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# REM sleep behavior disorder predicts functional dependency in early Parkinson's disease

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ABSTRACT

*Objective:* To determine whether non-motor symptoms predict the development of functional dependency in Parkinson's disease (PD).

*Methods:* This study using the PPMI data included 405 patients with newly diagnosed PD without functional dependency at baseline visit. We collected baseline demographic and clinical data. Non-motor symptoms were measured using well-validated instruments covering neuropsychiatric, sleep-related, olfactory, and autonomic symptoms. The development of dependency was defined to be present if a Schwab and England (S&E) score of less than 80% at any time point remained during the rest of the follow-up. Cox proportional-hazards regression analyses were performed to identify predictors of dependency. To further validate our findings, additional analysis was performed using an S&E cut-off of 60%.

*Results:* Over a 5-year follow-up period, 61 patients became functionally dependent. The cumulative incidence of dependency was 17% at the 5-year follow-up. Among the non-motor variables, only the REM sleep behavior disorder (RBD) screening questionnaire (RBDSQ) score was associated with the development of dependency. The bradykinesia subscore also predicted dependency. However, when using a cut-off score of 60% or below, the RBDSQ score but not the bradykinesia subscore increased the risk of dependency. The RBDSQ score was further inserted as a dichotomous variable in the multivariable Cox model. The presence of RBD was a significant predictor of dependency for both S&E cut-off scores.

*Conclusion:* The presence of RBD in early PD patients was associated with an increased risk of functional dependency. This finding supports the notion that RBD portends poor prognosis in PD.

## 1. Introduction

Maintaining functional independence in activities of daily living (ADL) is crucial for the quality of life and well-being of people [1]. Loss of independence leads to caregiver burden, high resource use, institutionalization, and increased risk of death [2,3]. Accordingly, it is considered to be an important outcome in the progression of Parkinson's disease (PD) [3]. Several demographic and clinical factors such as older age, a higher severity of bradykinesia, more severe axial symptoms, and a lower cognitive performance have been suggested as predictors of functional dependency in patients with PD [4–6].

Non-motor symptoms are increasingly recognized as an integral component of PD [7]. Growing evidence has shown that earlier development of non-motor symptoms is associated with a more rapid disease progression of PD [8–15], which suggests that such symptoms may be one of the most useful markers for predicting functional dependency. However, the impact of non-motor symptoms on the development of dependency has been unclear. Previous studies have focused only on neuropsychiatric symptoms, and thus, whether other non-motor symptoms including sleep-related, olfactory, and autonomic symptoms can predict functional dependency remains an open question. The aim of this study was therefore to investigate the association between non-motor symptoms and the risk of functional dependency in patients with early PD.

## 2. Methods

### 2.1. Patients

Study data were obtained from the Parkinson's Progression Markers Initiative (PPMI) database. The PPMI study is an ongoing cohort study that focuses on identifying biomarkers of PD progression [16]. A total of 423 patients with newly diagnosed, drug-naïve PD were enrolled in the PPMI study between July 2010 and May 2013, from 33 sites in the

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United States, Europe, Australia, and Israel. Details of the standardized protocols for patient selection, clinical assessments, and data acquisition are available on the PPMI website (ppmi-info.org) and have been published elsewhere [16]. At enrollment, PD participants were required to be over 30 years old; have 2 symptoms among bradykinesia, resting tremor, and rigidity, or only asymmetric resting tremor or bradykinesia; have been recently diagnosed within 2 years of study enrollment; be in Hoehn and Yahr stage 1 or 2; not be treated for PD; not be expected to require PD medication within at least 6 months of study enrollment; and have a dopamine transporter deficit on imaging. After enrollment, patients were followed up every 3 months for the first year and semi-annually for the subsequent years.

We downloaded data on PD patients from the PPMI database on August 6, 2018. For this analysis, data up to 5 years of follow-up were included. We excluded patients who were functionally dependent at baseline visit or were lost to follow-up in the first year following enrollment.

### 2.2. Standard protocol approvals, registrations, and patient consents

All procedures were approved by the Institutional Review Boards of the participating centers before the start of the study, and all participants provided written informed consent for the research before enrolling in the study.

### 2.3. Definition of functional dependency

Functional status was assessed using the Schwab and England (S&E) ADL scale which measures the ability to perform daily activities using a 0% (vegetative) to 100% (completely independent) score at 10% intervals [17]. Patients were asked to choose the answer that best described their functional status most of the time. The development of functional dependency was defined to be present if an S&E score of less than 80% (80% = completely independent in most chores; 70% = not completely independent) at any time point remained during the rest of the follow-up, as used previously [4,6]. To enhance the reliability of our findings, additional analysis was performed using an S&E cut-off score of 60% (some dependency).

### 2.4. Variables

Non-motor symptoms were evaluated using the University of Pennsylvania Smell Identification Test (UPSIT; scores range from 0 to 40, with lower scores indicating worse olfactory function), the REM sleep behavior disorder (RBD) Screening Questionnaire (RBDSQ; scores range from 0 to 13, with higher scores indicating more severe RBD symptoms), the Epworth Sleepiness Scale (ESS; scores range from 0 to 24, with higher scores indicating more severe daytime sleepiness), the Montreal Cognitive Assessment (MoCA; scores range from 0 to 30, with lower scores indicating worse cognitive function), the 15-item Geriatric Depression Scale (GDS; scores range from 0 to 15, with higher scores indicating more severe depression), the State-Trait Anxiety Inventory (STAI; scores range from 40 to 160, with higher scores indicating more severe anxiety), and the Scale for Outcomes in Parkinson's disease-Autonomic (SCOPA-AUT; scores range from 0 to 69, with higher scores indicating more severe autonomic symptoms).

We also collected data on age at enrollment, sex, disease duration, and the Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) motor score (scores range from 0 to 132, with higher scores indicating worse motor function). In this study, the score from the motor section of the MDS-UPDRS was broken down into subscales for bradykinesia (scores range from 0 to 52), rigidity (scores range from 0 to 20), tremor (scores range from 0 to 40), and axial function (scores range from 0 to 20), as previously described [18].

### 2.5. Statistical analysis

Baseline characteristics were assessed with the use of the chi-square test for categorical variables and the Student's *t*-test for continuous variables. The cumulative incidence of functional dependency was estimated with the use of the Kaplan-Meier method. After checking for the constancy of the proportional hazards over time, we used Cox proportional-hazards models to identify the predictors of dependency. Baseline variables associated with functional dependency with a $p$ value of less than 0.2 in the univariable analysis were included in a multivariable model with a backward elimination procedure ($p$ value removal = 0.1). We further inserted the RBDSQ score as a dichotomous variable in the multivariable Cox model, and cumulative incidence plots were obtained from this model. Both cut-off scores of 5 and 6 on the RBDSQ were used to differentiate patients with RBD from those without RBD [19]. Missing data were excluded from the analyses. All $p$ values were two-sided, and a $p$ value of less than 0.05 was considered to indicate statistical significance. Calculations were performed with SPSS 22.0 (SPSS Inc., Chicago, IL) and R version 3.4.2 (R Foundation for Statistical Computing, Vienna, Austria).

## 3. Results

Among the 423 patients, 2 exhibited functional dependency at the baseline visit, and 16 were lost to follow-up in the first year. Finally, 405 patients were included in this study. Of them, 310 patients completed 5-years of study follow-up. No data were missing for age at enrollment, sex, disease duration, MDS-UPDRS motor score, UPSIT score, RBDSQ score, ESS score, GDS score, and SCOPA-AUT score. Data were missing for the STAI score in 1 patient.

During a median follow-up of 5.0 years (mean ± standard deviation, 4.6 ± 0.9 years), 61 patients developed functional dependency. The cumulative incidence of dependency was 4% (95% confidence interval [CI], 2–6) at the 3-year follow-up, 9% (95% CI, 7–11) at the 4-year follow-up, and 17% (95% CI, 13–21) at the 5-year follow-up, respectively (Fig. 1). The baseline characteristics of the participants are shown in Table 1. MDS-UPDRS motor score, axial subscore, bradykinesia subscore, rigidity subscore, RBDSQ score, ESS score, GDS score, and SCOPA-AUT score were significantly higher in PD patients who developed functional dependency than in those who did not develop functional dependency. When using a cut-off of 60% on the S&E scale, 24 patients developed dependency during the follow-up period.

The results of the Cox proportional-hazards analysis are shown in

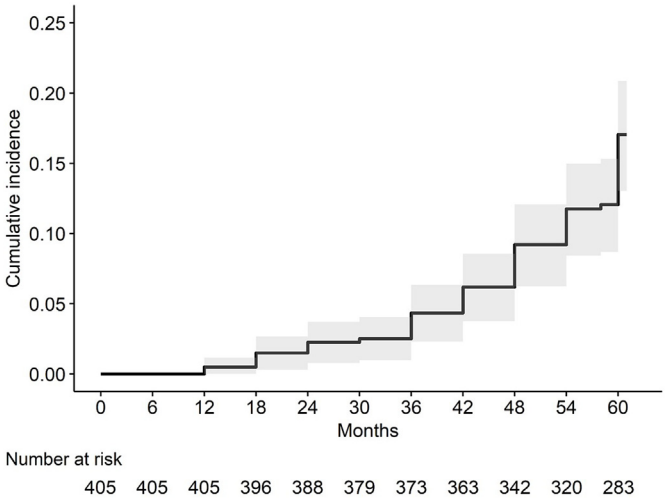


**Fig. 1.** Kaplan-Meier estimates showing the cumulative incidence of functional dependency in patients with early Parkinson's disease. Functional dependency was defined as a Schwab and England score of less than 80%.

**Table 1**
Baseline characteristics of the patients.

| | | Dependency defined by Schwab and England score < 80% | | |
|---|---|---|---|---|
| Variables | Total patients (n = 405) | Patients who developed dependency (n = 61) | Patients who did not develop dependency (n = 344) | *P* value |
| Age | 62.1 ± 9.8 [34, 85] | 64.4 ± 11.1 [36, 85] | 61.7 ± 9.6 [34, 83] | 0.047 |
| Male sex | 266 (66%) | 44 (72%) | 222 (65%) | 0.249 |
| Disease duration (months from diagnosis) | 6.8 ± 6.6 [0, 36] | 7.7 ± 7.2 [1, 36] | 6.6 ± 6.1 [0, 35] | 0.482 |
| MDS-UPDRS motor score | 20.8 ± 8.8 [4, 51] | 23.6 ± 8.0 [11, 41] | 20.3 ± 8.8 [4, 51] | 0.007 |
| Axial subscore | 1.8 ± 1.4 [0, 7] | 2.3 ± 1.4 [0, 5] | 1.8 ± 1.4 [0, 7] | 0.005 |
| Bradykinesia subscore | 10.8 ± 5.7 [1, 30] | 12.6 ± 6.1 [4, 26] | 10.5 ± 5.6 [1, 30] | 0.008 |
| Tremor subscore | 4.3 ± 3.1 [0, 18] | 4.2 ± 3.2 [0, 15] | 4.3 ± 3.1 [0, 18] | 0.795 |
| Rigidity subscore | 3.8 ± 2.6 [0, 13] | 4.5 ± 2.7 [0, 12] | 3.7 ± 2.6 [0, 13] | 0.030 |
| MoCA score | 27.1 ± 2.3 [17, 30] | 26.8 ± 2.7 [17, 30] | 27.2 ± 2.3 [17, 30] | 0.274 |
| UPSIT score | 22.3 ± 8.2 [1, 40] | 21.7 ± 9.0 [6, 38] | 22.4 ± 8.1 [1, 40] | 0.497 |
| RBDSQ score | 4.2 ± 2.6 [1, 12] | 5.5 ± 3.0 [1, 12] | 4.0 ± 2.5 [1, 12] | < 0.001 |
| RBDSQ ≥ 5 | 152 (38%) | 37 (61%) | 115 (33%) | < 0.001 |
| RBDSQ ≥ 6 | 102 (25%) | 28 (46%) | 74 (22%) | < 0.001 |
| ESS score | 5.7 ± 3.4 [0, 20] | 7.1 ± 4.1 [0, 20] | 5.5 ± 3.2 [0, 15] | 0.001 |
| GDS score | 2.3 ± 2.5 [0, 14] | 3.0 ± 2.6 [0, 12] | 2.2 ± 2.4 [0, 14] | 0.022 |
| STAI score | 65.0 ± 18.6 [0, 137] | 67.0 ± 18.9 [41, 120] | 64.6 ± 18.5 [0, 137] | 0.359 |
| SCOPA-AUT score | 9.4 ± 6.0 [0, 39] | 12.4 ± 7.3 [2, 32] | 8.8 ± 5.5 [0, 39] | < 0.001 |

Data are n (%) and the mean ± standard deviation [minimum, maximum].
*P* values reflect chi-square test for categorical variables and Student's *t*-test for continuous variables.
Abbreviations: ESS = Epworth Sleepiness Scale; GDS = Geriatric Depression Scale; MDS-UPDRS = Movement Disorders Society Unified Parkinson's Disease Rating Scale; MoCA = Montreal Cognitive Assessment; RBDSQ = REM Sleep Behavior Disorder Screening Questionnaire; SCOPA-AUT = Scale for Outcomes in Parkinson's disease-Autonomic; STAI = State-Trait Anxiety Inventory; UPSIT = University of Pennsylvania Smell Identification Test.

Table 2. Among the non-motor variables, the RBDSQ score, ESS score, GDS score, and SCOPA-AUT score were entered into a multivariable Cox model, but only the RBDSQ score was associated with the development of functional dependency (hazard ratio 1.20; 95% CI 1.10–1.30; $p = 0.016$) in the model after performing backward elimination. The bradykinesia subscore was also significantly predictive of dependency. However, at an S&E cut-off of 60% or below, the RBDSQ score but not the bradykinesia subscore significantly increased the risk of dependency (Supplementary Table 1).

The RBDSQ score was subsequently considered as a dichotomous variable. The number of patients with a RBDSQ score of 5 or more and 6 or more were 152 (38%) and 102 (25%), respectively. For both RBDSQ cut-off scores, the presence of RBD was significantly associated with an increased risk of dependency (Fig. 2 and Supplementary Table 2). This significant association persisted when using a cut-off of 60% on the S&E scale (RBDSQ cut-off 5, $p = 0.003$; RBDSQ cut-off 6, $p = 0.026$).

## 4. Discussion

In the current study, we examined various non-motor symptoms including neuropsychiatric, sleep-related, olfactory, and autonomic symptoms as a predictor of functional dependency in 405 patients with newly diagnosed PD over a 5-year follow-up period. The results showed that the 5-year cumulative incidence of dependency among the patients was 17%. We identified a significant relationship between the presence of RBD at the baseline visit and the development of dependency. To our knowledge, this is the first study to demonstrate an association of RBD with the risk of functional dependency in patients with PD. Although dependency was related to the severity of bradykinesia for an S&E cut-off of less than 80%, no significant association was found when using a cut-off of 60% or below.

While functional dependency in PD increases as the disease progresses, some patients become functionally dependent early in the disease course. The results of inception cohorts showed that 10–25% of the patients with PD were functionally dependent at the 5-year follow-up [5], which is roughly similar to our results. However, Bjornestad et al. [20] reported that the cumulative incidence of dependency in 189 patients with incident PD reached 6, 26, and 41% at the 1-year, 3-year, and 5-year follow-up, respectively, and these rates were higher than those found in the current study. Such a discrepancy might be attributed to methodological differences. In contrast to the study by Bjornestad et al. [20], we used sustained dependency as the outcome for the survival analyses reported in this study, suggesting a less common detection of dependency especially in the early stage. In addition, they investigated functional status using a standardized interview, which may be more sensitive to identify dependency rather than using the S&E ADL scale [3]. Alternatively, the mean age of the patients in the previous study (67.7 years) was higher than our patients, which might also affect the discrepancy of the results.

Previous longitudinal studies have shown that patients with PD and RBD are related to an increased risk of dementia [21,22] and psychosis [22,23], and greater worsening of motor function, particularly bradykinesia [24]. More specifically, another study using the PPMI data revealed that the presence of RBD is linked to a more rapid deterioration of motor symptoms in patients with PD with a more severe alpha-synuclein and dopaminergic pathology and to a more rapid cognitive decline in those with a more severe alpha-synuclein and amyloid pathology [9]. These observations indicate that the presence of RBD in PD reflects a distinct clinical subtype with a relatively poor prognosis, and may explain our findings. On the other hand, RBD is characterized by dream enacting behaviors which are one of the main causes of sleep-related injuries in PD [25,26]. Severe injuries such as limb fractures and subdural hematomas sometimes occur in relation to RBD [27]. Given the impact of injuries on the functional status of the elderly [28,29], we cannot exclude the possibility that injuries provoked by RBD partially contribute to the occurrence of functional dependency in our patients. Recently, a prognostic model to predict dependency in PD was established, in which age, smoking history, axial severity, and Mini-Mental State Examination score were included in the model [6]. Thus, our finding raises an important question regarding whether the addition of the variable associated with RBD can improve the model. Further studies will be necessary to clarify this issue.

We assessed the functional dependency using the same method described by Macleod et al. [4] However, in opposition to our result, they reported that older age at diagnosis of PD is an independent risk factor of dependency. Such conflicting results may be explained by the differences in age at diagnosis and follow-up periods. The patients included in the study by Macleod et al. [4] had an average age at diagnosis of 72.5 years, which is remarkably older than ours. Moreover, the patients in the current study were followed for up to 5 years, whereas the patients in the previous study were followed up between 5 and 12 years. The data from a prospective large cohort study including 495 patients with PD showed that the gap in the proportion of functional independence between the two age groups (> 70 years and ≤70 years) was approximately 10% at the 5-year follow-up, which was increased to about 30% at the 10-year follow-up [30]. This finding clearly shows

**Table 2**
Results of the Cox proportional-hazards analysis for the predictors of functional dependency.

| Dependency defined by Schwab and England score < 80% | | | | | |
|---|---|---|---|---|---|
| Univariable analysis | | | Multivariable analysis | | |
| Variables | HR (95% CI) | *P* value | Variables | HR (95% CI) | *P* value |
| Age (per year) | 1.03 (1.00–1.06) | 0.024 | Age (per year) | 1.03 (1.00–1.06) | 0.099 |
| Male sex | 1.34 (0.77–2.35) | 0.306 | | | |
| Disease duration (per month) | 1.03 (0.94–1.06) | 0.412 | | | |
| Axial subscore (per unit) | 1.28 (1.09–1.51) | 0.004 | Axial subscore (per unit) | – | – |
| Bradykinesia subscore (per unit) | 1.07 (1.03–1.11) | 0.001 | Bradykinesia subscore (per unit) | 1.05 (1.00–1.09) | 0.043 |
| Tremor subscore (per unit) | 0.99 (0.91–1.08) | 0.858 | | | |
| Rigidity subscore (per unit) | 1.10 (1.01–1.20) | 0.028 | Rigidity subscore (per unit) | – | – |
| MoCA score (per unit) | 0.94 (0.85–1.04) | 0.234 | | | |
| UPSIT score (per unit) | 0.99 (0.96–1.03) | 0.693 | | | |
| RBDSQ score (per unit) | 1.20 (1.10–1.30) | < 0.001 | RBDSQ score (per unit) | 1.20 (1.10–1.30) | 0.016 |
| ESS score (per unit) | 1.13 (1.05–1.21) | < 0.001 | ESS score (per unit) | 1.06 (0.99–1.14) | 0.094 |
| GDS score (per unit) | 1.11 (1.02–1.20) | 0.020 | GDS score (per unit) | – | – |
| STAI score (per unit) | 1.01 (0.99–1.02) | 0.333 | | | |
| SCOPA-AUT score (per unit) | 1.08 (1.04–1.11) | < 0.001 | SCOPA-AUT score (per unit) | 1.04 (1.00–1.08) | 0.063 |

Abbreviations: CI = confidence interval; ESS = Epworth Sleepiness Scale; GDS = Geriatric Depression Scale; HR = hazard ratio; MDS-UPDRS = Movement Disorders Society Unified Parkinson's Disease Rating Scale; MoCA = Montreal Cognitive Assessment; RBDSQ = REM Sleep Behavior Disorder Screening Questionnaire; STAI = State-Trait Anxiety Inventory; SCOPA-AUT = Scale for Outcomes in Parkinson's disease-Autonomic; UPSIT = University of Pennsylvania Smell Identification Test.

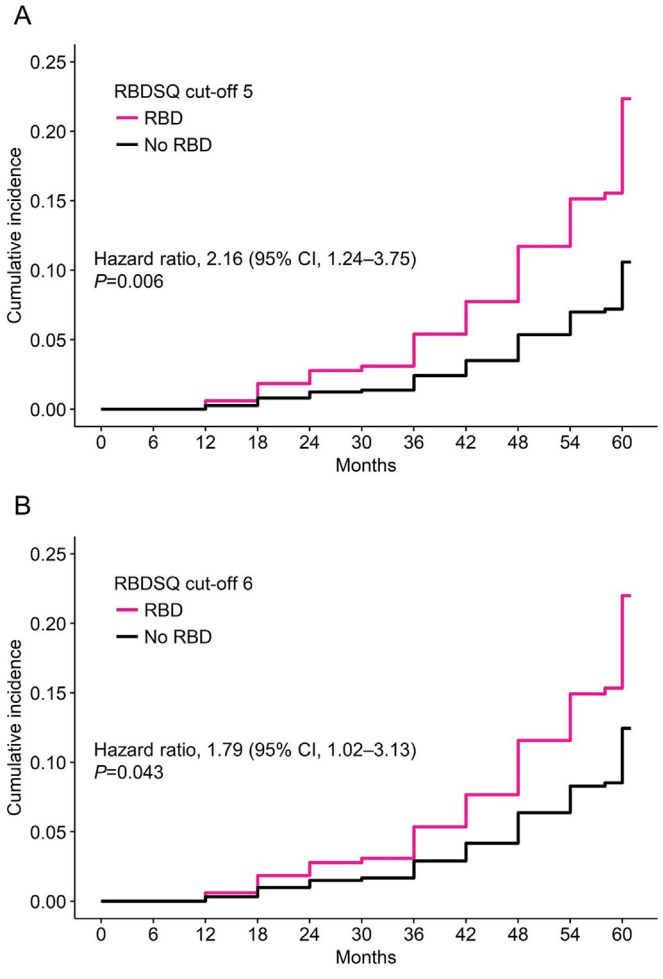


**Fig. 2.** Cox proportional hazards model cumulative incidence of functional dependency according to the presence of REM sleep behavior disorder in patients with early Parkinson's disease. (A) Using a REM sleep behavior Screening Questionnaire (RBDSQ) cut-off of 5; (B) Using a RBDSQ cut-off of 6. Functional dependency was defined as a Schwab and England score of less than 80%.

that dependency risk according to age is more prominent with a longer duration of follow-up.

The present study has a few limitations. First, the diagnosis of functional dependency was based on only a single questionnaire score. The addition of other functional assessment questionnaires should be considered to enhance the diagnostic accuracy in future studies. Furthermore, although the S&E ADL scale has been commonly used to measure the functional status of patients with PD, this scale has not been validated as a dichotomous measure. However, previous evidence suggests that it has face validity for defining functional dependency [4]. Second, the diagnosis of RBD was based on a questionnaire and not confirmed by objectively polysomnography. However, RBDSQ is a validated screening tool for diagnosis of RBD although there is inconsistency in the cut-off values of RBDSQ between studies [19]. To minimize this bias, we used both the cut-off scores of 5 and 6 on the RBDSQ and found consistent results. Thus, this limitation is not likely to be important. Third, we cannot exclude the possibility that unmeasured or unknown confounding factors accounted for the relationships observed in this study. In particular, comorbidity indexes may be important for predicting functional dependency. However, we could not control for this due to a lack of data. Last, the current study only included a follow-up of the first 5 years after enrollment, which might limit the generalization of the results when evaluated over longer periods.

In conclusion, the presence of RBD in patients with early PD was associated with an increased risk of functional dependency, whereas other non-motor symptoms were not related to the development of dependency. These findings may have important clinical implications and support the notion that RBD portends poor prognosis in PD.

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## Conflicts of interest

No conflicting relationship exists for the authors.

## Disclosure statement

Drs. R Kim, D Yoo, JH Im, HJ Kim and B Jeon report no disclosures relevant to the manuscript.

## Author roles

1. Research project: A. Conception, B. Organization, C. Execution;
2. Statistical Analysis: A. Design, B. Execution, C. Review and Critique;
3. Manuscript Preparation: A. Writing of the first draft, B. Review and Critique;

**R. Kim:** 1A, 1B, 1C, 2A, 2B, 2C, 3A.
**D. Yoo**: 2C, 3B
**J.H. Im:** 2C, 3B
**H.J. Kim**: 2C, 3B
**B. Jeon:** 1A, 2C, 3B

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.parkreldis.2019.07.025.

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