



Letter to the Editor

Methodological considerations for measuring the association between restless legs syndrome and premotor symptoms of Parkinson's disease: An epidemiologic approach


ARTICLE INFO

Keywords:

Epidemiologic methods
 Movement disorders
 Sleep disturbances
 Parkinson's disease

Dear Editor,

We recently read the article entitled “The association between restless legs syndrome and premotor symptoms of Parkinson's disease” by Iwaki and colleagues [1], published in *The Journal of the Neurological Sciences* (2018; 394: 41–44). We congratulate the authors for this impressive research, and at the same time offer some further considerations.

The authors noted that 30–60% of individuals suffering from the restless legs syndrome (RLS) are self-limiting in 2–10 years of follow-up, and that olfactory loss is a relatively late symptom of the prodromal stage of PD. While epidemiologic and clinical studies are often at the mercy of their data, the authors provided no information on how long the participants had RLS. These individuals may have had RLS before 2002, but from this study, we have no way of knowing the exposure history, as this information was left-censored. More importantly, the authors did not mention potential causes of RLS. These unmeasured factors may serve as risk factors for PD or pre-motor symptoms of PD. In that case, the participants' demographic characteristics that the authors adjusted for in their models did not provide a complete etiological picture of PD or outcomes that precede PD. It may be that the apparent association that the authors observed could be completely due to confounding induced by unmeasured covariates.

The selection of participants was also a concern. We understand that there could be some challenges in measuring the probable REM sleep behavior disorder (pRBD) outcome, and we can see how the authors wanted to do a complete case analysis that looks at multiple outcomes simultaneously from the same set of individuals. However, the exclusion of 5478 eligible participants was based on the following eligibility criteria: “If he reported being told by his sleep partner that he acted out his dreams while sleeping at least three times in the past.” This appears to have systematically excluded single men, potentially compromising representativeness. The consequence of this exclusion was unnecessary loss of information for the analysis of RLS-constipation and RLS-olfactory function relationships because many were excluded from the study even though they responded to questions concerning the latter two outcomes.

There is also ample potential for information bias in this study. In order for the proxy outcome to be reliable, the pre-motor PD symptom

has to have a strong association with PD, which remains unspecified in the current study. For example, the sensitivity of self-reported constipation may have decreased because of the patients' inability to recall past events, leading to outcome misclassification. Self-reported outcomes were used in the analysis without any indication of reliability other than pointing out that the questionnaires were “well-validated”.

For the statistical analysis, the authors used a regression model for the pRBD and constipation outcomes, taking a step-wise model selection approach to see whether demographic and lifestyle characteristics serve as confounders for the relationship between RLS and the outcomes. These covariates were only measured in 2002, but they might have changed over time. The lack of participant characteristics measured at a later date (to account for those with different exposure values between 2002 and 2008) did not allow for sensitivity analysis; hence, the robustness of the model results remains unknown. In terms of model specification, the log-binomial model with a log-link would have been more appropriate compared to the logistic regression model, since the former provides an adjusted risk ratio (RR) [2], which is more scientifically intuitive than an odds ratio (OR) [3]. Moreover, the outcomes themselves were not particularly rare in this study (3868 cases of constipation and 1926 cases of pRBD). While the OR may suffice in cases of hypothesis generation or simple prediction, the concern with the OR is that it can be dramatically further from the null than the corresponding RR when the outcome is not rare [4,5]. That is, the adjusted RR is substantially smaller than the results presented in Table 2. Hence, the conclusion about the degree of association between RLS and the premotor PD symptoms is somewhat misleading in magnitude [4].

As for the stepwise approach, indeed, very few previous studies looked at the relationship between RLS and the pre-motor symptoms of PD. From a hypothesis generating perspective, we can understand why the authors used this method, but it suffers from potentially biased regression coefficients because the model selection algorithm may lead to adjusting for the wrong covariates [6]. By unnecessarily controlling for non-confounders based on *p*-values and AIC/BIC scores, one could introduce bias in the estimate of the main coefficient(s) of interest [7]. Moreover, step-wise regression is generally based on methods that were intended to test pre-specified hypotheses, and a scientific approach to causal inference and model selection requires reliance not only on statistical significance but also on clinical relevance and plausibility

<https://doi.org/10.1016/j.jns.2018.12.009>

Received 8 November 2018; Accepted 5 December 2018

Available online 07 December 2018

0022-510X/ © 2018 Elsevier B.V. All rights reserved.

[8]. From the authors' statistical approach, it remains unclear whether the study was primarily intended to be predictive or explanatory [9]. There remains ambiguity, therefore, as to whether the model helped to identify either the population at elevated disease risk or the causal factors that may be targets of intervention, a distinction that is essential for valid interpretation and informing action.

While the associations in this study are not clinically relevant, we agree with the authors that the results may open up the possibility of future research. But clinical discrimination would have to show a much higher association in order to be useful in practice [10]. Nonetheless, we remain optimistic that the use of a data set from another comparable study, such as the Nurses' Health Study, to validate the results could enhance the study findings. If the authors could find effect modification or consistency across relevant characteristics and covariates, they may be able to address questions that are more scientifically meaningful to the clinical community.

References

- [1] H. Iwaki, et al., The association between restless legs syndrome and premotor symptoms of Parkinson's disease, *J. Neurol. Sci.* 394 (2018) 41–44.
- [2] L.A. McNutt, et al., Estimating the relative risk in cohort studies and clinical trials of common outcomes, *Am. J. Epidemiol.* 157 (10) (2003) 940–943.
- [3] I. Shrier, M. Pang, Confounding, effect modification, and the odds ratio: common misinterpretations, *J. Clin. Epidemiol.* 68 (4) (2015) 470–474.
- [4] M.J. Knol, et al., Overestimation of risk ratios by odds ratios in trials and cohort studies: alternatives to logistic regression, *CMAJ* 184 (8) (2012) 895–899.
- [5] H.T. Davies, I.K. Crombie, M. Tavakoli, When can odds ratios mislead? *BMJ* 316 (7136) (1998) 989–991.
- [6] E.W. Steyerberg, M.J. Eijkemans, J.D. Habbema, Stepwise selection in small data sets: a simulation study of bias in logistic regression analysis, *J. Clin. Epidemiol.* 52 (10) (1999) 935–942.
- [7] E.F. Schisterman, S.R. Cole, R.W. Platt, Overadjustment bias and unnecessary adjustment in epidemiologic studies, *Epidemiology* 20 (4) (2009) 488–495.
- [8] S. Greenland, Modeling and variable selection in epidemiologic analysis, *Am. J. Public Health* 79 (3) (1989) 340–349.
- [9] C.M. Schooling, H.E. Jones, Clarifying questions about "risk factors": predictors versus explanation, *Emerg. Themes Epidemiol.* 15 (2018) 10.
- [10] M.S. Pepe, et al., Limitations of the odds ratio in gauging the performance of a diagnostic, prognostic, or screening marker, *Am. J. Epidemiol.* 159 (9) (2004) 882–890.

Jihoon Lim^{a,b,*}, Jay S. Kaufman^a

^a *Division of Clinical Epidemiology, McGill University Health Centre, Allan Memorial Institute, 1025 Pine Ave West, Montreal, Quebec H3A 1A1, Canada*

^b *Department of Epidemiology, Biostatistics, and Occupational Health, McGill University, Purvis Hall, 1020 Pine Ave West, Montreal, Quebec H3A 1A2, Canada*

E-mail addresses: jihoon.lim@mail.mcgill.ca (J. Lim), jay.kaufman@mcgill.ca (J.S. Kaufman).

* Corresponding author at: Division of Clinical Epidemiology, McGill University Health Centre, Allan Memorial Institute, 1025 Pine Ave West, Montreal, Quebec H3A 1A1, Canada.