**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 < .01), especially in the MRI cohort. Compared to CN, participants in the MCI sample had a significantly lower percentage of females (χ2 = 1.5, p < .01), lower MMSE (t(424)=5.38, p < .001) and a higher percentage of amyloid positivity (χ2 = 43.7, p < .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)/  7.4 (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 (.85) | 28 (1.77) |
| Education [avg. years (SD)] | 16 (2.72) | 16 (2.70) | 16 (2.70) |

**2 Precision of brain-predicted age**

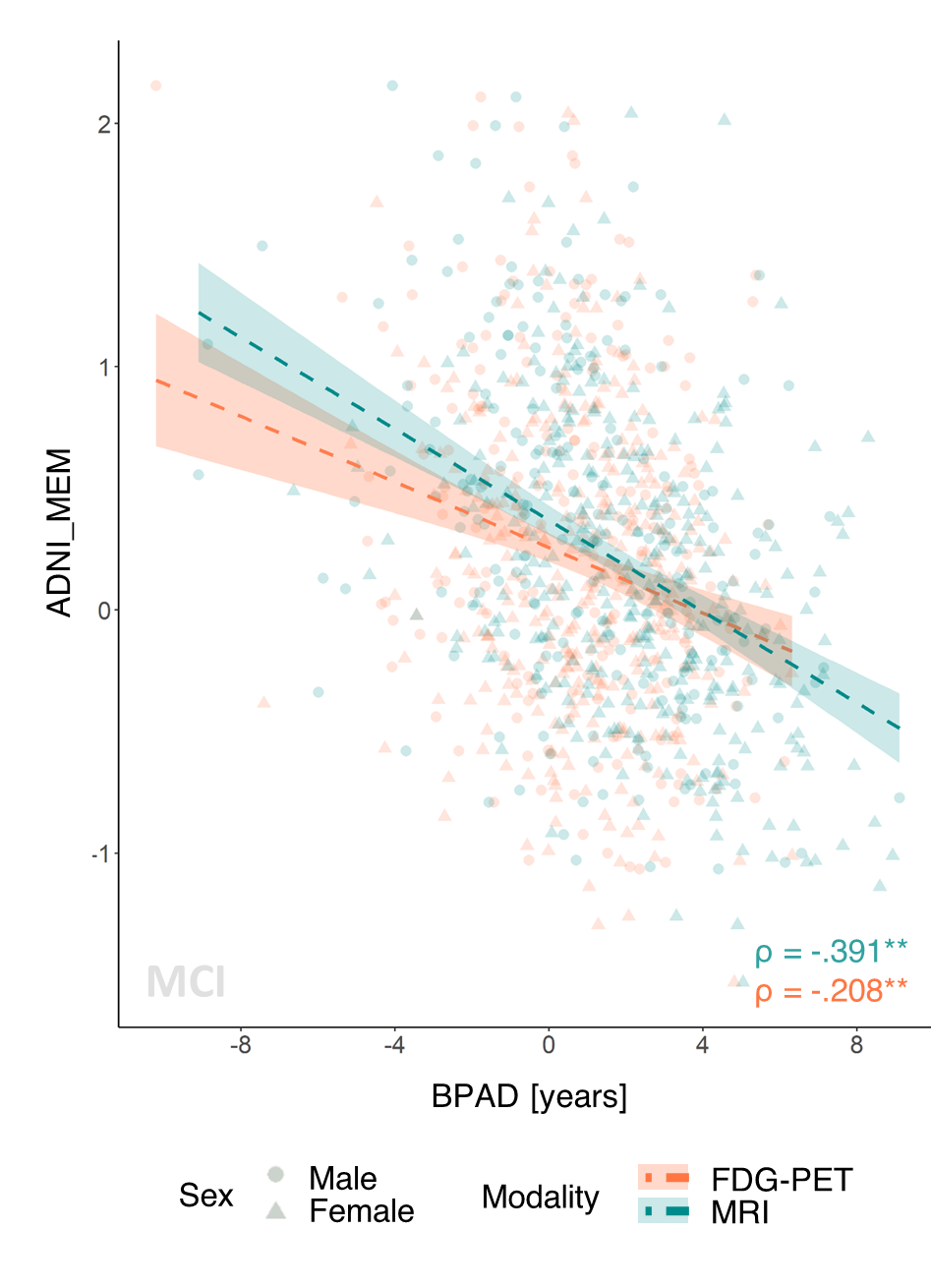
To compare the potential of FDG-PET SUVR and GMV to predict chronological age, we used a nested five-fold cross-validation approach, yielding one test prediction for (almost) every subject in the ADNI CN sample, and five test predictions for each subject in the CN\_validation and MCI sample. Regional 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 .10 and .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 .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 (.30) | 2.45 (.19) | 2.18 (.43) | | 2.50 (.12) | |
| Mean difference | -.10 | -.05 | -.80 | -.80 | .78 | | 1.75 | |
| Mean (SD) over 5 models | - | - | -.66 (.41) | -.92 (.16) | .77 (.26) | | 1.57 (.16) | |
| *Notes.* +After outlier exclusion using CN train set (IQR > 6) | | | | | | | |

**3 BPAD and Cognitive Performance**

Partial spearman correlations between cross-sectional BPAD and memory (ADNI-MEM) and executive function scores (ADNI-EF) were calculated to evaluate whether BPAD is associated with cognitive performance in the two modalities. Age and sex were used as covariates. To adjust for multiple comparison, threshold levels of significance were adjusted by Bonferroni correction (p = .025). In CN (n = 345), there was no significant partial correlation between BPAD and ADNI-MEM in either modality when controlling for age and sex. A weak, negative, partial correlation was detected between MRI-BPAD and ADNI-EF (*ρ*(341)=-.150, *p* = .005). Results of the zero order correlation yielded that there was a weak, negative correlation between MRI-BPAD and ADNI-MEM (*ρ*(343) = -.138, *p* = .010) and between MRI-BPAD and ADNI-EF (*ρ*(343) = -.137, *p* = .010).

In MCI (n = 512), significant, negative partial correlations between BPAD and ADNI-MEM, as well as between BPAD and ADNI-EF existed with BPAD derived from either FDG-PET or MRI and from each of the five models (Table 3). Fig.1 shows the association of FDG- and MRI-BPAD with ADNI-MEM scores in the respective first models. Across models, median correlation coefficients were significantly stronger between MRI-BPAD and ADNI-MEM (*z* = 3.56, *p* < .001) compared to FDG-BPAD.

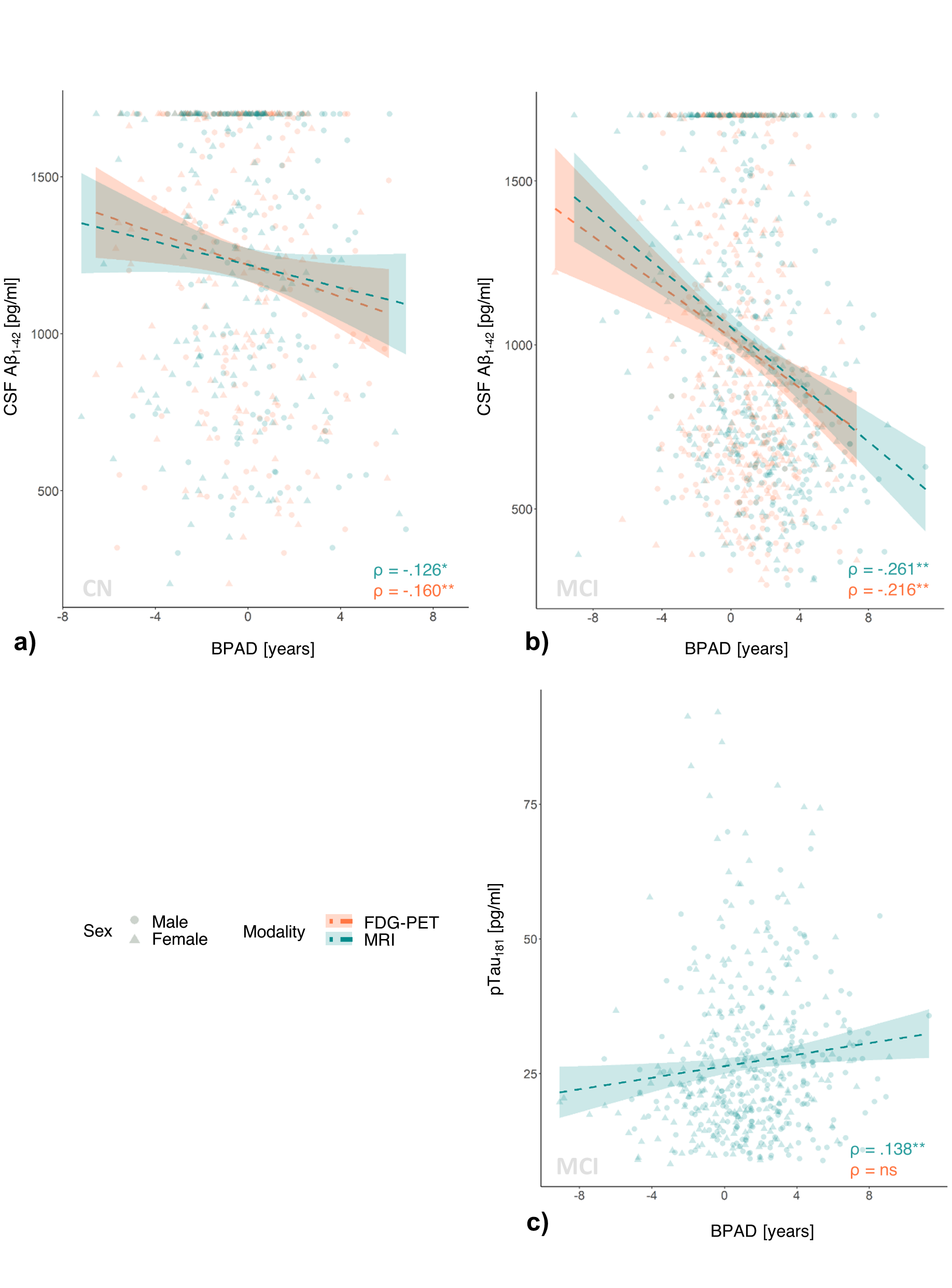


**Fig. 1 Cross-sectional correlation of BPAD and memory.**

**4 BPAD and AD Neuropathology**

Partial spearman correlations were calculated between cross-sectional BPAD and PET amyloid status (global AV45), CSF β-amyloid1–42 (CSF ABETA), CSF total-tau (CSF Tau) and CSF phospho-tau181 (CSF pTau) to evaluate whether BPAD is associated with AD neuropathology in the two modalities. Age and sex were used as covariates. To adjust for multiple comparison, threshold levels of significance were adjusted by Bonferroni correction (p = .0125). In CN (n = 266), a weak, negative, partial correlations existed between FDG-BPAD and CSF ABETA (*ρ(262)* = -.160, *p* = .009), controlling for age and sex (**Fig. 2** a)). MRI-BPAD was also partially correlated with CSF ABETA (*ρ(262)* = -.126, *p* = .040), however this correlation did not withstand Bonferroni correction. Other neuropathological measures were not associated with BPAD in CN. Results of the zero order correlation yielded a weak, negative correlation between FDG-BPAD and CSF ABETA (*ρ(264)* = -.157, *p* = .010), but not between MRI-BPAD and CSF ABETA (*ρ(264)* = -.102, *p* = .095).

In MCI (n = 392), partial correlations between BPAD and AD neuropathology revealed that FDG-BPAD was only marginally correlated with measures of amyloid across models (CSF ABETA: p < .05; global AV45: p = .018 - .070). MRI-BPAD was more significantly correlated with measures of amyloid (CSF ABETA: p < .001; global AV45: p < .001). Moreover, partial correlations were observed between MRI-BPAD and (p-)tau, which, however, did not withstand multiple comparison adjustment in the predictions of two (total tau) and one (phospho-tau) model(s) (CSF Tau: p = .006 - .046; pTau: p = .004 – .025). Table 3 presents an overview of partial correlation coefficients which were significant at p = .05 across models.



**Fig. 2 Cross-sectional correlation of BPAD and AD Neuropathology.** a) A more significant association between FDG-BPAD and CSF ABETA was observed compared to MRI-BPAD in CN. b) The opposite

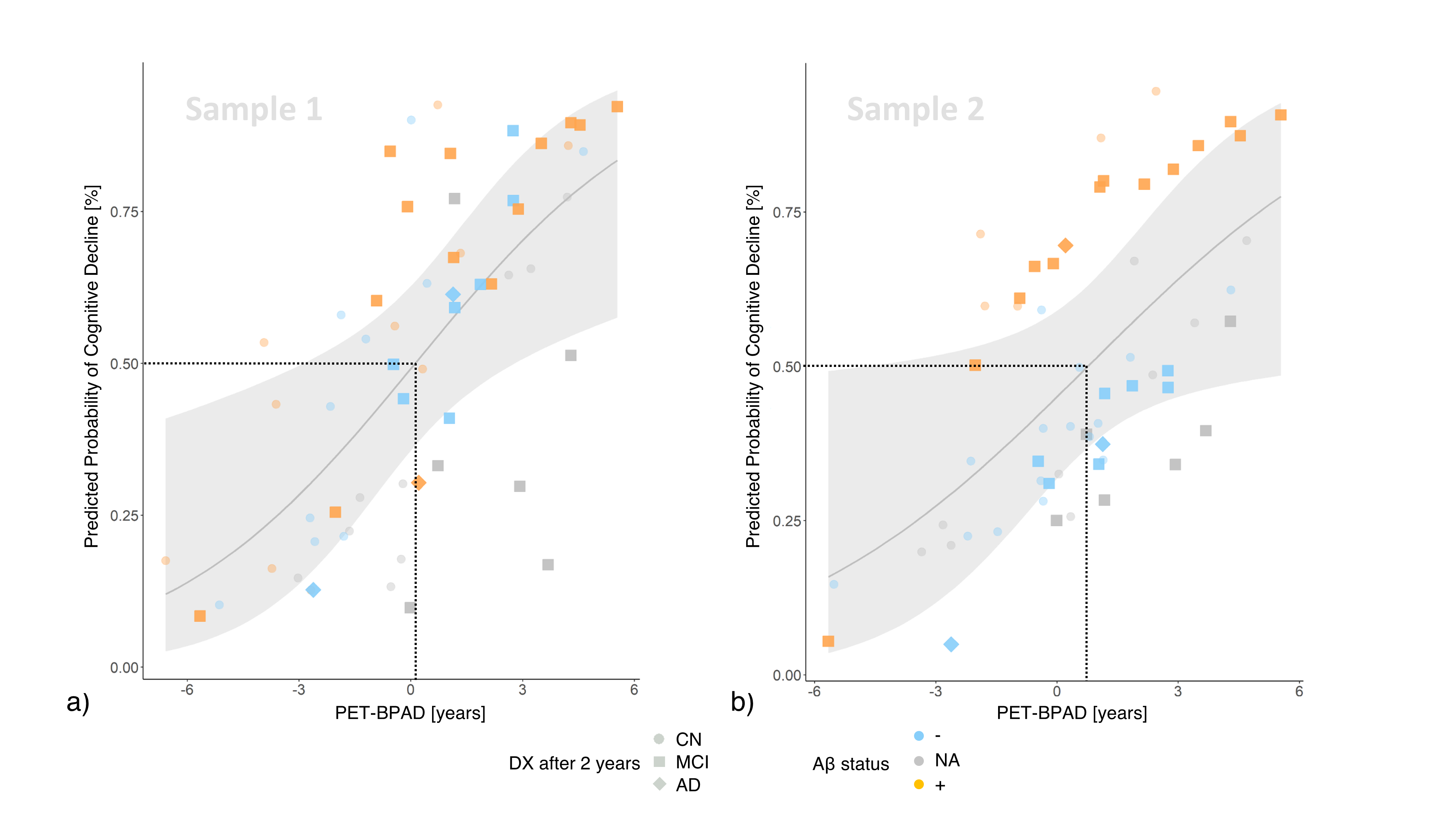
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| Table 3. Correlation strength between BPAD and neuropathology/cognitive function across five different models | | | | |
|  | FDG-PET | | MRI | |
|  | Zero-order | Partial | Zero-order | Partial |
| CSF ABETA | -.184  [-.215, -.150] | -.174  [-.216, -.120] | -.290  [-.294, .283] | -.262  [-.264, -.258] |
| Global AV45 | .121  [.112, .138] | ns | .204  [.189, .225] | .196  [.183, .205] |
| CSF Tau | ns | ns | .113  [.092, .123] | .128  [.101, .138] |
| CSF pTau | ns | ns | .126  [.107, .135] | .137  [.113, .145] |
| ADNI-MEM | -.236 [-.243; -.207] | -.208  [-.224; -.196] | -.437  [-.442; -.422] | -.409  [-.419; -.392] |
| ADNI-EF | -.237 [-.272; -.231] | -.224  [-.246; -.203] | -.300  [-.339; -.307] | -.290  [-.301; -.286] |
| *Notes.* Median [range] of Spearman correlation coefficients are displayed when significant (p<.05) correlation existed in brain-predicted age according to all five models. Coefficients are Spearman Rho unless marked by an asterisk. | | | | |

**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 education. Here, we performed 10-fold cross-validated logistic regression in two subsamples per group (CN/MCI), each containing all individuals who show cognitive decline within two years, and an exclusive matched sample of non-decliners (matched in number by age and sex). As amyloid status was not available for all individuals, analyses were conducted two-fold: once including individuals with missing amyloid information (NA values coded as separate category and amyloid negativity coded as reference; “whole samples”), and once excluding these individuals (“reduced samples”).

Table 4 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). Across the two matched sub-samples, PET- and MRI-BPAD were not significantly correlated. In sample one, the odds of CD were increased by 40% per one year PET-BPAD (OR = 1.404, 95% CI [1.113, 1.874]). 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, however, predictions in sample 2 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 .2 and .9 years in samples 1 and 2, respectively (*Fig. 1*). Sensitivity and specificity for prediction of CD at this threshold 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. In these reduced samples, higher PET-BPAD significantly predicted CD in sample 1 (OR = 1.46, 95% CI [1.101, 2.106], p = .018), whereas a positive amyloid status significantly predicted CD (OR = 4.704, 95% CI [1.135, 23.604], p = .041) in sample 2. 50% disease probability in sample 1 corresponded to a PET-BPAD of 0 years, yielding a sensitivity and specificity of 65 and 74%.

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| Table 4 Estimates (p-values) of logistic regression for prediction of cognitive decline. | | | | |
|  | CN | | MCI | |
|  | Sample  (n = 58) | Sample 2  (n = 58) | Sample 1  (n = 200) | Sample 2  (n = 200) |
| PET-BPAD [Years] | .340 (.008) | .261 (.052) | .132 (.122) | .172 (.040) |
| MRI-BPAD [Years] | .037 (.784) | .032 (.769) | .362 (<.0001) | .320 (<.0001) |
| Aβ+ | .026 (.973) | 1.612 (.036) | 1.407 (.009) | .603 (.292) |
| APOE-ε4+ | 1.464 (.104) | -.066 (.923) | .775 (.046) | 1.466 (<.001) |
| Education [Years] | -.136 (.221) | -.060 (.571) | -.031 (.646) | -.087 (.213) |



**Fig. 3 Cross-validated probability of CD within two years after a baseline diagnosis of CN by PET-BPAD.** PET-BPAD predicted CD within two years with variable control groups in the whole samples (displayed here) and in one reduced sample. Stable individuals made transparent for visibility. 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 CD; dotted line) was .2 years. b) Higher PET-BPAD and amyloid positivity predicted CD in sample two. The PET-BPAD-derived decision boundary in sample 2 was .9 years. CD = cognitive decline; DX = diagnosis.

In the whole samples of MCI, 393 individuals either maintained an MCI diagnosis until year two (“stables”; n = 293) or received a diagnosis of AD six months to two years after baseline (“decliners”; n = 100). Across the two matched sub-samples, PET- and MRI-BPAD were moderately strongly correlated (r­sample1 = .439; psample1 < .0001; rsample2 = .372; psample2 < .0001). In both samples, higher MRI-BPAD very significantly predicted CD (sample 1: OR = 1.436, 95% CI [1.241, 1.688]; (sample 2: OR = 1.377, 95% CI [1.202, 1.599]) together with APOE-e4 carriership (sample 1: OR = XX; sample 2: OR = XX), while a positive amyloid status and higher PET-BPAD predicted CD in only one sample. Notably, MRI-BPAD showed considerably higher significance compared to other risk factors (see Table 3). Odds ratios and confidence intervals of both samples are available in Supplementary Fig. 5. Based on these two samples, a clinically relevant MRI-BPAD threshold was between 2.3 (sample 1) and 2.7 years (sample 2, see *Fig. 4* a) and b)). With these thresholds, a sensitivity and specificity of 76% and 70% (sample 1) and 67% and 71% (sample 2) were reached. Fig. 3 c) and d) show a reduced MRI-BPAD threshold for APOE-ε4 carriers (sample one: 1.1 year; sample two: .7 years) compared to APOE-ε4 non-carriers (sample one: 3.8 years; sample two: 5.3 years).

86 MCI patients had full information on all considered variables, thus constituting the decliner group of the reduced samples. Results in the reduced samples compared well to those found in the whole samples. PET- and MRI-BPAD were significantly associated with each other (r­sample1 = .390; psample1 < .0001; rsample2 = .385; psample2 < .0001). Again, MRI-BPAD (ORsample1 = 1.43, 95% CI [1.221, 1.709], p < .0001; ORsample2 = 1.36, 95% CI [1.169, 1.613], p< .001) and APOE-e4 carriership (ORsample1 = 4.088, 95% CI [1.804, 1.9.580], p < .001; ORsample2 = 5.276, 95% CI [2.435, 11.989], p< .0001) were highly significant predictors of CD. PET-BPAD, in this reduced sample, was not predictive of CD, while a positive amyloid status predicted CD in sample one. 50% probability of CD corresponded to approximately 2.1 and 2.5 years in samples one and two, corresponding to a sensitivity and specificity of 76% and 69% in sample one and 68% and 65% 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 < .01 in all whole and reduced samples). However, 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 = 47%, Spesample2 = 28%), while amyloid status was more sensitive to CD (Sensample1 = Sensample2 = 92%). APOE-e4 carriership showed 73% sensitivity and 58% specificity in the whole samples, and 74% sensitivity and 66 – 67% specificity in the reduced samples and thus also showed reduced specificity, especially compared to the whole samples analyses. **Discussion**

In conclusion, BPAD can be reliably used to predict CD

analyses in the MCI sample revealed that both PET- and MRI-BPAD indicate conversion to AD. Notably, an MRI-BPAD greater than 2.3 years was identified as a specific and sensitive marker of CD, which outperformed other risk factors of CD in MCI in sample one in terms of significance and specificity. However, sensitivity and specificity scores are not high enough for MRI-BPAD to serve as a stand-alone biomarker of CD. Potentially, MRI-BPAD can serve as a reliable biomarker of CD together with APOE-e4 carriership, as Figure XX suggests different BPAD thresholds may apply as a function of the latter. XX

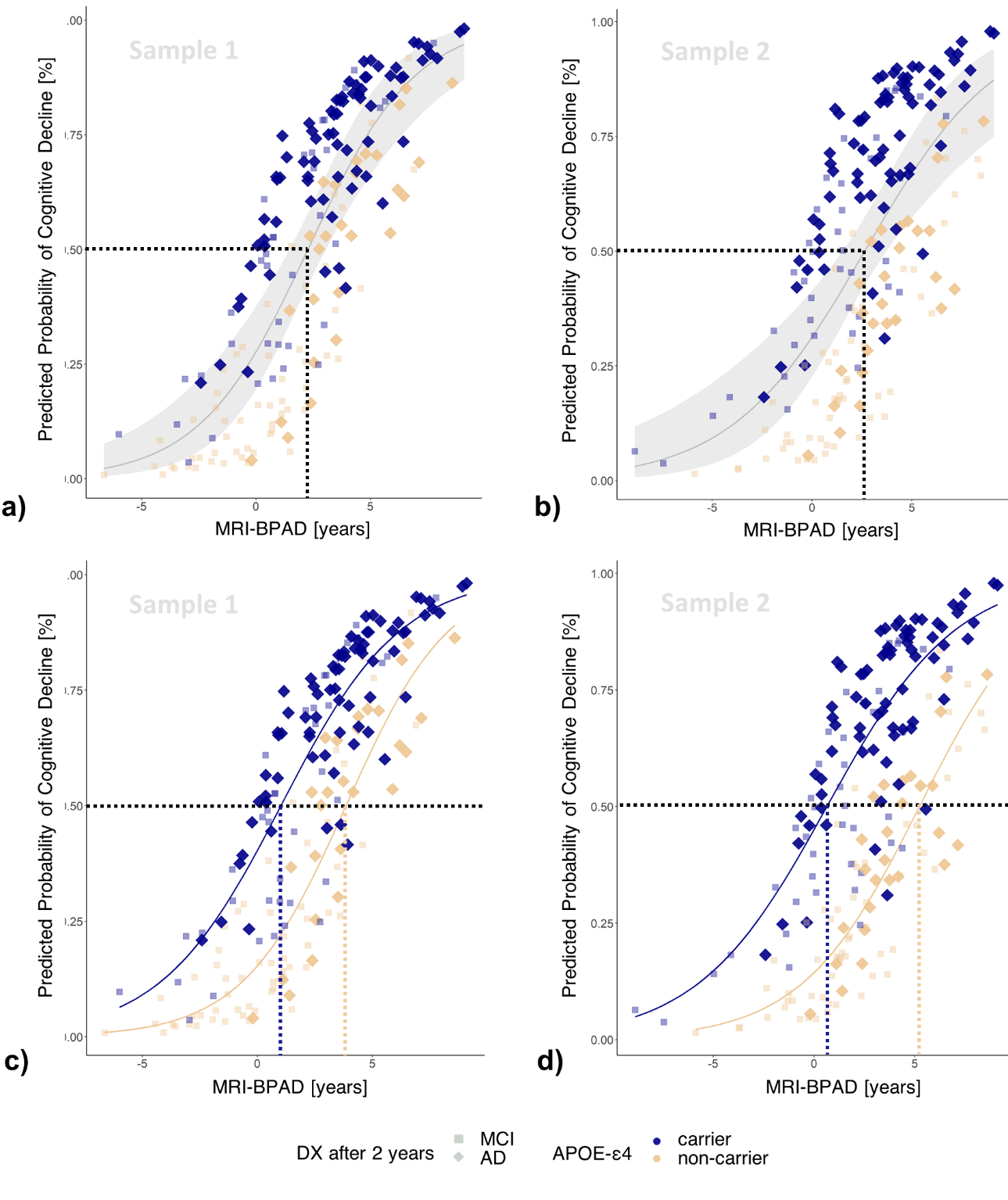


Fig. 4 Cross-validated probability of cognitive decline within two years after a baseline diagnosis of MCI by MRI-BPAD. Higher MRI-BPAD and a positive amyloid status, together with higher XX PET-BPAD and a positive APOE-ε4 carriership predicted CD within two years with variable control groups. Stable individuals made transparent for visibility. 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. *c) and d) 50% probability of cognitive decline requires a lower MRI-BPAD in APOE-e4 carriers compared to carriers.* 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.

**Supplementary Materials**

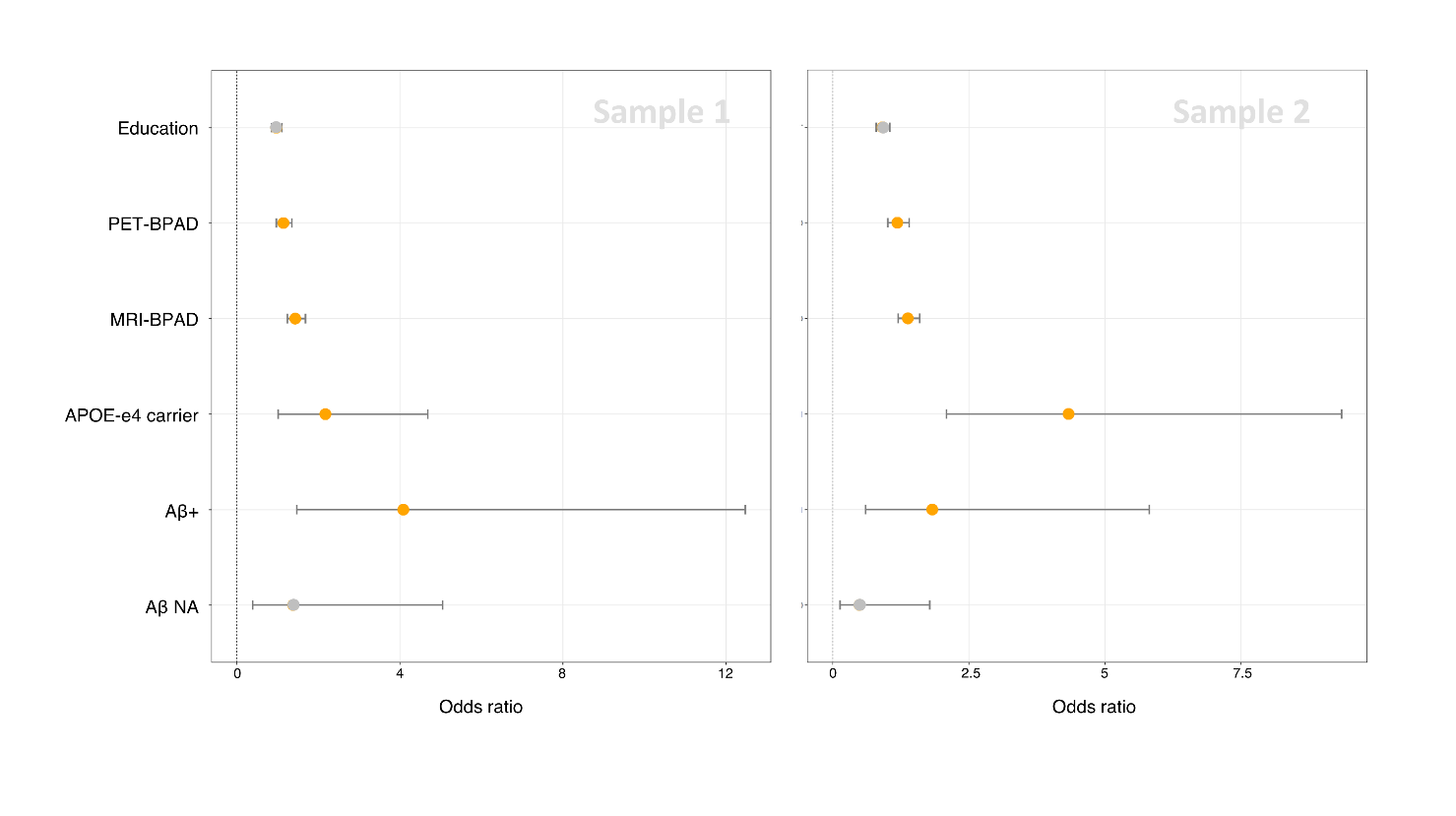


Fig. 5 Odds ratios of predicting cognitive decline in MCI patients. The odds of cognitive decline were increased by higher PET- and especially MRI-BPAD, as well as a positive APOE-e4 carriership and amyloid status.