Predicting Progression & Cognitive Decline in Amyloid-Positive Patients with Alzheimer's Disease

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Research

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Abstract

Background

In Alzheimer's disease (AD), amyloid- β (Aβ) peptides aggregate in the brain forming amyloid plaques, which are a key pathological hallmark of the disease. However, plaques may also be present in cognitively unimpaired elderly individuals. Therefore, it is of great value to explain the variance in disease progression among patients with Aβ pathology.

Methods

A cohort of n= 2293 participants from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database was selected to study heterogeneity in disease progression for individuals with Aβ plaque pathology. The analysis used baseline clinical variables including demographics, genetic markers and neuropsychological data to predict how the cognitive ability and AD diagnosis of subjects progressed using statistical models and machine learning. Due to the limited prevalence of Aβ pathology, models fit only to Aβ-positive subjects were compared to models fit to an extended cohort including subjects without established Aβ pathology, adjusting for covariate differences between the cohorts.

Results

Aβ pathology status was determined based the Aβ 42 /Aβ 40 ratio. The best predictive model of change in cognitive test scores for Aβ-positive subjects at the two-year follow-up achieved an R 2 score of 0.388 while the best model predicting adverse changes in diagnosis achieved a weighted F1 score of 0.791. Conforming to expectations, Aβ-positive subjects declined faster on average than those without Aβ pathology, but the specific level of Aβ plaques was not predictive of progression rate. For the four-year prediction task of cognitive score change, the best model achieved an R 2 score of 0.325 and it was found that fitting models to the extended cohort substantially improved performance. Moreover, using all clinical variables outperformed the best model based only on baseline cognitive test scores which achieved an R 2 score of 0.228.

Conclusion

Our analysis shows that levels of Aβ plaques are not strong predictors of the rate of cognitive decline in Aβ-positive subjects. Baseline assessments of cognitive function accounts for the majority of variance explained in the prediction of two-year decline but is insufficient for achieving optimal results in longer-term predictions. Predicting changes both in cognitive test scores and in diagnosis provides multiple perspectives of the progression of potential AD subjects.

Full Text

Due to technical limitations, full-text HTML conversion of this manuscript could not be completed. However, the latest manuscript can be downloaded and accessed as a PDF.

Figures

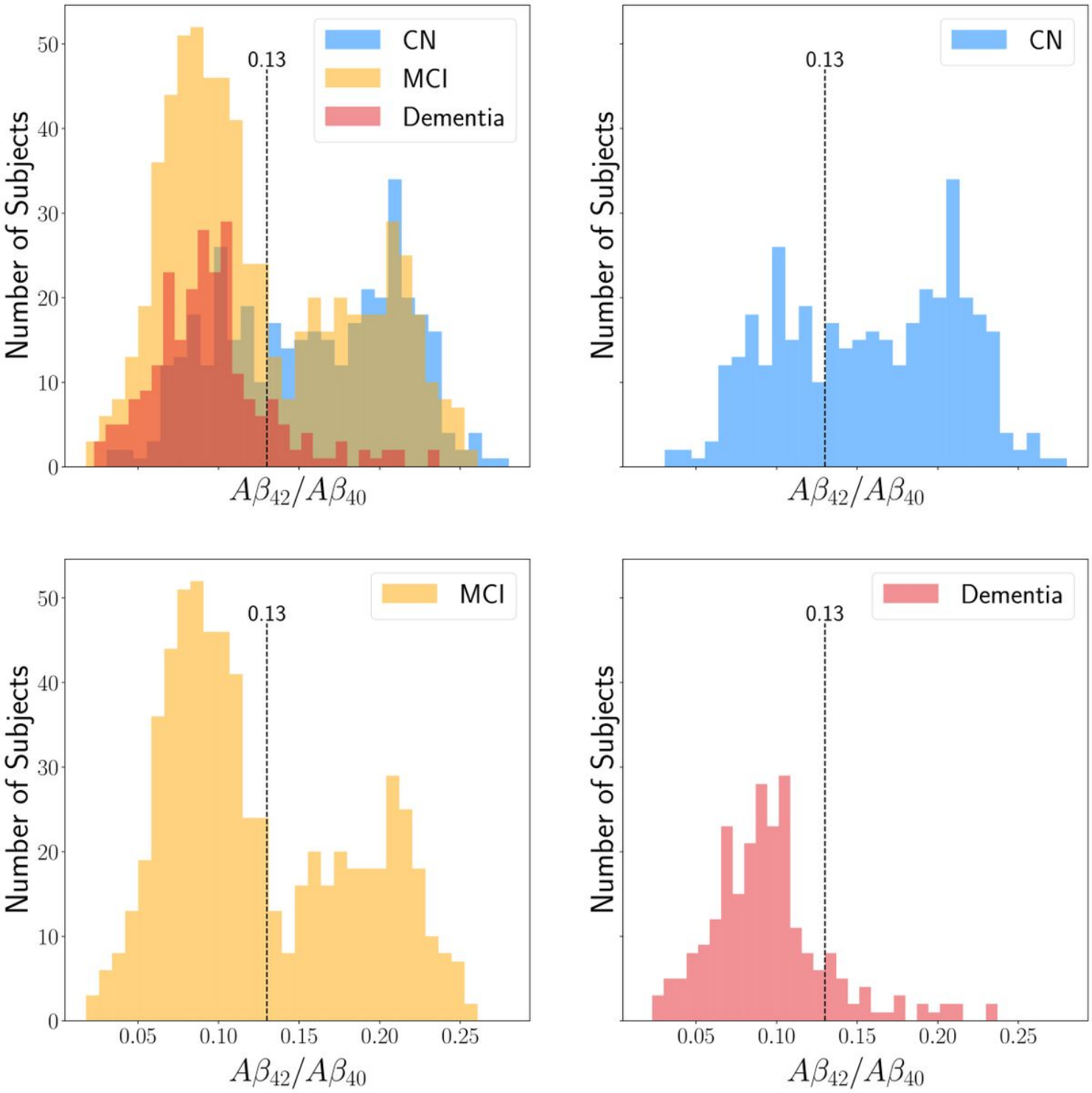

Figure 1

Histogram showing the A ratio of subjects at baseline. The different coloured groups represent different diagnoses: dementia, MCI and CN. The upper left histogram shows all diagnoses together and overlaps have blended colours like green and dark red.

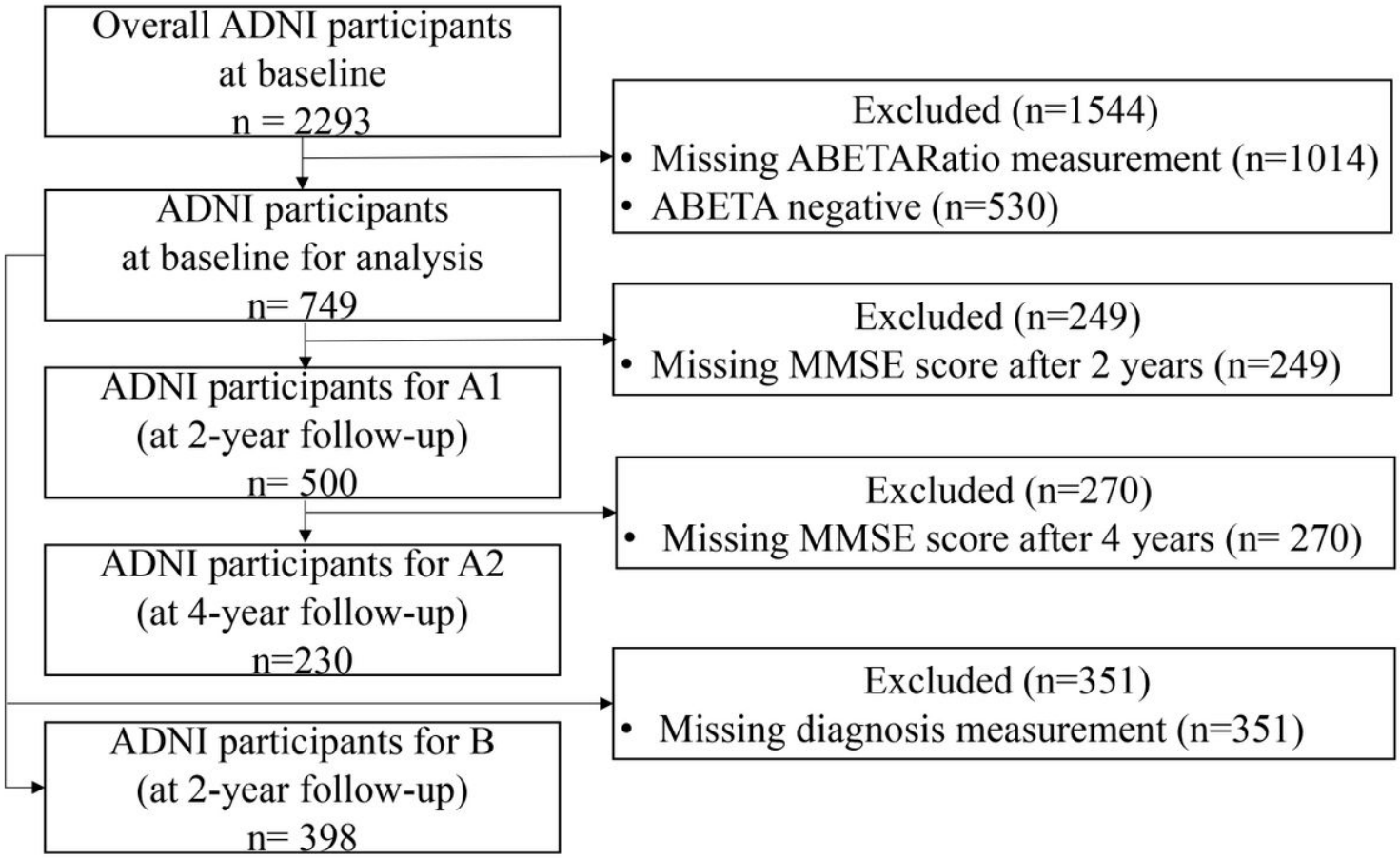

Figure 2

Exclusion procedure showing the A-positive subjects over time with various exclusion reasons. The graphs present the cohorts used for the prediction in the change in the MMSE score (A1 and A2) for the a change in the diagnosis after two years (B).

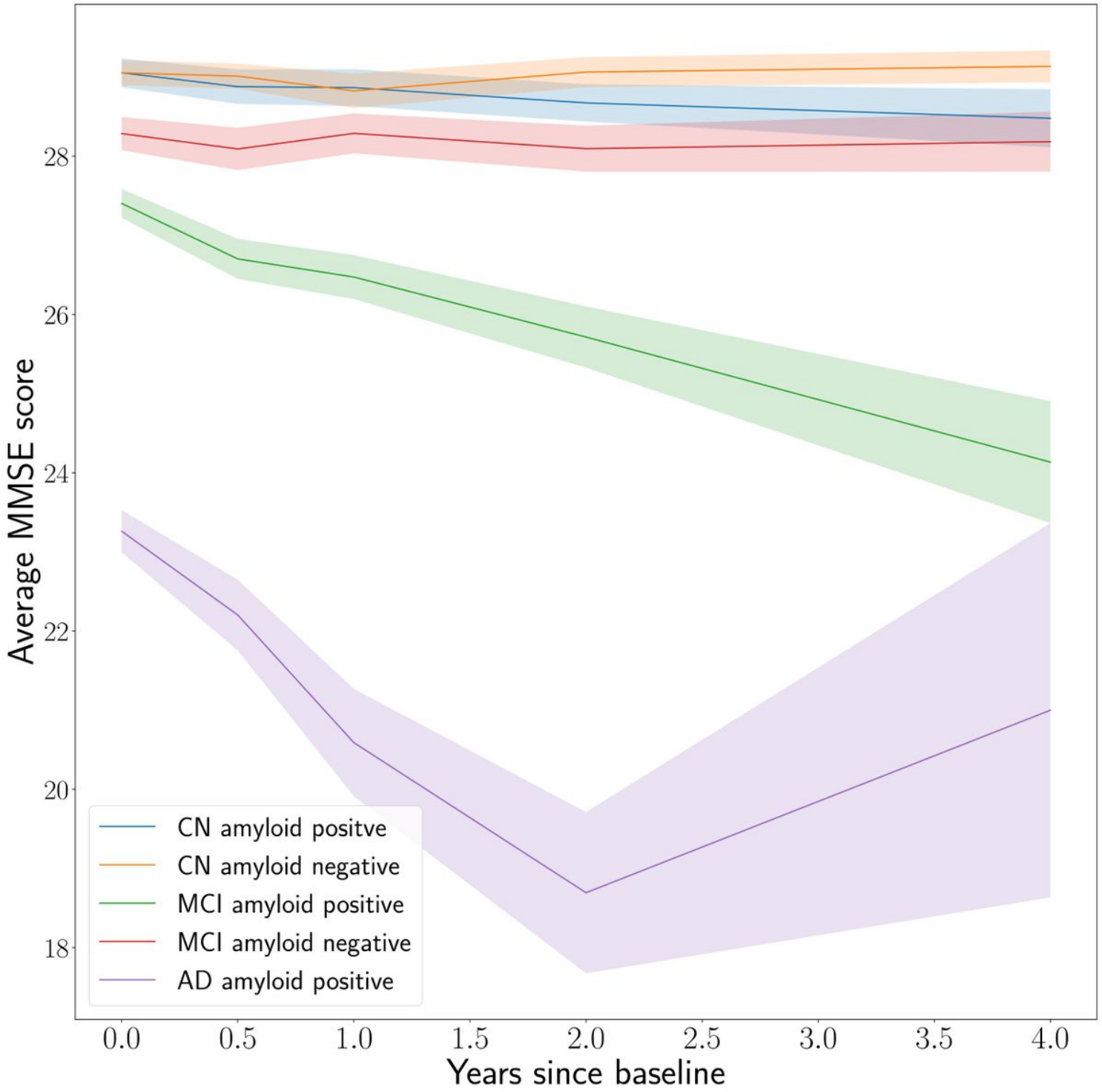

Figure 3

Graph showing the MMSE score development for CN, MCI and AD subjects split by A-status. The shaded areas represent 95% condence intervals for the mean values. The number of subjects decreases over time, hence the growing uncertainty bands.

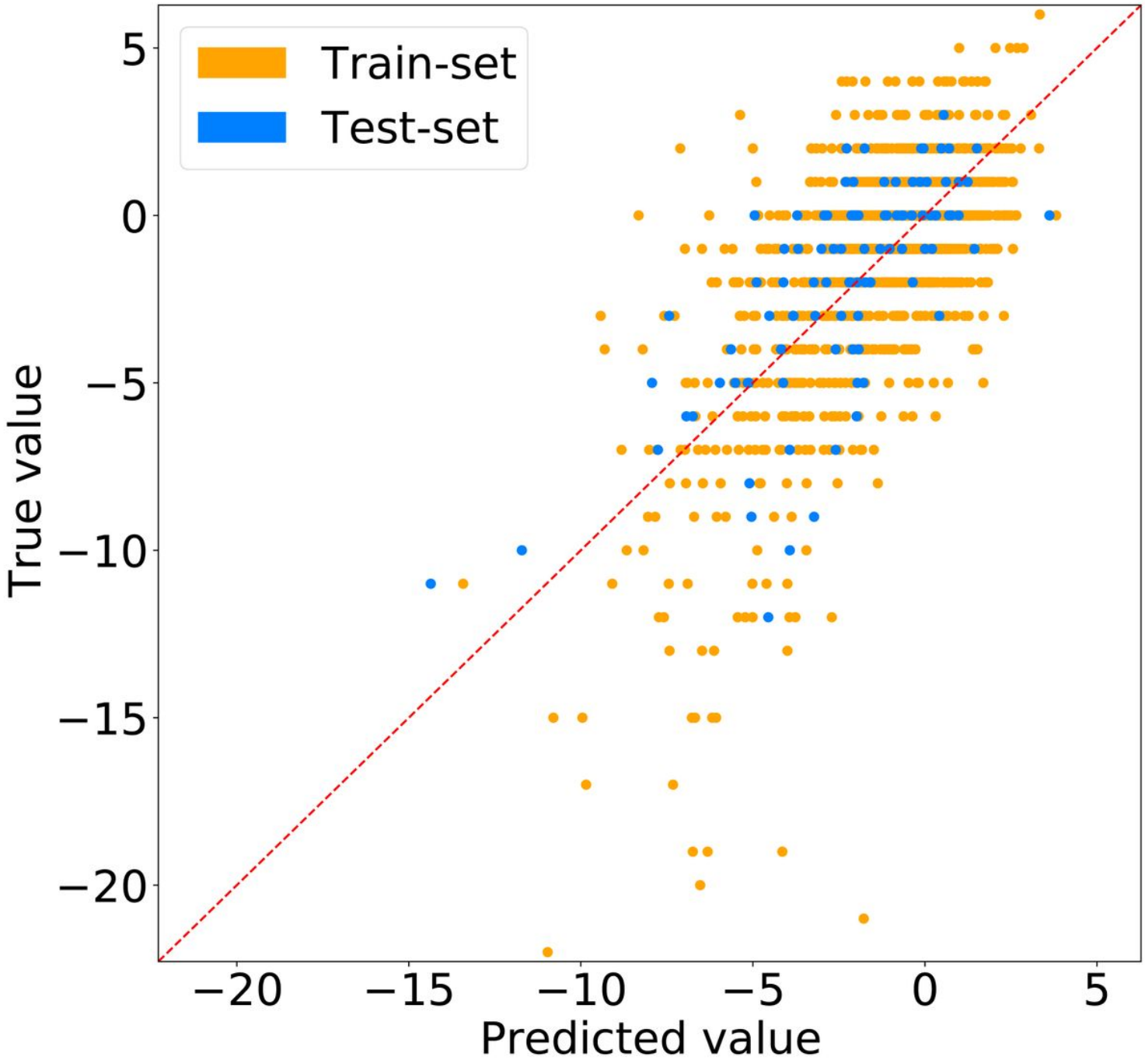

Figure 4

A calibration plot (true vs predicted values) for a linear regression model that predicts the change in MMSE score two years from baseline.

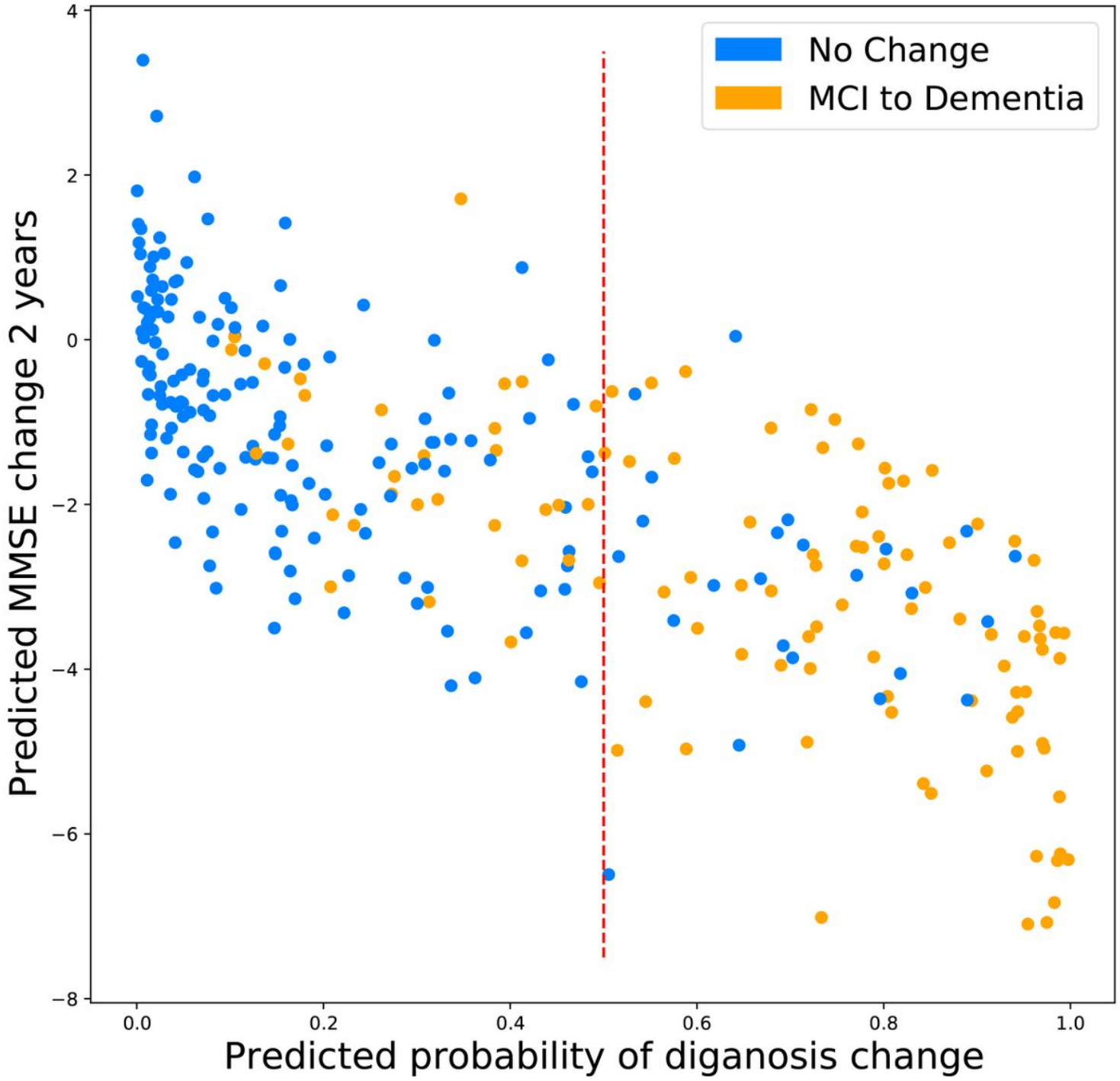

Figure 5

Predicted change in MMSE score and the predicted probability of a change in diagnosis after two years in the baseline-MCI group. Points are color-labeled based on their observed change in diagnosis.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Supplementarymaterial.pdf