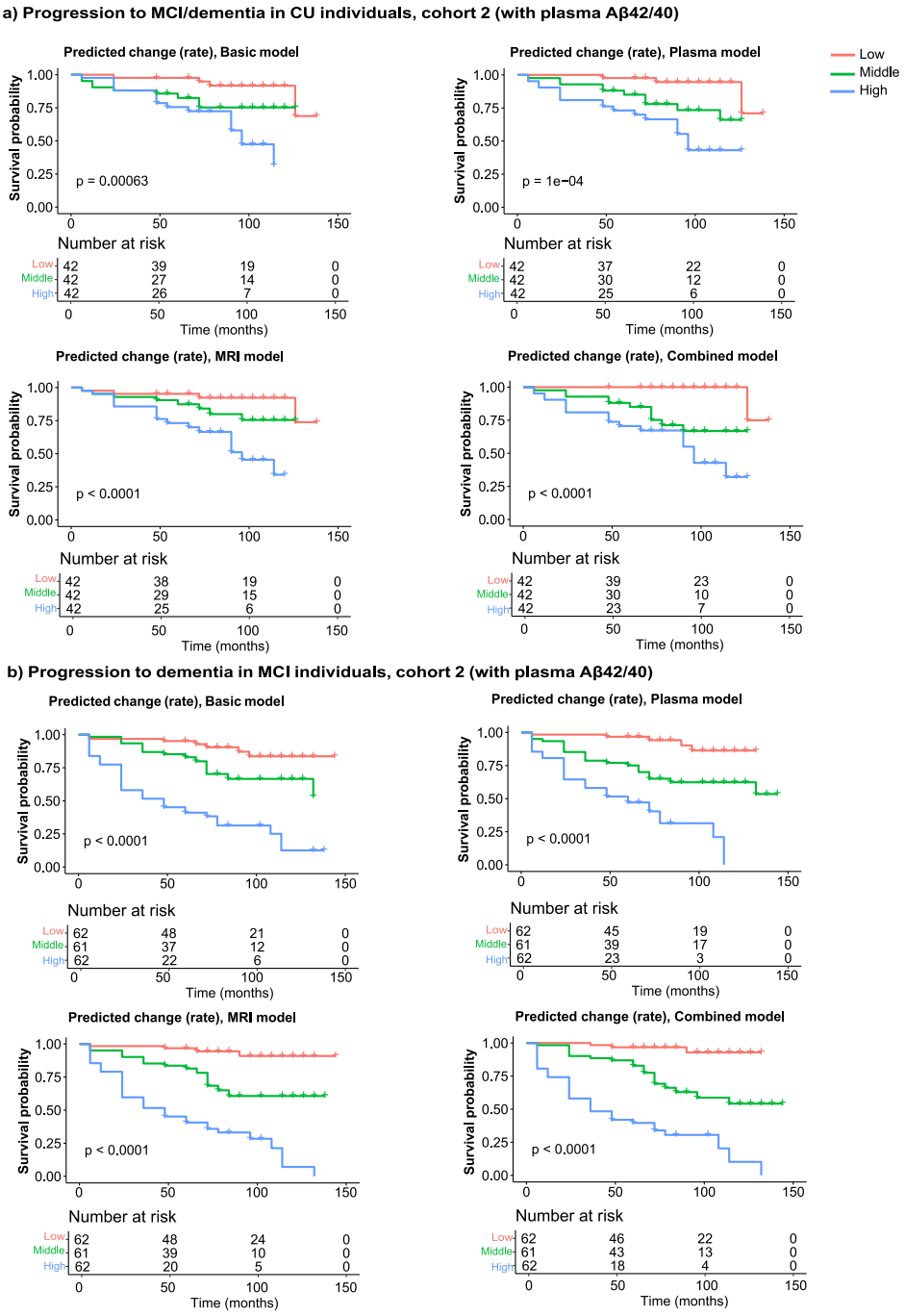

Fig. 5. Kaplan–Meier survival curves for progression to MCI/dementia in CU and MCI groups in cohort 2: The predicted rate of cognitive decline in ADNI-MEM score was divided into 3 tertiles (low, middle, high). Vertical tick marks on lines indicate times at which the individual was censored. p-values are for log-rank tests among the tertiles. (a) in CU individuals for progression to MCI/dementia, (b) in MCI individuals for progression to dementia. Basic model: Demographics, APOE4, Composite cognitive scores. Plasma model: Demographics, APOE4, Composite cognitive scores, plasma biomarkers. MRI model: Demographics, APOE4, Composite cognitive scores, MRI data. Combined model: Demographics, APOE4, Composite cognitive scores, plasma biomarkers, MRI data.

predicted decline). The risks for the MRI and plasma models were 7.9 and 9.7 times higher, respectively. Similarly, for MCI individuals, the combined model showed that those in the highest tertile had a risk of progressing to dementia that was over 29 times greater compared to the lowest tertile. The MRI and plasma models indicated risks of 21 and 14 times higher, respectively. The results in Cohort 1 were also similar to those in Cohort 2 (Supplementary Fig. 4).

The predicted rate of cognitive decline in other cognitive domains was not as strong as the one based on ADNI-MEM for predicting progression to dementia, especially in the early stages. The survival curves for the predicted rate of cognitive declines based on ADNI-EF, ADNI-VS, and ADNI-LAN show significant differences among the three groups in MCI individuals, as determined using all four models, but not in CU individuals (Supplementary Fig. 4–7).

4. Discussion

The objectives of this study were: (1) to investigate the role of plasma biomarkers, in combination with other non-invasive measures, in predicting the rate of cognitive decline in individuals without dementia; and (2) to predict the rate of decline across different cognitive domains — memory, executive function, language, and visuospatial

Table 3
Progression risk to dementia. Hazard ratios (HR) with 95% confidence intervals, p-values, and events/participants were calculated using Cox regression analysis. The first quartile is used as a reference. Events/Participants refers to the comparison group.

Group	Basic model			Plasma model			MRI model			Combined model		
	HR (95%CI)	p-val	Events/ N	HR (95%CI)	p-val	Events/ N	HR (95%CI)	p-val	Events/ N	HR (95%CI)	p-val	Events/ N
Risk of progression to MCI/dementia in CU individuals												
Low vs. Middle	3.02 (0.93–9.85)	0.066	4/42 vs. 9/42	4.51 (1.24–16.49)	0.023	3/42 vs. 10/42	2.72 (0.80–9.27)	0.110	4/42 vs. 8/42	16.21 (2.08–126.18)	0.008	1/42 vs. 11/42
Low vs. High	6.71 (2.20–20.47)	0.001	4/42 vs. 17/42	9.68 (2.80–33.48)	<0.001	3/42 vs. 17/42	7.88 (2.51–24.71)	<0.001	4/42 vs. 18/42	33.12 (4.39–250.12)	0.001	1/42 vs. 18/42
Risk of progression to dementia in MCI individuals												
Low vs. Middle	2.78 (1.14–6.77)	0.024	7/62 vs. 16/61	4.80 (1.81–12.75)	0.002	5/62 vs. 21/61	5.66 (1.90–16.89)	0.002	4/62 vs. 17/61	7.49 (2.22–25.33)	0.001	3/62 vs. 19/61
Low vs. High	11.01 (4.91–24.69)	<0.001	7/62 vs. 42/62	14.43 (5.62–37.04)	<0.001	5/62 vs. 39/62	21.02 (7.48–59.07)	<0.001	4/62 vs. 44/62	29.45 (9.06–95.74)	<0.001	3/62 vs. 43/62

abilities — and assess their associations with progression to dementia. To achieve this, we developed a two-stage machine learning framework. In the first stage, regularized linear regression (RLR) was applied to MRI data to derive an MRI score. In the second stage, the MRI score was combined with plasma biomarkers, demographics, APOE4, and baseline composite cognitive scores using random forest regression.

Our findings indicate that plasma biomarkers are effective in predicting distinct patterns of domain-specific cognitive decline and can potentially be used to predict progression to dementia, even in cognitively unimpaired individuals. While plasma biomarkers may not fully capture all the pathological changes occurring in the brain, they serve as a non-invasive source of information, offering valuable insights into disease mechanisms before the clinical onset of dementia (Brand et al., 2022; Palmqvist et al., 2019; Zhang et al., 2024; Yu et al., 2024; Smirnov et al., 2022; Mattsson-Carlgren et al., 2023).

We conducted multiple experiments using various feature combinations to identify the biomarkers most relevant to predicting cognitive decline. The ADNI-MEM-based model showed significant improvement when additional features were added, whereas other composite cognitive measures exhibited minimal or no gains. Specifically, for predicting decline based on the ADNI-MEM score, the correlation between actual and predicted rates increased from 0.38 in the basic model to 0.45 in the plasma model, which included plasma biomarkers along with demographics, APOE4, and baseline composite cognitive scores. Incorporating MRI data into the plasma model resulted in a further significant improvement, increasing the correlation to 0.50. In contrast, the inclusion of plasma or MRI features did not significantly improve predictions for other composite scores. An exception was the ADNI-LAN score: the combined model increased the correlation from 0.43 to 0.49, a significant gain over the basic model. All the correlation scores were clearly above zero and thus all the models offered meaningful insight to the future. Cognitive change in individuals without dementia is subtle and variable, making the prediction of the change challenging (Marinescu et al., 2020).

Assessing the importance of different features in the combined model revealed that while plasma biomarkers were useful for predicting the rate of cognitive decline, they were not the top predictors. Instead, the MRI and baseline composite cognitive scores were the strongest predictors, along with plasma biomarkers NfL and p-tau 181. Among the plasma biomarkers, the Aβ42/40 ratio was less predictive than NfL and p-tau 181. NfL consistently ranked among the top four predictors for memory (ADNI-MEM) and executive function (ADNI-EF) decline. This aligns with recent studies highlighting the limited predictive value of amyloid-beta measures compared to markers of neuronal injury and tau pathology. Both NfL and p-tau 181 have been linked to faster cognitive decline and increased risk of progression to dementia (Mendes et al., 2024; Smirnov et al., 2022). Interestingly, for the visuospatial domain (ADNI-VS), baseline cognitive scores were the most important predictors, while MRI, plasma biomarkers, and APOE4 had minimal impact. These findings highlight that the predictive value of biomarkers varies across cognitive domains.

We investigated the performance of cognitive decline rate prediction across different domains separately for CU and MCI groups. By using datasets with varying levels of cognitive impairment, we aimed to investigate the relationship between each cognitive measure and dementia. The results showed strong associations between the information detected by ADNI-MEM, ADNI-EF, and ADNI-LAN scores for different diagnostic groups, but not ADNI-VS. Prediction performance was significantly lower in the CU group compared to the MCI group. No significant relationship was observed between the prediction of ADNI-VS decline rate and diagnostic group. While our main analyses focused on individuals without dementia (as defined by cognitive assessments), we conducted analyses stratified by Aβ-positivity. Predictive performance was weaker in Aβ-negative individuals, consistent with the difficulty of detecting decline in the absence of biological signs of AD. Results from both stratifications, by cognitive status and Aβ status, were generally consistent. Prediction in CU individuals proved especially difficult, with very low correlations between predicted and actual decline, particularly in the memory domain. Although prediction was more challenging in Aβ-negative individuals than Aβ-positive ones, performance remained reasonably robust. While most Aβ-negative participants were cognitively healthy, a substantial proportion were individuals with MCI, which may explain why prediction in the Aβ-negative group was more successful than in the CU group alone.

We assessed the effectiveness of our prediction models for cognitive decline across different domains in predicting dementia progression in CU and MCI groups using survival analysis. Across all models, which varied in feature combinations and composite cognitive scores, significant predictive value was demonstrated for dementia progression in the MCI group. The predicted rate based on the ADNI-MEM score demonstrated the highest predictive power, while those based on the ADNI-VS score showed the lowest. In contrast, predicting progression to MCI/dementia in CU individuals proved more challenging. Only the predicted rate based on ADNI-MEM showed significant predictive power for dementia progression in this group. Among the models tested, the combined model demonstrated the highest predictive accuracy. Since memory impairment is often the earliest symptom of AD, driven by neurodegeneration in regions such as the hippocampus, the ADNI-MEM-based predictions were particularly effective in identifying progression to MCI or dementia, even in individuals without cognitive impairment.

Predictions for visuospatial decline diverged from those of other cognitive domains. While ADNI-MEM, ADNI-EF, and ADNI-LAN scores showed strong associations with diagnostic status (CU vs. MCI) and Aβ-positivity, ADNI-VS did not. In survival analyses, predicted memory decline had the highest power to predict progression to MCI or dementia, whereas visuospatial predictions had the lowest. This suggests that declines in memory, executive function, and language are more tightly linked to early disease stages, while visuospatial decline, although predictable, has limited utility as an early marker. Feature-importance analyses confirmed that the baseline ADNI-VS score was the primary driver of predicted visuospatial change, with other baseline cognitive

scores contributing modestly. Plasma biomarkers, MRI features, and APOE4 status added minimal predictive value for this domain. Although ADNI-VS predictions correlated with actual decline, they had limited clinical relevance for identifying early-stage dementia.

Previous research on plasma biomarkers in AD has primarily focused on detecting brain amyloidosis, often using the plasma Aβ42/40 ratio to detect PET or CSF Aβ positivity (West et al., 2021; Brand et al., 2022; Palmqvist et al., 2019). Fewer studies, however, have explored the role of plasma biomarkers in predicting cognitive decline. For example, Mattsson-Carlgren et al. (2023) evaluated combinations of plasma biomarkers, including p-tau 217, to predict cognitive decline in Aβ-positive CU individuals using MMSE and modified Preclinical Alzheimer Cognitive Composite (mPACC) scores. Their findings highlighted the strong predictive power of plasma p-tau 217 in detecting cognitive decline in preclinical AD patients. Similarly, Zhang et al. (2024) investigated the association of plasma biomarkers such as Aβ42/40, p-tau 181, NfL, and glial fibrillary acidic protein (GFAP) with cognitive decline across different domains. Their study showed that memory decline was most strongly associated with p-tau 181, while attention, executive function, and visuospatial abilities were more closely linked to NfL levels. Aβ42/40 emerged as the most efficient marker for distinguishing memory decline, whereas GFAP was particularly effective in identifying decline patterns in language and visuospatial functions. Our study shares similarities with Zhang et al. (2024) in assessing cognitive decline across domains but differs in methodology. We employed machine learning for predictive modeling, prioritizing high-accuracy forecasting of future outcomes, rather than exploratory analysis aimed at understanding relationships and generating hypotheses (Shmueli, 2010). Additionally, compared to Zhang et al. (2024), we assessed the impact of combining plasma biomarkers with other non-invasive measures to improve predictive accuracy. Finally, we evaluated the effectiveness of our predictive models in forecasting progression to MCI or dementia in CU and MCI groups. These analyses offer a more nuanced understanding of the potential of plasma biomarkers in early AD detection.

Our findings emphasize the strengths and limitations of plasma biomarkers in dementia research. While they excel in predicting memory decline and dementia progression, their predictive power is limited in non-memory domains. This may be due to the focus on AD-specific plasma biomarkers, i.e., Aβ42/40, p-tau 181, and NfL, which primarily reflect amyloid plaques, tau aggregation, and neurodegeneration—core pathological features of AD. These biomarkers are highly relevant for detecting AD-related pathology and demonstrate stronger predictive value for cognitive decline in memory-related domains. However, they tend to be less predictive in non-memory domains like visuospatial abilities, where neurodegeneration may not be as directly influenced by amyloid or tau pathology. This likely explains the reduced effectiveness of plasma biomarkers in predicting cognitive decline in these areas and their limited performance in early AD prediction.

A possible limitation of this study is its focus on AD-specific biomarkers, which restricted our ability to explore relationships between other pathologies and types of dementia across different cognitive domains. Moreover, since our experiments were conducted using the ADNI cohort, which predominantly focuses on AD, the results may not generalize well to non-memory domains where AD-specific biomarkers are less relevant. The memory domain is most closely associated with AD, which explains why our predictions were more accurate in this area. These findings underscore the need for future studies that incorporate a broader range of biomarkers and pathologies to enhance understanding and prediction of cognitive decline across various types of dementia.

5. Conclusion

Our study investigates the role of plasma biomarkers, particularly when combined with non-invasive measures such as MRI data and cognitive assessments, in predicting domain-specific cognitive decline and progression to dementia. We introduce three key contributions: (1) modeling the rate of cognitive decline rather than single-time-point outcomes, (2) building domain-specific models for memory, executive function, language, and visuospatial abilities, and (3) linking predicted decline rates to real-world clinical progression, showing that individuals predicted to decline more rapidly are significantly more likely to progress from CU to MCI/dementia or from MCI to dementia.

Among the various cognitive domains, memory decline was the most accurately predicted, with plasma biomarkers (Aβ42/40, p-tau181, NfL) providing substantial added value, likely due to their strong association with AD pathology. However, plasma biomarkers were less predictive for non-memory domains. While MRI emerged as a stronger overall predictor compared to plasma biomarkers, combining these biomarkers with APOE4 and cognitive scores proved especially effective. This multimodal approach had a synergistic effect, particularly in predicting memory decline and assessing the risk of progression to MCI/dementia in CU individuals.

Our findings also emphasize the challenge of predicting cognitive decline in the early stages of AD, particularly among CU individuals. However, when CU individuals are analyzed alongside those who have slightly progressed toward AD, such as those in the MCI stage, ML algorithms can help predict cognitive changes to some extent and even predict progression to MCI/dementia with a certain level of accuracy. This has important clinical implications, as current methods struggle to accurately predict cognitive decline in CU individuals, an area of critical importance given the development of AD-modifying therapies that are most effective when administered during the earliest stages of the disease. Future research should focus on individuals near the Aβ-positivity threshold, as this subgroup may offer critical insights into the early continuum of disease progression.

Abbreviations

Aβ: amyloid-β; AD: Alzheimer's disease; ADAS-cog: AD Assessment Schedule-Cognition ADNI: Alzheimer's Disease Neuroimaging Initiative; ADNI-MEM: Memory; ADNI-EF: Executive function; ADNI-LAN: Language; ADNI-VS: Visuospatial functioning; APOE4: Apolipoprotein E ε4; ATN: Amyloid, tau, and neurodegeneration; CI: Confidence interval; C-index: Concordance index; CSF: Cerebrospinal fluid; CN: Cognitively normal; CU: cognitively unimpaired CV: Cross-validation EMCI: Early mild cognitive impairment; LMCI: Late mild cognitive impairment; MAE: Mean absolute error; MCI: Mild cognitive impairment; ML: Machine learning; MMSE: Mini-Mental State Examination; MoCA: Montreal Cognitive Assessment; MRI: Magnetic resonance imaging; NfL: Neurofilament light PET: Positron emission tomography; R: Pearson correlation coefficient RAVLT: Reys Auditory Verbal Learning Test; RF: Random forest; RLR: Ridge linear regression; SMC: Subjective memory concern;

CRediT authorship contribution statement

Elaheh Moradi: Writing – original draft, Writing – review & editing, Visualization, Validation, Software, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Robert Dahnke:** Writing – review & editing, Resources. **Vandad Imani:** Investigation, Writing – review & editing. **Christian Gaser:** Writing – review & editing, Resources, Funding acquisition. **Alina Solomon:** Writing – review & editing. **Jussi Tohka:** Writing – review & editing, Supervision, Resources, Funding acquisition, Conceptualization.

Declaration of Generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the authors used GPT-4 from OpenAI to improve language and readability. After using this tool/service, the authors reviewed and edited the content as needed. The authors take full responsibility for the content of the publication.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary material related to this article can be found online at https://doi.org/10.1016/j.neurobiolaging.2025.06.010.

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