

# Risk of Parkinson's Disease Dementia Related to Level I MDS PD-MCI

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## ABSTRACT

**Background:** The International Parkinson and Movement Disorders Society criteria for mild cognitive impairment in PD need validation. The objectives of this present study were to evaluate prognostic validity of level I (abbreviated) International Parkinson and Movement Disorders Society mild cognitive impairment in PD criteria for development of PD dementia and compared them with level II (comprehensive) criteria.

**Methods:** We analyzed data from 8 international studies (1045 patients) from our consortium that included baseline data on demographics, motor signs, depression, detailed neuropsychological testing, and longitudinal follow-up for conversion to Parkinson's disease dementia. Survival analysis evaluated their contribution to the hazard of Parkinson's disease dementia.

**Results:** Level I mild cognitive impairment in PD, increasing age, male sex, and severity of PD motor signs independently increased the hazard of Parkinson's disease dementia. Level I and level II mild cognitive impairment in PD classification had similar discriminative ability with respect to the time to Parkinson's disease dementia.

**Conclusions:** Level I mild cognitive impairment in PD classification independently contributes to the hazard of Parkinson's disease dementia. This finding supports the prognostic validity of the abbreviated mild

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Parkinson's disease (PD) is often associated with cognitive decline, which is commonly described in terms of mild cognitive impairment (PD-MCI) and Parkinson's disease dementia (PDD). PD-MCI can occur early in the disease and occurs more frequently with increasing age and disease duration.<sup>1,2</sup> Furthermore, PD-MCI has been identified as a risk for PDD,<sup>3-5</sup> which makes it of particular importance in the early identification and management of PD patients.

International Parkinson and Movement Disorders Society (MDS) clinical criteria have been formulated for both PD-MCI and PDD over the last decade.<sup>6,7</sup> The criteria for PD-MCI are operationalized in 2 ways: level I, abbreviated neuropsychological assessment or a global cognitive screening tool; and level II, comprehensive neuropsychological assessment. The MDS PD-MCI Validation Study Group recently showed that PD-MCI, when assessed using level II criteria, independently increased the hazard of PDD after accounting for the effects of age, sex, years of education, depression, and the severity of PD motor signs (with PD-MCI and age having the largest influence).<sup>4</sup> However, comprehensive neuropsychological testing is not always possible because of time, cost, or patients' inability to cooperate with a long assessment. Therefore, the abbreviated level I PD-MCI criteria might be more suitable in certain clinical and research settings. The criteria state that an abbreviated neuropsychological assessment may consist of a small test battery that does not fulfill level II criteria or a global cognitive screener.

The aims of the current study were (1) to evaluate whether the level I PD-MCI criteria, based on an abbreviated neuropsychological examination using 1 test for each of the 5 cognitive domains, are a prognostic indicator of PDD in a large international study using longitudinal individual patient data, and (2) to compare level I versus level II PD-MCI in a subset of the data in which both these sets of criteria could be applied.

## Methods

This study is based on data from the PD-MCI Validation Study Group.<sup>8</sup> The methods were closely matched to those described in our article on level II PD-MCI<sup>4</sup> to enhance comparability, and are summarized below.

A more detailed description is available in the online supplementary material.

## Data Inclusion

Individual studies were included if they used at least 1 neuropsychological test for each of the 5 PD-MCI criteria cognitive domains at baseline,<sup>7</sup> included  $\geq 75$  patients at baseline, and had any follow-up on PDD status for  $\geq 67\%$  of the baseline population. Based on these criteria, 8 studies were included.<sup>2,9-16</sup> A total of 1045 patients were included in the final analyses. Figure 1 schematically displays the inclusion process, and Supplementary Table 1 provides cohort details.

Demographic and clinical data included age, sex, years of education, PD duration, neuropsychological test scores, either Unified Parkinson's Disease Rating Scale (UPDRS) part III<sup>17</sup> or MDS-UPDRS III score,<sup>18</sup> Hoehn and Yahr score,<sup>19</sup> and an indicator of depression. Conversion guidelines were used to derive a unified measure of UPDRS-III, as described elsewhere,<sup>4,20</sup> which will further be referred to as UPDRS-III\*.

## Application of the PD-MCI Criteria and PDD Assessment

Level I PD-MCI criteria were applied based on 1 test per cognitive domain. Impairment was rated crossing cutoffs of -1 SD, -1.5 SD, and -2 SD from the mean for at least 2 tests (of 5). For example, a patient with the lowest scores of -2.3 and -1.7 SD was classified to meet the -1.5 SD cutoff. The measures used to assess subjective cognitive decline varied over studies and are described in Supplementary Table 1.

Six of the 8 included studies used MDS PDD criteria<sup>6</sup> for the PDD diagnosis; one used both MDS and DSM-IV criteria, and one used a combination of MMSE and functional impairment (detailed description in the supplementary methods section and Supplementary Table 1).

## Statistics

Multiple imputation was used to account for incomplete data. Cox proportional hazards models were used to evaluate the contributions of age, sex, years of education, UPDRS-III\* score, PD-MCI, and depression at first measurement on the hazard of PDD. Time was measured from PD symptom onset until PDD or censoring. The relative influence of both level I and level II criteria on the hazard risk of PDD was assessed in the subset of 4 studies (CARPA, NZBRI, Toronto, and AZSAND cohort) that included data meeting level II criteria. Discriminative ability was of primary interest, for which C-statistics were derived and internally cross-validated by means of bootstrapping. As a secondary analysis, contribution to the model fit of level II criteria over level I criteria was tested by comparison of nested models.

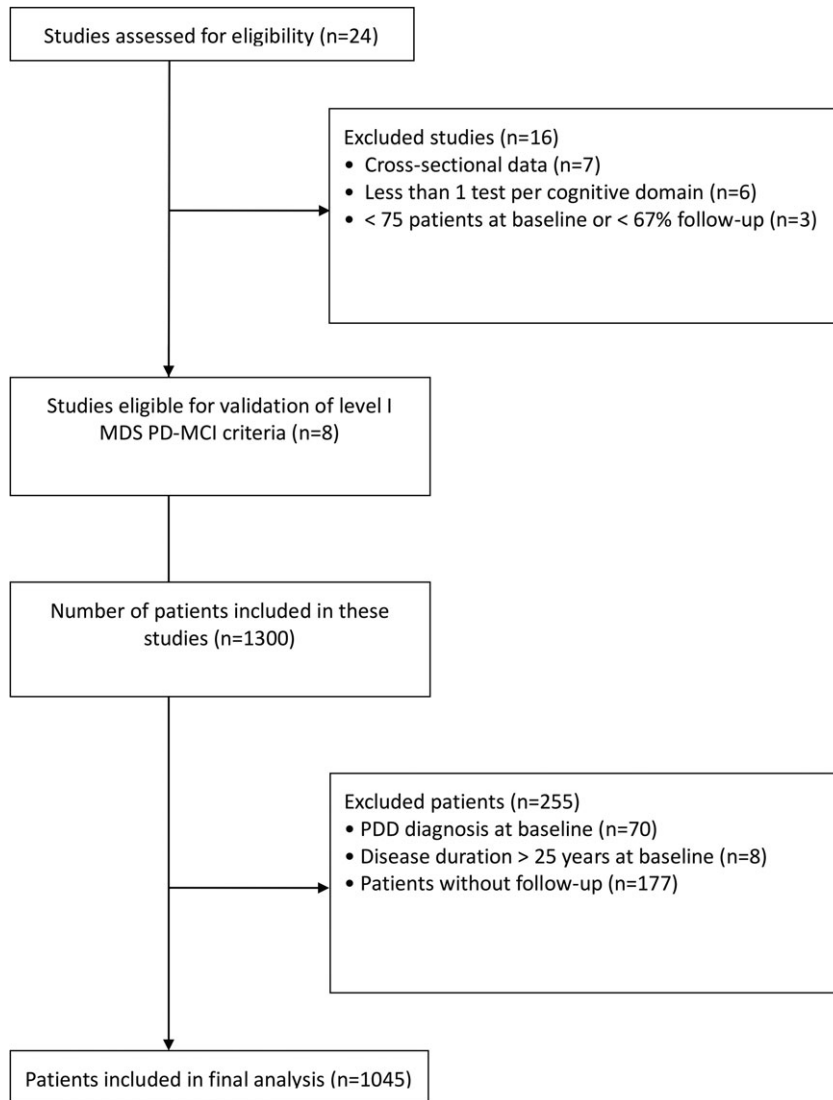


FIG. 1. Flowchart showing the data inclusion process.

TABLE 1. Multivariate Cox proportional hazards models evaluating the hazard of PDD (n = 1045 from 8 studies)

	$\beta$	SE	95% CI	HR ( $e^{\beta}$ )	z Statistic	P
Age (per year)	0.06	0.01	(0.04-0.09)	1.06	5.00	< 0.005
Sex (male)	0.41	0.21	(0.00-0.81)	1.51	1.98	0.047
Years of education	-0.01	0.04	(-0.08 to 0.06)	0.99	0.32	0.746
Level I PD-MCI -1 to -1.5 SD	0.99	0.26	(0.48-1.50)	2.69	3.79	< 0.005
Level I PD-MCI -1.5 to -2 SD	1.86	0.33	(1.20-2.51)	6.41	5.48	< 0.005
Level I PD-MCI below -2SD	2.65	0.30	(2.06-3.24)	14.1	8.82	< 0.005
Depression indicator	0.58	0.39	(-0.21 to 1.37)	1.79	1.45	0.147
UPDRS-III* (non-linear <sup>†</sup> )					20.7 (3) <sup>a</sup>	< 0.005

<sup>a</sup>Chi square statistic (df)

The reference categories were female and no cognitive impairment. For continuous variables, hazard ratios are expressed per unit difference on their scale of measurement (years of age and education). Hazard ratios for a certain variable are interpreted holding the other variables constant. For example, holding the other characteristics constant, the hazard of PDD for someone fulfilling level I PD-MCI according to the -1 but not -1.5 SD cutoff is 2.69 (the HR) times higher than for some without any signs of cognitive impairment. Likewise, for a year increase in age, the hazard is 1.06 times higher. For multiple units, for example, 2 years, the effects multiply, and the hazard is 1.06 × 1.06 times higher. The proportionality assumption was met (P = 0.64). <sup>†</sup>Modeled using restricted cubic splines. HR, hazard ratio; SE, standard error of  $\beta$ ; 95% CI, 95% confidence interval for  $\beta$ .

## Results

### Descriptive Statistics

Descriptive statistics are shown in Supplementary Table 2 ( $n = 1045$ ). Seventeen percent of the patients had PD-MCI at baseline, defined by at least 2 impairments, with 10% crossing only the -1 SD cutoff, 3.8% also the -1.5 SD cutoff, and 3.3% crossing the -2 SD cutoff. Median follow-up was 2.8 years (IQR, 1.9-3.5 years; range, 0.5-9.0 years), and 151 patients developed PDD (14.4%). Only 9% of patients without any cognitive impairment at first measurement developed PDD during follow-up, progressively increasing to 77% of the PD-MCI group with 2 impairments below the -2 SD cutoff on first neuropsychological evaluation. An overview of the available data over time is shown in online Supplementary Figure 1.

### Survival Analyses

The results for the final model are shown in Table 1. A diagnosis of PD-MCI progressively raised the hazard of PDD (ie, while fulfilling more impaired cutoffs on neuropsychological testing). The hazard of PDD was also higher with increasing age, male sex, and increasing UPDRS-III\* score. The contribution of the latter was significantly nonlinear ( $P = 0.001$ ) as shown in Supplementary Figure 2.

As a measure of the prognostic value of the survival model, the median observed and bootstrap corrected C-statistics were 0.79 (the observed and bootstrap-corrected estimates were 0.794 and 0.786, respectively, and the small correction disappeared because of rounding.). That is, in 79% of the pairs of patients in the data for which the time to PDD could be ordered, the patient with the shortest observed time to PDD also had the shortest predicted time to PDD according to the model.

Results for application of the level I and level II criteria in the subset of data in which both could be applied are shown in Supplementary Table 3. Removing PD-MCI from the full model, the observed (bootstrap-corrected) C-statistic was 0.76 (0.70). This clearly improved on adding either level I or level II PD-MCI to the model to 0.86 (0.79) for both. Therefore, level I and level II criteria increased the discriminative ability to the same amount. Using both level I *and* level II PD-MCI as operationalized above did not increase the C-statistic. In agreement with this assessment, removal of level II PD-MCI from this model did not significantly deteriorate the model ( $P = 0.23$ ). To summarize, level II criteria did not show added value to the level I criteria by means of discrimination index or model fit.

## Discussion

In the current study, we found that level I MDS PD-MCI — based on a single neuropsychological test for each of 5 cognitive domains — is related to the hazard

of PDD, with worse performance on neuropsychological assessment increasing this hazard. These findings were corrected for demographic and clinical characteristics such as age, motor signs, and depression. Increasing age, disease severity, and male sex also increased the hazard for PDD.

The pattern of increase in hazard with each successive degree of neuropsychological impairment, as reported here for level I PD-MCI and reported previously for level II PD-MCI criteria,<sup>4</sup> is in line with the view that mild cognitive impairment reflects a stage between normal cognition and PDD.<sup>1</sup> Furthermore, the large sample size allowed for detection of a nonlinear contribution of UPDRS-III\*, with differences in the lower regions of the sum score having a larger impact on the hazard of PDD than differences in the higher regions. In contrast to our earlier findings, the effect of male sex on the hazard of PDD was borderline significant. This difference might be spurious because no correction for multiple testing was performed.

In addition to these confirmatory results, level I and level II criteria were compared with each other and had similar discriminant ability, while level I PD-MCI identified fewer cases as impaired for equal cutoffs and associated these cases with relatively higher hazard ratios. This may relate to level I criteria reflecting greater cognitive decline when measured by the same cutoff as level II criteria, that is,  $\geq 2$  of 5 tests have to be impaired for level I, versus  $\geq 2$  of 10 tests for level II.

Regarding the practical implications of our findings, the hazard ratio is a relative measure and communicates relative increase or decrease in the rate of developing PDD. Therefore, the absolute effect of mild cognitive impairment depends on the underlying rate of conversion to PDD, having a larger effect in those already at increased risk and a smaller effect in those at low risk. The current clinical meaning of mild cognitive impairment is in the objectification of possible complaints and the relative increase in risk of PDD. The added value of level II PD-MCI classification is its higher sensitivity.

A limitation of our study, because of its retrospective nature, is the variability in methods across the included studies. These include different methods for patient recruitment, neuropsychological evaluation, assessment of motor signs, and evaluation of the end point of interest. Although the pooled results still showed a clear contribution of level I PD-MCI, the influence of these varying methods could not be quantified because of the relatively large number of differences compared with the amount of data (i.e., subsets of data with the same methods were too small to accurately estimate the effects of interest). Furthermore, the lack of information on loss to follow-up because of mortality may have induced bias because both PDD and mortality might share a common cause and we could not account for this in the analyses.

Strengths of our study include the use of a large multicenter, international sample, uniform application of the MDS PD-MCI criteria across studies based on all cognitive domains, and side-by-side comparison of level I and level II PD-MCI criteria. Furthermore, although the relationship between PD-MCI, age, and PDD has been reported separately in previous studies,<sup>1,21</sup> the current study made use of the MDS PD-MCI criteria and analyzed the effects jointly.

We assessed PD-MCI using an abbreviated neuropsychological battery, but we do recognize there are other possibilities. Future studies might focus on global cognitive measures, cognitive decline on serial testing, and decline from premorbid levels as ways to assess PD-MCI to arrive at a more standardized operationalization of level I PD-MCI criteria.

In conclusion, level I PD-MCI criteria classification, based on a brief neuropsychological assessment, confers an independent contribution to the hazard of PDD while taking age, sex, education, PD motor sign severity, and depression into account. This finding supports the role of level I PD-MCI as a risk factor for PDD. ■

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## Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's website.