Genetic liability to bipolar disorder and onset of postpartum mental disorders

Trine Munk-Olsen,1,2,3 Arianna Di Florio,4 Veerle Bergink,5 Esben Agerbo,2,3 Kathrine Bang Madsen,2,3 Liselotte Vogdrup Petersen,2,3 Xiaoqin Liu 2,3

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.3 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-auto5 PGSs from the latest genome-wide association study (GWAS) by Psychiatric Genomics Consortium. We also calculated PGSs 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 and the first 10 principal components to account for population stratification.7

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). Similarly 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.5 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

© Author(s) (or their employer(s)) 2023. Re-use permitted under CC BY-NC. Published by BMJ.

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

To view, please visit the journal online (http://dx.doi.org/10.1136/bmjment-2023-300835)
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 (R313-2019-5690). XL is supported by the European Union’s Horizon 2020 research and innovation programme under the Marie Skłodowska-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.

Supplemental material This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/.

ORCID iD Xiaoqin Liu http://orcid.org/0000-0003-4519-1536

REFERENCES

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

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Women with no previous psychiatric history (N=1854)</th>
<th>Women with a previous psychiatric history (N=1120)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Timing at PMD onset after delivery</strong></td>
<td>0–30 days</td>
<td>31–365 days</td>
</tr>
<tr>
<td>No of women</td>
<td>250</td>
<td>1604</td>
</tr>
<tr>
<td>Age at delivery (years)</td>
<td>&lt;24</td>
<td>25–29</td>
</tr>
<tr>
<td></td>
<td>97 (38.8)</td>
<td>114 (45.6)</td>
</tr>
<tr>
<td></td>
<td>852 (53.1)</td>
<td>593 (37.0)</td>
</tr>
<tr>
<td></td>
<td>57 (42.9)</td>
<td>59 (44.4)</td>
</tr>
<tr>
<td></td>
<td>539 (54.6)</td>
<td>377 (38.2)</td>
</tr>
<tr>
<td></td>
<td>≥30</td>
<td>2018</td>
</tr>
<tr>
<td></td>
<td>39 (15.6)</td>
<td>201 (80.4)</td>
</tr>
<tr>
<td></td>
<td>159 (9.9)</td>
<td>1066 (66.5)</td>
</tr>
<tr>
<td></td>
<td>17 (12.8)</td>
<td>102 (76.7)</td>
</tr>
<tr>
<td></td>
<td>71 (7.2)</td>
<td>697 (70.6)</td>
</tr>
</tbody>
</table>

Fig. 1 The ORs of postpartum psychiatric disorders diagnosed 0–30 days versus 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.