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# Combination of $^{18}$F-FDG PET and Cerebrospinal Fluid Biomarkers as a Better Predictor of the Progression to Alzheimer's Disease in Mild Cognitive Impairment Patients

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**Abstract**. The biomarker-based new diagnostic criteria have been proposed for Alzheimer's disease (AD) spectrum. However, any biomarker alone has not been known to have satisfactory AD predictability. We explored the best combination model with baseline demography, neuropsychology, $^{18}$F-fluorodeoxyglucose positron emission tomography (FDG-PET), cerebrospinal fluid (CSF) biomarkers, and apolipoprotein E (APOE) genotype evaluation to predict progression to AD in mild cognitive impairment (MCI) patients. A longitudinal clinical follow-up (mean, 44 months; range, 1.6–161.7 months) of MCI patients was done. Among 83 MCI patients, 26 progressed to AD (MCI-AD) and 51 did not deteriorate (MCI-Stable). We applied that univariate and multivariate logistic regression analyses, and multistep model selection for AD predictors including biomarkers. In univariate logistic analysis, we selected age, Rey Auditory Verbal Retention Test, parietal glucose metabolic rate, CSF total tau, and presence or not of at least one APOE $\varepsilon$4 allele as predictors. Through multivariate stepwise logistic analysis and model selection, we found the combination of parietal glucose metabolic rate and total tau representing the best model for AD prediction. In conclusion, our findings highlight that the combination of regional glucose metabolic assessment by PET and CSF biomarkers evaluation can significantly improve AD predictive diagnostic accuracy of each respective method.

Keywords: Biomarkers, combination, mild cognitive impairment, predictor

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## INTRODUCTION

Neuropathological and biomarkers studies of Alzheimer's disease (AD) have demonstrated that cerebral pathological changes commence for up to decades before the onset of symptoms [1–4].

The new biomarker-based diagnostic criteria have been proposed to enhance the clinical detection of AD in early prodromal stages of the disease [5, 6]. The importance of using biomarkers in diagnosis is that these biological tests may enable us to detect AD pathology to determine whether mild cognitive impairment (MCI) symptoms are due to AD pathology and represent early stage, prodromal AD. Such an etiological classification is invaluable for clinical trials of disease modifying drugs under development, to prevent or slow down the clinical manifestation of AD.

Biomarkers recommended by the new diagnostic criteria are amyloid tracer uptake and $^{18}$F-fluorodeoxyglucose (FDG) using positron emission tomography (PET), medial temporal lobe atrophy as assessed by structural magnetic resonance imaging (MRI), and cerebrospinal fluid (CSF) biomarkers including amyloid-β $(A\beta)_{1\text{-}42}$, total tau (tTau), and phosphorylated tau (pTau). However, their standardization efforts are underway and quantitative analytic techniques are in evolution for some time. Moreover, researchers might not have found any biomarker which has satisfactory AD predictability alone. Recently, there have been several longitudinal follow-up studies evaluating AD prediction with combination of different classes of biomarkers as well as clinical information [7–11]. Most of them used a combination of MRI and CSF biomarkers, and one study applied the combination of FDG-PET and CSF [10]. The results suggested that CSF biomarkers do not have significant additive prediction accuracy on imaging biomarkers or cognitive tests. In contrast, a recent two-year follow-up study demonstrated that combination of CSF $A\beta_{42}$/tau and hippocampal volume could be useful to identify prodromal AD [11]. So far, there are no consistent findings for a combined AD prediction model.

In this study, we first examined the clinical outcomes of MCI individuals during a 44 months mean follow-up period. We then tried to compare the abilities of demography, cognitive test, regional glucose metabolism, CSF biomarkers, apolipoprotein E (APOE) genotype, and possible combinations of these methods to predict MCI individuals who would develop AD and to search for the best prediction model.

The main hypothesis of this study was that combination of any two or all five measures would be a better predictor for the progression to AD in MCI individuals than any one of them alone.

## MATERIAL AND METHODS

### *Subjects*

Eighty-three MCI patients were recruited from the Department of Geriatric Medicine, Karolinska University Hospital Huddinge, Stockholm, Sweden. The patients had been referred from the primary care centers in the community for investigation of suspected dementia development. They underwent comprehensive clinical examination, electroencephalogram, CT or MRI, CSF and blood analysis including APOE genotype, and neuropsychological testing. The diagnosis of MCI followed the clinical criteria as defined by Petersen et al. [12]: memory complaint, objective memory impairment (1.5 SD below age matched controls) [13], normal general cognitive function, intact daily living, not fulfilling the DSM-IV criteria for dementia [14]. They were clinically followed up every 6 months (mean, 44 months; standard deviation, 35.4; range, 1.6–161.7 months). The variation in length of follow-up is explained by that there was no fixed type of clinical follow-up but follow-up was based upon clinical need. At follow-up, subjects were diagnosed as having not deteriorated (MCI-Stable) or as having converted to AD (MCI-AD) on the basis of the DSM-IV criteria for dementia and the National Institute of Neurological and Communication Disorders, Alzheimer's Disease and Related Disorders Association (NINCSD-ADRDA) criteria for AD [15]. Follow-up diagnosis of reversal to cognitively normal was based on Mini-Mental Status Exam (MMSE) scores and neuropsychological assessment, and no memory complaint.

All patients and their caregivers provided written informed consent to participate in the study, which was conducted according to the declaration of Helsinki and subsequent revisions. Ethical approval was obtained from the regional human ethics committee of Stockholm and the Faculty of Medicine and Radiation, Protection Committee of Uppsala University Hospital, Sweden.

### *FDG-PET*

All subjects underwent PET examinations with $^{18}$F-FDG (FDG) at Uppsala PET Centre/Imanet. The tracer was produced according to good manufacturing

standards at Uppsala PET center. PET examinations were performed under resting conditions, in dimmed light room, and with the patients' head suitably fixed to prevent movement and fasting before for 4 h. The scanners employed on the earlier occasion (GEMS 2048-15 and GEMS 4096- 15WB, General Electric Medical Systems, WI, USA) had a spatial resolution of 6 mm (full-width at half-maximum) that covered 100 mm, with 6.5 mm slice spacing, producing 15 tomographic slices. Recent PET scans were performed by a Siemens ECAT EXACT HR + scanner (CTI PET systems Inc.) with a field of view of 155 mm, providing 63 contiguous 2.46 mm slices with 5.6 mm transaxial and 5.4 mm axial resolution. Images were reconstructed from the data and corrected for tissue attenuation of 511-keV gamma radiation photons by employing an external $^{68}$GE source [16]. Venous blood was arterialized by heating the hand and subsequently collected from the back of the hand for measurement of plasma levels of radioactive FDG and glucose. Accumulation of FDG in the brain was monitored for 60 min, during which 13 samples were taken to examine variations in FDG concentration. Three more blood samples were collected during scanning period for the determination of plasma glucose concentrations. The cerebral metabolic rate of glucose (CMRglc), expressed in μmol/min/100 g, was calculated by a graphical procedure [17], including a lumped constant of 0.418 to correct for differences in utilization between FDG and glucose.

*Region of interest (ROI) analysis*

For FDG-PET from the GE scanners, a set of 46 regions of interest (ROIs) was defined using a Scanditronix program (IDA, Images Display and Analyses GE 1994). All ROIs were paired for the right and left hemisphere, except for the pons and the whole brain. Cortical ROIs (1×3 cm) were defined in the frontal (two slices), parietal (four slices) and parieto-temporal (one slice) cortices. At the level of the thalamus, ROIs encompassing the caudate nucleus were defined. Two circular ROIs (1.5 cm in diameter) were defined in two slices in the pons and then linked. Regions in frontal association cortices were defined at a level of four slices above the level of the thalamus. On the two slices below, ROIs for the posterior cingulate cortex were drawn. Cortical ROIs (0.7×(1–3) cm) were defined in the temporal cortex in coronal slices of 8 mm, and in two slices in each of the following regions: anterior/posterior inferior, lateral, and uncus. To correct for inter-subject variations in global CMRglc, ROI data were normalized to metabolic rate for consumption of pons.

For the ECAT EXACT HR + scanner, FDG-PET was co-registered and resliced to their individual T1 reference image. All T1 reference images were segmented into gray matter (GM) and white matter tissue classes using the unified segmentation algorithm of SPM8. The resultant probabilistic GM map for each participant had a threshold of 0.5 applied to it, and a binary GM mask was created (0, no tissue, and 1, tissue with a $\geq$ 50% probability belonging to GM). The inverse nonlinear transformation parameter file from SPM's segmentation algorithm was used to warp a simplified digital probabilistic atlas [18], consisting of 24 cortical and subcortical regions, into each individual's native T1 space. These atlases were multiplied by the corresponding binary GM mask, which generated a GM-specific digital atlas for each participant. Raw co-registered and resliced FDG-PET data for each patient were sampled using the same individual digital atlases previously created. A mean FDG-PET uptake was measured for each atlas region using this method. Regional metabolic rate of glucose were created for FDG-PET and each atlas region by dividing by the respective mean pons metabolic rate.

For regional glucose metabolism analysis of this study, we finally used 5 ROIs (frontal, temporal, parietal, posterior cingulate cortex (PCC), caudate) which were mean of each compatible right and left, 10 ROIs selected from each manually drawn 46 ROIs of GE scanner for 76 MCI subjects and 24 ROIs of ECAT EXACT HR + scanner analyzed by Hammers atlas from additional 8 MCI cases. Composite ROI was also calculated by mean of aforementioned 5 ROIs.

*Cerebrospinal fluid measurements*

CSF was obtained by lumbar puncture performed in non-fasting subjects between 8–11 am at the Karolinska University Hospital. CSF samples with more than 500 erythrocytes/μl were excluded. All samples were centrifuged for 10 min at 3000 x g and 4°C immediately after collection. The supernatant was aliquoted after careful mixing to avoid gradient effects, and were stored at –80°C until analysis. Measurement of tTau, pTau, and $A\beta_{1\text{-}42}$ in CSF was performed using a sandwich enzyme-linked immunosorbent assays (ELISA) (INNO-BIA AlzBio3 assay, Innogenetics, Ghent, Belgium) [19–21]. For CSF biomarker data of the subjects, $A\beta_{1\text{-}42}$, tTau, and pTau were available for 33, 36, and 28 patients, respectively.

*Neuropsychological assessments*

An experienced neuropsychologist (O.A.) performed cognitive assessments. These neuropsychological tests assess specific domains such as verbal abilities (Similarities and Information), visuospatial abilities (Block Design and Rey-Osterrieth copy), episodic memory (Rey Auditory Verbal Learning and Retention after 30 min; Rey-Osterrieth Retention after 30 min), and attention and executive function (Trail Making Test A and B). Detailed information regarding the above-mentioned tests has been described previously [22]. All cognitive raw scores were z-transformed by using reference data from healthy adults at the Geriatric Clinic, Karolinska University Hospital Huddinge [23].

*Statistical analysis*

The subjects were categorized into two groups, i.e., those who progressed to AD (MCI-AD) and those who did not progress (MCI-Stable). The MCI-Stable group included those subjects who still remained in the MCI, or improved to cognitively normal at the follow-up. *t*-tests were conducted to examine the differences in the mean age, education, and cognitive test scores at the baseline, and chi-square tests were conducted to compare the male/female ratio and the frequency of APOE ε4 allele between those two groups. Logistic regression analyses were conducted to examine the ability of the demography, cognitive tests, APOE genotype, cerebral regional glucose metabolism, CSF biomarkers, and various combinations of these measures to predict those subjects who would convert to AD and test the main hypothesis of this study. We used the difference of –2 log likelihood (–2LL) to statistically compare the predictive ability of various variables with different numbers of independent variables. –2LL is a quantity generated by the logistic regression procedure and is directly proportional to the contribution of variables to the separation of groups. A smaller –2LL means a better discriminative or predictive ability of the model. The –2LL is convertible to a chi-square value and allows the direct statistical comparison of predictive models of different complexity (likelihood ratio test) [24]

Table 1
Baseline characteristics of the group that progressed to Alzheimer's disease (MCI-AD) and the group that did not progress to AD (MCI-Stable)

| | MCI-Stable ($n=51$) | MCI-AD ($n=26$) |
|---|---|---|
| Age, mean (SD), y | 59.7 (7.5) | 63.5 (8.2)* |
| Education, mean (SD), y | 13.3 (4.0) | 12.9 (4.2) |
| Gender, M (F), No | 26 (25) | 8 (18) |
| APOE | | |
| ε2/ε3, No | 1 | 0 |
| ε2/ε4, No | 1 | 0 |
| ε3/ε3, No | 24 | 7 |
| ε3/ε4, No | 20 | 11 |
| ε4/ε4, No | 2 | 7 |
| APOE ε4 positivity, % | 46 | 72† |
| MMSE, mean (SD) | 28.5 (1.6) | 26.6 (2.6)** |
| CSF data | | |
| $A\beta_{42}$, mean (SD), pg/mL | 639.1 (255.3) | 485.0 (93.5)* |
| tTau, mean (SD), pg/mL | 313.3 (145.0) | 488.5 (154.6)** |
| P-tau, mean (SD), pg/mL | 76.6 (69.3) | 78.9 (26.1) |
| $A\beta_{42}$/P-tau ratio, mean (SD) | 11.8 (6.3) | 6.8 (2.4)* |

Significantly different from MCI-Stable *$p<0.05$, **$p<0.01$ by two-tailed *t*-test; †$p<0.05$ by chi-square test.

## RESULTS

*Follow-up status of MCI*

Of the 83 participants, 26 (31.3%) progressed to AD (MCI-AD), 41 (49.4%) continued to be in the MCI state (MCI-Stable), 6 (7.2%) to other dementia, and 10 (12.0%) improved to cognitively normal (MCI-Stable). Out of the six MCI subjects who progressed to other dementia, one was diagnosed as with frontotemporal dementia, another with Parkinson's disease dementia, and the other four with vascular dementia. Consequently, these six individuals were excluded from the subsequent analyses, because progression to AD was the main focus of this study.

*Baseline characteristics of MCI-Stable and MCI-AD group*

The baseline characteristics of the MCI-Stable and MCI-AD groups are shown in Table 1. The MCI-AD were older than the MCI-Stable ($t_{[75]}=-2.02$, $p=0.047$), but no significant group difference was found in the mean education level of the two groups ($t_{[75]}=0.315$, $p=0.754$). There was no significant group difference in male/female ratio ($\chi^2=2.853$, $p=0.091$). APOE carriers of at least one ε4 allele were significantly more frequent in MCI-AD than in MCI-Stable ($\chi^2=4.544$, $p=0.033$). Regarding CSF evaluations, MCI-AD had significantly lower $A\beta_{1\text{-}42}$ and $A\beta_{1\text{-}42}$/pTau and higher tTau values than MCI-Stable ($t_{[31]}=2.719$, $p=0.011$; $t_{[25]}=3.041$, $p=0.006$; $t_{[34]}=-3.172$, $p=0.003$). There were significant differences between the two groups regarding baseline MMSE scores ($t_{[75]}=4.016$, $p<0.001$), Similarities ($t_{[72]}=3.153$, $p=0.002$), Information

Table 2
Baseline neuropsychological test results (z-score)

| | MCI-Stable | MCI-AD |
|---|---|---|
| Similarities | −0.07 (0.86) | −0.67 (1.13)* |
| Information | −0.25 (0.92) | −1.46 (1.45)** |
| Block Design | −0.38 (1.32) | −0.78 (1.19) |
| Rey complex figure test copy | −0.37 (0.88) | −0.59 (1.94) |
| Rey complex figure test delay | −0.40 (1.07) | −1.57 (1.02)** |
| Rey auditory verbal learning test | −0.39 (0.74) | −1.25 (0.98)** |
| Rey auditory verbal retention test | −0.59 (0.95) | −1.90 (0.95)** |
| Trail making test A time | −0.47 (1.47) | −1.47 (1.68)* |
| Trail making test B time | −0.32 (1.00) | −1.63 (1.98)** |

Significantly different from Stable-MCI, *$p<0.05$, **$p<0.01$ by two-tailed $t$-test.

($t_{[66]}=4.186$, $p<0.001$), Rey Auditory Verbal Learning ($t_{[72]}=4.265$, $p<0.001$), Rey Auditory Verbal Retention ($t_{[68]}=5.327$, $p<0.001$), Rey-Osterrieth Retention ($t_{[71]}=4.538$, $p<0.001$), Trail Making Test (TMT)-A time ($t_{[72]}=2.645$, $p=0.010$), and TMT-B time ($t_{[72]}=3.786$, $p<0.001$). No significant group differences were found in the Block Design ($t_{[71]}=1.266$, $p=0.210$) or in Rey-Osterrieth copy ($t_{[69]}=0.658$, $p=0.513$) (Table 2).

### *Selection of significant prediction models for progression to AD*

#### *Univariate logistic regression analysis*

For univariate logistic regression analysis, we categorized AD progression risk factors as five domains of demography, cognitive tests, CSF biomarkers, cerebral glucose metabolism by FDG-PET, and presence or not of at least one APOE $\varepsilon$4 allele (APOE).

For demographic data of age, gender, and education, only age showed significant prediction for AD. Among cognitive tests, the MMSE as well as Similarities, Information, Rey-Osterrieth Retention, Rey Auditory Verbal Learning/Retention, and TMT-A/B showed significant prediction. For further analysis, we selected the Rey Auditory Verbal Retention Test (RAVRT) with lowest -2LL among significant eight tests as predictor of cognitive test domain in logistic regression analysis for model selection. For FDG-PET ROI biomarkers, the parietal/frontal/temporal/caudate/PCC/composite CMRglc had significantly differentiated MCI-AD from MCI-Stable. We selected the parietal CMRglc which showed lowest -2LL as predictor of cerebral glucose metabolism domain in logistic regression analysis for model selection (Fig. 1). Among the CSF biomarkers, only tTau remained significant (Fig. 1). APOE was also observed as significant variable (Table 3).

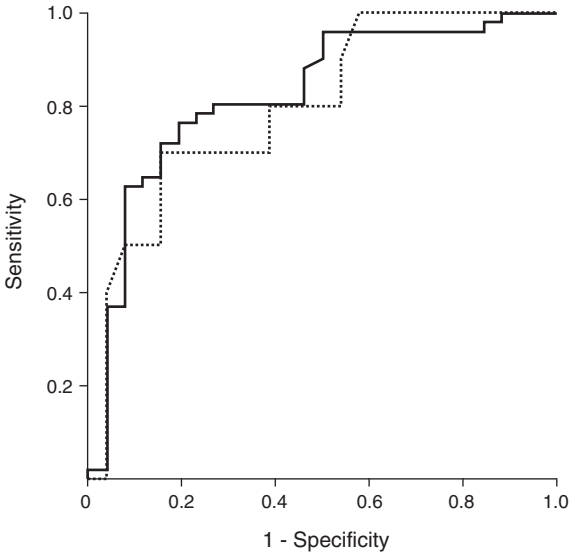


Fig. 1. Receiver operating characteristic curves of finally selected two AD predictors (parietal glucose metabolic rate and total tau) in MCI patients. Solid black line indicates parietal glucose metabolic rate with the area under the curve (AUC) of 0.83. The dotted line indicates total tau with AUC of 0.80.

#### *Selection of final model predicting MCI to AD*

The multivariate stepwise logistic regression analyses and the final model selection were conducted in three steps (Table 4). In the first step, we tested the following 10 combined pair models with each selected variable of five risk domains: [Age + RAVRT]; [Age + Parietal CMRglc]; [Age + tTau]; [Age + APOE]; [tTau + RAVRT]; [RAVRT + APOE]; [Parietal CMRglc + tTau]; [Parietal CMRglc + APOE]; [Parietal CMRglc + RAVRT]; [tTau + APOE]. Of these models, the combination [Parietal CMRglc + RAVRT] was deleted considering for multicollinearity, because we found significant correlation between the two variables ($r=0.44$, $p<0.001$). We selected [Parietal CMRglc + tTau] model as fitness (-2LL = 25.76). Furthermore, we statistically compared the -2LL between selected "two-predictor model" of [Parietal CMRglc + tTau] and each Parietal CMRglc and tTau of selected models in the univariate analysis. The results showed significant differences in both comparisons ([Parietal CMRglc + tTau] versus Parietal CMRglc: $p<0.001$; [Parietal CMRglc + tTau] vs tTau: $p=0.004$).

In the second step, we performed analysis adding age or APOE to selected "two-predictor models". The two "three-predictor models" of [Parietal CMRglc + tTau + Age] and [Parietal CMRglc + tTau + APOE] had same –2LL value of 25.76 with selected

Table 3
Results from univariate logistic regression analyses for 5 categorized domains

| | Model | Chi-square | OR | 95% CI | df | *p* value | -2LL |
|---|---|---|---|---|---|---|---|
| Demographics | | | | | | | |
| Age | **A** | 3.96 | 1.06 | 1.00–1.13 | 1 | 0.046 | 94.50 |
| Gender | | 2.91 | 2.34* | 0.86–6.35 | 1 | 0.09 | 95.57 |
| Education | | −0.05 | 0.99 | 0.87–1.12 | 1 | 0.83 | 95.48 |
| Neuropsychological Tests | | | | | | | |
| MMSE | | 13.6 | 1.56 | 1.20–2.03 | 1 | <0.001 | 84.84 |
| Information | | 15.3 | 2.70 | 1.46–4.98 | 1 | <0.001 | 70.34 |
| Similarities | | 9.13 | 2.16 | 1.26–3.69 | 1 | 0.003 | 85.53 |
| Rey Auditory Verbal Learning | | 16.00 | 3.38 | 1.71–6.69 | 1 | <0.001 | 78.66 |
| Rey Auditory Verbal Retention | **B** | 23.90 | 4.25 | 2.04–8.86 | 1 | <0.001 | 63.25 |
| Rey Complex Figure Copy | | −0.42 | 1.13 | 0.78–1.64 | 1 | 0.515 | 89.43 |
| Rey Complex Figure Retention | | 18.50 | 2.98 | 1.64–5.43 | 1 | <0.001 | 75.33 |
| Block Design | | −1.62 | 1.29 | 0.87–1.91 | 1 | 0.203 | 92.46 |
| TMT-A | | 6.48 | 1.49 | 1.08–2.07 | 1 | <0.001 | 88.18 |
| TMT-B | | 12.85 | 1.97 | 1.27–3.05 | 1 | <0.001 | 81.81 |
| FDG-PET | | | | | | | |
| Parietal | **C** | 19.06 | 1.74 | 1.27–2.40 | 1 | 0.001 | 79.42 |
| PCC | | 14.22 | 1.42 | 1.15–1.76 | 1 | <0.001 | 83.43 |
| Temporal | | 14.47 | 1.89 | 1.28–2.78 | 1 | <0.001 | 84.01 |
| Frontal | | 11.04 | 1.45 | 1.13–1.85 | 1 | <0.001 | 87.44 |
| Caudate | | 4.20 | 1.20 | 1.00–1.44 | 1 | <0.001 | 93.45 |
| Composite | | 15.75 | 1.70 | 1.25–2.31 | 1 | <0.001 | 81.90 |
| CSF | | | | | | | |
| Aβ1-42 | | 3.72 | 1.00 | 1.00–1.01 | 1 | 0.082 | 34.96 |
| tTau | **D** | 8.22 | 1.01 | 1.00–1.01 | 1 | 0.012 | 34.32 |
| pTau | | 0.10 | 1.00 | 0.99–1.02 | 1 | 0.924 | 35.17 |
| Aβ1-42/pTau | | 6.24 | 1.30 | 0.99–1.68 | 1 | 0.051 | 28.13 |
| APOE | **E** | 4.67 | 3.04 | 1.07–8.61 | 2 | 0.028 | 89.16 |

OR = odds ratios; –2LL = –2 log likelihood; PCC = posterior cingulate; APOE = presence or not of at least one apolipoprotein ε4 allele; tTau = total tau; pTau = phosphorylated tau; *Reference: Male; For neuropsychological test, FDG-PET, Aβ1-42 and Aβ1-42/pTau, high scores are references. In FDG-PET, glucose metabolic ratio values were changed to tenfold.

Table 4
Logistic regression analyses to select best model for Alzheimer's disease prediction in MCI

| | Model | Chi-square | df | *p* value | –2LL | Significance Test for –2LL Difference |
|---|---|---|---|---|---|---|
| Age + RAVRT | AB | 27.34 | 2 | <0.001 | 59.77 | |
| Age + Parietal | AC | 22.00 | 2 | <0.001 | 76.48 | |
| Age + tTau | AD | 8.29 | 1 | 0.004 | 34.25 | |
| Age + APOE | AE | 10.04 | 2 | 0.007 | 83.79 | |
| tTau + RAVRT | BD | 13.71 | 2 | 0.001 | 28.83 | |
| RAVRT + APOE | BE | 25.24 | 2 | <0.001 | 57.33 | |
| Parietal + tTau | **CD** | 16.78 | 2 | <0.001 | 25.76 | Model CD versus D: $p = 0.004$<br>Model CD versus C: $p < 0.001$ |
| Parietal + APOE | CE | 22.80 | 2 | <0.001 | 71.03 | |
| tTau + APOE | DE | 8.29 | 1 | 0.004 | 34.25 | |
| Parietal + tTau + APOE | CDE | 16.78 | 2 | <0.001 | 25.76 | |
| Parietal + tTau + Age | ACD | 16.78 | 2 | <0.001 | 25.76 | |

RAVRT = Rey Auditory Verbal Retention Test; Parietal, Parietal glucose metabolic rate; tTau, total tau; APOE, presence or not of at least one apolipoprotein ε4 allele; –2LL, –2 log likelihood.; Considering for multicollinearity combination of Parietal and RAVRT was deleted, because two predictors have significant correlation ($r = 0.454$; $p < 0.001$).

two-predictor model, and theses also only had two significant variables of Parietal CMRglc and tTau in stepwise logistic regression analysis using backward elimination method.

In the third step, considering one/two/three-predictor models, we finally selected the combination of Parietal CMRglc and tTau as best fitted model for predicting MCI to AD (Table 5).

Table 5
Finally selected regression model (Model CD) for Alzheimer's disease prediction in MCI

| Variables | Regression coefficient | Standard error | Odd ratios | 95% Confidence interval | *p*-value |
|---|---|---|---|---|---|
| Intercept | −3.59 | 3.09 | | | |
| Parietal | 0.56 | 0.23 | 1.75 | 1.11–2.76 | 0.017 |
| tTau | −0.01 | 0.00 | 0.99 | 0.98–0.99 | 0.005 |

Parietal, Parietal glucose metabolic rate; tTau, total tau.

### *Cox regression analysis of the prediction of time to conversion from MCI to AD*

When age, RAVRT, Parietal CMRglc, tTau, and APOE were entered in cox regression analysis using backward elimination method, the combination of Parietal CMRglc ($B = -4.245$, SE = 1.681, $p = 0.012$) and tTau ($B = -0.007$, SE = 0.002, $p = 0.001$) significantly predicted time to conversion from MCI to AD (Fig. 2).

## DISCUSSION

In the univariate AD prediction analysis, we selected five predictors: age; Rey Auditory Verbal Retention Test; Parietal glucose metabolism; CSF total tau; and APOE genotype. Using multivariable stepwise logistic analysis and three step model selections of variables combination, we finally found that the combination of the parietal glucose metabolism and CSF total tau best fitted as AD predictor model.

In contrast to our results, several previous studies have not included CSF biomarkers as a final combined predictive model for AD [7, 9, 10]. An Alzheimer's Disease Neuroimaging Initiative (ADNI) study with predictor variables such as volumetric MRI measures, CSF biomarkers, and neuropsychological tests demonstrated that single-predictor models of entorhinal cortex volume or TMT-B may be as good as any more complex models that include CSF biomarkers for predicting conversion to AD [7]. Another ADNI study showed that the combination of delayed logical memory, left middle temporal lobe thickness, and RAVRT was denoted as the "Winners" model [9]. A third study evaluated FDG-PET as well as APOE $\varepsilon 4$ allele frequency, CSF biomarkers, hippocampal volume, and episodic memory performance to find prognostic abilities [10]. The results demonstrated that abnormal baseline values of both FDG-PET and Rey Auditory Verbal Learning Test significantly predicted the MCI subjects who converted to AD [10].

Regarding the inclusion of CSF biomarkers in the final model, there are possible explanations for the discrepancy between prior studies and our results. Our subjects are on average <65 years; younger than other studies which typically included subjects >75 years. Overall a conversion rate of 31.3% to AD in the current study is also relatively low compared to

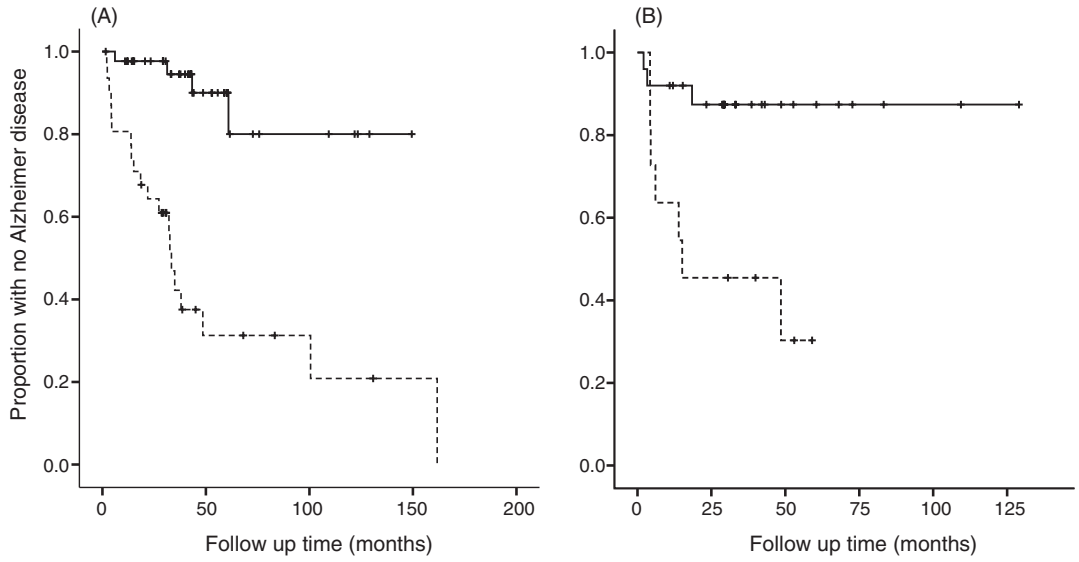


Fig. 2. Survival curves illustrate the finally selected predictors for (A) parietal glucose metabolic rate and (B) total tau. Both curves show that for each variable, a higher proportion of normal values (solid black line) remained Alzheimer's disease free over time compared to abnormal values (dotted line). + indicates censored. Normal and abnormal values were acquired from cut off values of ROC curves.

previous reports of conversion rates at approximately 15% per year reported [10–12], which might be related to younger age. Moreover, there are differences in the follow-up duration between our study and earlier studies performed. We followed up the MCI patients for 44 mean months (maximum 162 months), while in the previous studies the follow-up durations varied between 18 and 40 months. We did not have a fixed follow-up time but followed-up the MCI patients as long as it was clinically of value. The longer follow-up duration of our study could decrease censoring effects of CSF biomarkers. A meta-analysis study of CSF biomarkers and MRI showed that with increased time from diagnosis CSF biomarkers gave more accurate diagnosis than MRI or memory tests [25]. These findings support our final AD predictor model of parietal glucose metabolism and CSF tTau. Recent long term follow-up studies with baseline CSF biomarkers for AD prediction also have consistently reported high prediction accuracy of CSF biomarkers [11, 26–32]. Our study findings of an AD prediction model including CSF biomarker are in line with them and might give additional FDG-PET information for biomarker prediction model. A further reason might be due to high variability of CSF assays. Hort and colleagues [33] reported that even when using the same assay, considerable variability in absolute concentrations of AD biomarkers has been found between different centers. Similarly, most of ADNI studies did not demonstrate CSF biomarkers as final combined predictive model [7, 9, 10, 34].

When using FDG-PET as measure for AD prediction, we found significant AD predictability of hypometabolism for the parietal, temporal, PCC, frontal, caudate ROIs, and composite region on univariate logistic regression analysis. Considering previous studies and –2LL value, we selected parietal glucose metabolism as predictive model candidate of cerebral glucose metabolism domain. In agreement with our results, longitudinal FDG-PET studies in MCI have demonstrated that regional hypometabolism are associated with incipient AD, and MCI individuals are detectable more than one year before the clinical AD diagnosis [35–40]. These studies showed that hypometabolism of the parietal, PCC, or temporoparietal regions are related to MCI progression. Two studies [36, 39] evaluated APOE genotype influence on MCI conversion and showed that when combing FDG-PET and APOE increased sensitivity or specificity was found for classification of MCI-Stable and MCI-AD. However, these data must be considered as limited information due to short follow up duration of less than 2 years, small numbers of subject, and no assessment of CSF biomarkers.

In the present study, we also selected the APOE genotype, the most common susceptibility gene for AD, as one of five predictive domains. Univariate logistic regression analysis showed that APOE $\varepsilon 4$ carrier status has significant AD predictive ability. Although the addition of the APOE genotype to the 4 other variables (age; RAVRT; Parietal CMRglc; tTau) selected from other 4 domains improved predictability, we selected the combination of Parietal CMRglc and tTau as the best predictive model. Addition of APOE genotype to the selected two-predictor combination model did not significantly increase the AD prediction. Both hospital-based cross-sectional [41] and a population-based longitudinal study [42] reported that by adding the APOE genotype to the clinical information, an increase was observed in discrimination or predicting accuracy of AD. These findings are mainly consistent with ours; however, they used only clinical information, while our study applyed biomarkers of FDG-PET and CSF in addition to clinical information. Taken together, our findings suggest that although APOE genotype alone might be an important AD predictor, the combination of FDG-PET and CSF tTau became a stronger model to predict AD.

For cognitive tests as the early indicators for AD in non-demented elderly people, many studies have reported that episodic memory tasks are good predictors for AD progression [43–47]. Consistent with these observations, we also selected RAVRT as a predictor in cognitive test domain. However, this test was not selected as a predictor in the final prediction model but it showed a significant correlation with parietal glucose metabolism. Therefore, RAVRT could be used in a situation where FDG-PET may be unavailable.

We applied Cox regression analysis for the prediction of time to conversion from MCI to AD. The analysis also showed significant contribution of the combination of the parietal CMRglc and tTau to predict time to conversion from MCI to AD. This result also supports our final model of AD prediction. Hypometabolism has been known to reflect synaptic failure and tTau, a non-specific marker of neuronal damage. These two biomarkers are categorized as neuronal injury markers in the newly suggested diagnostic criteria [6]. At this point, our results imply that the combination assessment for neuronal injury biomarkers could increase early detection of preclinical AD. Moreover, they afford the evidence that these preclinical MCI patients should take possible preventive treatment.

Amyloid imaging with PET offers high molecular specificity for the major pathologic marker of AD that has accumulated for many years before clinical AD. Recent PIB follow-up studies have showed that subjects with high *in vivo* amyloid uptake have high MCI conversion rate to AD [48, 49]. There is so far no combination study of amyloid imaging and other biomarkers including FDG-PET and CSF to evaluate AD predictability.

The strengths of the current study include its long duration of follow-up and using three biomarkers including FDG-PET, CSF, and APOE genotype in addition to clinical information. Clinically, our results suggest that with CSF biomarkers, FDG-PET, which is known as having earlier change than MRI in the AD continuum, could be very useful for early detection of AD.

Some possible limitations of this study should be discussed. One concern is that we did not measure all three CSF biomarkers for all subjects. The other concern is that MRI volume measurements such as for the hippocampus or entorhinal cortex in combination with PIB-PET could be used as complementary imaging biomarkers to evaluate structural and amyloid changes in a comprehensive manner. Visual inspections of MRI scans were included in the clinical assessment for diagnosis of MCI. Since the quality of the scans did not allow measurement of cortical volume or thickness, they were not included in the present biomarker evaluation which would have been of interest.

In conclusion, our results highlight that the combination of regional glucose metabolic assessment and CSF biomarkers evaluation could significantly improve the preclinical predictive ability of each method alone. However, APOE genotype did not make any additional contribution to AD prediction in MCI patients.

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