ORIGINAL RESEARCH

Dementia Risk Prediction in a Longitudinal Geriatric Parkinson's Disease Cohort: Evaluation and Application of the Montreal Parkinson Risk of Dementia Scale

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ABSTRACT

Background

Parkinson's disease (PD) increases risk for dementia and cascading adverse outcomes. The eight-item Montreal Parkinson Risk of Dementia Scale (MoPaRDS) is a rapid, in-office dementia screening tool. We examine predictive validity and other characteristics of the MoPaRDS in a geriatric PD cohort by testing a series of alternative versions and modelling risk score change trajectories.

Methods

Participants were 48 initially non-demented PD patients (Mage = 71.6 years, range = 65–84) from a three-year, three-wave prospective Canadian cohort study. A dementia diagnosis at Wave 3 was used to stratify two baseline groups: PD with Incipient Dementia (PDID) and PD with No Dementia (PDND). We aimed to predict dementia three years prior to diagnosis using baseline data for eight indicators that harmonized with the original report, plus education.

Results

Three MoPaRDS items (age, orthostatic hypotension, mild cognitive impairment [MCI]) discriminated the groups both independently and as a composite three-item scale (area under the curve [AUC] = 0.88). The eight-item MoPaRDS reliably discriminated PDID from PDND (AUC = 0.81). Education did not improve predictive validity (AUC = 0.77). Performance of the eight-item MoPaRDS varied across sex (AUCfemales = 0.91; AUCmales = 0.74), whereas the three-item configuration did not (AUCfemales = 0.88; AUCmales = 0.91). Risk scores of both configurations increased over time.

Conclusions

We report new data on the application of the MoPaRDS as a dementia prediction tool for a geriatric PD cohort. Results support the viability of the full MoPaRDS, and indicate that an empirically determined brief version is a promising complement.

Key words: Parkinson's disease, incipient dementia, longitudinal change, risk factors, Montreal Parkinson Risk of Dementia Scale (MoPaRDS)

INTRODUCTION

Parkinson's disease (PD) is associated with a nearly sixfold increased risk of dementia as compared to populations without PD.(1) Parkinson's disease dementia (PDD) is related to additional adverse outcomes including morbidity, institutionalization, and death.(2) Because there are currently no disease modifying therapies available to treat PDD, growing research attention has been directed towards developing assessment tools that may be applied in clinical and geriatric care settings in order to identify at-risk PD patients. Findings from such investigations will advance Canada's national dementia strategy(3) by promoting early and targeted interventions that may offset or delay PDD incidence and progression.

Established PDD risk factors include older age, male sex, prodromal dementia symptoms (hallucinations, gait disturbance), orthostatic hypotension, axial and symmetrical motor impairment, rapid eye movement sleep behaviour disorder, and mild cognitive impairment (MCI).(4) Recent multicentre research assembled baseline data for these clinical predictors

and 4.4-year dementia outcomes. The goal was to operationalize and validate the eight-item Montreal Parkinson Risk of Dementia Scale (MoPaRDS) as a rapid, in-office screening tool for PDD.[5] Study participants included four diverse cohorts (Eastern Canada (two), Japan, and USA-Australia-Europe) of PD patients (N = 607; Mage = 63.4, SD = 10.1) who were initially non-demented. Results showed that (a) each of the eight MoPaRDS items independently predicted PDD at follow-up; (b) baseline full-scale risk scores had high predictive validity; (c) the MoPaRDS performed slightly better for males as compared to females; and (d) the optimal cut-off point was an overall risk score ≥4. The authors highlighted the need for follow-up validation research to examine whether (a) incorporating education into the MoPaRDS increases predictive validity; and (b) overall risk scores increase over time, which would allow clinicians to monitor changes in PDD risk.

We evaluated these research directions with harmonized longitudinal data from a three-wave (three-year) study of a well-characterized[6–13] Western Canadian cohort of geriatric (aged 65+) PD patients. Five research goals (RG) were stipulated. For RG1, we examined whether two subgroups of an initially non-demented cohort of persons with PD (i.e., those who later converted to PDD and those who remained dementia free) were independently discriminated by baseline values for (a) each of the eight constituent MoPaRDS items, and (b) education. Because not all clinics or research cohorts will have access to all eight of the MoPaRDS items, for RG2 we examined predictive validity of overall risk scores on three alternative configurations: (a) the full (eight-item) MoPaRDS; (b) the full MoPaRDS plus education; and (c) an empirically derived abbreviated configuration. For RG3, we explored whether prediction patterns of overall risk scores varied across sex. For RG4, we determined the optimal cut-off points for a positive screen result. For RG5, we examined change trajectories of overall risk scores across the three waves.

METHODS

Study Design and Participants

Geriatric PD patients were recruited between 2003 and 2009 from the University of Alberta Movement Disorder clinic, the Parkinson's Society of Alberta, and neurologist referrals. Prior to study enrollment, an experienced neurologist confirmed PD diagnoses and non-demented status. Individuals with a clinical history of atypical PD, stroke, unstable health conditions, or baseline dementia were excluded. Eligible participants underwent a three-wave longitudinal protocol with 18-month interwave intervals (for a complete reporting of exclusionary criteria and the study protocol see[6,8,10,13]). The University of Alberta Research Ethics Board approved the study protocol. Participants provided written informed consent.

We assembled data for 48 PD patients (Mage = 71.6 years; SD = 4.8; 56% male) who were (a) missing no baseline data across the individual MoPaRDS items or education; (b) non-demented at baseline; and (c) evaluated for dementia at the third and final wave of participation. As detailed elsewhere,[6,8,10] dementia diagnoses were determined by an experienced clinician using the prevailing diagnostic criteria. Briefly, participants were diagnosed with PDD if they presented with (a) impairment in two cognitive domains and (b) functional impairment. Diagnoses were based on: (a) clinical assessment; (b) independent PD patient and informant interviews; (c) Clinical Dementia Rating Scale;[14] (d) Standardized Mini-Mental Status Examination;[15] (e) Dementia Rating Scale;[16] and (f) Short Blessed Information-Memory-Concentration Test.[17] Fourteen participants (29.2%) had developed dementia at Wave 3 and were retroactively classified at baseline as PD with Incipient Dementia (PDID). The remaining participants (n = 34; 70.8%) did not develop dementia and were retroactively classified as PD with No Dementia (PDND).

Measures Representing the Eight-Item MoPaRDS

An important application feature of the MoPaRDS is that the eight constituent items are typically accessible in exact or similar form in many geriatric clinics and research databases. The overall MoPaRDS performance is expected to be robust to minor variations in item details. Accordingly, we assembled data for eight variables that (a) corresponded to a single parallel item in the original MoPaRDS;[5] and (b) were accessible at each of the three waves. Briefly, the measures matching corresponding MoPaRDS items included: (a) age > 70 years; (b) male sex; (c) falls and/or freezing of gait; (d) bilateral disease; (e) history suggestive of rapid eye movement sleep behaviour disorder; (f) orthostatic hypotension; (g) MCI; and (h) visual hallucinations. As in the original report,[5] each item was scored dichotomously (0 = absent, 1 = present) and overall risk scores were calculated by summing responses (0 = no deficits, 8 = all deficits endorsed). In Table 1, we (a) present detailed scoring criteria; (b) denote items with operational definitions that varied slightly from the original report (bilateral disease, rapid eye movement sleep behaviour disorder, hallucinations, and MCI); and (c) display baseline item frequencies.

Education

We assembled three waves of data for education (years of formal schooling). Because the definition of high versus low education has yet to be standardized in the PD literature[18] and the original report did not include education (but adopted a dichotomous scoring approach), we dichotomized education using a median split (median = 14.0 years). Participants falling below this cut-point were assigned a value of 1 to indicate risk (see Table 2 for descriptives).

Analytical Approach

Baseline values on the MoPaRDS were evaluated for prediction accuracy in discriminating PDID from PDND using binary logistic regression and receiver operating characteristic (ROC) curves. Separate analyses were performed for (a) each of the constituent MoPaRDS items (RG1); (b) overall risk scores on the three configurations (RG2); and (c) males and females

TABLE 1.
MoPaRDS scoring criteria[a] and baseline item frequencies

MoPaRDS item, n (%)	*Total Sample*	*PDND*	*PDID*	*Scoring Criteria*
MCI	14 (29.2%)	3 (8.8%)	11 (78.6%)	Defined according to MDS Task Force level II PD-MCI guidelines.[28] For further details see[6,29]
Bilateral disease	16 (33.3%)	9 (26.5%)	7 (50.0%)	Asymmetry index score < 1.5 [ratio of the UPDRS[37] laterality scores (sum of questions 3.3–3.8) for the side of the body with the higher score vs. the side with the lower score] or an absolute difference < 3 [when the lower score is 0][5]
RBD	28 (58.3%)	22 (64.7%)	6 (42.9%)	NPI-Q[38] question 11 scoring = yes and/or UPDRS 1.2 scoring = 1
Hallucinations	3 (6.3%)	2 (5.9%)	1 (7.1%)	NPI-Q question 2 scoring = yes
Falls and/or freezing of gait	12 (25.0%)	6 (17.6%)	6 (42.9%)	UPDRS 2.14 scoring > 0 and/or UPDRS 2.15 scoring > 0
Orthostatic BP drop > 10mmHg	22 (45.8%)	11 (32.4%)	11 (78.6%)	Systolic blood pressure drop > 10 mmHg upon standing compared to supine after 2 minutes[5] or an inability to complete the task due to dizziness upon standing or use of a mobility aid
Male sex	27 (56.3%)	21 (61.8%)	6 (42.9%)	Self-reported as male or female
Age > 70	24 (50.0%)	13 (38.2%)	11 (78.6%)	Calculated based on self-reported birth date
MoPaRDS total, M (SD)	3.0 (1.5)	2.6 (1.4)	4.2 (1.2)	Calculated by summing responses across the eight constituent MoPaRDS items

[a]We note the following minor variations in our items relative to the original report:[5] (a) due to unavailability, we evaluated bilateral disease onset using data from the UPDRS[37] as opposed to the MDS UPDRS;[33] (b) RBD and hallucinations were measured using the NPI-Q[38] as opposed to clinical expert interview, RBD screening questionnaire, or a polysomnogram; and (c) MCI was consistently evaluated using MDS Task Force PD-MCI guidelines.[6,28] In the original report, MCI was evaluated using either the latter criteria, the Montreal Cognitive Assessment,[39] or was missing (n = 82) and imputed as 0.5.
MoPaRDS = Montreal Parkinson Risk of Dementia Scale; PDND = Parkinson's Disease with No Dementia; PDID = Parkinson's Disease with Incipient Dementia; MCI = mild cognitive impairment; MDS = Movement Disorder Society; NPI-Q = Neuropsychiatric Inventory Questionnaire; UPDRS = Unified Parkinson's Disease Rating Scale; RBD = rapid eye movement sleep behaviour disorder; BP = blood pressure. Each item was scored dichotomously (0 = absent, 1 = present).

TABLE 2.
Baseline demographic and clinical characteristics

Characteristic, M (SD)	*Total Sample (n = 48)*	*PDND (n = 34)*	*PDID (n = 14)*	*p value*
Age (years)	71.6 (4.8)	70.0 (3.5)	75.4 (5.3)	[b]
Male sex n (%)	27 (56.3)	21 (61.8)	6 (42.9)	ns
Age at PD diagnosis	62.68 (5.3)	61.35 (4.9)	65.93 (4.9)	[c]
PD duration (years)	8.9 (4.5)	8.6 (4.4)	9.5 (5.1)	ns
UPDRS part III	16.6 (8.1)	14.4 (7.0)	21.7 (8.5)	[c]
UPDRS total	26.6 (12.9)	22.62 (9.9)	36.29 (14.5)	[b]
MMSE	28.1 (1.7)	28.62 (1.5)	26.79 (1.6)	[b]
Modified Hoehn and Yahr	2.2 (0.7)	2.0 (0.5)	2.6 (0.7)	[c]
Education (years)	14.1 (3.0)	14.3 (3.2)	13.6 (2.3)	ns
Education n (%) below median[a]	20 (41.7)	15 (44.1)	5 (35.7)	ns

[a] Median = 14.0 years.
[b]p value < .001.
[c]p value ≤ .01.
M = mean; SD = standard deviation; PDND = Parkinson's Disease with No Dementia; PDID = Parkinson's Disease with Incipient Dementia; PD = Parkinson's disease; UPDRS = Unified Parkinson's Disease Rating Scale; MMSE = Mini-Mental Status Exam; ns = non-statistically significant. Comparisons were made using independent samples t-test or chi-square test, as appropriate.

(RG3). That is, each of the RGs examined the independent (or direct) effect of one predictor on one binary outcome (PDID, PDND). For RG3, the sex item was excluded from the calculation of overall risk scores on the full MoPaRDS. We ascertained whether prediction patterns varied across sex using prevailing statistical conventions regarding the interpretation and comparison of independent area under the ROC curves (AUC).[19] Briefly, AUC is the most widely used metric for evaluating the overall discriminatory ability of a classifier model.[20] Values are interpreted such that 0.5 represent chance, 0.5–0.69 represents poor discrimination, 0.7–0.79 represents acceptable discrimination, 0.8–0.89 represents excellent discrimination, and ≥ 0.9 represents outstanding discrimination. We determined the optimal cut-off points for a screen positive result on the MoPaRDS using ROC curves with coordinate points (RG4). We modeled the nature (i.e., extent of between-person differences in within-person changes) and rate (i.e., average number of risk characteristics accumulated per wave) of change in overall risk scores using growth curve analyses (RG5; see[21,22] and Appendix A for further details). Analyses were performed using SPSS 26 (IBM SPSS Statistics, Armonk, NY) or Mplus 8.0 (Mplus, Los Angeles, CA).

RESULTS

Demographic and Clinical Characteristics

Detailed demographic and clinical characteristics of the initially non-demented study sample disaggregated by the two derived baseline groups (PDND, non-demented at Wave 3; PDID, demented at Wave 3) are presented in Table 2.

RG1: Predictive Validity of Individual MoPaRDS Items and Education

We used baseline data to test whether each of the constituent MoPaRDS item independently discriminated PDID from PDND. Detailed results are presented in Appendix B. Findings showed that the two groups were discriminated by three of the eight MoPaRDS items: age (odds ratio [OR] = 5.92; 95% confidence interval [CI] = 1.38–25.30; $p = .02$); MCI (OR = 37.89; 95% CI = 6.64–216.27; $p < .001$); and orthostatic hypotension (OR = 7.67; 95% CI = 1.77–33.18; $p = .01$). There was a trend for falls and/or freezing (OR = 3.50; 95% CI = 0.88–13.88; $p = .08$). Education did not independently discriminate PDID from PDND (OR = 0.70; 95% CI = 0.20–2.55; $p = .59$). We conducted a series of follow-up analyses in which we verified that education did not independently discriminate the groups when (a) tested as a continuous variable (OR = 0.92; 95% CI = 0.73–1.15; $p = .46$); (b) dichotomized using a cut-point of 12 years of formal education (n below this threshold = 7; OR = 0.97; 95% CI = 0.16–5.69; $p = .97$); and (c) dichotomized using a cut-point of >1SD below the mean (11 years of formal education; n below this threshold = 5; OR = 1.72; 95% CI = 0.26–11.62; $p = .58$).

RG2: Predictive Validity of Overall Risk Scores

Detailed results are presented in Table 3. Overall, our findings showed that full scale risk scores on the eight-item MoPaRDS discriminated the PDID and PDND groups at baseline (OR = 2.45; 95% CI = 1.37–4.38; $p = .002$). The ROC curve is depicted in Figure 1 (AUC = 0.81; 95% CI = 0.68–0.93; $p = .001$). Education did not improve predictive validity (median split OR = 1.94; 95% CI = 1.20–3.13; $p = .007$; AUC = 0.77; 95% CI = 0.63–0.91; $p = .004$) and was therefore not consid-ered in subsequent analyses.

We tested whether the combination of the three MoPaRDS items that were independent predictors would similarly discriminate PDID from PDND. The three items were age, MCI, and orthostatic hypotension. Findings showed that overall risk scores on this brief configuration discriminated the two groups (OR = 5.72; 95% CI = 2.18–15.03; $p < .001$). See Figure 1 for the ROC curve (AUC = 0.88; 95% CI = 0.75–1.0; $p < .001$). Because there was a trend for falls and/or freezing, we also examined predictive validity of a four-item configuration. The AUC of this scale (0.88; 95% CI = 0.78–0.98; $p < .001$) was equivalent to that of the three-item configuration and was therefore not considered further.

RG3: Sex Stratification Analyses

Results for the eight-item MoPaRDS showed that AUC for females and males were quite different and resided in differ-ent interpretive categories. For females, AUC was 0.91 ($p = .002$), indicating outstanding discrimination. For males, AUC was 0.74 ($p = .08$), indicating acceptable—but not excellent or outstanding—discrimination. These results, together with the overall pattern of findings reported in Table 3, suggest that the eight-item MoPaRDS performed better for females. Nota-bly, the three-item MoPaRDS performed well and similarly for females and males (see Table 3 for detailed results). For females and males, the AUC was 0.88 and 0.91, respectively.

RG4: Optimal Cut-Off Points for Screen Positive

The optimal cut-off on the eight-item MoPaRDS, as indicated by the extreme upper-left point of the ROC curve (see Figure 1), was a total score ≥ 4. A screen positive distinguished PDID and PDND groups (positive predictive value [PPV] = 50%; negative predictive value [NPV] = 85.7%) with an acceptable level of accuracy (AUC = 0.71; 95% CI = 0.55–0.88; $p = .02$).

The optimal cut-off on the three-item MoPaRDS was a total score ≥ 2 (see Figure 1). A screen positive (PPV = 63.2%; NPV = 93.1%) discriminated PDID from PDND with a good level of accuracy (AUC = 0.83; 95% CI = 0.69–0.96; $p < .001$). Complete results for both configurations are reported in Table 3.

RG5: Risk Score Change Trajectories

Growth curve analyses[21,22] indicated that a random intercept, fixed slope model provided the best fit to longitudinal data for both the eight- and three-item configuration of the MoPaRDS (for model comparisons and fit indices see Appendix C). These results permit three conclusions: (a) baseline overall risk scores statistically differed across participants (8-item: $\hat{\sigma}^2 = 1.65$, $p < .001$; 3-item: $\hat{\sigma}^2 = 0.70$, $p < .001$); (b) overall risk scores increased over time (i.e., statistically differed from 0; 8-item: M increase per wave = 0.30, p = .002; 3-item:

TABLE 3.
Research Goals 2–4: Binary logistic regression models for overall risk scores on baseline configurations of the MoPaRDS discriminating PDID from PDND[a]

MoPaRDS Configuration	R^2	*OR*	*PAC*	*Sens*	*Spec*	*PPV*	*NPV*	*LR*	*LR-*	*AUC*
8-item	0.30	2.45[g]	75.0%	42.9%	88.2%	60.0%	78.9%	3.6	0.7	0.81[f]
8-item + education	0.26	1.94[f]	70.8%	21.4%	91.2%	50.0%	73.8%	2.4	0.9	0.77[f]
3-item	0.53	5.72[e]	85.4%	57.1%	97.1%	88.9%	84.6%	19.7	0.4	0.88[e]
4-item	0.52	4.22[e]	81.3%	64.3%	88.2%	69.2%	85.7%	5.4	0.4	0.88[e]
8-item stratified by sex[b]										
Females	0.61	3.81[g]	81.0%	75.0%	84.6%	75.0%	84.6%	4.9	0.3	0.91[f]
Males	0.19	2.04[h]	81.5%	16.7%	100%	100%	80.8%	--	0.8	0.74[h]
3-item stratified by sex										
Females	0.60	5.52[g]	85.7%	75.0%	92.3%	85.7%	85.7	9.7	0.3	0.88[f]
Males	0.57	11.64[f]	85.2%	50.0%	95.2%	75.0%	87.0%	10.4	0.5	0.91[f]
8-item total ≥ 4[c]	0.20	6.00[g]	70.8%	71.4%	70.6%	50.0%	85.7%	2.4	0.4	0.71[g]
3-item total ≥ 2[d]	0.45	23.14[e]	81.3%	85.7%	79.4%	63.2%	93.1%	4.2	0.2	0.83[e]

[a]We verified in follow-up analyses that the MoPaRDS continued to discriminate the two baseline groups when the MCI item was removed from (a) the full configuration (OR = 1.87, $p = 0.27$; AUC = 0.71, $p = 0.21$) and (b) the abbreviated configuration (OR = 4.78, $p = .003$; AUC = 0.79, $p = .002$).
[b]Sex was removed from the MoPaRDS for these analyses (i.e., maximum score = 7).
[c]Participants were stratified into two groups according to whether their overall risk score on the eight-item MoPaRDS fell at or below this cut-off at baseline.
[d]Participants were stratified into two groups according to whether their overall risk score on the three-item MoPaRDS fell at or below this cut-off at baseline.
[e] p value < .001.
[f] p value < .01.
[g] p value < .05.
[h] p value < .10.
MoPaRDS = Montreal Parkinson Risk of Dementia Scale; PDND = Parkinson's Disease with No Dementia; PDID = Parkinson's Disease with Incipient Dementia; R^2 = Nagelkerke R^2; OR = odds ratio; PAC = percentage accuracy in classification; Sens = sensitivity; Spec = specificity; PPV = positive predictive value; NPV = negative predictive value; LR^+ = positive likelihood ratio; LR- = negative likelihood ratio; AUC = area under the receiver operating characteristic curve.

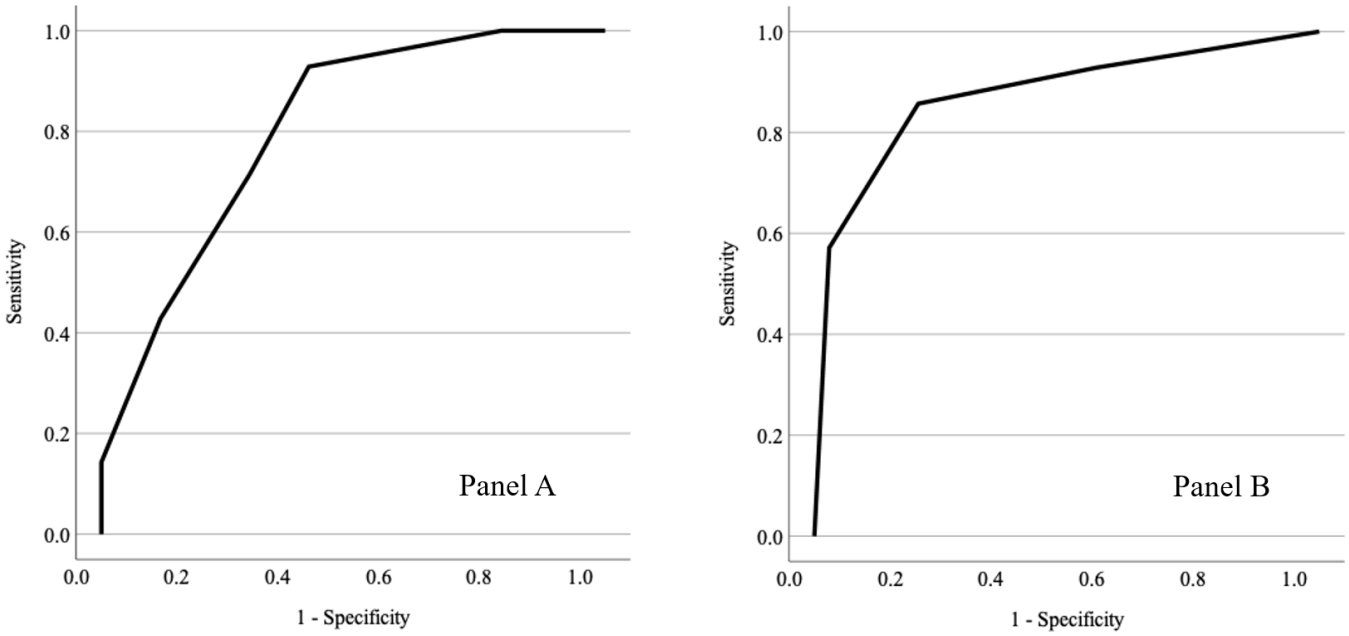

FIGURE 1. Receiver operating characteristic curve (ROC) for baseline scores on the eight-item (Panel A) and three-item (Panel B) Montreal Parkinson Risk of Dementia Scale (MoPaRDS) discriminating Parkinson's Disease with Incipient Dementia (PDID) from Parkinson's Disease with No Dementia (PDND). For the eight-item MoPaRDS, area under the ROC curve (AUC) is 0.81 (95% confidence interval [CI] = 0.68–0.93; $p = .001$). For the three-item MoPaRDS, AUC is 0.88 (95% CI = 0.68–0.93; $p = .001$).

M increase per wave = 0.23, p < .001); and (c) the rate at which scores increased did not vary across participants (i.e., participants tended to accumulate deficits at the same rate). Collectively, these results indicate that overall risk scores on both configurations of the MoPaRDS generally increased across the study duration, although the rate of increase was slightly slower for the three-item version. Change trajectories are presented in Figure 2.

DISCUSSION

The MoPaRDS[5] was developed as an inexpensive and non-invasive dementia screening tool for identifying at-risk PD patients in routine care settings. The eight constituent items represent demographic, motor, and non-motor features that are regularly evaluated in office-based care settings. Because fluid biomarkers, neuroimaging, and genetic features are not

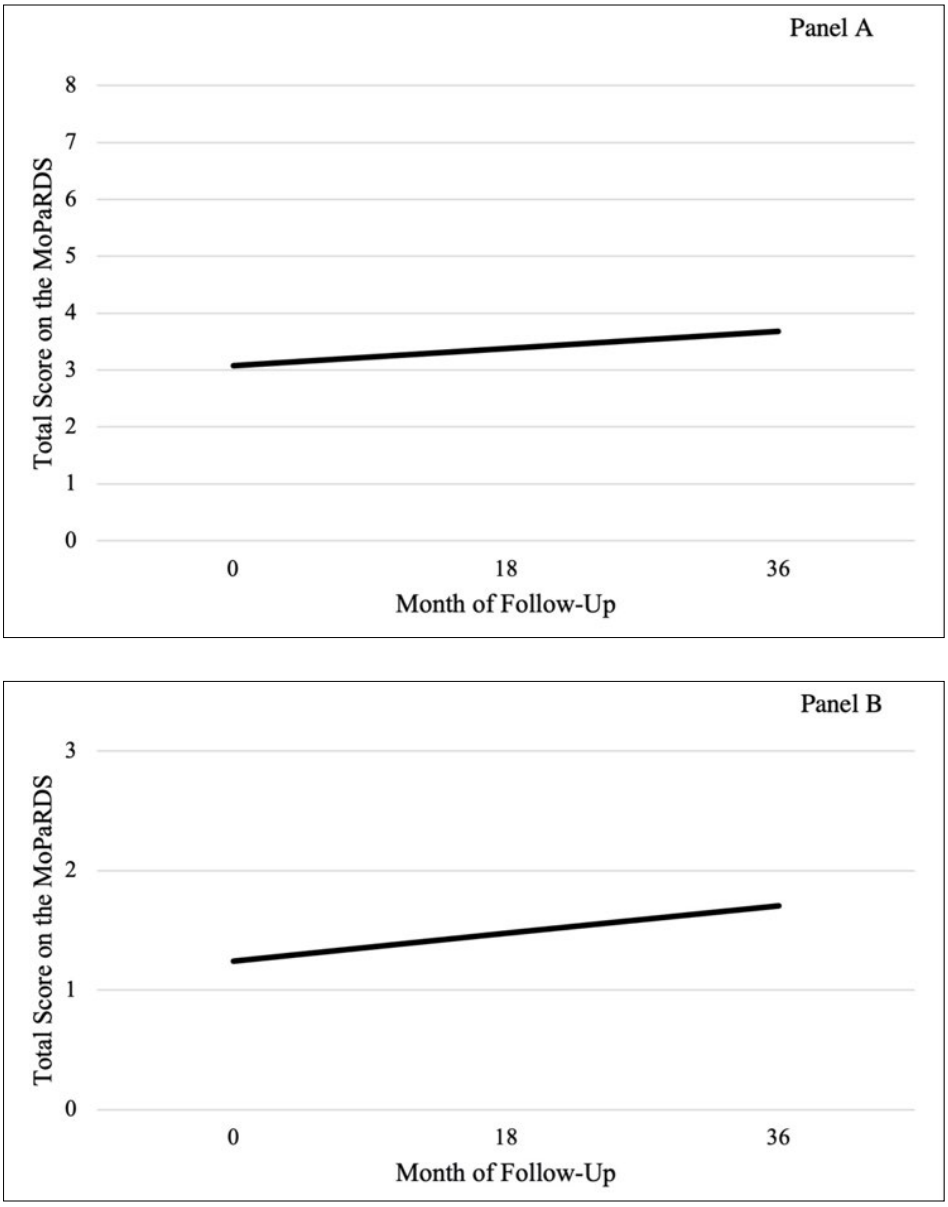

FIGURE 2. Predicted growth curve model for overall risk scores on the eight-item (Panel A) and three-item (Panel B) Montreal Parkinson Risk of Dementia Scale (MoPaRDS). Baseline overall risk scores on the eight-item MoPaRDS statistically differed across participants ($\hat{\sigma}^2 = 1.65$, $p < .001$). Overall risk scores on the eight-item MoPaRDS increased across the three waves (*M* increase per wave = 0.30, $p = .002$). Baseline overall risk scores on the three-item MoPaRDS statistically differed across participants ($\hat{\sigma}^2 = 0.70$, $p < .001$). Overall risk scores on the three-item MoPaRDS increased across the three waves (*M* increase per wave = 0.23, $p < .001$).

required, overall risk scores can be compiled within a single office visit. This follow-up validation study is the first to our knowledge to (a) address important research directions noted in the original report (i.e., integrate education into overall risk scores and evaluate longitudinal change trajectories); and (b) examine whether the MoPaRDS performs screening robustly across minor variations in constituent items and PD cohorts varying in age (geriatric), longitudinal follow-up (shorter), and geographic location (Western Canada). We assembled three waves of data for a well-characterized[6-13] geriatric PD cohort, including 48 patients who were non-demented at baseline, a subset of which (29%) had converted three years later to PDD.

A principal finding was that, for a geriatric PD cohort, the full eight-item MoPaRDS discriminated PDID from PDND (three years prior to dementia) at a level (AUC = 0.81) that was similar to that reported for the international cohort examined in the Dawson and colleagues article[5] (AUC = 0.88). These results support the key interpretations that the full MoPaRDS (a) can be clinically useful in older non-demented PD patients; and (b) is robust for minor item variations which are likely to appear across active clinics. In addition, results of the planned item-level analyses led us to a follow-up examination of a three-item configuration. In the present dataset, we observed that this brief version of the MoPaRDS also discriminated the PDID and PDND groups at an excellent level (AUC = 0.88). The three items in the brief configuration have been separately linked with concurrent PDD in other reports.[5,7,23] However, this configuration was not tested in the original report,[5] and we are unaware of any previous study describing such a brief MoPaRDS-derived screening tool to identify at-risk geriatric PD patients three years prior to the onset of clinically detectable dementia.

In an effort to validate the present novel results, we used shared data from the original 2018 study[5] (N = 607) to test whether the new three-item version predicted PDD at a comparable level to (a) that observed the present study; and (b) the full MoPaRDS in the validation data.[5] Both findings were strikingly supportive of validation. Specifically, in the validation data (a) the three-item MoPaRDS reliably predicted PDD (AUC = 0.84); and (b) this value was similar to the original full-MoPaRDS prediction (AUC = 0.88). A content inspection of the three-item version indicated that it represented a concentration of the dementia-intensive items (especially age and MCI). Because the shorter version accomplished three-year PDD prediction without representation of PD-related items in both data sets, we recommend further research testing the generalizability of this configuration in other geriatric samples. Moreover, because the third item was orthostatic hypotension, we suggest additional research on its role in elevating PDD risk.[23]

Regarding sex, the full MoPaRDS in the 2018 study[5] reported somewhat higher predictive validity for males (AUCmales = 0.92; AUCfemales = 0.81), whereas we observed that the full MoPaRDS performed substantially better for females (AUCmales = 0.91; AUCfemales = 0.74). The reasons for these divergent patterns are unclear,[24] but may reflect the comparatively older age of the current cohort.[25] This aging-related possibility merits future examination. Increased understanding of sex differences in PDD—and the early prediction of elevated risk—may allow clinicians to tailor timely intervention and prevention strategies more precisely. Importantly, the three-item MoPaRDS showed high and nearly equivalent performance for females (AUC = 0.88) and males (AUC = 0.91), suggesting that this brief version may be similarly applicable for both sexes in generally older adults.

Notably, our cut-off score results on the eight-item MoPaRDS were convergent with the original study.[5] Specifically, we found that an overall risk score ≥ 4 was the optimal cut-off for a screen positive result, yielding 71.4% sensitivity and 70.6% specificity (AUC = 0.71). The previous study also adopted this cut-off and reported 77.1% sensitivity and 87.2% specificity (AUC = 0.83). Although these findings confirm the viability of applying the full scale to a geriatric PD cohort, our findings with the three-item MoPaRDS should also be mentioned. The optimal cut-off was an overall risk score ≥ 2, which yielded 85.7% sensitivity and 79.4% specificity (AUC = 0.83), a comparable set of results.

The previous study[5] identified education as a potentially useful component of the MoPaRDS that was unavailable in the international data set. In our study, education was examined in several operational variations but did not independently or in combination demonstrate predictive validity for PDD. Although education may be associated with cognitive reserve in PD, which in turn is correlated with motor and cognitive performance,[26] cognitive reserve might affect dementia risk differentially in asymptomatic aging as compared to people already aging with PD, a substantial dementia risk factor.[27] Because relatively few studies have examined education-PDD associations (including related measures such as continuing late life learning),[18] we support future work exploring whether this factor increases prediction accuracy of the MoPaRDS.

A novel contribution of the present study is that we used longitudinal growth curve modelling techniques[21,22] to demonstrate that overall risk scores on both the full and brief MoPaRDS configurations increased over the three waves. The results of these longitudinal analyses are noteworthy, given that some items do not change over time (sex) or may be more likely to appear earlier in the clinical course of PD (orthostatic hypotension). To our knowledge, no prior studies have examined actual change trajectories of the MoPaRDS. Consequently, we propose this as a priority area of continued research attention. Findings from this line of investigation may support integrating this screening tool into routine care settings in order to monitor transitional changes in PDD risk. Early identification of at-risk individuals may allow for targeted interventions that mitigate or offset subsequent risk for PDD and the associated downstream negative effects.[2,3]

We note several methodological strengths and limitations. First, among the former, we tested our research questions using longitudinal data for an extensively characterized[6–13] geriatric cohort of initially non-demented PD patients. Second, participants completed a comprehensive testing battery at all

three waves and (a) were missing no baseline data across the constituent MoPaRDS items or education; and (b) were evaluated for both MCI[6,28,29] and PDD[6,8,10] using the prevailing clinical diagnostic criteria. Third, we verified that the new empirically indicated three-item MoPaRDS also accurately predicted PDD in the validation cohort.[5] Among study limitations is, first, the relatively small sample size. However, we note that our study was sufficiently powered to obtain reliable estimates in binary logistic regression analyses[30] and growth curve analyses,[21] and has been successful in previous biomarker prediction studies.[6–13] Second, in the present data, only three of eight individual MoPaRDS items discriminated PDID from PDND. We note that this pattern is consistent with an attribution related to the older age of this cohort and the concurrent possibility that geriatric PD patients might present alternative dementia risk profiles given age-associated comorbidities, such as white matter disease[31] and Alzheimer's co-pathology.[32] This possibility could be tested in future studies.

CONCLUSIONS

Overall, our results suggest that the recently established eight-item MoPaRDS is also a promising tool for rapidly screening for dementia risk in a geriatric PD cohort. We tested and confirmed that an abbreviated configuration (a) performed well and similarly across sex; and (b) reliably predicted PDD in the validation cohort[5] of a comparatively younger international PD patient group. Because the risk factors comprising the three-item version are not specific to PD, this abbreviated screening tool may be of relevance to other aging cohorts and has potential for broader application in busy clinical-geriatric settings. We verified that education (as variously defined) did not increase predictive validity of the MoPaRDS and that risk scores on both configurations increased over time. These results have implications not only for research purposes, but also for clinical guidance and decision-making. Early detection of PDD risk (in this case up to three years prior to diagnosis) may encourage closer medication monitoring, surveillance for medical conditions that exacerbate dementia risk, and advance care planning.[33–35] Future work could examine the generalizability of these findings across a longer duration of follow-up and in larger clinical cohorts with sample characteristics that complement the present study. In the interim, the MoPaRDS can be used judiciously in clinical geriatric settings as informative, but not definitive, regarding dementia risk in persons diagnosed with PD.

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CONFLICT OF INTEREST DISCLOSURES

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APPENDIX A. Further information on growth curve analyses

Growth Curve Analyses

We established the functional form of change for the Montreal Parkinson Risk of Dementia Scale (MoPaRDS) using growth curve models.[21,22] We identified the best-fitting model by testing the following four models in sequence: (a) fixed intercept (no slope) model, which assumes that there is no variability between or within persons; (b) random intercept (no slope) model, which allows for variability across persons in overall level but assumes no intraindividual change; (c) random intercept, fixed slope model, which allows for variability across persons in level but assumes that each person changes at the same rate; and (d) random intercept, random slope model, which allows for variability across persons in both level and change.[22] We compared each successive model using the chi-square difference test. This statistic is interpreted such that positive values indicate that the less restrictive model provides a better fit to the data relative to the preceding, more restrictive model.

Model Fit

The extent to which each model provided a good fit to the data was evaluated using the following standard indices: (a) comparative fit index for which ≥ .95 was judged a good fit and between .90 and .94 was judged an adequate fit; (b) root mean square error of approximation, for which ≤ .05 would be judged as good and between .06 and .08 would be judged adequate; and (c) chi-square for which a good fit would produce a non-statistically significant result (i.e., $p > .05$; indicates that the data do not statistically differ from model-based estimates).

Missing Data

A small number of participants were missing data across a subset of the items used to calculate overall risk scores on the eight- and three-item MoPaRDS at the second (n = 6) or third wave (n = 7). Risk scores for these participants were estimated using full information maximum likelihood. We selected this approach to handling missing data based on literature indicating that generalizations from studies using full information maximum likelihood are superior to those from studies using such approaches to handling missing data as listwise or pairwise deletion.[36]

APPENDIX B. Research Goal 1: Binary logistic regression models for the constituent MoPaRDS items independently discriminating PDID from PDND

Item	*OR*	*p value*	*95% CI*	*AUC*	*p value*	*95% CI*
Male sex	0.46	.46	[0.13–1.64]	0.41	.31	[0.23–0.58]
Age > 70	5.92	.02	[1.38–25.30]	0.70	.03	[0.54–0.86]
Mild cognitive impairment	37.89	< .001	[6.64–216.27]	0.85	< .001	[0.71–0.99]
Bilateral disease onset	2.78	.12	[0.76–10.15]	0.62	.20	[0.44–0.80]
RBD	0.41	.17	[0.12–1.46]	0.39	.24	[0.21–0.57]
Hallucinations	1.23	.87	[0.10–14.78]	0.51	.95	[0.32–0.69]
Falls and/or freezing	3.50	.08	[0.88–13.88]	0.63	.17	[0.44–0.81]
Orthostatic BP drop	7.67	.01	[1.77–33.18]	0.73	.01	[0.57–0.89]
Education < 14 years[a]	0.70	.59	[0.20–2.55]	0.46	.65	[0.28–0.64]

[a] Findings stemming from follow-up analyses exploring (a) continuous education; and (b) alternate cut-points are presented in the Results section.
MoPaRDS = Montreal Parkinson Risk of Dementia Scale; PDID = Parkinson's Disease with Incipient Dementia; PDND = Parkinson's Disease with No Dementia; OR = odds ratio; CI = confidence interval; AUC = area under the receiver operating characteristic curve; RBD = rapid eye movement sleep behaviour disorder; BP = blood pressure drop > 10 mmHg. Each item was scored dichotomously (0 = deficit absent, 1 = deficit present) and tested as an independent predictor in separate binary logistic regression analyses (i.e., we serially tested each item for prediction of the binary outcome PDID, PDND).

APPENDIX C. Research Goal 5: Goodness-of-fit indices fo MoPaRDS growth curve models

Model	*AIC*	*BIC*	*CFI*	*RMSEA*	χ^2 *(df)*	*D*	*Δdf*
8-item MoPaRDS							
Fixed intercept, no slope	500.97	508.46	0	0.49	62.69 (5)[c]	--	--
Random intercept, no slope	452.73	462.09	0.85	0.21	12.45 (4)[d]	50.24[c]	1
Random intercept, fixed slope[a]	446.52	457.75	0.98	0.09	4.24 (3)	8.21[d]	1
Random intercept, random slope[b]	--	--	--	--	--	--	--
3-item MoPaRDS							
Fixed intercept, no slope	389.70	397.18	0	0.50	65.45 (5)[c]	--	--
Random intercept, no slope	339.77	349.12	0.84	0.22	13.54 (4)[d]	51.91[c]	1
Random intercept, fixed slope[a]	329.24	340.46	1.00	0	1.01 (3)	12.53[c]	1
Random intercept, random slope[b]	--	--	--	--	--	--	--

[a]Best fitting model.
[b]This model was not considered due to a not positive definite covariance matrix.
[c]*p* value < .001.
[d]*p* value < .01.
MoPaRDS = Montreal Parkinson Risk of Dementia Scale; χ^2 = chi-square test of model fit; df = degrees of freedom; AIC = Akaike information criterion; BIC = Bayesian information criterion; CFI = comparative fit index; RMSEA = root mean square error of approximation; *D* = chi-square difference test; Δ*df* = change in degrees of freedom.