Childbirth and Delayed Parkinson's Onset: A Reproducible Nonbiological Artifact of Societal Change

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ABSTRACT: Background: Uncontrolled studies have reported associations between later Parkinson's disease onset in women and a history of giving birth, with age at onset delayed by nearly 3 years per child. We tested this association in two independent data sets, but, as a control to test for nonbiological explanations, also included men with PD.

Methods: We analyzed valid cases from the Parkinson's Progressive Markers Initiative incident sample (145 women, 276 men) and a prevalent sample surveyed by the New Zealand Brain Research Institute (210 women, 394 men).

Results: The association was present in both women and men in the Parkinson's Progressive Markers Initiative study, and absent in both in the New Zealand Brain Research Institute study. This is consistent with generational differences common to men and women, which confound with age at onset in incident-dominant samples.

Conclusions: Despite being replicable in certain circumstances, associations between childbirth and later PD onset are an artifact of generational cohort differences. © 2020 International Parkinson and Movement Disorder Society

Key Words: cohort effects; epidemiology; Parkinson's disease; pregnancy; sex differences; sex hormones

The incidence of Parkinson's disease (PD) is substantially lower in women[1,2] (at least outside China and Japan).[1,3] The reason is unknown, but could include greater male exposure to risk factors (eg, head injury or occupational use of toxins)[4] or protective factors applying differentially to women (eg, greater exposure to hormones like estrogens and progestogens).

Plausible mechanisms have been proposed for how female sex hormones could play a neuroprotective role in neurodegenerative conditions,[5] and hence observational studies have tested associations between increased hormone exposure and protection against PD. Lifetime hormonal exposure has been operationalized using endogenous measures such as fertile life span (the duration between age at menarche and age at menopause) or exogenous exposure through oral contraceptives or hormone replacement therapy. Despite some positive findings,[6] most reviews,[7] large prospective,[8] or case-control[9] studies, and meta-analyses[10,11] have shown little support for relationships between any such measures and a lowered risk of PD.

Eight studies have examined the effect of parity (number of childbirths) on the risk of women subsequently developing PD.[10] Meta-analysis showed no effect, with the relative risk of PD between the highest and lowest number of births being 0.99 (95% CI, 0.79–1.25).[10] However, 3 studies have independently reported another childbirth-related association not specifically addressed in that meta-analysis: among women diagnosed with PD, they found that a history of childbirth was associated with later age at onset.[12-14] That is, although having children might not reduce the risk of Parkinson's disease per se, it might still slow the pathological process. The associations were surprisingly large and consistent, with symptom onset reported as later by 2.7 years (95% CI, 0.8–4.6 years, Netherlands, n = 97)[12] or 2.6 years per childbirth (95% CI, 0.05–5.1 years, Germany, n = 79)[14]

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or to have a correlation coefficient of 0.35 between parity and onset age (India, n = 81, $P = 0.001$).[13]

A challenge in such observational studies is applying valid control comparisons. Women without Parkinson's disease lack the disease outcome measures (such as age at onset), whereas men with PD lack the predictor hormonal measures. For this specific association, however, defining the predictor as "number of biological children" rather than "number of childbirths" allows men with Parkinson's disease to be a suitable control for nonbiological explanations. We propose that if the relationship between number of children and onset age is absent in men, it would strengthen claims for a protective female sex hormone effect. Conversely, if that relationship *does* hold for men, it would strongly support the cause being nonbiological.

Methods

Data Sets

PPMI: The openly available Parkinson's Progressive Marker Initiative[15] is a data set of incident cases, with a mean of 7 months between diagnosis and recruitment (see Table 1 and Acknowledgments). Valid data on number of children were available from 421 of PPMI's 423 idiopathic Parkinson's disease cases.

NZBRI: At the New Zealand Brain Research Institute, we combined 2 previously conducted risk-factor surveys, in which 604 people with idiopathic Parkinson's disease provided valid responses on age at diagnosis and number of biological children (Table 1). Cases ranged from recently diagnosed to those with long-standing disease. Responses were mostly collected online, with some submitting via paper or telephone. Respondents with dementia had assistance to complete the questions. One survey (192 valid cases) recruited from our ongoing longitudinal study of a convenience sample of prevalent cases in the local Canterbury region. The other (412 valid cases) was nationwide, recruiting from the membership (excluding Canterbury) of the Parkinson's New Zealand charitable trust. Age at diagnosis was self-reported in the national survey and confirmed from clinical records in the Canterbury survey. Canterbury respondents had the diagnosis confirmed by a neurologist. The remainder required a diagnosis to receive care from Parkinson's New Zealand, which might have been made by a neurologist, other specialist, or general practitioner.

Analyses

Onset age was defined as when Parkinson's disease was diagnosed because symptom onset age was not collected in the NZBRI nationwide survey. Data were fitted with simple Bayesian linear models, using the R[16] package *brms*.[17] Weakly informative Student t test priors were used for the intercept (df = 3, mean is 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 nonnegative. The scale values were chosen so the prior distributions had moderate probability mass fully covering the range of plausible parameter values. Based on the 3 previous studies,[12-14] we used a proper informative normal prior (mean, $\pm$2.5; SD, 2) for the effect of the number of children (being positive for the dependent variable of age and negative for year of birth). We ran 4 chains of 20 000 iterations each.

When testing hypotheses of associations between the number of children and age at onset (or year of birth), in each case we compared a model containing the number of children as a predictor to an intercept-only model (ie, a model of no association). Bayes factors give 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 ("flat-line") model.

Reproducibility

The code and the anonymized data set extracts used to conduct the analyses and generate this article are available at https://github.com/nzbri/pd-parity.

Results

PPMI Sample

We first attempted to replicate the association between number of children and later disease onset in the PPMI women. The linearly modeled delay in diagnosis was 1.1 years per child (credible interval, 0.15–2.1), being the slope of the line in the upper-right panel of Figure 1B. However, a Bayes factor (BF) of 1.5 indicated very weak evidence for an association compared with the intercept-only model. Stronger results were found for the PPMI men, with a slope of 1.4 years per child (0.4–2.3), BF = 4.9. That the relationship occurred in men argues against the underlying cause being pregnancy- or birth related.

TABLE 1 Demographic characteristics of the PPMI and NZBRI samples

Study	Sex	n	Mean age	Mean age at diagnosis	Mean disease duration (years)
PPMI	Men	276	62.2 (9.7)	61.6 (9.7)	0.5 (0.5)
	Women	145	60.7 (9.6)	60.1 (9.6)	0.6 (0.6)
NZBRI	Men	394	71.7 (7.5)	63.8 (9)	7.9 (5.8)
	Women	210	70.3 (7.3)	62.9 (9)	7.5 (5.8)

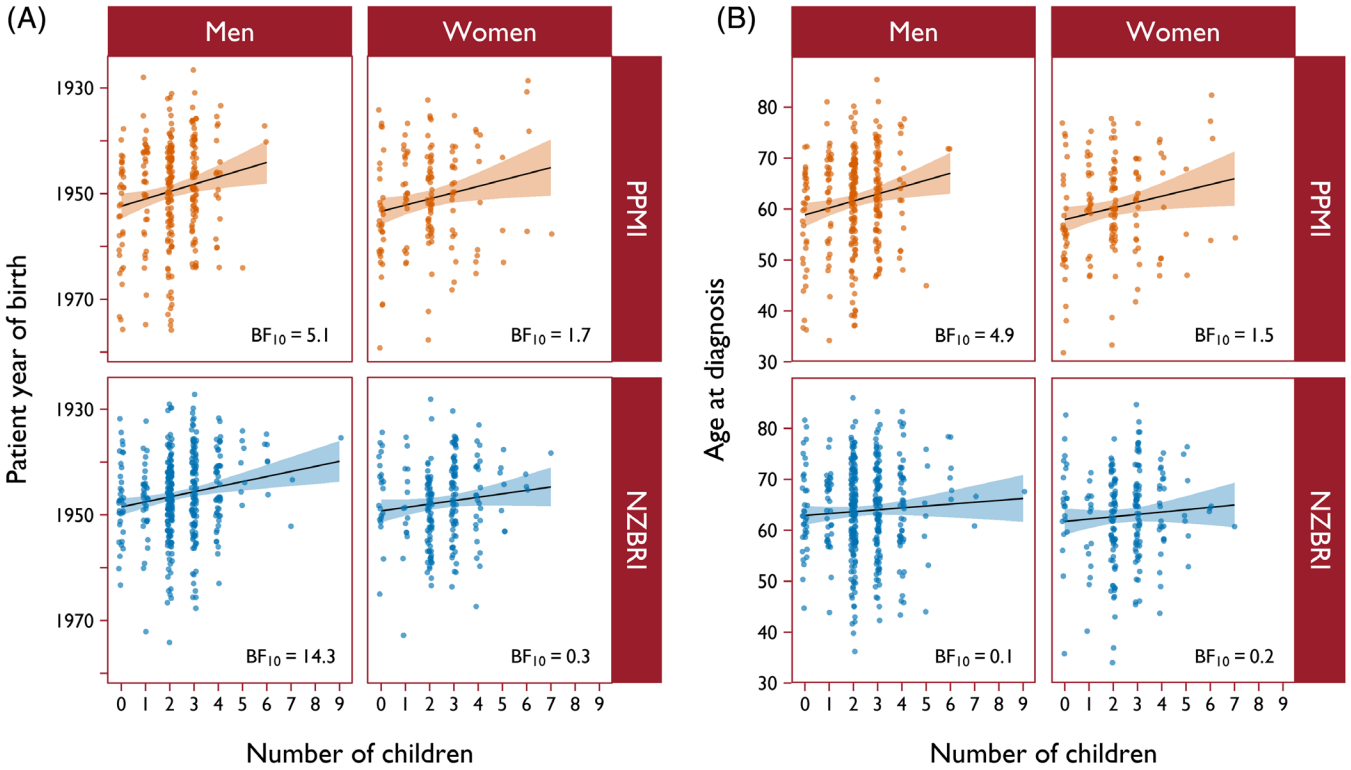

FIG 1. (**A**) In the PPMI (orange) and NZBRI (blue) studies, there was a background cohort effect in which older patients tended to have had more children than had patients who were born more recently (for ease of comparison with the age-of-onset associations, we plot number of children on the x-axis, although this does not reflect the direction of causality). The magnitude of this effect (i.e. the slope of each line) was such that each additional child was associated with the average patient having been born (approximately) one year earlier. The association was more strongly evident in men than in women in these samples. (**B**) PPMI is an incident study and hence patient age and age-of-diagnosis are tightly correlated. Accordingly, the PPMI age-of-diagnosis association almost perfectly reflects the underlying background societal association of older people having more children (at a similar magnitude of approximately one year per child). By contrast, the NZBRI survey was of a prevalent sample, in which a patient's current age and their age of diagnosis are no longer necessarily coupled. That is, a patient of a given age might have been recently diagnosed, or they could have long-standing disease. Accordingly, the age-of-diagnosis association was absent for both the NZBRI men and women, as indicated by the small BF (Bayes factor) values. Figure by MacAskill (2020), distributed at https://doi.org/10.6084/m9.figshare.9928460. [Color figure can be viewed at wileyonlinelibrary.com]

For completeness, we also examined whether women did actually have a later age of disease onset. As indicated in Table 1, the mean age at diagnosis was similar between the sexes, occurring earlier for women by just −0.8 years (-2.5 to 1.0 years).

NZBRI Sample

In the NZBRI sample, the slope for women was only 0.5 years per child (−0.5 to 1.4 years), with a Bayes factor of 0.2, indicating strong evidence against an association. The results were similar for men, with a slope of 0.4 years per child (−0.3 to 1.1 yaers), BF = 0.1.

The NZBRI mean age at diagnosis was again similar between the sexes, occurring earlier for women by just −0.5 years (−1.9 to 0.9 yaers).

Testing a Nonbiological Alternative Explanation

In many countries, because of late-20th-century societal changes, older people on average had larger families than people born more recently. Figure 1A shows such effects for the men and women in both studies. We then modeled how many years earlier we would expect a patient to have been born, given how many children he or she had. The coefficients are negative, as for consistency across studies with recruitment at different times, we modeled year of birth rather than age.

PPMI study. Women: −1.2 years per child, credible interval (−2.19 to −0.2 yars)], BF = 1.7. Men: −1.4 years per child (−2.38 to −0.4 years), BF = 5.1.

NZBRI study. Women: −0.6 years per child (−1.43 to 0.1 yaers), BF = 0.3 (although the association was not present in this sample, we know that the population fertility for New Zealand women did indeed decline markedly in the late 20th century[18]). Men: −1.0 years per child (−1.54 to −0.4 yaers), BF = 14.3.

Discussion

The PPMI men showed a clear association between having more children and later disease onset (although the data set is limited by having few patients with more than 4 children). This is sufficient to discount the proposed hormonal cause for this relationship, previously reported in women only.[12-14] We tested a nonbiological explanation, common to both

men and women, in which older patients are simply more likely than younger ones to have had larger families. In incident studies like PPMI, there is a near-perfect correlation between patient age and age at diagnosis. Accordingly, the diagnosis-age effect in the PPMI study (top row, Fig. 1B) very closely resembles the simple background generational cohort effect (top row, Fig. 1A). The previously reported associations are therefore likely an example of the classic epidemiological trap of mistaking an age effect for a generational cohort one.[19] As patient age and age at onset are almost perfectly correlated in this study, it is not possible to use age to statistically "correct for" generational membership.

Associations between number of children and diagnosis age were absent in both sexes in the NZBRI study (bottom row, Fig. 1B), although the background generational effect (bottom row, Fig. 1A) was similar to that in the PPMI study. This is consistent because in a prevalence sample, people with long-standing disease somewhat decouple the relationship between patient age and the age at diagnosis. Consider one person diagnosed at age 50 and another at 75. In an incident study, with recruitment soon after diagnosis, these people would necessarily come from different generations. In a prevalent sample, however, this relationship can break down. They could even be the same age, if one was recently diagnosed at age 75, whereas the other, also currently aged 75, had a 25-year history of disease. Artifactual associations between number of children and age at onset are therefore most likely in samples with a preponderance of incident cases. In a pure incident sample, the magnitude of the association should closely match the background societal association between age and family size (as shown in the roughly 1-year-per-child associations in the PPMI sample). Two of the previous studies defined disease duration from symptom onset: with mean duration of 2.5 years[12] and 5.8 years,[14] this indeed places them closer to the PPMI incident study (2.1 years mean female symptom duration) than to the NZBRI prevalent sample (in which the mean duration since diagnosis was 7.5 years, implying a much longer time relative to symptom onset). The third study had a median disease duration of 5 years, although it was not specified if that was defined from symptom onset or diagnosis.[13] The magnitude of the effect we found (approximately 1 year later onset per child) was smaller than in the previous studies. This is consistent with the complex web of social, cultural, financial, and health factors that influence family size, with generational cohort being only one contributor (evident in the large variability in Fig. 1A).

If there were a causal association between childbirth and delayed disease onset, women's mean onset age should be measurably later than men's (unless some other competing female risk factors could somehow balance the putative protective childbirth effect). We found male and female onset age was similar in both the PPMI and NZBRI samples. In the previous studies, women's onset age (57.1 years) was either similar to men's (57.3 yaers)[14] or nonsignificantly later (53.4 vs 51.3 years, $P = 0.06$)[12]; the remaining study[13] had no male comparison. That is, not only is the association between childbirth and later disease onset artifactual, there is likely no female age-at-onset advantage in need of explanation.

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