BMJ Mental Health

Genetic liability to bipolar disorder and onset of postpartum mental disorders

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► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/bmjment-2023-300835).

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Received 7 July 2023
Accepted 1 August 2023

To cite: Munk-Olsen T, Di Florio A, Bergink V, *et al*. *BMJ Ment Health* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/bmjment-2023-300835

INTRODUCTION

Childbirth triggers a broad range of diagnoses jointly defined as postpartum mental disorders (PMDs),[1] but immediate onset within the first 30 days after delivery has been linked to an increased probability of converting to bipolar disorder (BD) diagnoses later.[2] Building on these specific observations, we hypothesised that PMDs occurring within the first month after delivery have a higher bipolar genetic liability, measured as polygenic score (PGS), compared with those diagnosed 31–365 days post partum, and further speculated this association is specific to the PGS for BD compared with genetic liability to other severe mental disorders, such as major depressive disorder (MDD) and schizophrenia (SCZ).

METHODS

We conducted a cohort study linking Danish national registers to the Integrative Psychiatric Research (iPSYCH) study,[3] which included 93 608 individuals diagnosed with a major mental illness and a random sample of 50 615 subjects from the entire Danish population born during 1981–2005 (the subcohort). DNA was extracted from the blood and genotyped. We identified 2974 women with genetic data who had PMD, defined as any hospital admission or outpatient contact for mental illness (International Classification of Diseases, 10th Revision (ICD-10) codes F00–F99, excluding F10–F19 and F70–F79) 0–12 months after delivery.[4] We similarly defined previous psychiatric history as hospital contact for mental illness at any time before the delivery. DNA was extracted from the blood and genotyped. We derived LDpred2-auto[5] PGS from the latest genome-wide association study (GWAS) by Psychiatric Genomics Consortium. We also calculated PGS using the iPSYCH individual data. We then combined the PGS obtained from summary statistics and individual-level data through a linear combination.[6]The sample size for the discovery GWAS without the iPSYCH sample can be found elsewhere.[6] We converted PGSs into z-scores using PGS distributions in women from the subcohort born during 1981–1997. We used logistic regression to estimate the odds ratios (ORs) of PMD that occurred within 30 days vs 31–365 days after delivery by the BD PGSs in the form of both per SD increase (continuous variable) and tertiles and adjusted for all the covariates listed in table 1 and the first 10 principal components to account for population stratification.[7] To show the degree of specificity for genetic liability to BD, we also calculated PGSs for MDD and SZ as negative controls, as we did not expect to find an association between these estimates and the specific early onset of PMD. Given PMD among women without a psychiatric history prior to childbirth may be a distinct psychiatric phenotype, we, for additional comparative purposes, examined the associations in women with and without previous psychiatric history separately. Since we specified the hypotheses a priori, no corrections for multiple comparisons are needed.[8]

RESULTS

Of 2974 women with PMDs, 1120 had a psychiatric history and 1854 did not have a psychiatric history (table 1). Distributions of PGSs are shown in online supplemental eFigures 1 and 2.

Among women without psychiatric history, the odds of PMD that occurred within 30 days vs 31–365 days after delivery were marginally associated with a per-SD increase of BP PGS (OR 1.13, 95% CI 0.97 to 1.32) but not for our negative control PGSs (MDD or SCZ) (figure 1). Further, the ORs differed by tertiles of BD PGS, with the highest OR seen for the highest tertile (OR 1.40, 95% CI 1.00 to 1.96) in comparison to the lowest tertile (online supplemental eFigure 3A). Similar associations were not seen among women with a psychiatric history (online supplemental eFigure 3A, B, C).

DISCUSSION

This study is based on relatively few cases but provides preliminary evidence that the link between childbirth and the immediate onset of PMDs, in part, could be ascribed to a BD genetic liability. Interestingly, our findings suggest that this genetic link exists among women with no previous psychiatric history, in line with our previous population-based research indicating that incident PMDs within the first 30 days after delivery are linked explicitly to BD diagnoses.[2] Further, our findings suggest that first-onset PMD appears distinct from PMDs in women with a history of mental disorders.

The specificity of the association between BD genetics and the timing of PMD onset is intriguing, especially considering the lack of association for the analyses that applied negative controls using MDD and SCZ PGSs. However, we acknowledge the considerable genetic overlap between BD, MDD and SCZ, and MDD and SCZ PGSs may not act as the perfect negative controls. Therefore, we encourage future studies to consider alternative

Table 1 Characteristics of the study population at the timing of the first psychiatric episode by previous psychiatric history

Characteristics	Women with no previous psychiatric history (N=1854)		Women with a previous psychiatric history (N=1120)	
Timing at PMD onset after delivery	**0–30 days**	**31–365 days**	**0–30 days**	**31–365 days**
No of women	250	1604	133	987
Age at delivery (years)				
<24	97 (38.8)	852 (53.1)	57 (42.9)	539 (54.6)
25–29	114 (45.6)	593 (37.0)	59 (44.4)	377 (38.2)
≥30	39 (15.6)	159 (9.9)	17 (12.8)	71 (7.2)
Primiparity	201 (80.4)	1066 (66.5)	102 (76.7)	697 (70.6)
Parental country of origin				
Denmark	225 (90.0)	1418 (88.4)	120 (90.2)	884 (89.6)
At least one parent outside Denmark	25 (10.0)	186 (11.6)	13 (9.8)	103 (10.4)
Parental psychiatric history				
Any psychiatric disorder*	14 (5.6)	136 (8.5)	43 (32.3)	395 (40.0)
No history of psychiatric disorders	236 (94.4)	1468 (91.5)	90 (67.7)	592 (60.0)
Calendar year at delivery				
2000–2005	13 (5.2)	121 (7.5)	6 (4.5)	49 (5.0)
2006–2010	76 (30.4)	565 (35.2)	39 (29.3)	380 (38.5)
2011–2015	161 (64.4)	918 (57.2)	88 (66.2)	55.8 (56.5)

Values are numbers (percentages) unless stated otherwise.
*Less than 0.5% of women were born to parents with bipolar history, and we were not able to include a separate group due to Danish legislation.
PMD, postpartum mental disorder.

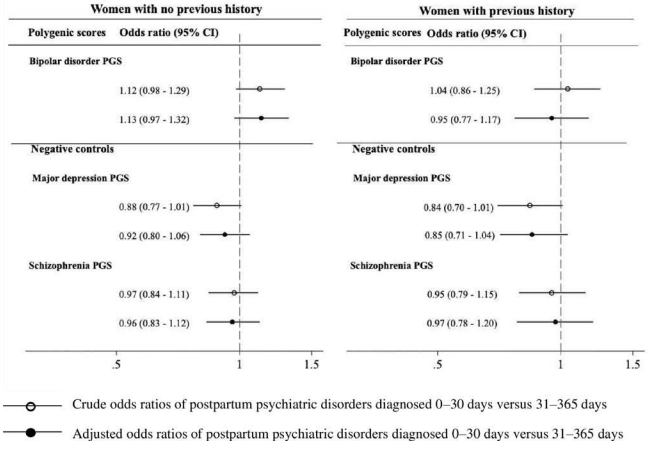

Figure 1 The ORs of postpartum psychiatric disorders diagnosed 0–30 days vs 31–365 days by per 1-SD increase in the polygenic risk scores (PGS). Adjusted for age at delivery, primiparity, parental country of origin, parental psychiatric history, calendar year at delivery and the first 10 principal components.

controls. If replicated, our findings could (1) argue against broad definitions of postpartum mental illness in mechanistic and clinical studies, (2) add to evidence that if women have early onset PMDs, bipolar spectrum disorders should be a diagnostic consideration and (3) encourage distinguishing PMDs identified as first onset versus recurrent episodes. Finally, moving forward, we tentatively speculate how the timing of onset in itself can be a diagnostic tool to identify a subgroup of PMDs.

Acknowledgements The authors gratefully acknowledge the Psychiatric Genomics Consortium (PGC) and the research participants and employees of 23andMe, Inc., for providing the summary statistics used to generate the polygenic risk scores.

Contributors XL conducted the data analysis and has complete access to all study data, ensuring data integrity and accuracy of the analysis. TM-O wrote the first draft of the manuscript. TM-O, ADF and XL conceived and designed the study. All authors contributed to the result interpretation, providing critical reviews of the paper and have approved the final manuscript.

Funding This work is funded by R01 MH122869. TM-O is also supported by the Lundbeck Foundation (R313-2019-569). XL is supported by the European Union's Horizon 2020 research and innovation programme under the Marie Sklodowska-Curie grant agreement No 891079. The genotyping was funded by the Lundbeck Foundation and the Clarman Foundation.

Competing interests None declared.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement XL has full access to all data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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