

**How helpful are clinical variables and biomarkers to predict cognitive decline in early  
Parkinson's disease?**

**Analysis of the Parkinson's Progression Markers Initiative cohort study over two years**

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## **Abstract**

### **Objective**

To evaluate the contribution of clinical information and biomarkers to the prediction of cognitive decline in newly diagnosed Parkinson's disease (PD) patients.

### **Method**

Cognitive performance (Montreal Cognitive Assessment (MoCA) score), demographic and clinical data, and biomarkers (ApoE status, cerebrospinal fluid (CSF) and dopamine-transporter (DAT) imaging results were evaluated in 390 newly diagnosed PD patients in the Parkinson's Progression Markers Initiative. Using i) change in MoCA score over two years, ii) MoCA scores at year two follow-up, and iii) a diagnosis of cognitive impairment (combined MCI or dementia) at two years as outcome measures, the predictive values of (i) baseline clinical variables and (ii) separate or combined additions of ApoE status, DAT-imaging and CSF biomarkers were assessed. In addition, a prediction model using logistic regression analysis was run. Bootstrap analysis, 10-fold cross validation and cohort splitting were performed for model validation.

### **Results**

In multivariate analyses, baseline age, University of Pennsylvania Smell Inventory Test (UPSIT) score, CSF A $\beta$ 1-42/t-tau ratio and ApoE status were associated with change in MoCA score over time; and baseline age, MoCA and UPSIT scores, and CSF A $\beta$ 1-42/t-tau ratio with MoCA score at 2 years. Accuracy of prediction of cognitive impairment using age alone (AUC 0.68, 95% CI 0.60-0.76) improved significantly by addition of clinical scores (UPSIT, REM-Sleep Behavior Disorder-Screening Questionnaire (RBDSQ), Geriatric Depression Scale and MDS-UPDRS motor scores; AUC 0.76, 95% CI 0.68-0.83), CSF variables

(AUC 0.74, 95% CI 0.68-0.81), or DAT-imaging results (AUC 0.76, 95% CI 0.68-0.83)). In combination, the five variables showing the most significant associations with cognitive impairment (age, UPSIT, RBDSQ, CSF A $\beta$ 1-42 and caudate uptake on DAT-imaging) allowed prediction of cognitive impairment at 2 years with an AUC 0.80 (95% CI 0.74-0.87,  $p < 0.001$ ).

### **Conclusion**

In early PD, the occurrence of cognitive impairment two years later can be predicted with good accuracy using a combination of age, non-motor assessments, DAT-imaging and CSF examination.

## Introduction

Cumulative incidence of dementia in Parkinson's disease (PD) is as high as 80% after 8 years disease duration<sup>1</sup>, and deterioration in cognition is a significant contributor to the disability associated with PD<sup>2;3</sup>. Mild cognitive impairment (PD-MCI) is a term used to denote cognitive impairment falling short of dementia in PD<sup>4</sup>, with current evidence suggesting that almost all patients with PD-MCI will subsequently convert to dementia in the course of PD<sup>4;5</sup>. Early identification of those at risk of developing cognitive impairment in PD may help stratify the early PD population for clinical trials and prognostic information, and improve understanding the pathophysiology of cognitive decline in PD.

There are several possible mechanisms by which cognitive impairment develops in PD. Pathological studies demonstrate that AD ( $\beta$ -amyloid plaques and tau neurofibrillary tangles) and PD pathology (cortical Lewy bodies) commonly coexist<sup>12</sup>. Dopaminergic deficits *per se* are associated with cognitive impairment, as evidenced by the fact the administration of levodopa early in the disease course can alleviate cognitive symptoms, especially the frontal-executive type<sup>14</sup>, and that neuroimaging studies have shown relationships between caudate and putamen dopamine transporter density and with prefrontal dysfunction in PD patients<sup>15</sup>.

In terms of clinical predictors, age, male sex, education, lower baseline cognitive score, severity of motor symptoms, hyposmia and REM-sleep behavior disorder (RBD) have all been suggested to predict cognitive decline in PD<sup>6-9</sup>. Biomarker studies reported that dopamine depletion on DAT-

imaging is associated with subsequent cognitive decline in PD<sup>10-13</sup>. A number of studies have also examined the association of cognitive impairment in PD with CSF levels of  $\alpha$ -synuclein, A $\beta$ 1-42, total tau (t-tau), phosphorylated tau 181p (p-tau), and A $\beta$ 1-42/t-tau ratio as well as ApoE4 status<sup>13;16;17</sup>. However, the results of previous studies have been conflicting on the contribution of these CSF parameters for the prediction of cognitive impairment in PD<sup>18-22</sup> and to our knowledge no study has previously combined clinical, CSF and DAT imaging parameters or calculated the predictive value of these variables for development of cognitive impairment in PD. In this study we aimed to evaluate the extent to which the various clinical, imaging, biomarker and genetic metrics can predict the development of cognitive impairment, both individually, and in combination. Specifically, we hypothesized that adding CSF and DAT imaging results to clinical assessments would significantly contribute to prediction of cognitive deterioration at 2 years.

## **Methods**

The current study investigated clinical and biomarker predictors of cognitive decline in the early stage of PD from the Parkinson's Progression Marker Initiative (PPMI; <http://www.ppmi-info.org/wp-content/uploads/2013/02/PPMI-Protocol-AM5-Final-27Nov2012v6-2.pdf>). The PPMI is an ongoing, multicenter longitudinal study to assess progression of clinical features, imaging and biomarkers of PD patients compared to healthy controls<sup>23</sup>. Assessments comprise clinical evaluation of motor and non-motor features as well CSF examination and ioflupane iodine-123 DAT SPECT (DATSCAN) imaging at baseline. The de-identified data is made available to investigators. Baseline clinical and cognitive data<sup>24</sup> and the association of

CSF A $\beta$ 1-42 with cognitive impairment at 2 years have previously been reported<sup>13</sup>.

## **Participants**

Only data from PD patients with 2 year follow up were included in this analysis. At baseline participants were required to (1) have an asymmetric resting tremor or asymmetric bradykinesia, or two of bradykinesia, resting tremor, and rigidity; (2) have a recent PD diagnosis; (3) be untreated with medications for PD; and (4) have a dopamine transporter (DAT) deficit on imaging. For comparison, we also analysed results in the HC group (n=178). The study was approved by the Institutional Review Board at each site, and participants provided written informed consent<sup>24</sup>. Data were downloaded on 1st April 2015.

## **Assessments included in this analysis**

Outcomes: Cognitive decline was evaluated using (1) change in Montreal Cognitive Assessment (MoCA), a scale for global cognitive abilities validated for use in PD<sup>25-27</sup>, from baseline to two-year follow-up, (2) MoCA score at the 2-year assessment and (3) categorization as cognitively impaired at 2 years. Cognitive tests that were performed and used to allow classification of cognitive function were, (1) memory: Hopkins Verbal Learning Test—Revised (HVLT-R)<sup>28</sup>; (2) visuospatial function: Benton Judgment of Line Orientation<sup>29</sup> 15-item (split-half) version; (3) processing speed-attention: Symbol-Digit Modalities Test (SDM)<sup>30</sup>; (4) executive function and working memory: Letter-Number Sequencing (LNS)<sup>31</sup>; and (5) semantic (animal) fluency<sup>32</sup>. Individuals were categorized as having “Normal cognition”, “PD-MCI” or “Dementia”, according to the PPMI protocol: PD-MCI was defined as scores on two or more of the HVLT Total Recall,

HVLT Recognition Discrimination, Benton Judgment of Line Orientation, LNS, SFT, or SDM > 1.5 standard deviation below normal, and no functional impairment due to cognition impairment.

A diagnosis of dementia also required evidence of functional impairment.

*Clinical variables* included in the current study, as they have previously been reported to be associated with cognitive decline in PD, included: age, sex, years of education, disease duration, sense of smell assessed using the University of Pennsylvania Smell Identification Test (UPSIT)<sup>33</sup>, RBD measured using the RBD Screening Questionnaire (RBDSQ)<sup>34</sup>, depression measured using the 15-item Geriatric Depression Scale (GDS)<sup>35</sup>, PD severity measured using the MDS-UPDRS motor score, and tremor-dominant, postural instability gait difficulty (PIGD) subtype, and indeterminate motor subtypes<sup>36</sup>. For biomarker studies, we included DAT imaging data for mean caudate and putaminal uptake relative to uptake in the occipital area, and asymmetry of caudate and putaminal uptake (side with highest/side with lowest uptake) (<http://www.ppmi-info.org/study-design/research-documents-and-sops>); Apo-E e4 status (e4 homozygous, heterozygous, or negative ); and CSF results for  $\alpha$ -synuclein (repeated for those with CSF hemoglobin < 200 ng/ml as the high  $\alpha$ -synuclein content in blood may lead to high  $\alpha$ -synuclein levels in traumatic taps), A $\beta$ 1-42, total (t-tau) and phosphorylated tau<sub>181</sub> (p-tau), and total protein (as described previously<sup>16;23</sup>).

### **Statistical Analysis**

Analyses were performed with data collected at baseline/screening (MoCA and DAT imaging) and at 2-year follow up. MoCA change score was calculated as MoCA baseline score – MoCA 2-year score. Variables were analysed for missing data. Comparisons between groups were made

using Chi-Square tests, t-tests for normally distributed variables, and Mann-Whitney tests for non-parametric data. We examined the residuals to ensure they fulfilled all linear regression assumptions. The residuals were not negatively skewed when tested in the final model, checking both graphically and using normality tests, while homoscedasticity and independence also applied. Univariate and multivariate linear analyses with MoCA change scores between baseline and two years assessment and with MoCA score at 2 years as dependent variables were conducted using backwards linear regression analysis. Variables were entered as independent variables if they had a univariate association with a p-value of less than 0.20<sup>37;38</sup>. If variables were highly correlated, the variable with the lower p-value was entered as independent variable. MoCA scores at baseline were not included in multivariate linear regression analysis to predict the change of MoCA score from baseline to 2 years to avoid including them on both sides of regression equation<sup>39</sup>, but they were included in analysis with MoCA scores at 2 years<sup>40</sup>. Univariate logistic regression analysis was used to identify possible risk factors for cognitive impairment (defined as either PD-MCI or dementia) at 2 years. We used the Benjamini-Hochberg procedure<sup>41</sup> controlling for a false discovery rate(FDR) of 0.05, resulting in a significance level of  $p < 0.0167$  for this univariate comparison.

Several multivariate logistic regression models were then developed with cognitive impairment at 2-year follow-up as dependent variable: using age only; then (a) age with clinical variables; (b) age with DAT imaging results; (c) age with CSF biomarkers; and (d) age with clinical, DAT imaging and CSF biomarkers. For these logistic regression models, independent variables were included if they were not highly correlated ( $r > 0.5$ ) and were significantly different between those with and those without cognitive impairment



( $p \leq 0.05$ )<sup>42</sup>. For the model with combined clinical and biomarker variables, only independent variables with a p-value of  $< 0.005$  were included to restrict the number of predictors for ease of use in clinical practice and to avoid overfitting of the model<sup>43;44</sup>. A bootstrap resampling procedure with 1000 repetitions was applied to the final risk model. In order to confirm the accuracy of prediction for internal validation, 10-fold cross-validation and cohort splitting were used. Bootstrapping replicates the process of sample generation from an underlying population by drawing samples with replacement from the original data set, which is of the same size as the original data set, whereas in 10-fold cross-validation the data set is divided into k subsets, and the holdout method is repeated k times. Each time, one of the k subsets is used as the test set and the other k-1 subsets are put together to form a training set<sup>45</sup>. Moreover, we separated the original dataset in development and validation samples, comprising 70% and 30% of the original data set respectively (cohort splitting). Discrimination of the models was quantified via an area under a receiver operating characteristic (ROC) curve;<sup>46</sup> the predictive ability was determined with Nagelkerke's R2 index, and the calibration was tested with the Hosmer-Lemeshow test for goodness of fit<sup>47</sup>. The logistic regression models were repeated and presented with imputation of missing data in the independent variables using variable means. Statistical analysis was carried out STATA 13.

To predict risk of individual patients, a risk model was constructed to calculate predicted risk in the following way:

Patient's risk of cognitive impairment at 2 years =  $\exp(\text{patient's risk score}) \div (1 + \exp(\text{patient's risk score}))$ ;

where patient's risk score = intercept + (bvariable 1×variable1) + (bvariable 2×variable2) + (bvariable 3× variable3) + (bvariable4 ×variable4) + (bvariable5×variable5); and bvariable1, bvariable2, bvariable3, bvariable4, and bvariable5 are the regression coefficients.

Reference Range= $\exp(\text{patient's risk score} \pm 1.96 \times \text{Std.Error}) \div (1 + \exp(\text{patient's risk score} \pm 1.96 \times \text{Std.Error}))$

## **Findings**

393 subjects fulfilling PPMI criteria for newly diagnosis PD had 2-year follow-up. Three did not have a baseline MoCA and were excluded. 318 had 2-year MoCA results available at the time of data download, of whom 314 had undergone classification for cognitive impairment. There was no significant difference in the tested variables between those with and without 2-year cognitive follow-up data, except mean caudate asymmetry which was greater in those without cognitive assessment at 2 years ( $p=0.02$ ).

There were no missing values in age, gender, education years, disease duration, baseline MoCA scores, UPSIT scores, MDS-UPDRS motor scores and motor subtype, two for GDS and 34 for RBDSQ. Apo E status data was missing in 37 patients. No DAT imaging data were missing.

Baseline CSF data were missing in 10 patients for A $\beta$ 1-42 and  $\alpha$ -synuclein, 12 patients for p-tau, 14 patients for t-tau and 31 for total protein. We repeated analyses by imputing missing predictor variable data with average means. These did not alter the overall results of any analysis.

### Predictors of change in cognitive function over 2-year follow up

In multivariate analyses, change in MoCA scores from baseline to 2-year follow-up was associated with age, UPSIT score, Apo E status, and CSF A $\beta$ 1-42/t-tau ratio (table 1). For Healthy Controls, change in MoCA score from baseline to 2-year follow-up was associated with age, gender, and CSF A $\beta$ 1-42 (Table 1 Supplementary material).

### Predictors of cognitive function at 2 years follow up

In multivariate analyses, MoCA score at 2-years was associated with age, baseline MoCA and UPSIT scores and CSF A $\beta$ 1-42/t-tau ratio (Table 1). For Healthy Controls, MoCA score at 2-years was associated with age, gender, baseline MoCA score and CSF A $\beta$ 1-42. (Table 1 Supplementary material).

### Prediction of classification of cognitive Impairment at 2 years follow up

Forty-nine participants with PD were classified as having PD-MCI at 2-year follow up, three as demented and 262 judged as cognitive normal. Only two HC were classified as having MCI and none as demented at two years and were not analysed further. At follow-up 233 of those without and 48 with cognitive impairment had been treated with antiparkinsonian medication ( $p=0.47$ ). Four patients in the group with cognitive impairment had been started on medication for cognitive impairment. At baseline, participants with PD judged as cognitively impaired (MCI or dementia) were older, had higher RBDSQ scores at baseline, lower UPSIT scores, lower CSF A $\beta$ 1-42 and A $\beta$ 1-42/t-tau ratios, and lower mean caudate uptake and caudate and putaminal asymmetry (table 2).

Using those clinical variables showing univariate association ( $p < 0.05$ ) with cognitive impairment at 2 years (age, MDS-UPDRS motor score, GDS, UPSIT and RBDSQ scores) as independent variables in logistic regression analysis, prediction accuracy was greater than for age alone ( $p = 0.025$ ; figure 1a). DAT imaging parameters with univariate association with cognitive impairment (mean caudate uptake, caudate and putaminal asymmetry) also increased the AUC over age alone ( $p = 0.018$ ; figure 1b), as did CSF A $\beta$ 1-42 ( $p = 0.0195$ ; figure 1c). Combining the five variables most strongly associated with cognitive impairment in univariate analysis, (age, UPSIT and RBDSQ scores, CSF A $\beta$ 1-42 and mean caudate uptake) gave an AUC of 0.80 (95% CI 0.74-0.87;  $p = 0.0003$  compared to age alone; figure 1d). All risk models produced good discrimination and calibration, with the final risk model giving an AUC 0.80, Nagelkerke's R<sup>2</sup> of 0.20 and acceptable goodness of fit (Hosmer-Lemeshow Chi-Square 6.27; 8 df;  $p = 0.62$ ) in the final risk model. Whilst each model was significantly better than age alone at predicting cognitive impairment at 2 years, there was no statistically significant difference in AUCs between the models with Clinical variables, CSF and DAT imaging parameters combined with age when they were compared in pairs. However, AUCs of both the models with Clinical and with CSF parameters combined with age were statistically significant different from the final model ( $p = 0.03$  and  $p = 0.02$ ) and there was a trend for the model with DAT imaging parameters ( $p = 0.13$ ; Supplementary Figure 1).

The results of the bootstrapped logistic regression analysis of the final model are given in table 3. Association of mean caudate uptake with cognitive impairment failed to reach significance in this model ( $p = 0.09$ ) but removal of mean caudate uptake from the analysis did not change the scores derived for the other factors.

The results of the 10-fold cross-validation confirmed the final model, showing no statistically significant difference in the performance of the final model between 10 different samples ( $p=0.88$ ); the results of the cohort splitting also showed no statistically significant difference in the AUCs for the same model in the development and validation sample (Supplementary Figures 2 and 3).

Using an example for the final model, a 70 year old patient with newly diagnosed PD who has an UPSIT score of 22 and an RBDSQ score of 5 with a CSF A $\beta$ 1-42 of 399 pg/ml and a mean caudate uptake of 1.99 has a predicted risk of cognitive impairment at 2 years of 13% (7 – 18%). If the patient was 50 years old, the predicted risk with these results would be 5% (1-9%). If the 70 year old patient had a CSF A $\beta$ 1-42 of 310pg/ml, an UPSIT score of 17, an RBDSQ score of 7 and a mean caudate uptake of 1.79, it would be 34% (25-43%).

### **Interpretation**

In this study we have identified clinical and biomarker predictors of cognitive impairment in the first two years following initial diagnosis of PD. Early cognitive decline, a strong predictor of development of dementia in PD, was associated with a number of clinical variables, whether outcome at year 2 was change in MoCA scores, absolute MoCA scores, or classification of cognitive impairment (MCI or dementia) based on investigator assessment and detailed cognitive testing. Beside higher age, the strongest clinical predictors were reduced sense of smell, the presence of REM sleep behavior disorder and, to a lesser degree, depression and motor scores. There was evidence for a relationship between APOE genotype and MoCA change score, similar to what has been reported previously in the general population and in PD<sup>48,49</sup>. A significant association was also seen between MoCA change scores and lower CSF

A $\beta$ 1-42/t-tau ratio. DAT imaging results, i.e. reduced mean caudate uptake and asymmetry and, to a lesser degree, lower putaminal asymmetry, were also predictive of cognitive impairment after two years in multivariate analysis.

The prevalence of cognitive impairment in both the population and in patients with PD is known to increase with advancing age<sup>50;51</sup>, and age was the strongest clinical predictor of cognitive impairment in this analysis in patients and healthy controls. Although a trend was seen towards cognitive impairment being associated with less formal education, which has previously been reported to be a risk factor for cognitive deterioration in the general population and PD<sup>50;52</sup>, this association failed to reach significance in the multivariate analyses; male sex also did not further contribute to prediction of cognitive deterioration in participants with PD, although this previously identified risk factor for cognitive decline<sup>6</sup> was confirmed in our healthy control population.

Patients with more severe motor symptoms and those with greater depression scores were more likely to be classified as cognitively impaired, in line with previous reports of motor severity and depression being predictors of cognitive deterioration in PD<sup>6;51;53</sup>. The previously postulated association of the PIGD subtype with worse cognition<sup>51;54;55</sup> was not seen in this early phase study, which may in part be due to instability of this categorization.

Some of the strongest associations with cognitive decline were seen with baseline UPSIT and RBDSQ scores. Hyposmia has been reported as a risk marker for both PD<sup>56</sup> and AD<sup>57</sup> and has previously been associated with cognitive decline in PD<sup>9;58</sup>. It has been postulated that sense of smell reflects extrastriatal neurodegeneration in both AD and PD, and whilst the underlying pathological basis for this unclear this may reflect early involvement of the olfactory bulb in

both disorders<sup>59-62</sup>. Similarly, RBD, even when assessed using a questionnaire (RBDSQ) rather than a formal sleep study, was a useful predictor of cognitive impairment in this early disease sample. Reduced and asymmetric DAT-tracer uptake particularly in the caudate was associated with cognitive deterioration in line with previous studies which have implicated the caudate, and to a lesser degree the putamen, in cognitive function in both health individuals<sup>63</sup> and patients with PD<sup>64-67</sup>.

CSF A $\beta$ 1-42 results at baseline also contributed to predicting cognitive deterioration. CSF A $\beta$ 1-42 level is a marker of CSF amyloid pathology of AD, inversely correlating to brain  $\beta$ -amyloid plaque load. Reduced CSF A $\beta$ 1-42 is a core feature of Alzheimer's disease but is also seen in other neurodegenerative disease and notably in Dementia with Lewy bodies and Parkinson's disease dementia, likely due to the deposition of both Parkinson's and Alzheimer pathology in the brain.<sup>68</sup> This study is not able to determine to what extent the underlying pathology of this cognitive decline is concomitant Alzheimer's versus Lewy Body pathology, but suggests that amyloid deposition is an important contributor to development of cognitive impairment in early PD. It is noteworthy that CSF t-tau was also associated with MoCA score at two years, reflecting the contribution of neuronal loss in this neurodegenerative process. At least in AD studies levels of CSF tau levels correlate more with measures of neurodegeneration (e.g. atrophy) and cognitive decline than CSF A $\beta$ 1-42 level<sup>69</sup>. Previous studies examining the value of CSF constituents as predictors of cognitive decline in PD have produced inconsistent results. In some studies, lower levels of CSF A $\beta$ 1-42 without a contribution of p-tau or t-tau were reported<sup>18;20;70;71</sup>, whereas higher levels of CSF p-tau but not lower levels of A $\beta$ 1-42 were associated with cognitive decline in early PD in the DATATOP study<sup>21</sup>. Some studies also reported that higher  $\alpha$ -

synuclein predicted cognitive decline<sup>20;71</sup> but the results from the DATATOP suggested this is only seen in early disease<sup>19</sup>, whereas higher p-tau and p-tau/A $\beta$ 42 ratio in the same study were associated with cognitive decline in more advanced disease suggesting different mechanisms involved at these different disease stages<sup>21</sup>. In the present study CSF  $\alpha$ -synuclein and p-tau levels, which have previously been reported to be significantly lower than in controls in this PD population<sup>16</sup>, were not helpful in predicting early cognitive deterioration in this population. These differences between studies may reflect differences in sample sizes<sup>18;20</sup>, disease stages<sup>18;20</sup>, variability in measurements of the different CSF proteins, or in assessments methods between these studies, and highlight the need for improved standardization of CSF protein measurements.

The main purpose of this analysis was to determine the value of clinical markers as well as various widely available biomarkers at the time of diagnosis of PD in predicting the development of cognitive impairment over two years. Clinical markers, particularly age, UPSIT and RBDSQ, provided useful discriminative value over and above age alone. Similarly, addition of CSF A $\beta$ 1-42, or caudate uptake and caudate and putaminal asymmetry on DAT imaging markers increased discriminative value of age for prediction of cognitive impairment, with similar predictive values in all three models. Compared to age alone which has a predictive value AUC of 0.68 (95% CI 0.60-0.76), a model taking into account both clinical variables and biomarkers increased the AUC to 0.80 (95% CI 0.74-0.87). Therefore, combining these clinical and biomarker variables may be most helpful in clinical practice and, importantly, in clinical trials aiming to identify those at risk of cognitive decline. Thus, calculating a 5% risk with a reference range of 1-9%, compared to a 13% (7-18%) or a 34% (25-43%) risk is likely to be



clinically useful.

In the absence of pathological confirmation, the current data cannot determine the pathological underpinning of early cognitive decline in PD, which is likely to be multifactorial. Furthermore, the nigrostriatal dopaminergic deficit demonstrated on DAT imaging does not necessarily reflect dopaminergic deficits in other brain areas. However, this analysis suggests that the nigrostriatal deficit, which underlies the motor symptoms of PD, is not the primary driver of cognitive changes seen at this early post-diagnostic stage.

#### *Limitations of this study*

This assessment only included the first two years post-diagnosis, with median duration since diagnosis of 4 (IQR 2-8) months at baseline. Therefore, few patients had developed frank dementia by clinical cognitive assessment. Whilst MCI is considered a pre-dementia phase, not all patients will develop dementia. Nevertheless, previous studies have reported a very high conversion rate of MCI to dementia in patients with PD with new diagnosis of MCI<sup>5</sup>. Our results should therefore be considered in the context of predicting cognitive impairment rather than dementia. In addition, classification of cognitive impairment was not usually performed at the start of the study. However, even if MCI had been noted at inclusion, this may have reflected this symptom already being present given the long pre-diagnostic phase of PD, as time of diagnosis depends on many variables, including health-seeking behaviour and availability of specialist access<sup>72</sup>. The changes in the main outcomes in the early phase of PD examined are too small to distinguish those with slower or faster progression to clinical dementia, for which longer follow-up will be required. Finally, the prediction formula should be further validated in other samples and interpreted in the appropriate clinic context.

However, strategies to identify which individuals with PD are at risk of developing cognitive impairment may have prognostic implications for patients, and may allow for clinical trials to prevent or slow the onset of cognitive decline with major implications for patients, families and society. It is for instance unclear whether there are benefits of trialing AChEI medications, with proven benefit in PDD, at very early stages. Whilst considerably more work is required to determine the pathological features underlying risk for cognitive impairment at this stage, these results suggest that using clinical markers and currently available biomarkers it is possible to define a population at high risk of cognitive decline who may benefit for interventions as well as being the subject of future trials. Whilst these results need confirmation in further studies, our results demonstrate that a simple algorithm combining age, presence of hyposmia and of RBD, as well as CSF and DAT imaging parameters improves the predictive accuracy for cognitive decline and, in the appropriate clinical context, clinicians and researchers can use the proposed method to calculate risk of cognitive decline over two years for individuals with early with PD.

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All authors declare no conflict of interest.

## **Appendix.**

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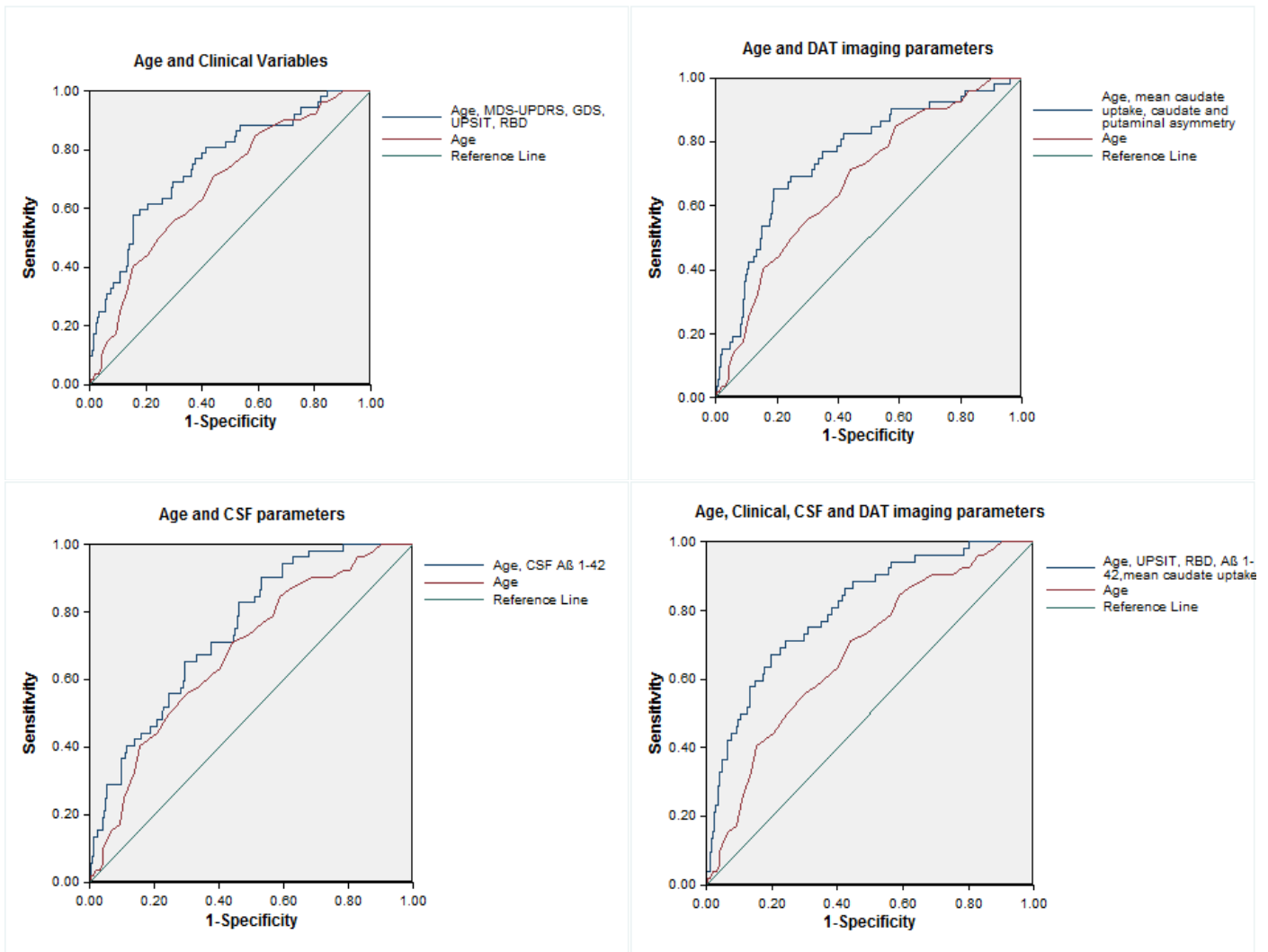


Figure 1. Receiver Operating Characteristic Curves (ROC) for Prediction of Cognitive Impairment at 2 years following diagnosis of Parkinson's disease. Predictive value of a) Age only (AUC 0.68 (95% CI 0.60-0.76)) and Age with clinical variables (MDS-UPDRS motor, GDS, UPSIT and RBDSQ scores; AUC 0.76 (95% CI 0.68-0.83)), b) Age with DAT imaging (mean caudate uptake, and caudate and putaminal asymmetry; AUC 0.76 (95% CI 0.68-0.83)), c) Age with CSF A $\beta$ 1-42 (AUC 0.74 (95% CI 0.68-0.81)), d) Age with clinical and personal variables, DAT imaging results and CSF A $\beta$  1-42 combined (AUC 0.80 (95% CI 0.74-0.87)).

Table 1. Associations of MoCA change scores from baseline to two year follow up and MoCA scores at two years

Clinical markers	MoCA change score				MoCA follow up score			
	Univariate		Multivariate		Univariate		Multivariate	
	Coefficient	p-value	Coefficient	p-value	Coefficient	p-value	Coefficient	p-value
Age (yrs)	0.061	<b>0.0001</b>	0.045	0.01	-0.106	<b>&lt;0.0001</b>	-0.049	<b>0.003</b>
Gender								
	Female*							
	Male	0.167	0.61			-0.764	<b>0.03</b>	
Education (yrs)		-0.059	0.28			0.064	0.30	
Disease duration (mths)		-0.034	<b>0.13</b>			-0.001	0.96	
Motor subgroup								
	TD*							
	PIGD	0.268	0.57			-0.047	0.96	
	Inderminate	0.585				0.172		
MoCA baseline score						0.667	<b>&lt;0.0001</b>	0.572
GDS score		0.070	0.25			-0.063	0.35	<b>&lt;0.0001</b>
MDS-UPDRS motor score		0.038	<b>0.03</b>			-0.068	<b>0.0004</b>	
UPSIT score		-0.064	<b>0.001</b>	-0.035	0.08	0.089	<b>&lt;0.0001</b>	0.045
RBDSQ score		0.075	<b>0.15</b>			-0.078	<b>0.18</b>	0.01
	<b>Biomarkers</b>							
Apo E e4 status								
	No Apo e4 allele*							
	Heterozygous	0.740	<b>0.03</b>	0.658	0.01	-0.532		
	Homozygous	2.240		3.701		-1.047	0.33	
DAT imaging								
	Mean putaminal uptake	-0.798	<b>0.14</b>			1.122	<b>0.06</b>	
	Mean caudate uptake	-0.641	<b>0.02</b>			0.574	<b>0.06</b>	
	Putaminal asymmetry	-0.470	0.21			0.900	<b>0.03</b>	
	Caudate asymmetry	0.804	0.39			0.414	0.69	
CSF markers (pg/ml)								
	Abeta1-42	-0.006	<b>0.0002</b>			0.004	<b>0.02</b>	
	Alphasynuclein	-0.0003	0.21			0.0001	0.57	
	Alphasynuclein in those with haemoglobin<200ng/ml^	-0.0003	0.23			0.0001	0.68	
	total tau	0.019	<b>0.03</b>			-0.035	<b>0.0004</b>	
	Phosphorylated tau	-0.003	0.83			-0.010	0.56	
	abeta/tau ratio	-0.197	<b>0.0002</b>	-0.125	0.03	0.271	<b>&lt;0.0001</b>	0.162
	Total protein	0.015	<b>0.07</b>			-0.018	<b>0.05</b>	0.002

\*Reference Category

In bold are variables included in multivariate linear regression analysis



Table 2: Characteristics of patients with Parkinson's disease with and without Cognitive Impairment at 2 years

Clinical markers	Patients without Cognitive Impairment at 2 years		Patients with Cognitive Impairment at 2 years		p-value*
	Mean (SD) or n (%)	SD	Mean (SD) or n (%)	SD	
<b>Clinical markers</b>					
<b>N</b>	<b>262</b>		<b>52</b>		
Age (yrs)	66.18	9.926	66.12	7.833	<b>&lt;0.0001</b>
Male gender (%)	170 (64.9)		38 (73.1)		0.25***
Education in years	15.65	2.598	14.62	3.748	0.06
Disease duration (mths)	6.66	6.6822	6.869	7.0968	0.84**
MoCA score	27.25	2.32	26.94	2.235	0.38
GDS score**	2	2	2	2	<b>0.03</b>
MDS-UPDRS motor score	20.44	8.404	23.21	10.434	<b>0.04</b>
UPSIIT score	22.92	8.043	17.48	8.347	<b>&lt;0.0001</b>
RBDSQ score	5.24	2.827	6.98	3.529	<b>0.0003</b>
Subgroup					
TD	227(86.6%)		39 (75%)		
PIGD	18 (6.9%)		8 (15.4%)		
Indeterminate	17 (6.5%)		5 (9.6%)		0.11***
<b>Genetic/Biomarkers</b>					
Apo E e4 (%) heterozygous - DAT imaging	53 (22.4%) - 5 (2.1%)		11 (25.0%) - 1 (2.3%)		0.93***
Mean putaminal uptake	0.84	0.28	0.76	0.29	0.07
Mean caudate uptake	2.07	0.54	1.77	0.55	<b>0.0003</b>
Putaminal asymmetry	1.54	0.42	1.40	0.35	<b>0.03</b>
Caudate asymmetry	1.22	0.17	1.15	0.13	<b>0.009</b>
<b>CSF markers (pg/ml)</b>					
<b>N</b>	<b>255</b>		<b>50</b>		
Abeta1-42	381.58	97.89	310.51	80.93	<b>&lt;0.0001</b>
Alphasynuclein	1863.97	799.16	1753.13	688.45	0.36
with haemoglobin<200ng/ml^	1819.86	737.13	1849.52	677.46	0.22
total tau	44.49	16.79	46.03	21.15	0.57
Phosphorylated tau**	12.00	7.40	11.55	10.20	0.49
Abeta1-42/tau ratio	9.44	2.97	7.84	3.06	<b>0.0006</b>
Total protein	42.92	18.91	48.93	23.65	0.06

\*Wilcoxon, \*\*non-parametric statistics (median, IQR, Mann-Whitney test) or \*\*\* Chi Square Tests  
Significance level controlled for False Discovery Rate p<0.0167; TD: Tremor dominant; PIGD, Postural instability.

Table 3. Model for Prediction of Early Cognitive Impairment in Parkinson's Disease

	Regression	OR	95% C.I.for OR		p-value
	Coefficient		Lower	Upper	
RBDSQ	0.123	1.131	1.001	1.277	0.048
CSFalpha1-42	-0.006	0.994	0.990	0.997	0.001
UPSIT	-0.061	0.941	0.896	0.988	0.015
Mean Caudate Uptake	-0.578	0.561	0.283	1.113	0.090
Age	0.051	1.053	1.005	1.103	0.029
Intercept	-1.051	0.350			0.605

Bootstrapped results of multivariate logistic regression with all statistically significant ( $P < 0.0005$ ) clinical and biomarker variables (including imputed missing values)