**1 Participants**

This study included 880 FDG-PET and MRI scans (respectively) from the Alzheimer’s Disease Neuroimaging Initiative (ADNI) database (“CN” and “MCI” samples, adni.loni.usc.edu) and 59 from the Open Acces of Imaging Studies-3 database (OASIS-3). Scans from the ADNI were selected such that FDG-PET and MRI scans from the same individual were not more than one year apart. Data was split into three samples: the “main” ADNI sample of CN individuals (“CN”, n = 367) was used to train models and yield predictions for later association of BPAD with cognitive performance, neuropathology and cognitive decline in CN. The small sample of CN derived from the OASIS-3 (“CN\_validation”, n = 59) was used to validate prediction accuracy (mean absolute error, MAE) in an external dataset. Finally, predictions for the ADNI sample of MCI patients (“MCI”) were used to associate BPAD with cognitive performance, neuropathology and cognitive decline in MCI. All individuals included in this study were 65 years or older, while OASIS participants were significantly younger than ADNI participants (p < 0.01), especially in the MRI cohort. Compared to CN, participants in the MCI sample had a significantly lower percentage of females (χ2 = 10.5, p < 0.01), lower MMSE (t(424)=5.38, p < 0.001) and a higher percentage of amyloid positivity (χ2 = 43.7, p < 0.001).

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| Table 1. Overview of samples | | | | |
|  | **CN** | **CN\_validation** | **MCI** |
| ***n* total** | **367** | **59** | **513** |
| Age [avg. years (SD)] | 74.2 (5.68) XX PET/MRI | 71.7 (4.15) (PET)/  70.4 (4.17) (MRI) | 74.9 (5.77) |
| Sex [%female] | 51 | 59 | 40 |
| CSFAβ1-42 Status  (-/+/NA) | 171/111/85 | NA | 121/270/122 |
| MMSE [avg. score] | 29 (1.24) | 29 (0.85) | 28 (1.77) |
| Education [avg. years (SD)] | 16 (2.72) | 16 (2.70) | 16 (2.70) |

**2 Precision of brain-predicted age**

To compare the potential of FDG-PET SUVR and GMV to predict chronological age, we used a nested five-fold cross-validation approach, yielding one test prediction for (almost) every subject in the ADNI CN sample, and five test predictions for each subject in the CN\_validation and MCI sample. Regional FDG-PET- and MRI-predicted chronological age comparably well (Table 2) with a mean absolute error (MAE) of 1.99 and 1.89 years, respectively. In the ADNI-derived CN test sets, individuals’ brain-predicted age as assessed with FDG-PET and MRI was on average 0.10 and 0.05 years younger than their chronological age, respectively, thus demonstrating high average potential to capture brain aging in a CN cohort. The OASIS-derived CN\_validation sample was used to validate our findings in an external dataset and showed similar MAEs as the ADNI sample, although chronological age was slightly better predicted from FDG-PET as compared to MRI, reflected in a lower MAE across the five models (see Table 2). A probable explanation for the higher MAE in the CN\_validation MRI sample is that the age distribution in this sample deviated more from the age distribution in the ADNI train sets compared to CN\_validation PET samples. In the MCI test sets, individuals’ brain-predicted age as assessed with FDG-PET and MRI was on average 0.77 and 1.57 years older than their chronological age, respectively, thus reflecting an advanced brain age. The bias elimination procedure successfully eliminated the correlation between chronological age and BPAD in the CN test set. For the CN\_validation and MCI sample, bias elimination was successful in 3/5 CN\_validation FDG-PET and all CN\_validation MRI sets, while bias in MCI sets was only eliminated in 1/5 sets for both FDG-PET and MRI. Therefore, chronological age was included as a covariate in subsequent analyses.

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| Table 2. Precision of predicting chronological age from FDG-PET and MRI scans. For CN\_validation and MCI, results of the first model and metrics over all five models are shown. | | | | | | |
|  | **CN** | | **CN\_validation** | | **MCI** | |
|  | **FDG** | **MRI** | **FDG** | **MRI** | **FDG** | **MRI** |
| ***n* total** | 345⁺ | 345⁺ | 59 | 59 | 513 | 513 |
| **MAE** | 1.99 | 1.89 | 1.83 | 2.43 | 1.96 | 2.68 |
| MAE before bias correction | 4.04 | 3.97 |  |  |  |  |
| Mean (SD) over 5 models | - | - | 2.04 (0.30) | 2.45 (0.19) | 2.18 (0.43) | 2.50 (0.12) |
| **Mean difference** | -0.10 | -0.05 | -0.80 | -0.80 | 0.78 | 1.75 |
| Mean (SD) over 5 models | - | - | -0.66 (0.41) | -0.92 (0.16) | 0.77 (0.26) | 1.57 (0.16) |
| *Notes.* +After outlier exclusion using CN train set (IQR > 6) | | | | | | |

**3 BPAD in CN**

**3.1 BPAD and Cognitive Performance**

**3.2 BPAD and AD Neuropathology**

**4 BPAD in MCI**

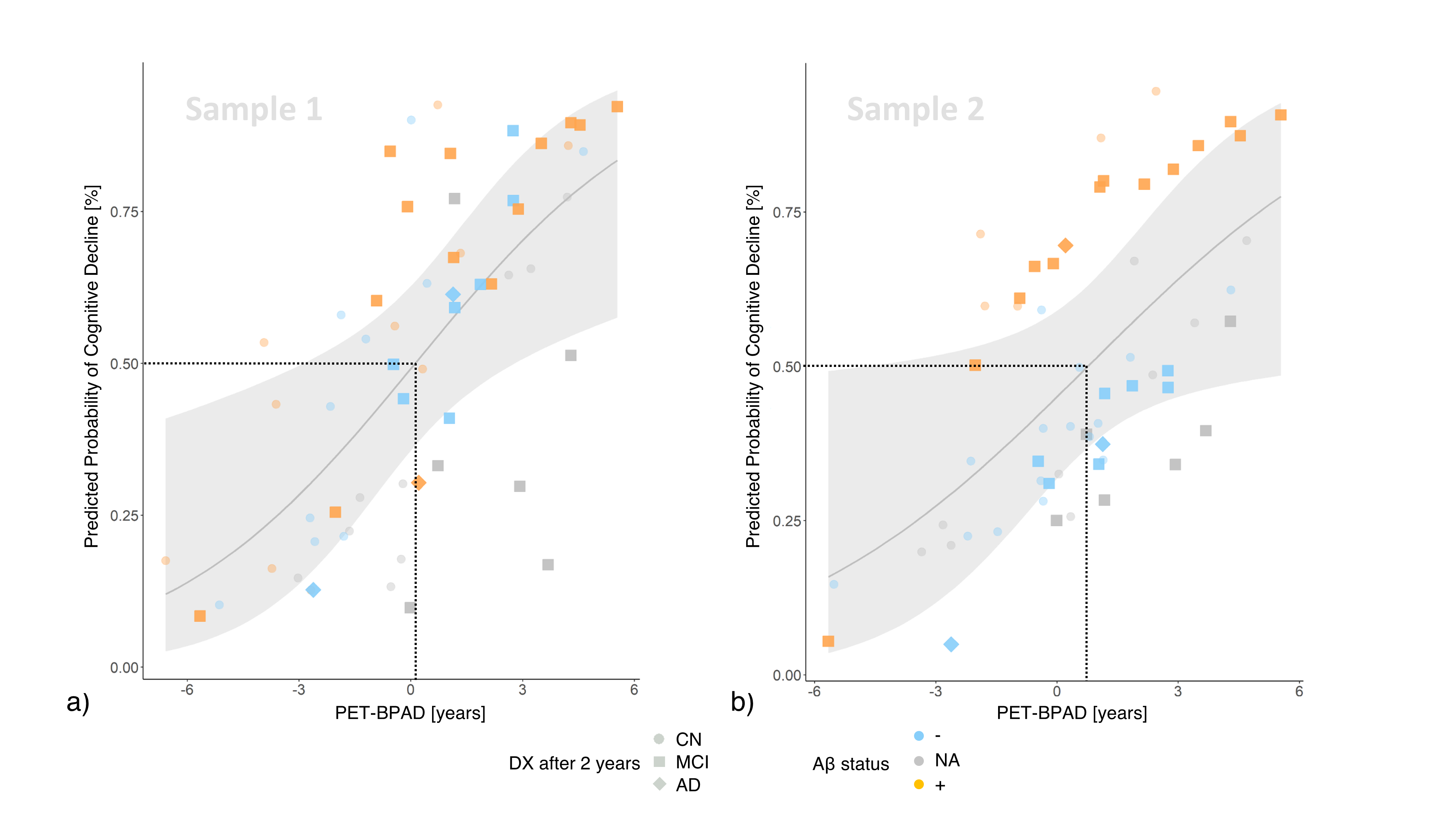
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| --- | --- | --- | --- | --- |
| **XX OLD XX Table 3. Correlation strength (rho or r) between BPAD and neuropathology/cognitive function across five different models** | | | | |
|  | **FDG-PET** | | **MRI** | |
|  | **Zero-order** | **Partial** | **Zero-order** | **Partial** |
| **CSF ABETA** | **-0.222  [-0.237; -0.172]** | **-0.186  [-0.224; -0.135]** | **-0.316  [-0.319; 0.305]** | **-0.269  [-0.279; -0.266]** |
| **AV45 (global SUVR)** | **0.137  [0.113; 0.154]** | **--** | **0.197  [0.176; 0.217]** | **0.173  [0.163; 0.202]** |
| **CSF Tau** | **--** | **--** | **0.127  [0.121; 0.138]** | **0.124  [0.114; 0.138]** |
| **CSF PTau** | **--** | **--** | **0.146  [0.141; 0.157]** | **0.139**  **[0.131; 0.153]** |
| **ADNI-MEM** | **-0.279 [-0.321; -0.234]** | **-0.250  [-0.257; -0.234]** | **-0.455  [-0.459; -0.443]** | **-0.409  [-0.420; -0.397]** |
| **ADNI-EF** | **-0.272 [-0.323; -0.241]\*** | **-0.255  [-0.258; -0.219]\*** | **-0.325  [-0.339; -0.307]\*** | **-0.290  [-0.301; -0.286]\*** |
| ***Notes.* Median [range] of correlation coefficients are displayed when significant (p<0.05) correlation existed in brain-predicted age according to all five models. Coefficients are Spearman Rho unless marked by an asterisk (\*: Pearson’s r coefficient).** | | | | |

**CONV**

To assess the potential of BPAD in the two modalities to serve as an indicator of cognitive decline (CD), as well as to compare BPAD to existing risk factors, individuals’ diagnosis at year two was predicted from PET-BPAD, MRI-BPAD, APOE-e4 carriership, amyloid status and years of. To achieve reliable results, 10-fold cross-validated logistic regression was performed in two subsamples per group (CN/MCI), matched for age and sex. As amyloid status was not available for all individuals, analyses were conducted in two ways, once including individuals with missing amyloid information (NA values coded as separate category; “whole samples”), and once excluding these individuals (“reduced samples”).

Table 3 presents an overview of logistic regression estimates and p-values on the whole samples. Two hundred ninety eight individuals from the baseline CN sample received either a CN diagnosis at year two (“stables”; n = 269), or a diagnosis of cognitive impairment (MCI or AD) six months to two years after baseline (“decliners”; n = 29). The two matched sub-samples included 58 individuals (29 decliners and 29 stables). Across these two samples, PET- and MRI-BPAD were not significantly correlated. In sample 1, the odds of CD were significantly increased by 40% per one year PET-BPAD (OR = 1.404, 95% CI [1.113, 1.874], see Table 3 for p-values). In sample 2, PET-BPAD (OR = 1.298, 96% CI [1.013, 1.734]) and amyloid status (OR = 5.011, 95% CI [1.197, 25.363]) marginally to significantly predicted CD. Predictions in this sample were predominantly driven by amyloid status (see ***Fig. 1*** b)). To determine a clinically relevant threshold of BPAD, we approximated the PET-BPAD corresponding to 50% disease probability, which was 0.2 and 0.9 years in sample one and two, respectively (***Fig. 1***). Sensitivity and specificity of the PET-BPAD to indicate CD were 68% and 68% in sample 1 and 62% and 66% in sample 2. After removing those individuals who did not have information on amyloid status available, a reduced sample of 23 decliners remained, thus constituting a sample size of 46 (23 decliners and 23 stables). Comparable results as in the whole sample were found: In one sample, higher PET-BPAD significantly predicted CD (OR = 1.46, 95% CI [1.101, 2.106], p = 0.018) and in the other sample, a positive amyloid status significantly predicted CD (OR = 4.704, 95% CI [1.135, 23.604], p = 0.041), while neither PET- nor MRI-BPAD reached significance levels. 50% disease probability in sample 1 corresponded to a PET-BPAD of 0 years, yielding a sensitivity and specificity of 65 and 74%. Taken together, these findings show that in combination with other information such as e.g. amyloid status PET-BPAD offers potential in identifying individuals at risk of CD in a CN stage.

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| Table 3 Estimates (p-values) of logistic regression for prediction of cognitive decline. | | | | |
|  | CN | | MCI | |
|  | Sample 1 | Sample 2 | Sample 1 | Sample 2 |
| PET-BPAD [Years] | 0.340 (0.008) | 0.261 (0.052) | 0.151 (0.057) | 0.189 (0.017) |
| MRI-BPAD [Years] | 0.037 (0.784) | 0.032 (0.769) | 0.350 (<0.001) | 0.337 (<0.001) |
| Aβ+ | 0.026 (0.973) | 1.612 (0.036) | 1.577 (0.002) | 0.888 (0.078) |
| APOE-ε4+ | 1.464 (0.104) | -0.066 (0.923) | 0.774 (0.034) | 1.433 (<0.001) |
| Education [Years] | -0.136 (0.221) | -0.060 (0.571) | -0.014 (0.833) | -0.048 (0.445) |

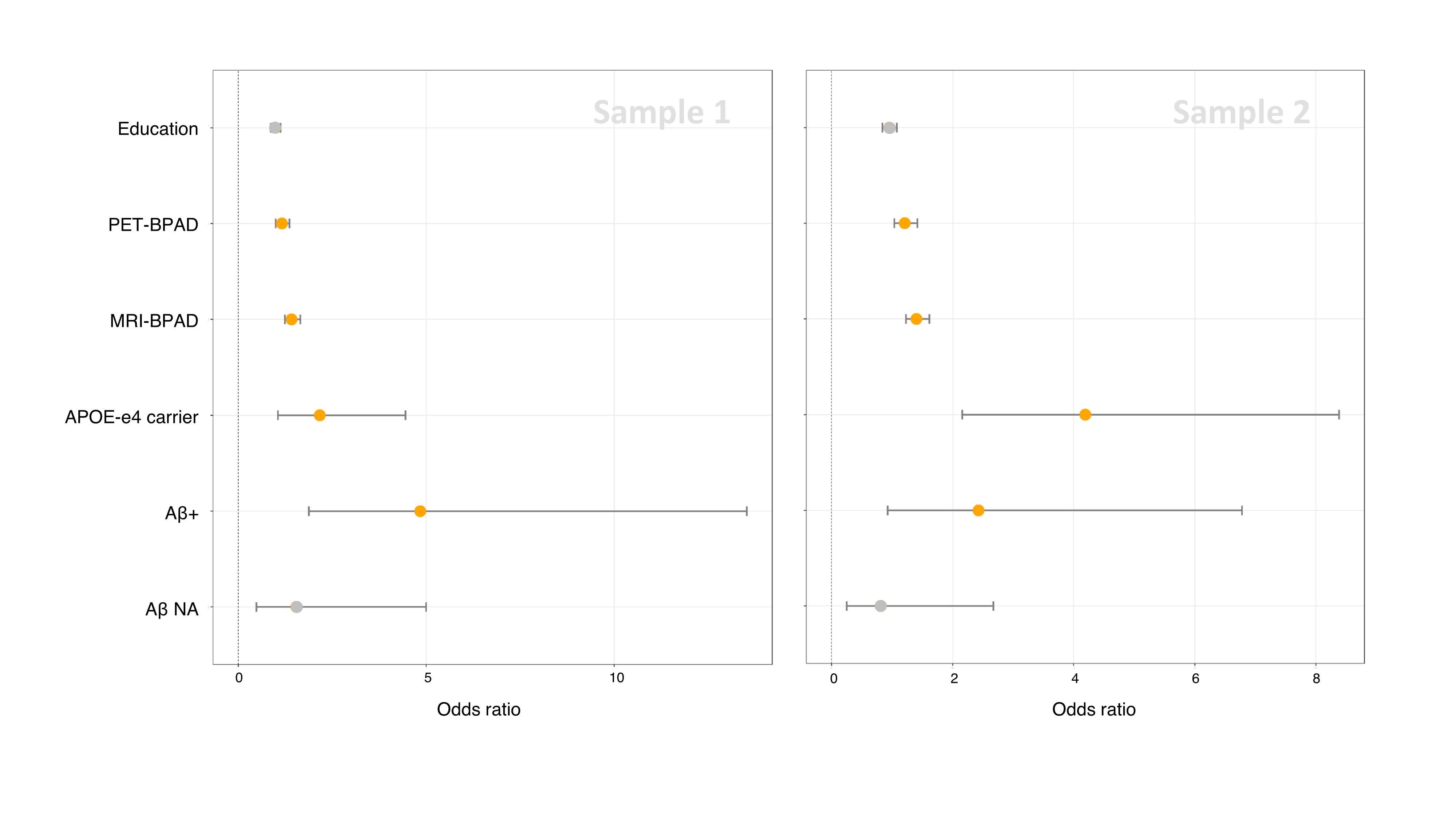


**Fig. 1 Cross-validated probability of cognitive decline within two years after a baseline diagnosis of CN by PET-BPAD.** PET-BPAD predicted CD within two years with variable control groups. a) Higher PET-BPAD was the only predictor of CD in sample one. The PET-BPAD-derived threshold for CD in sample 1 (50% probability of disease progression; dotted line) was 0.2 years. b) Higher PET-BPAD and amyloid positivity predicted CD in sample two. The PET-BPAD-derived decision boundary in sample 2 was 0.9 years. CD = cognitive decline; DX = diagnosis.

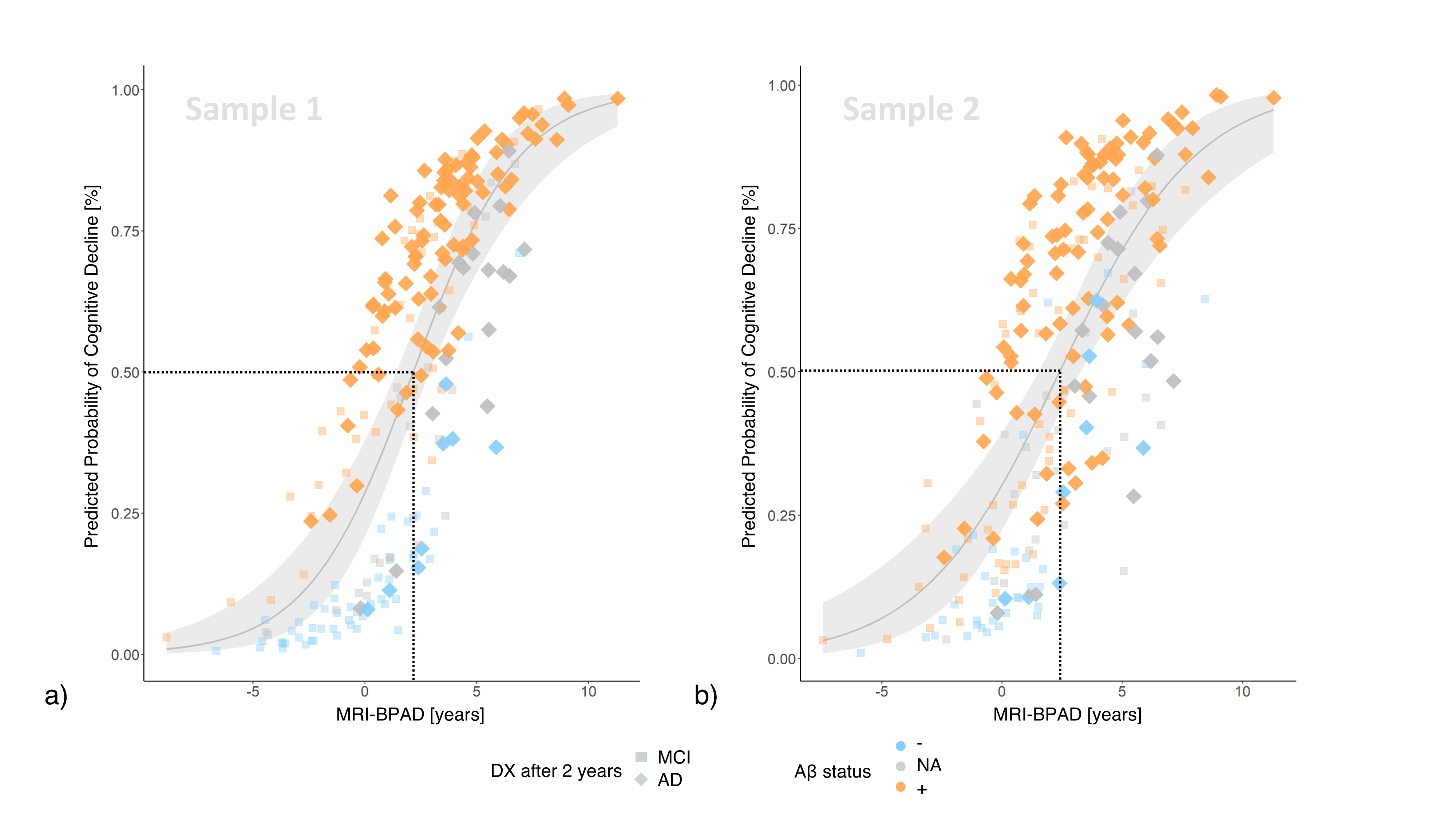
In the whole samples of MCI, 476 individuals either maintained an MCI diagnosis until year two (“stables”; n = 362) or received a diagnosis of AD six months to two years after baseline (“decliners”; n = 114). The two matched sub-samples included 228 individuals (114 decliners and 114 stables). Across these samples, PET- and MRI-BPAD were moderately strongly correlated (r­sample1 = 0.406; psample1 < 0.0001; rsample2 = 0.348; psample2 < 0.0001). In both samples, higher MRI-BPAD very significantly predicted CD together with a positive amyloid status, APOE-e4 carriership, as well as higher PET-BPAD, although the latter was only marginally significant in sample 1. Notably, MRI-BPAD showed considerably higher significance compared to other risk factors (see Table 3); the odds of CD were increased by 40% (sample 2: OR = 1.401, 95% CI [1.228, 1.617]) to 42% (sample 1: OR = 1.419, 95% CI [1.238, 1.652]) per one year MRI-BPAD for individuals with MCI. Odds ratios and confidence intervals of both samples are presented in ***Fig. 2***. Based on these two samples, a clinically relevant MRI-BPAD threshold, where 50% probability of disease progression is reached lies between 2.1 (sample 1) and 2.2 years (sample 2, see ***Fig. 3***). With these thresholds, a sensitivity and specificity of 75% and 65% (sample 1) and 75% and 68% (sample 2) were reached.

In the reduced samples, 97 decliners remained, thus two matched samples of size n = 194 (97 decliners and 97 stables) were created. Results in the reduced samples were highly similar to those found in the whole samples in that MRI-BPAD was the most significant predictor of CD in both samples, while amyloid status, APOE-e4 carriership and PET-BPAD were also significantly associated with pending CD. PET-BPAD significantly predicted CD in both reduced samples. 50% disease probability corresponded to approximately 2.1 and 2.2 years in samples one and two, corresponding to a sensitivity and specificity of 73% and 71% in sample one and 73% and 63% in sample two. Finally, due to the correlation observed between PET- and MRI-BPAD in the MCI sample, we additionally assessed logistic regression models with unimodal BPAD [1]. Considered in separate models, both MRI- and PET-BPAD very significantly predicted (Supplementary Table XX) CD together with APOE-e4 carriership and amyloid status (p < 0.001 in all whole and reduced samples), although MRI-BPAD continued to show higher significance compared to PET-BPAD.

In the current MCI samples, MRI-BPAD showed higher specificity compared to amyloid status (assessed with reduced sample (without NA); Spesample1 = 49%, Spesample2 = 38%), while amyloid status was more sensitive to CD (Sensample1 = Sensample2 = 92%). APOE-e4 carriership showed 72% sensitivity and 61% specificity in the whole samples, and 73% sensitivity and 63 – 64% specificity in the reduced samples, thus proving to be slightly less predictive of CD compared to MRI-BPAD. In conclusion, analyses in the MCI sample revealed that both PET- and MRI-BPAD indicate conversion to AD. Notably, an MRI-BPAD greater than ~ 2.2 years was identified as the single-most predictive variable in the logistic regression models. These findings were stable against variation in the control group, as well as to sample size reductions. However, especially limited specificity scores strongly suggest limited interpretability of stand-alone biomarkers for AD and suggest the combined observation of e.g. MRI-BPAD and amyloid status.



**Fig. 2 Odds ratios of predicting cognitive decline in MCI patients.** The odds of cognitive decline were increased by higher PET- and especially MRI-BPAD, as well as a positive APOE-e4 carriership and amyloid status.



**Fig. 3 Cross-validated probability of cognitive decline within two years after a baseline diagnosis of MCI by MRI-BPAD.** Higher MRI-BPAD and a positive amyloid status, together with higher PET-BPAD and a positive APOE-ε4 carriership predicted CD within two years with variable control groups. a) The MRI-BPAD-derived threshold for CD in sample 1 (50% probability of disease progression; dotted line) was 2.1 years. b) The MRI-BPAD-derived decision boundary in sample 2 was 2.2 years. CD = cognitive decline; DX = diagnosis.

**Method**

Participants

The primary goal of ADNI has been to test whether biological markers and clinical and neuropsychological assessment can be combined to measure the progression of MCI and AD.