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Tau-PET is superior to phospho-tau when predicting cognitive decline in symptomatic AD patients

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Abstract

INTRODUCTION: Biomarkers for prediction of cognitive decline in patients with amnesic mild cognitive impairment and amnesic mild dementia are needed for both clinical practice and clinical trials.

METHODS: We evaluated the ability of tau-PET, cortical atrophy on MRI, baseline cognition, *APOE*-status, plasma and cerebrospinal fluid levels of phosphorylated tau-217, neurofilament light, and amyloid- $\beta_{42/40}$ (individually and in combination) to predict cognitive decline over two years in BioFINDER-2 and ADNI.

RESULTS: Baseline tau-PET and a composite baseline cognitive score were the strongest independent predictors of cognitive decline. Cortical thickness and neurofilament light provided some additional information. Using a predictive algorithm to enrich patient selection in a theoretical clinical trial led to a significantly lower required sample size.

DISCUSSION: Models including baseline tau-PET and cognition consistently provided the best prediction of change in cognitive function over 2 years in patients with amnesic mild cognitive impairment or mild dementia.

Keywords

AD; Tau; PET; blood biomarkers; cognition

Introduction

Amyloid β ($A\beta$) plaques and tau tangles are the pathologies that define Alzheimer's disease (AD).[1] Cerebrospinal fluid (CSF) $A\beta$ was shown to be associated with an increased risk of progression from mild cognitive impairment (MCI) to AD dementia already 20 years ago,[1-3] and the first PET tracer for $A\beta$ was developed shortly thereafter.[4] More recently, methods to accurately measure $A\beta$ in plasma have been developed.[1, 5-7] Over the past several years, new methods have been developed to visualize tau pathology *in vivo* using tau positron emission tomography (PET) imaging[8] and to determine levels of phosphorylated tau (p-tau) in CSF[9, 10] and plasma.[1, 11-16] The rapid development of tau-PET tracers has led to the recent approval, by the United States Food and Drug Administration, of [¹⁸F]flortaucipir as a diagnostic agent in AD dementia.[17] Tau-PET has been shown to reliably detect the tau aggregates formed in AD,[18, 19] and shows strong associations with both cognitive decline [20-24] and neurodegeneration. [25, 26] Levels of p-tau in CSF and plasma have been shown to begin increasing at the asymptomatic (preclinical) stage of AD in response to very early $A\beta$ pathology. [27-30] Higher baseline concentrations of p-tau have also been shown to accurately predict progression to AD dementia in both cognitively unimpaired (CU) individuals and in patients with MCI.[12, 31-33] Neurofilament Light (NfL), a more general marker of neurodegeneration, has been reported to be increased in AD [34], and to be associated with conversion from MCI to AD dementia.[32]

As mentioned above, we and others have recently shown that blood-based biomarkers of A β (A), tau (T) and neurodegeneration (N) can predict both future cognitive decline and conversion to AD dementia.[11-16, 31-33] Further, tau-PET has also been shown to be an important predictor of cognitive decline in AD.[26, 35, 36] However, there is a clear lack of head-to-head comparisons of these type of promising fluid and imaging biomarkers, and there is also an urgent need to determine optimal biomarker combinations for prediction of cognitive decline in patients with MCI or mild dementia over a clinically relevant time span such as 24 months. This information is of great importance both in clinical settings to establish the risk of cognitive decline in symptomatic patients at a subject level, and in the settings of clinical trials directed against symptomatic AD where follow-up time typically ranges between 18 and 24 months [37-39].

We therefore aimed to determine the ability of different blood and CSF, as well as imaging ATN biomarkers associated with AD, to independently predict cognitive decline in patients with objective memory impairment. To this end, we analysed the ability of i) the most relevant plasma and CSF biomarkers (i.e. p-tau217, neurofilament light (NfL) and the ratio of A β 42 to A β 40 [A β _{42/40}]), ii) tau-PET ([¹⁸F]RO948 standardized uptake value ratios (SUVRs)) in three different regions-of-interest (ROIs)), iii) baseline cognition, iv) MRI (cortical thickness in an “AD-signature” temporal-ROI[40]), and v) the main genetic risk variant for sporadic AD (the *APOE* *ϵ 4* allele), to predict longitudinal cognitive performance over two years in patients presenting with amnesic mild cognitive impairment (MCI) or amnesic mild dementia. We included patients with amnesic MCI or mild amnesic dementia without requiring them to already have evidence of A β pathology (defined by CSF or PET) to be able to identify which markers best predict cognitive decline independent of A β -status. This is a relevant situation in clinical practice, where most patients with amnesic memory impairment have an unknown A β -status. In a sensitivity analysis we restricted the participants to only include A β -positive participants to mimic a clinical trial setting. Based on the main results presented in this study, including all participants, we have developed a prototype of an on-line prognostic tool that can be used to predict cognitive decline over 24 months, either to provide individualized prognostic information in clinic practice or when recruiting suitable participants to clinical trials. Importantly, the main results were replicated in an independent cohort (ADNI).

Methods

Participants

We included participants from the Swedish BioFINDER-2 study (n=118; May 2017 – March 2021; www.biofinder.se). The inclusion criteria for the present study were 1) either amnesic MCI (n=90) or early amnesic dementia (n=28) and 2) a baseline Mini-Mental State Examination (MMSE) score of \geq 22 points. 3) A complete dataset for all studied biomarkers. In addition to presenting with amnesic memory problems patients with MCI either fulfilled established DSM-5 clinical criteria for mild neurocognitive disorder, or met the DSM-5 criteria for major neurocognitive disorder possibly due to AD.

BioFINDER-2 participants underwent a medical history and neurological examination, brain MRI, blood and CSF sampling, [¹⁸F]RO948 tau-PET and repeated neuropsychological

testing after 1, 2 and 3 years. Only participants with cognitive follow-up data extending over 2 years were included in the analysis, but results from all available time points were used for cognitive slope calculation. At baseline, participants also underwent a cognitive battery including trailmaking test-A & B (TMT-A, TMT-B), animal fluency (AF) and the wordlist delayed recall part of the ADAS-cog. These tests were used to calculate a baseline cognitive composite score by computing z-scores based on the mean and standard deviation of cognitively unimpaired (CU) participants (n=465) from the BioFINDER2 study. The baseline cognitive composite was calculated as $-ADAS-cog_{z-score} + -TMT-B_{z-score} + AF_{z-score}$. These three cognitive tests were used in combination since they were shown to be the best predictors of conversion to AD dementia.[33] For a sensitivity analysis using a modified Preclinical Alzheimer Cognitive Composite (PACC) as an outcome we calculated a modified PACC z-scores using the formula: $MMSE_{z-score} + 2 \times (-ADAS-cog_{z-score}) + -TMT-A_{z-score} + AF_{z-score}$. TMT-A was used instead of TMT-B in the longitudinal analysis to minimize the loss of AD participants at follow-up visits. Written informed consent was obtained from all participants prior to entering the study and the study was approved by the regional review board for human research ethics at Lund University. Details on ADNI participants are provided in the supplement.

Image acquisition, processing and biofluid biomarker collection and processing

Image acquisition and processing as well as biofluid biomarker handling are described in detail in the supplementary information. In an initial analysis we found that Braak III/IV was the best predictor (highest t-value) of cognitive decline of these three meta-ROIs, and consequently only the Braak III/IV (temporal ROI) region was used in further analyses, to avoid multiple dependent tau-PET predictors (Supplementary Table 1).

Statistics

Linear regression modelling was used to predict change in cognition with each biomarker measured separately as the main predictor and in combination. Age, sex, education and baseline MMSE were included as covariates. Change in MMSE (slope) was calculated for each individual as the slope of a linear regression based on all available follow-up visits. Only individuals who had all available biomarker measurements were included in order to ensure direct comparability of model results. Models were evaluated using t-values, R^2 and change in Akaike Information Criterion (AIC) values. A model with an AIC value more than two points lower than another model can be considered significantly different.[32] To find the most parsimonious model that could predict cognitive decline we performed an initial selection using the R package MuMIn, which tests all possible variable combinations and then ranks the models according to their AIC.[41] As a complementary model, stepwise removal of the variable with the highest p-value from the full model was performed and the model with the lowest AIC was considered as the optimal model with the best tradeoff between model fit and complexity. The parsimonious model selected was the model with the fewest predictors within 2 AIC points from the optimal model. Note that before starting the analyses, to limit the number of biomarkers studied and minimize the risk of random false-positive findings, we selected biomarkers shown in previous studies to be associated to cognitive decline in AD. To avoid collinearity due to dependent predictors (such as for example pTau measured in CSF and plasma), and since in clinical practice or clinical trial

settings often blood, but not CSF, is sampled, we performed the analysis of plasma and CSF biomarkers separately.

Finally, we performed a simulated clinical trial power analysis in which the ability of each measure to increase trial power was determined when used for inclusion screening. First, the number of trial participants needed to achieve 80% power to detect a reduction in cognitive change was calculated for each group without any additional inclusion criteria (“unenriched scenario”). Next, the same calculation was performed when assuming that only individuals in the 25%, 30%, 35% etc. top percentile of risk for cognitive decline as predicted by the parsimonious model would be included in the trial (“enriched scenario”). The percent difference in number of trial participants needed between the unenriched and enriched scenarios was then reported along with p-values based on the proportion of 1000 bootstrap trials in which the enriched scenario required fewer participants than the unenriched scenario. All statistical tests were two-tailed with a significance level of 0.05. All analyses were performed using the R programming language (v 4.0).

Results

Participants and biomarkers

118 participants presenting with memory impairment (either amnesic MCI or amnesic mild AD dementia) from the Swedish BioFINDER-2 study were included in the study. The mean age was 71.0 ± 8.6 years, mean education duration was 12.8 ± 4.4 years, 48% were females, and mean baseline MMSE was 26.4 ± 2.4 (range 22-30). Participant demographics for the included cohort are provided in Table 1. MMSE scores were obtained at baseline and at annual follow-up for up to three years. Cognitive decline was computed as the change (slope) in MMSE score per year and correlated to ten biomarkers: plasma and CSF p-tau217, plasma and CSF NfL, plasma and CSF $A\beta_{42/40}$ ratio, tau-PET SUVR in a temporal ROI (corresponding to Braak imaging stages III-IV), *APOE* $\epsilon 4$ status, cortical thickness in “AD-signature” cortex and the cognitive baseline composite score.

Prediction of cognitive decline by individual biomarkers

We found that baseline tau-PET SUVR in the temporal ROI showed the highest t-values, R^2 and lowest AIC values when each biomarker was used individually to predict change in cognition ($t = -6.26$, $R^2 = 0.33$, AIC -33 compared to a model including only the covariates; Figure 1 and Supplementary Tables 2 and 3). Baseline cognition, cortical atrophy, CSF NfL and plasma and CSF p-tau217 also individually significantly predicted cognitive decline (Figure 1, Supplementary Tables 2 and 3). As expected, models including all biomarkers provided better model fit (higher R^2 -values). They also provided better AIC-values as compared to the best single predictor tau-PET (Supplementary Tables 2 and 3).

Prediction of cognitive decline by biomarker combinations

We next determined the most parsimonious model that could provide a non-inferior prediction of future cognitive decline compared to the full models combining all predictors. We therefore sequentially removed one biomarker at a time from the full model in a stepwise

fashion (the biomarker with the highest p-value in the model was removed) and refit the model. Data showing the change in AIC and R^2 upon biomarker removal are presented in Table 2. The combination of tau-PET, baseline cognition, cortical atrophy and NfL provided the most parsimonious models (with the fewest number of predictors, and AIC within <2 from the model with the lowest AIC), where tau-PET and baseline cognition were the strongest predictors (Table 2). We next confirmed this model using an automated data-driven model selection (MuMin) to evaluate the ability of all possible biomarker combinations to predict cognitive decline. Again we found that for both plasma and CSF analyses, the combination of tau-PET, cortical atrophy, NfL and baseline cognition provided the lowest AICs.

In a sensitivity analysis, when restricting the analysis to only amnesic MCI participants ($n=90$), we found similar results (Supplementary Table 4). Further, when including only participants that were $A\beta$ -positive (Supplementary Table 5) to mimic the scenario of a clinical trial, tau-PET and baseline cognition were significant predictors, while NfL and cortical atrophy were no longer significant predictors. Finally, when using change in modified PACC over time as the cognitive outcome (instead of change in MMSE), we again found that tau-PET and baseline cognition were the strongest predictors of cognitive decline in the parsimonious models, but with minor contributions from plasma NfL and plasma p-tau217 (Supplementary Table 6). In another sensitivity analysis we found no added value of plasma or CSF glial fibrillary acidic protein (GFAP) or CSF levels of the synaptic marker Neurogranin in the BioFINDER cohort (data not shown).

To validate our findings we included 50 participants from the ADNI cohort, having a complete set of biomarkers for: age, sex, education, baseline and longitudinal MMSE, baseline cognition, tau-PET ($[^{18}F]$ flortaucipir), *APOE* $\epsilon 4$ -status, $A\beta$ -status, plasma NfL, plasma p-tau181 and cortical thickness. We found that tau-PET and baseline cognition were again the best predictors for longitudinal cognitive decline, but plasma NfL and cortical atrophy did not contribute to the model (Supplementary Table 7).

Enrichment for clinical trials using biomarkers

With the aim of studying the importance of screening biomarker data for clinical trial design we next calculated the impact of biomarker enrichment on group sizes needed to achieve a preset statistical power of 80%. We found that using the parsimonious models defined in BioFINDER-2, i.e. tau-PET, baseline cognition, NfL and cortical thickness, to enrich for higher risk of cognitive decline resulted in significant reduction in group sizes with preserved statistical power (Figure 2 and Supplementary Figure 1; full details provided in Supplementary Table 8). These results are independent of the assumed treatment effect. There were no statistically significant differences in the reduced group sizes between using CSF or plasma biomarkers (Supplementary Figure 1). The results indicated that restricting inclusion to the 50% of participants with the highest predicted risk for cognitive decline resulted in a need for ~52% fewer participants compared to having no enrichment strategy (Figure 2). Biomarker enrichment further resulted in removal of $A\beta$ negative individuals even if $A\beta$ biomarkers were not used in the parsimonious selection model. For example, in an unselected population, 65% of amnesic individuals were $A\beta$ -positive, compared to ~80%

using a 75% cut off (i.e. including the 75% with the most pathological values, and excluding the 25% with most normal values), 92-93% using a 50% cut off and 97% using a 25% cut off. In a sensitivity analysis, a more simple model only containing the most important predictors (that is: tau-PET and cognition) performed similarly to the full models for study enrichment (Supplementary Figure 2).

Generation of a prediction algorithm for future cognitive decline

To simplify the use of the data provided herein we have generated a web-based application for calculating the risk for cognitive decline over a two-year period, based on the full BioFINDER2 dataset. The web-application is available at: <https://brainapps.shinyapps.io/PredictMMSE/> (Figure 3).

Discussion

Plasma [12, 33], CSF [42, 43] and imaging biomarkers [35, 36, 42-48] of A, T and N have previously been used individually or in combination to predict cognitive decline and conversion to AD dementia. However, a comprehensive direct head-to-head comparison of the relative contributions of plasma, CSF and tau-PET biomarkers to the prediction of cognitive decline is lacking. To address this gap and to allow direct comparisons of the relative contribution of the different biomarkers to the prediction we used a dataset where data for all studied biomarkers were available in all participants. In short we found that models consisting of tau-PET and baseline cognition, were most strongly and consistently associated with subsequent cognitive decline in heterogeneous populations of patients with amnesic MCI or mild amnesic dementia. Further, there were more modest and more variable contributions of NfL and cortical thickness, but neither plasma (or CSF) p-tau, plasma (or CSF) A β 42/A β 40, or *APOE4* genotype were included in the main models.

The present results are in line with a recent study showing that tau-PET is superior to A β -PET and MRI when predicting subsequent cognitive change in AD, [35] but in that large multicenter cohort neither plasma biomarkers, CSF biomarkers, nor baseline cognition were studied.

The present finding that NfL and cortical atrophy provides modest, but independent, information compared to tau-PET alone might be expected, considering that NfL and cortical atrophy reflects ongoing axonal degeneration and substance loss of the brain, which is clearly different to the tau aggregates detected with tau-PET imaging. [1] Previous studies have suggested a role for structural cortical volumetric or thickness MRI measures [43, 45, 48, 49] in prediction of cognitive decline in AD. Cross-sectionally we and others have reported that temporal cortical atrophy on MRI and tau-PET are associated with cognitive performance. [42, 44, 46, 47, 50] However, neither NfL, nor cortical atrophy were significant predictors in the ADNI validation cohort, possibly reflecting the smaller sample size and potentially also the lower number of early AD dementia participants in the ADNI dataset.

The main explanation why plasma (or CSF) p-tau was not selected in the main parsimonious models is likely because this biomarker, similar to A β 42/A β 40 and A β -PET, becomes abnormal much earlier than tau-PET, in the case of A β 42/A β 40 likely already 10-30 years

before onset of objective memory impairment.[1, 11, 15] Tau-PET is more closely related to neurodegeneration and cognitive decline during the symptomatic stages of AD[1, 35], likely explaining why we found that plasma (and CSF) p-tau does not seem to contribute with independent information beyond tau-PET in patients with MCI and mild dementia. CSF p-tau 217 was pathological in 60% of participants at baseline (including all AD-dementia participants). In comparison, 38% of participants had a pathological RO948 PET at baseline. That said, plasma p-tau might be more useful during preclinical stages of AD, where it can predict future increase in tau-PET uptake.[51]

Further, baseline cognition (here evaluated using composites of memory and executive function) showed an association with future cognitive decline even after adjusting for baseline MMSE, but performed significantly inferior compared to the parsimonious model or tau-PET when used alone (Table 2, Supplementary tables 2 and 3). Still, including baseline cognition added independent information to the parsimonious models on top of tau-PET, cortical thickness and NfL data, showing the value of brief cognitive testing in the clinic when predicting subsequent cognitive decline. Similarly, we have previously found that the same three cognitive tests together with plasma p-tau can predict conversion to AD dementia in patients with SCD or MCI, but again tau-PET was not available in that study.[33]

Conducting clinical studies is very expensive since large populations need to be included to have a sufficient number of progressors over a relatively short time interval to show an effect of the treatment. In an unselected population, only a minority of patients with MCI or mild dementia will progress significantly over a two-year period. Optimizing the trial design by selecting patients that are more likely to progress is therefore of great importance for reducing the number of required participants. We consequently aimed to see whether preselecting study participants for a theoretical clinical trial based on their baseline biomarker levels could reduce the number of required participants without compromising statistical power. Restricting the study population using the parsimonious model to more pathological biomarker values resulted in a significant reduction in sample sizes needed (Figure 2; Supplementary Table 8 and Supplementary Figure 1). Importantly for the use of these biomarkers in selection of participants for future clinical studies of AD, selection based on the parsimonious model including only tau-PET, baseline cognition, cortical atrophy, and NfL also selected for A β positivity, thereby decreasing the need for performing both A β - and tau-PET in the selection process.

In light of the recently published Phase II study of donanemab in early AD[38] where cognitive decline continued despite the clearance of A β plaques as assessed by A β -PET, it may be argued that including patients based on tau-positivity, as assessed by tau-PET, may be too late since the treatment may not be able to halt disease progression. The parsimonious model presented in this article may therefore prove more suitable for anti-tau trials, acting at a later stage of the disease progression.

From a clinical perspective, knowing the likelihood that a patient in the clinic will remain stable or is likely to significantly deteriorate over a relevant time interval is of great importance. “How quickly does my memory deteriorate?” was recently listed as the most

important question to be answered by both AD patients and caregivers in a survey study[52], followed by other questions related to cognition. Being able to address these questions is therefore of large interest to meet the concerns of the patients affected by the disease. By knowing the tau-PET status, the baseline performance on a few brief cognitive screening tests, NfL, a prediction can now be made using an easy-to-use on-line tool developed using the results of the present study (<https://brainapps.shinyapps.io/PredictMMSE/>).

There are limitations of this study. First, the follow-up period is rather short, although it is within the range of many therapeutical trials in symptomatic AD (ClinicalTrials.gov: Clarity AD, EMERGE, GRADUATE 1&2, and ENGAGE, and [37-39]), and represents a foreseeable time perspective from a clinical point of view. Second, the number of participants is relatively low, especially for the number of AD dementia participants, and the majority are of European descent. We cannot exclude that there may be small predictive effects seen with the non-significant biomarkers if the sample size was increased, and the results would benefit from being replicated in additional large independent cohorts. Likewise, we cannot exclude that other biomarkers may show better predictive abilities with a more diverse ethnic background. Third, MMSE may not be the optimal readout for longitudinal cognition in all settings, even though it often performs well to detect decline in populations with patients with MCI or mild dementia and it is often included in clinical trials as a secondary outcome. A sensitivity analysis using a modified PACC, designed to be an earlier marker of cognitive decline, as the cognitive outcome resulted in a similar outcome compared to using longitudinal MMSE. Fourth, we aimed at making a comprehensive comparative study of biomarkers for cognitive decline in early AD, but still important biomarkers, such as for example FDG PET, were not available in the dataset and have not been included in the present study.

Conclusions

We found that tau-PET, baseline cognition, cortical thickness, p-tau217-levels in blood and CSF as well as CSF NfL, can all individually predict future cognitive decline in patients with amnesic MCI or mild dementia. However, models including tau-PET and baseline cognition consistently provided the best prediction of cognitive decline in this heterogenous patient population, implying that tau-PET might be an important addition to the diagnostic work-up in situations when prognostic information is of importance. We further found that selecting a study population based on these biomarkers can result in clearly reduced number of participants needed in clinical trials, e.g. anti-tau trials, with cognitive decline as primary outcome.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data Sharing

Anonymized data will be shared by request from a qualified academic investigator for the sole purpose of replicating procedures and results presented in the article and as long as data transfer is in agreement with EU legislation on the general data protection regulation and decisions by the Swedish Ethical Review Authority, which should be regulated in a material transfer agreement.

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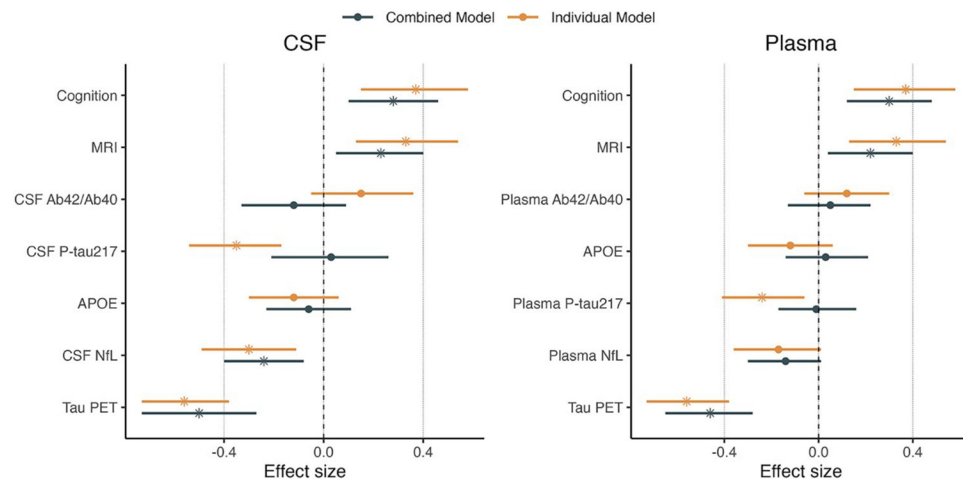


Figure 1. Prediction of cognitive decline using biomarkers individually or in combination. The figure shows the effect sizes for each biomarker in predicting future cognitive decline either alone (orange bars, on top) or in a combined model (black bars, below). Significant biomarkers are represented with a star. The model using cerebrospinal fluid (CSF) biomarkers is shown in the left panel and the model using plasma biomarkers in the right panel. Bars represent 95% Confidence Intervals.

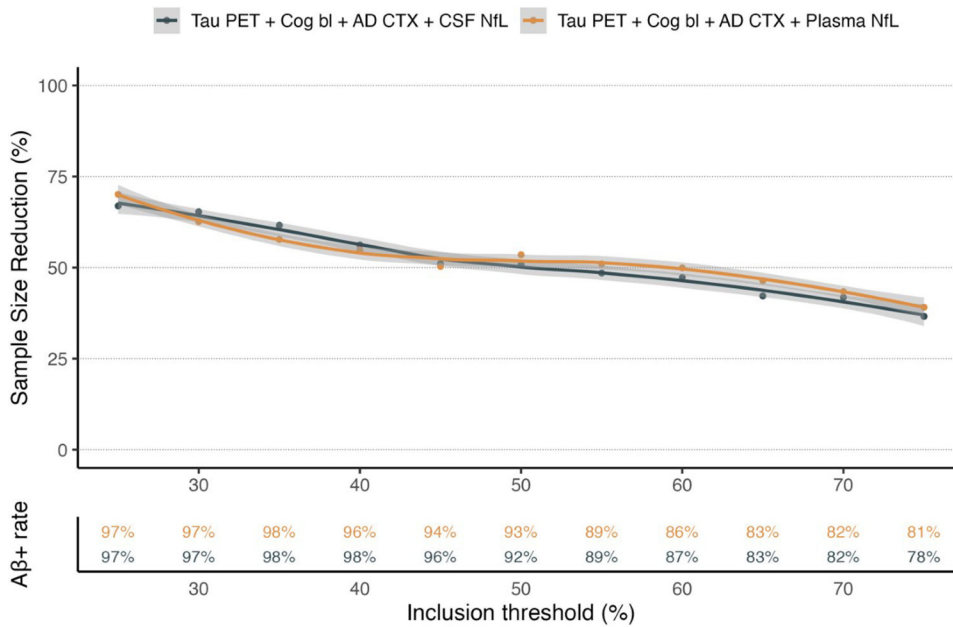


Figure 2. Enrichment for clinical trials using the parsimonious model biomarkers.

The top panel of the graph shows the effect on group size needed to include in a clinical trial to retain statistical power when enriching for pathological values for the tau-PET, Baseline cognition, cortical thickness and NfL biomarkers (cerebrospinal fluid (CSF) NfL in black, plasma NfL in orange). The bottom panel shows the rate of A β positivity with the different inclusion thresholds (CSF in black, plasma in orange).

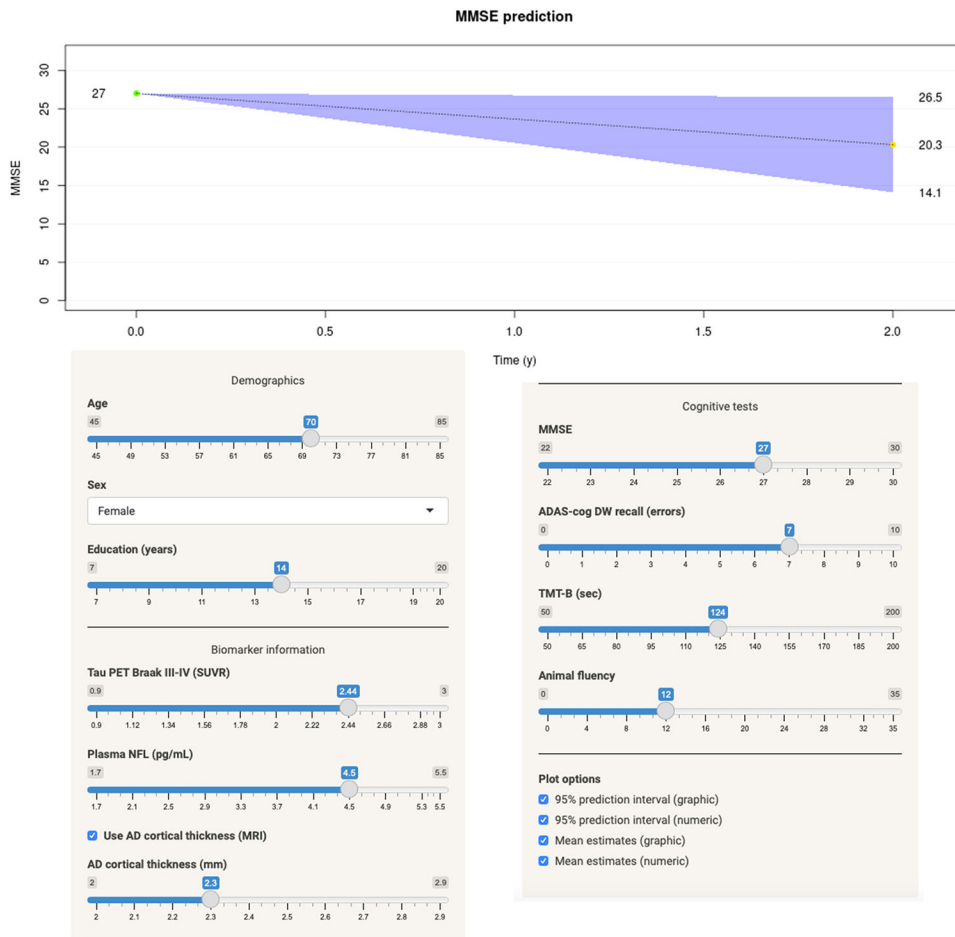


Figure 3. Prediction algorithm for cognitive decline

Example of the implementation of the regression models at <https://brainapps.shinyapps.io/PredictMMSE/>. At this web-site it is possible to enter basic demographic data (age, sex and education), biomarker data (tau-PET temporal ROI SUVR and plasma NfL (pg/ml)) as well as raw cognitive test scores (MMSE, ADAS delayed recall, TMT-B and animal fluency). The example shows the predicted individual change in cognition for a 70-year old female who has 14 years of education, a pathological tau-PET (2.44 SUVR), a plasma NfL of 4.5 pg/ml, and a cortical thickness of 2.3 mm (please note that entering cortical thickness is optional). She has a baseline MMSE score of 27, scores seven errors on a ten-word delayed recall test, completes the Trail-Making Test B in 124 seconds and names twelve animals in 1 min.

Table 1.

Demographic information

	Participants
n	118
Sex (F/M)	57/61
Age (years \pm SD)	71.0 \pm 8.6
Education (years \pm SD)	12.8 \pm 4.4
Baseline MMSE (mean \pm SD)	26.4 \pm 2.4
MMSE slope (mean \pm SD)	-1.40 \pm 1.92
mPACC slope (mean \pm SD) [§]	-1.30 \pm 2.67
Cognitive baseline z-score (mean \pm SD)	-6.3 \pm 3.2
[¹⁸F]RO948 temporal SUVR (mean \pm SD)	1.47 \pm 0.47
Plasma p-tau217 (ng/ml; mean \pm SD)	3.97 \pm 5.02
Plasma NFL (ng/ml; mean \pm SD)	21.2 \pm 24.4
Plasma Aβ42/40 ratio (mean \pm SD)	0.21 \pm 0.04
CSF p-tau217 (ng/ml; mean \pm SD)	278 \pm 286
CSF NFL (ng/ml; mean \pm SD)	234 \pm 182
CSF Aβ42/40 ratio (mean \pm SD)	0.07 \pm 0.03
Aβ positive (%)	77/118 (65)

CSF = cerebrospinal fluid; F = female; M = male; MMSE = minimal state exam; SD = standard deviation; SUVR = standardized uptake value ratio.

[§] modified PACC measurement used for a sensitivity analysis (n=103).

Table 2.

Selection of the most parsimonious model for predicting cognitive decline in patients with amnestic MCI and amnestic mild dementia

Model	Plasma p-tau217	APOE $\epsilon 4$ status	Plasma A β ratio	Plasma NfL	MR AD cortex	Baseline cognition	Tau-PET	R ²	p-value	AIC
Full plasma model	-0.11 (0.91)	0.38 (0.71)	0.54 (0.59)	-1.85 (0.07)	2.43 (0.02)	3.27 (0.001)	-4.89 (<0.0001)	0.44	<0.0001	108
plasma model -1	-	0.37 (0.71)	0.54 (0.59)	-1.87 (0.06)	2.48 (0.01)	3.28 (0.001)	-5.30 (<0.0001)	0.44	<0.0001	106
plasma model -2	-	-	0.41 (0.68)	-1.99 (0.05)	2.47 (0.02)	3.27 (0.001)	-5.34 (<0.0001)	0.44	<0.0001	104
plasma model -3	-	-	-	-2.02 (0.046)	2.48 (0.01)	3.29 (0.001)	-5.49 (<0.0001)	0.44	<0.0001	103
plasma model -4	-	-	-	-	2.36 (0.02)	3.19 (0.002)	-5.59 (<0.0001)	0.42	<0.0001	105
plasma model -5	-	-	-	-	-	3.18 (0.002)	-6.08 (<0.0001)	0.39	<0.0001	109
plasma model -6	-	-	-	-	-	-	-6.26 (<0.0001)	0.33	<0.0001	117
Model	CSF p-tau217	APOE $\epsilon 4$ status	CSF A β ratio	MR AD cortex	CSF NfL	Baseline cognition	Tau-PET	R ²	p-value	AIC
Full CSF model	0.22 (0.82)	-0.67 (0.51)	-1.16 (0.25)	2.56 (0.01)	-2.90 (0.005)	3.13 (0.002)	-4.27 (<0.0001)	0.47	<0.0001	102
CSF model -1	-	-0.69 (0.49)	-1.32 (0.19)	2.59 (0.01)	-2.91 (0.004)	3.13 (0.002)	-5.26 (<0.0001)	0.47	<0.0001	100
CSF model -2	-	-	-1.13 (0.26)	2.66 (0.009)	-2.84 (0.005)	3.17 (0.002)	-5.32 (<0.0001)	0.47	<0.0001	98.8
CSF model -3	-	-	-	2.70 (0.008)	-2.90 (0.005)	3.04 (0.003)	-5.29 (<0.0001)	0.46	<0.0001	98.2
CSF model -4	-	-	-	-	-2.58 (0.01)	3.04 (0.003)	-5.85 (<0.0001)	0.42	<0.0001	104
CSF model -5	-	-	-	-	-	3.18 (0.002)	-6.08 (<0.0001)	0.39	<0.0001	109
CSF model -6	-	-	-	-	-	-	-6.26 (<0.0001)	0.33	<0.0001	117

Results from the stepwise regression model. The variable with the highest p-value was removed from the model and the R² and AIC of the new model assessed. For both plasma and CSF analyses the lowest AIC was achieved with models containing [18F]RO948 (tau-PET), Neurofilament Light (NfL), and baseline cognitive data (data highlighted with light orange). All models included sex, education, age, and baseline MMSE as covariates. Tau-PET = [18F]RO948 Standardized Uptake Ratio values in a temporal ROI; MR AD cortex = Cortical thickness in "AD signature cortex" (see methods for details); A β ratio = A β 42/40 ratio. Biomarker values indicate t-values (p-values).