Response to Reviews

We thank both editors and the associate editor for their constructive comments. In particular, the queries about the specification of priors led us to revise the statistical analysis and to calculate more accurate Bayes factor values than we provided with the original submission.

Response to Reviewer 1

Overall the paper is very well written and the conclusion that the association seen in prior studies is due to a secular trend in family size is well-reasoned.

I did have some concerns about the use of the New Zealand cohort which could be subject to ascertainment bias, inaccurate self-reported diagnosis, and bias towards younger patients given that the surveys were web-based. The PPMI analysis alone is adequate to demonstrate the author's point, although admittedly the average age of PPMI participants is quite young.

We agree that the PPMI data is sufficient to argue against a biological cause for the previously-reported association. The New Zealand data provides additional value by allowing further conclusions to be made, such as why the association will not always be evident in a given sample, depending on the sampling design.

With regards to the concerns about the New Zealand study, we note that

- The Canterbury sub-sample (n = 192) was entirely of patients with a formal diagnosis from a neurologist. In most cases, diagnosis was by a movement disorders specialist (TJA), as these patients had all participated previously in research projects at our centre.
- The remaining 412 cases from other regions were recruited from clients of the New Zealand Parkinson's Society, which provides nursing and allied-health support to people diagnosed with Parkinson's. In many cases, this diagnosis would also have been via a neurologist, but some would have been diagnosed by other specialists (such as geriatricians) or by general practitioners.

That is, this was an invitation-only survey, sent to people with a formal Parkinson's diagnosis. It did not rely upon self-selecting volunteers. This is now stated explicitly in the manuscript.

Online surveys do have a risk of systematic bias towards younger participants, although we note that the New Zealand cases were nonetheless on average a decade older than those in the PPMI study. Participants in the Canterbury sub-sample could opt to fill in the survey in a paper form rather than online, and in the national survey, a small number chose to answer the questions verbally, over the phone. These alternative means of response are also now stated explicitly stated in the manuscript.

The fact that there are few participants with 4 or more children in either cohort could limit the generalizability of their finding. Replicating the results in a large registry study (such as the one used by Greene et al.) would be ideal.

This is true, and is now noted as a limitation in the first sentence of the Discussion. The reviewer's recommendation of Yadav (2012), a study from India that included women with much higher fertility than in the other studies, does now provide an additional compelling display of the (artefactual) association between number of children and age-of-onset, at least in women.

Minor points:

1) Yadav, 2012 can also be cited in the introduction.

We thank the reviewer for pointing us to this reference, which is now incorporated throughout the manuscript. As noted above, it provides useful additional evidence, as it included a number of women who had given birth up to nine times. It also brings to four the number of studies that have shown the parity vs age-of-onset association (including PPMI). Graphically, the relationship appears strong in this paper and of a similar magnitude to the other studies, although unfortunately it was reported only via a correlation coefficient, rather than a direct regression effect size in terms of years-per-child.

2) How was diagnosis confirmed in the NZBRI cohort? How exactly were participants identified and recruited?

This query is covered in the earlier response to reservations about the NZBRI sample.

Response to Reviewer 2

This is an interesting and well-written paper. The findings are important and the explanations for those findings are clearly articulated in the Discussion. I have the following suggestions for the authors:

• At the top of page 4, the authors state that in the two previous studies that examined this issue, the associations between number of children and age at onset of PD were not linear. It would be helpful to expand upon this point and describe the nature of the relationships found in these studies.

Upon further consideration (including of the additional Yadav (2012) paper suggested by Reviewer 1), we have removed the statement about non-linearity. The three papers to have previously reported the association all depicted the data using bar graphs, showing the mean age of onset at each number of children. That is, this form of data visualisation summarises the data rather than directly depicting the analysis (regression or correlation based upon an individual, independent data point from each woman). Without being able to see the distributions of raw data points, we can't claim strongly that the relationships in the Haaxma and Frentzel papers were non-linear, as the mean values can be unstable when there are only small numbers of women with a given number of children. The Yadav paper, meanwhile, is perhaps the most useful previous dataset, as it includes the largest range of childbirths (up to nine per woman). The association there does appear convincingly linear, despite the bar-graph presentation.

• On page 5, the authors should be explicit about the prior distributions that were used. Were these improper flat priors over the real line? Something else?

We thank the reviewer for this comment and question, which has led us to not only revise this manuscript but also improve our practices in other ongoing analyses. When revising both the manuscript and the underlying analysis code to be more explicit about the specification of priors, we found that the originally submitted statement "Parameters were given default weakly-informative priors" was incorrect — the *brms* package actually applies an improper prior for regression coefficients by default. An improper prior is not appropriate when calculating Bayes factors and hence this resulted in the Bayes factors in our originally submitted manuscript being inflated.

We now explicitly define the priors in the analysis code (publicly available on the Github page). We have also updated the manuscript to more explicitly state the priors in use, as follows: "Weakly-informative Student *t* priors were used for the intercept (df = 3, mean = data mean, SD = 10) and standard deviation (df

= 3, mean = 0, SD = 10). Based upon the three previous studies, (Haaxma *et al.,* 2007; Yadav *et al.*, 2012; and Frentzel *et al.*, 2017) we used a proper informative normal prior (mean = ±2.5, SD = 2) for the effect of the number of children (being positive when the dependent variable was age, and negative for year of birth)."

• The term "Bayes factor" should be defined more precisely, i.e., as the ratio of the likelihood of the data given a model including the number of children to the likelihood of the data given an intercept-only model.

We now use this definition, and have deleted the redundant definition in the caption of Figure 1.

• Throughout the text, the term "uncertainty interval" should be replaced by "credible interval".

We have replaced "uncertainty" with the more commonly-used "credible" throughout.

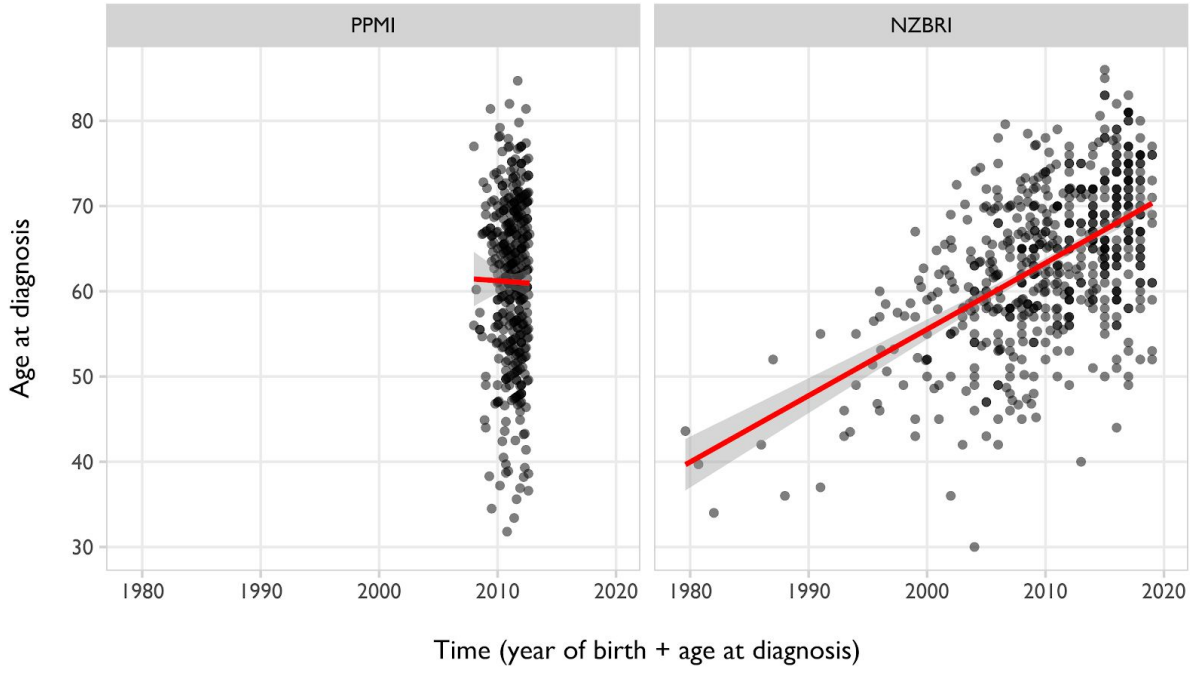
• The rationale for the comparisons of men and women with respect to age at diagnosis of PD is unclear. There may be biological or social factors other than childbirth that affect age at diagnosis of PD in women.

This is true, although such factors would have to neatly cancel out the additive effects of each childbirth. We now state this possibility in the final paragraph of the discussion, and have shortened that paragraph to put less emphasis on this claim.

Response to Associate Editor

If their conclusions are correct, then I would think that age at onset should be rising in men and women over time. This was not tested.

Unfortunately, we cannot assess this formally with our datasets. In the PPMI sample, all diagnoses occurred within several years of study commencement. Change in onset age as a function of time cannot be measured meaningfully over such a narrow window. In the NZBRI sample, however, diagnoses span a much wider time window, but there is a survivorship bias effect in operation:



For example, only people with an early age of onset could survive from diagnosis in the early 1980s until being recruited several decades later. This creates a very strong apparent relationship of onset age seeming to rise over time, but we would argue that this is (again) artefactual. The change is too large to be believable (with onset age increasing from approximately 40 to 70 over the span of four decades). Such a strong effect is most likely due to the massive survivorship bias. If there is any potential remaining genuine temporal trend, it would not be able to be disentangled from the survivorship bias. Hence it is not possible to look for changes over time in age of onset in either the PPMI or NZBRI samples – this would require recruiting patients over a span of decades, or combining data from many historical studies.

Also the year of birth difference per child seems surprisingly small.

Figure 1 shows the massive variability in this data. For example, knowing that a man in the PPMI study had two children does not allow us to predict his year of birth with any confidence – that is, men with two children span almost the entire age range in the study. There are a multitude of other social, environmental, health, and financial factors that would contribute to how many children a given person has. The year of birth is just one contributor to that mix, but does apply some constraints: for example we can see that no man born after 1965 in that study has had more than two children, although that was quite common for older men in that study.

A summary statement in the conclusion about the implications for these findings would help those readers less familiar with the topic - e.g. that other environmental factors associated with earlier year of birth may explain the child number associations.

We now have such a statement in the second paragraph of the Discussion: "The small magnitude of the relationship between year of birth and number of children (approximately one year per child) is smaller than in the previous studies, but is consistent with the complex web of social, cultural, financial, and health factors that influence a person's family size, with generational cohort being only one contributor (as shown in the large variability in Figure 1A)."