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Letter to the Editor

Response to letter to Editor

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Dear Editor,

We appreciate the comments from Lim and Kaufman on our study titled "The association between restless legs syndrome and premotor symptoms of Parkinson's disease" [4]. Their points are important and we are grateful to have the opportunity for further discussion.

Firstly, the statement that "30–60% of restless legs syndrome (RLS) symptoms are self-limiting" was based on the previous studies [1–3]. In the study cohort, we observed two thirds of people with RLS symptoms in 2002 didn't report the symptoms in 2008. Although we did not have the information about RLS symptoms before 2002, there were clear changes from 2002 to 2008. In addition, 3.8% of people who didn't have RLS symptoms in 2002 had them in 2008. These numbers were well agreed with the previous reports supporting the representativeness of the study cohort. Moreover, considering this relative transient nature of RLS, using the combination of RLS status asked twice in a 6-years interval provided uniqueness to our study.

The authors' second point regarding potential unadjusted confounders is important because no observational research is free from this concern. We cannot adjust unmeasured confounders but as a practical approach to evaluating the potential bias, we conducted the sensitivity analyses. In these analyses, we used a model similar to the original study but adjusted for major risk factors for Parkinson's disease, such as categorical age (< 60, 60–64, 65–69, 70–74, 75–79, 80+ years old), categories of smoking status (non-smoker, past smoker, current smoker), body mass index (< 23, 23–24.9, 25–26.9, 27–29.9, 30+ kg/m^2), alcohol intake (0, 0.1–9.9, 10.0–19.9, 20.0–29.9, 30+ g/d), and quintiles of physical activity level, caffeine intake, and lactose intake. The results from this model are shown in Table 1 with those from the original model we have reported. The estimates are very close in the two models and this sensitivity analyses indicates the robustness of the associations in the original study.

The author also raised a concern regarding our excluded 5478 participants without a sleeping partner. We analyzed the association between RLS status and constipation including those who were excluded in the original study. The odds ratio was 1.39 [1.14, 1.17] (95% C.I.) for transient RLS,1.43 [1.21, 1.71] for developed RLS, and 1.46 [1.12, 1.92] for continuous/repeated RLS compared to controls. Our conclusion that the history of RLS was associated with constipation didn't change. The smell test was only introduced to the participants that had a sleeping partner, so our analysis of the association between RLS and olfactory function lost no participants through the exclusion criteria.

The authors also pointed out the possibility of information bias. Although information bias is often a concern in epidemiological studies, it is unlikely to have affected constipation, because most people will know their bowel movement frequency. Moreover, the health professional follow-up study is a prospective study and these variables were determined by participants' records collected before the analyses, further reducing the possibility of information bias.

We also like to mention the authors' comment on the impact of changing covariates over time. We do have information on covariates during follow-up, and we intentionally adjusted for baseline (2002) only because changes during follow-up may reflect the onset or progression of hyposmia and other prodromal features.

We appreciate the comments from authors and we are encouraged by their interest in further studies. Identifying the high risk population for Parkinson's disease is crucial for developing disease modifying or protective treatment for this devastating disease.

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Table 1
Number of cases and age-adjusted odds ratio of having the outcomes by RLS status compared with no RLS.

Outcomes	RLS status			
	Control (n = 15,362)	Transient (n = 441)	Developed (n = 601)	Continuous/recurrent (n = 232)
Constipation				
Case	3491	125	178	74
Odds ratio (age-adjusted)	1 (ref)	1.26 [1.02, 1.56]*	1.38 [1.15, 1.65]**	1.50 [1.13, 1.99]**
Odds ratio (full model)	1 (ref)	1.26 [1.02, 1.57]*	1.32 [1.1, 1.59]**	1.49 [1.12, 1.99]**
pRBD				
Case	1760	51	77	38
Odds ratio (age-adjusted)	1 (ref)	1.01 [0.75, 1.36]	1.14 [0.89, 1.45]	1.52 [1.07, 2.16]*
Odds ratio (full model)	1 (ref)	0.99 [0.73, 1.35]	1.11 [0.87, 1.43]	1.52 [1.07, 2.16]*
Both symptoms				
Case	503	15	22	21
Odds ratio (age-adjusted)	1 (ref)	0.99 [0.59, 1.67]	1.09 [0.70, 1.68]	2.83 [1.79, 4.48]**
Odds ratio (full model)	1 (ref)	1.03 [0.61, 1.73]	1.00 [0.63, 1.58]	2.81 [1.77, 4.47]**

RLS, Restless Legs Syndrome; pRBD, probable REM sleep behavior disorder. Age-adjusted model is the same as reported in the original manuscript. Full model is adjusted for age, smoking status, body mass index, physical activity level, caffine intake, alcohol intake, and lactose intake.

* $p < .05$.

** $p < .01$.

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Nothing to report.

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