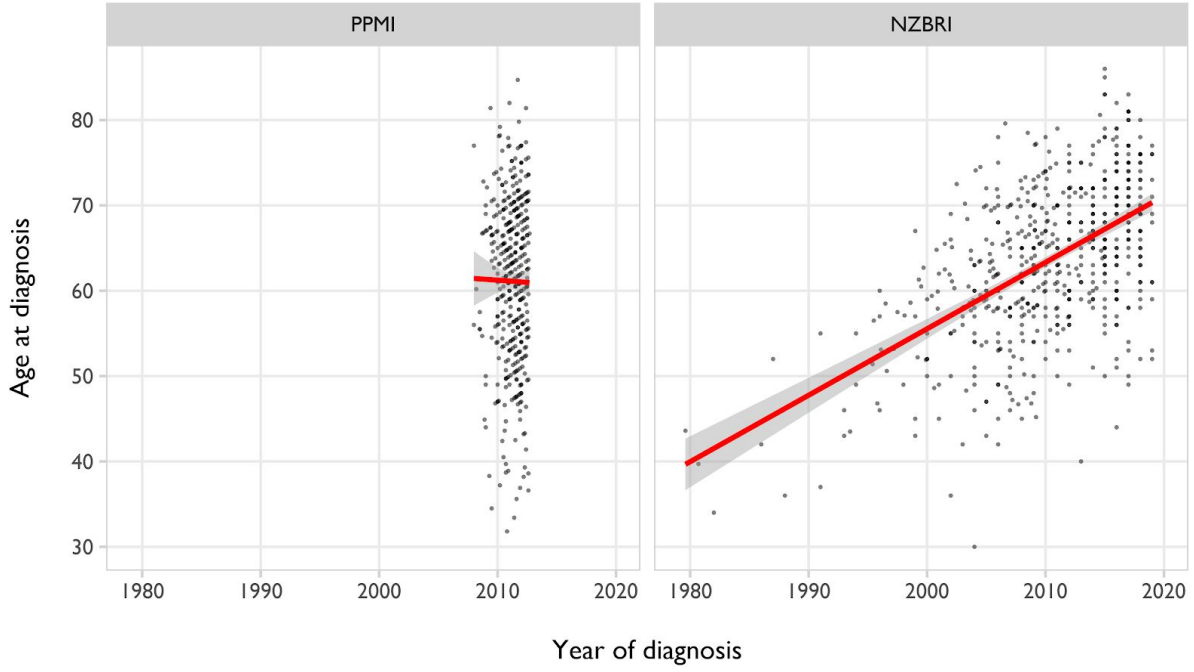
Response to Second Review

Dear Professor Stoessl,

Thanks for your ongoing engagement with this paper – it is enjoyable for us to be challenged to wrestle with these concepts. Your question is a natural one, which we had discussed internally, but only informally prior to this.

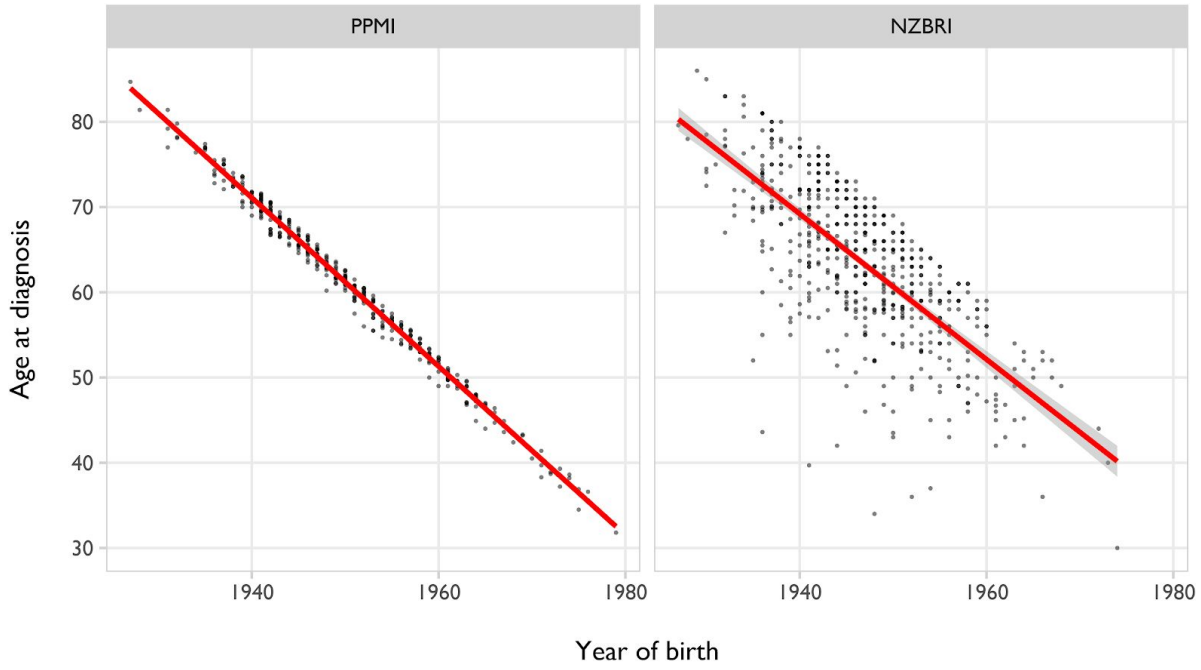
If your hypothesis is correct, should it not be possible to 'correct' for a generational cohort effect by including both year of birth and number of children in the model and test associations with age at diagnosis? If you are correct, then the effect of number of children should be of lower magnitude or non-significant - essentially, despite shifts in overall practices over time, there are surely modern day women who have a lot of children and in the past, there were women who did not?

Before answering this question, it might be useful to review the figure below, which was contained in our response to the last review. This was created to show why neither the PPMI nor NZBRI studies can answer whether the age of diagnosis of PD is changing over time. The PPMI study can't address the question at all, because (being an incidence study), recruitment (and hence diagnosis) occurred only over a very narrow time period. In the NZBRI prevalence study, however, diagnoses span four decades, and appear to show a strong relationship of diagnosis age getting later over time. Although we can't rule out a small effect existing, the large magnitude of the effect shown is too large to be believable, and is more parsimoniously explained as being due to survivorship bias. For example, for people diagnosed in 1980, only those with an early age of onset could have survived to be surveyed in the last couple of years, rotating the line of best fit to have an artefactual strongly positive slope:



So this brings us to your current question, of whether we could correct for cohort effects by simultaneously including year of birth, age at onset, and number of children in a model. This could potentially be applied if we had comprehensive data, derived from multiple incidence studies, conducted serially over a span of

decades. Unfortunately, it isn't feasible with either of the datasets we have to hand. This can be shown if we look at the correlation between age at diagnosis and year of birth (as a measure of generational cohort):



In the PPMI study, year of birth and age at diagnosis are almost perfectly anti-correlated, a consequence of this being an incidence study. In such a design, year of birth doesn't explain age of onset, but is a simple arithmetic transformation of it (i.e. age at diagnosis is simply the result of subtracting year of birth from the (almost constant) year of recruitment). So if we were to include year of birth in a model, it would appear to nearly perfectly "predict" age at diagnosis. Consequently, the term for number of children would necessarily drop out of the model, as there would be no variance left for it to explain. This is the result you predicted: that "the effect of number of children should be of lower magnitude or non-significant", but it isn't a fair test. That is, year of birth can't be used to correct just for the generational cohort effect, as it effectively explains *all* of the variance in the outcome variable. So we can't usefully include both diagnosis age and year of birth in a model simultaneously.

The situation is different with the NZBRI data: year of birth does not perfectly fit the age of diagnosis, leaving over some variability that could be tested to see if it is accounted for by the number of children. But according to the first figure, this "fan-shaped" spread of the data is really just a consequence of the survivorship bias inherent in such a prevalence study. If we included number of children in that model, unlike in PMMI, it would likely be a significant predictor. But we would argue that it would not be safe to interpret its effect, given how much of the residual variance here is due to the survivorship bias that arises from simultaneously examining year of birth and age of diagnosis.

So in summary, we would say:

- One can't correct for cohort effects in the PPMI study, because it works too well: being an incidence study, cohort accounts for *all* of the variance in age of diagnosis.
- One can't correct for cohort in the NZBRI data, as the variance it leaves to be explained is created by the very strong survivorship bias inherent in the prevalence study design, rather than reflecting real generational differences.

We appreciate being asked the question: having to deal with it formally, and to graph the various relationships, has certainly clarified our own thoughts on the issues involved. The same question will likely arise for many readers, and hence we have now added this sentence to the end of the first paragraph in the discussion, with reference to the PPMI data: "As patient age and age-of-onset are almost perfectly correlated in this study, it is not possible to use age to statistically "correct for" generational membership."

Response to Statistical Reviewer

The authors have satisfactorily addressed nearly all of the issues raised in the initial review. The one aspect that requires some attention is the description of the prior distributions used by the authors.

We've taken this further feedback to heart and amended not only the description of the priors in manuscript, but also (in greater detail) the descriptions in the publicly-available analysis code.

The prior distribution used for the standard deviation (presumably of the residuals) is not entirely clear.

In the manuscript, we now explicitly state that the standard deviation applies to the residuals (changes in red): "Weakly-informative Student *t* priors were used for the intercept (df = 3, mean = data mean, scale = 10) and standard deviation of the residuals (df = 3, mean = 0, scale = 10)"

The standard deviation is necessarily a positive quantity, so a Student t prior distribution would not be appropriate, nor would specification of a mean of zero. The prior distribution that the authors specified is more likely a folded Student t distribution with lower bound (not mean) at zero and a scale factor (not standard deviation) of 10.

In the same paragraph, we now state: "Weakly-informative Student *t* priors were used for the intercept (df = 3, mean = data mean, scale = 10) and standard deviation of the residuals (df = 3, mean = 0, scale = 10) with rejection sampling used to ensure the standard deviation was non-negative. The scale values were chosen so the prior distributions had moderate probability mass fully covering the range of plausible parameter values."

Similarly, it is not clear what the "SD" specified for the Student t prior distribution for the intercept represents since it is not the actual standard deviation associated with the t-distribution (which depends solely on the degrees of freedom). The authors need to specify these prior distributions more carefully and not rely on the language used in the documentation of the brms R package, which does not accurately describe what the prior distributions actually represent.

We have now replaced the term “SD” with “scale”, indicating the scale factor of the distribution: “Weakly-informative Student *t* priors were used for the intercept (df = 3, mean = data mean, scale = 10)

Additionally, , we now provide much more detail in the comments of the publicly-available code used to generate the manuscript, made publicly available at https://github.com/nzbri/pd-parity/blob/master/PD_parity_and_onset_age.Rmd:

```
########
# Define priors
# See https://github.com/stan-dev/stan/wiki/Prior-Choice-Recommendations
#
# Use weakly-informative priors for intercept and standard deviation of
# residuals.
# For intercept: Student-t distribution, df = 3, mean = 0, scale = 10
# For standard deviation of residuals: Student-t distribution, df = 3,
# mean = 0, scale = 10 with rejection sampling on the prior to ensure greater
# or equal to 0.
# Matches the defaults for brms.
#
# Probability density function definition for the Student-t distribution:
# https://mc-stan.org/docs/2_22/functions-reference/student-t-distribution.html
#
# To transform scale of Student-t to standard deviation:
# https://jrnold.github.io/bugs-examples-in-stan/resistant.html
# \sigma^{*} &amp;\sim \mathsf{HalfCauchy}{(0, 5)} \\
# \sigma &amp;= \sigma^{*} \sqrt{\frac{\nu - 2}{\nu}} \\
#
# For Bayes Factors need proper priors on non-common parameter between model.
# By default brms has improper priors on regression coefficients.
#
# We use informative priors for the effect of number of children, based upon
# three previous studies cited in the paper: Haaxma et al. (2007), Yadav et
# al. (2012), and Frentzel et al. (2017).
#
# Older age == earlier birth year, thus reversal of sign for effect:
#
# For  age: Normal distribution with mean =  2.5, sd = 2
# For year: Normal distribution with mean = -2.5, sd = 2
########
```