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Genetic liability to posttraumatic stress disorder and its association with postpartum depression

Kathrine Bang Madsen[1,2], Xiaoqin Liu[1,2], Clara Albiñana[1,2], Bjarni Jóhann Vilhjálmsson[1,2,3], Esben Agerbo[1,2,4], Preben Bo Mortensen[1,2,4], David Michael Hougaard[2,5], Merete Nordentoft[2,6,7], Thomas Werge[2,7,8,9], Ole Mors[2,10], Anders D. Børglum[2,11,12] and Trine Munk-Olsen[1,2,13]

[1]NCRR – National Centre for Register-based Research, Business and Social Sciences, Aarhus University, Aarhus, Denmark; [2]iPSYCH, The Lundbeck Foundation Initiative for Integrative Psychiatric Research, Denmark; [3]Bioinformatics Research Centre, Aarhus University, Aarhus, Denmark; [4]CIRRAU – Centre for Integrated Register-based Research, Aarhus University, Aarhus, Denmark; [5]Department for Congenital Disorders, Statens Serum Institut, Copenhagen, Denmark; [6]CORE – Copenhagen Research Centre for Mental Health, Mental Health Centre Copenhagen, Mental Health Services in the Capital Region of Denmark, Copenhagen, Denmark; [7]Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark; [8]Institute of Biological Psychiatry, Mental Health Services, Copenhagen University Hospital, Copenhagen, Denmark; [9]Lundbeck Foundation Center for GeoGenetics, GLOBE Institute, University of Copenhagen, Copenhagen, Denmark; [10]Psychosis Research Unit, Aarhus University Hospital – Psychiatry, Aarhus, Denmark; [11]Department of Biomedicine and the iSEQ Center, Aarhus University, Aarhus, Denmark; [12]Center for Genomics and Personalized Medicine, CGPM, Aarhus, Denmark and [13]Research Unit of Psychiatry, Institute for Clinical Research, University of Southern Denmark, Odense, Denmark

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Author for correspondence:
Kathrine Bang Madsen,
E-mail: kathrine.bang@econ.au.dk

Abstract

Background. Childbirth may be a traumatic experience and vulnerability to posttraumatic stress disorder (PTSD) may increase the risk of postpartum depression (PPD). We investigated whether genetic vulnerability to PTSD as measured by polygenic score (PGS) increases the risk of PPD and whether a predisposition to PTSD in PPD cases exceeds that of major depressive disorder (MDD) outside the postpartum period.

Methods. This case-control study included participants from the iPSYCH2015, a case-cohort of all singletons born in Denmark between 1981 and 2008. Restricting to women born between 1981 and 1997 and excluding women with a first diagnosis other than depression ($N = 22\,613$), 333 were identified with PPD. For each PPD case, 999 representing the background population and 993 with MDD outside the postpartum were matched by calendar year at birth, cohort selection, and age. PTSD PGS was calculated from summary statistics from the Psychiatric Genomics Consortium with LDpred2-auto. Odds ratios (ORs) were estimated using conditional logistic regression adjusted for parental psychiatric history and country of origin, PGS for MDD and age at first birth, and the first 10 principal components.

Results. The PTSD PGS was significantly associated with PPD (OR 1.42, 95% CI 1.20–1.68 per standard deviation increase in PTSD PGS) compared to healthy female controls. Genetic PTSD vulnerability in PPD cases did not exceed that of matched female depression cases outside the postpartum period (OR 1.10, 95% CI 0.94–1.30 per standard deviation increase).

Conclusions. Genetic vulnerability to PTSD increased the risk of PPD but did not differ between PPD cases and women with depression at other times.

Introduction

Childbirth increases the risk of mental disorders, including postpartum depression (PPD), inferring that PPDs and related disorders are triggered by some components related to either pregnancy, delivery, or the postpartum period (Howard et al., 2014; Meltzer-Brody et al., 2018). PPD is the most common complication of childbirth, with prevalence estimates ranging from 12% to 19% (O'Hara & McCabe, 2013; Shorey et al., 2018). As with other mental disorders, the etiology of PPD is not established, but is likely due to a combination of genetic, biological, and environmental factors (Batt, Duffy, Novick, Metcalf, & Epperson, 2020). A Swedish twin study demonstrated a heritability of perinatal depression at 44%, notably higher than non-perinatal depression (32%) suggesting that PPD may be genetically distinct from depression (Viktorin et al., 2016). However, a recent study found a strong association between genetic liability to depression and risk of PPD confirming the genetic overlap between these phenotypes (Bauer et al., 2019).

As PPD is linked directly to delivery, it seems plausible that the birth itself, if experienced as traumatic, could act as a trigger for PPD. This hypothesis is supported through evidence documenting how factors related to a traumatic birth, including preterm birth and cesarean section, increase risk of PPD and acute stress reactions postpartum (de Paula Eduardo, de Rezende, Menezes, & Del-Ben, 2019; Meltzer-Brody et al., 2017).

Birth trauma can impact the psychological wellbeing of the mother, with loss of control, excessive pain, and fear of the baby's health considered the most general elements of childbirth that make it potentially traumatizing (Agius, Xuereb, Carrick-Sen, Sultana, & Rankin, 2016; Lefkowitz, Baxt, & Evans, 2010; Zaers, Waschke, & Ehlert, 2008). There is increasing evidence that women may develop posttraumatic stress disorder (PTSD) as a result of a traumatic birth and the prevalence of PTSD resulting from childbirth events has been estimated at 4% postpartum (Yildiz, Ayers, & Phillips, 2017).

The high prevalence of PTSD and depression comorbidity in non-postpartum samples has been repeatedly reported and a meta-analysis reported a co-occurrence of 52% (Rytwinski, Scur, Feeny, & Youngstrom, 2013). Also, genetic variation associated with PTSD has been shown to positively correlate with PGS for depression (Nievergelt et al., 2019). In relation to the postpartum period, some studies indicate that women experiencing PTSD specifically related to childbirth often report symptoms of depression (Dikmen-Yildiz, Ayers, & Phillips, 2017; Söderquist, Wijma, Thorbert, & Wijma, 2009; White, Matthey, Boyd, & Barnett, 2006), suggesting that postpartum depressive reactions can be implicated in trauma exposure.

Based on the above considerations, we hypothesized that vulnerability to PPD is influenced by genetic vulnerability to PTSD, and the aim of this study was to investigate (1) if genetic vulnerability to PTSD measured by polygenic scores (PGSs) increase the risk of PPD and (2) to which extent a predisposition to PTSD in PPD cases exceeds that of matched female depression cases outside the postpartum period.

Methods

Data sources

We obtained data from the Danish national registers linked with genetic data from the Integrative Psychiatric Research (iPSYCH) study, through the use of unique Central Person Register (CPR) numbers. The iPSYCH2015 was sampled as a case-cohort study and included a subset of the Danish Civil Registration System (Pedersen, 2011) of all singletons born from 1 May 1981 to 31 December 2008, who were alive and resided in Denmark at their 1-year birthday (i.e. the full cohort), and is an expansion of the iPSYCH2012 cohort (Bybjerg-Grauholm et al., 2020; Pedersen et al., 2018). In total, the expanded iPSYCH2015 sample consists of 93 608 individuals with a diagnosis of schizophrenia, autism, attention-deficit/hyperactivity disorder, or affective disorders by the end of 2015 identified from the Danish Psychiatric Central Research Register, which holds information on inpatient contacts at psychiatric hospitals and wards during 1969–1994 and outpatient contacts since 1995 (Mors, Perto, & Mortensen, 2011). In the register, diagnoses are recorded using the International Classification of Diseases, 8th Revision (ICD-8) codes until 1993, and ICD-10 codes from 1994 and onwards. Also, a random sample of 50 615 population controls was drawn from the full cohort, which may also have psychiatric disorders later (Fig. 1). A detailed description of the iPSYCH2015 sample has been published previously (Bybjerg-Grauholm et al., 2020). In the present study, iPSYCH2012 refers to the original data selection while iPSYCH2015i refers to the second selection and iPSYCH2015 to the combined. DNA was extracted from the Danish Newborn Screening Biobank and genotyped using the Infinium PsychChip v1.0 array for the iPSYCH2012 sample and the Global Screening Array v2 for the iPSYCH2015i sample, both from Illumina (Illumina, San Diego, CA, USA). The genotyping, quality control, and variant calling process for the samples and markers have been described in detail elsewhere (Bybjerg-Grauholm et al., 2020; Pedersen et al., 2018). Non-genotyped markers were imputed using the Haplotype Reference Consortium as reference panel (The Haplotype Reference Consortium, 2016) following the RICOLPILI pipeline (Lam et al., 2020), as well as quality control. For the PGS calculation, the number of variants was restricted to the common set of variants described in the HapMap3 project.

Definition of postpartum depression

Depression was defined by a diagnosis of single and recurrent depressive disorders (ICD-8 codes: 296.09, 296.29, 298.09, and 300.49; ICD-10 codes F32–33) recorded in the Danish Psychiatric Central Research Register (Mors et al., 2011). Women were categorized as PPD cases if their first depressive episode occurred within 12 months after delivery and major depression (MDD) cases otherwise, meaning the PPD cases did not have a previous depressive episode.

Study population

PPD case identification

The iPSYCH2015 sample comprised 50 057 women born between 1981 and 1997. We excluded 4586 women with no available genetic data and 374 women with no linkage to their parents. Moreover, we excluded 22 484 women with other psychiatric disorders (all ICD-10 F diagnoses except F32–33) as the first psychiatric episode from the case cohort since these women would not contribute to the identification of PPD or MDD cases or controls. Of the remaining 22 613 women, we identified PPD cases by obtaining information on the date of delivery from the Danish Medical Birth Registry, established in 1973 (Bliddal, Broe, Pottegård, Olsen, & Langhoff-Roos, 2018) (Fig. 1).

Each PPD case was matched to three control women from the subcohort representing a *healthy female background population* to explore aim 1 (if genetic vulnerability to PTSD is associated with increased risk of PPD). Criteria for matching were by the cohort selection (iPSYCH2012 sample or iPSYCH2015i) to account for the change of array in genotyping, and calendar year at birth for women who did not have a psychiatric episode when their matched PPD case had the first depressive episode.

Each PPD case was further matched with up to three MDD cases by a single year of age at first depression diagnosis, calendar year at birth, and the cohort selection (iPSYCH2012 sample or iPSYCH2015i). This was done in order to explore aim 2 (to which extent predisposition to PTSD in PPD cases exceeds that of depression outside the postpartum period).

After matching, 333 women in the PPD group, 999 women in the control group, and 993 in the MDD group were included in the analysis.

Polygenic score for PTSD

The PTSD PGS was calculated using LDpred2-auto (Privé, Arbel, & Vilhjálmsson, 2021) on the latest PTSD GWAS summary statistics from the Psychiatric Genomic Consortium (Nievergelt et al., 2019) restricted to individuals of European ancestry. We restricted the model to the Single Nucleotide Polymorphisms (SNPs) in

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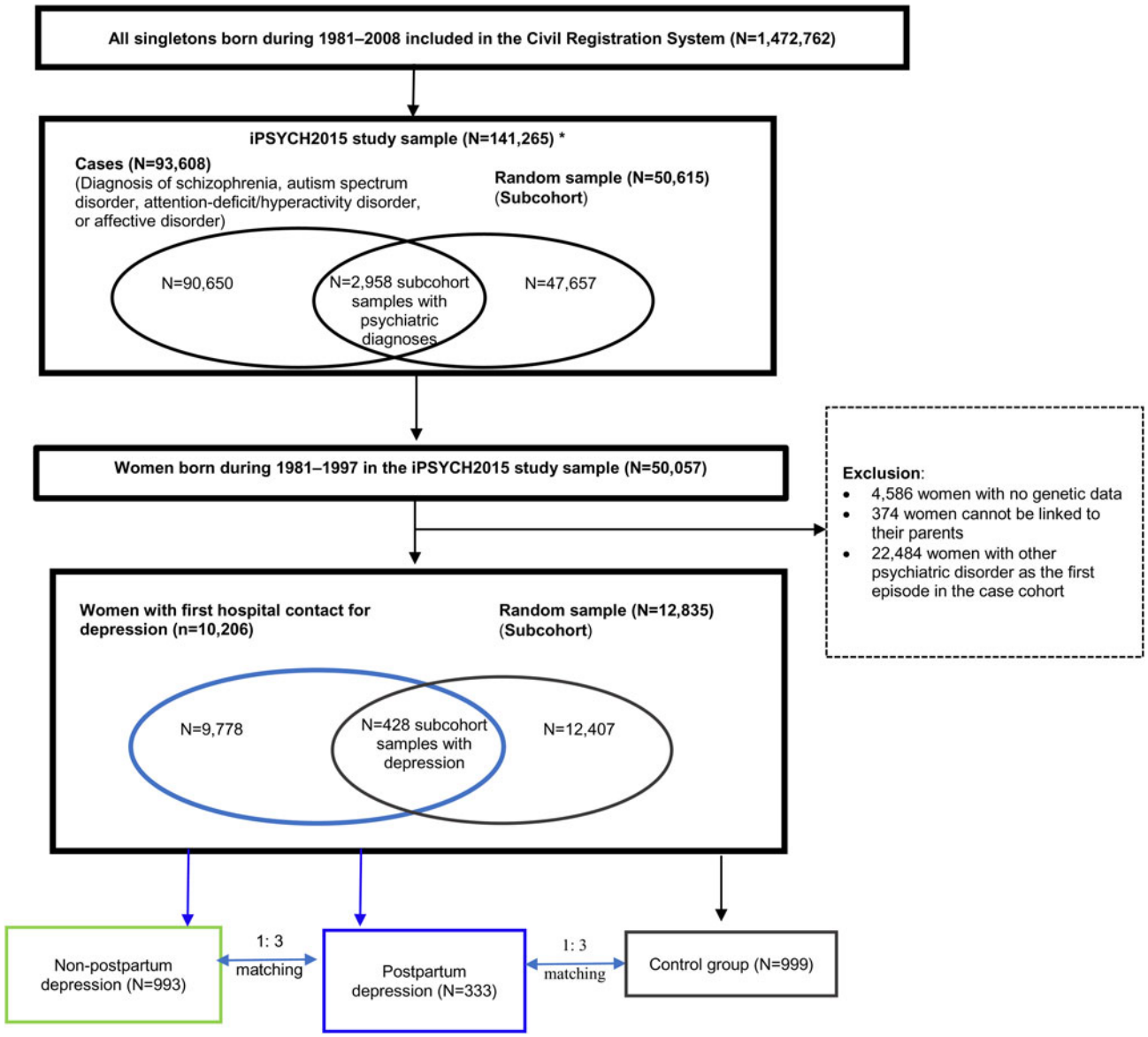

Fig. 1. Flowchart illustrating the identification of the study population. *Ascertainment refers to whether the individuals were from the cases or the random sample of the entire Danish population.

common between the iPSYCH2015 imputed dataset, the GWAS summary statistics, and the HapMap3 set of common variants (https://www.sanger.ac.uk/resources/downloads/human/hapmap3.html), leaving a total of 1 107 677 SNPs. For LDpred2-auto, we used the PTSD LDSC SNP-heritability estimate (3.75%) as the initiation parameter.

Polygenic score for MDD

The MDD PGS was calculated using LDpred2-auto on the latest MDD GWAS summary statistics from the Psychiatric Genomic Consortium (Howard et al., 2019). We restricted the model to the SNPs in common between the iPSYCH2015 imputed dataset, the GWAS summary statistics, and the HapMap3 set of common variants (https://www.sanger.ac.uk/resources/downloads/human/hapmap3.html), leaving a total of 1 108 585 SNPs. For LDpred2-auto, we used the MDD LDSC SNP-heritability estimate (8.9%) as the initiation parameter.

Statistical analysis

Descriptive statistics were used to describe and summarize the characteristics of PPD cases, healthy controls, and MDD (non-PPD) cases. PGSs were converted into *z*-scores and into quintiles according to the PGS distributions in women born during 1981–1997 from the subcohort. We calculated the standardized PGSs based on the following formula: (observed value–mean)/standard deviation. Conditional logistic regression was performed to estimate the odds ratios (ORs) with 95% confidence intervals (95% CIs) of developing PPD or MDD *v.* controls by PGSs in the form of both per standard deviation increase (continuous variable) and quintiles in comparison to the lowest quintile. We compared the associations pairwise, i.e. the PPD case with her controls and MDD cases with the controls of their matched PPD case.

First, we calculated the ORs of PPD *v.* controls (and MDD *v.* controls), with the following interpreation: An OR of more than

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1 means the odds of PPD *v.* controls increases with the change in PGS, i.e. per standard deviation increase or a higher quintile *v.* the lowest quintile. We then calculated the ORs of PPD *v.* MDD. All comparisons were performed only between PPD case and her matched MDD cases. We adjusted the analyses for the first 10 principal components, maternal psychiatric history (yes/no), and paternal psychiatric history (yes/no). Parental (maternal or paternal) psychiatric history was defined as having a hospital contact for any psychiatric disorders (all ICD-10 F diagnoses) or receiving psychotropic medication before the first depression episode. Associations between PGS for mental illness and PPD could be explained by an earlier age at childbirth in the PPD group (age at becoming a mother). To account for the genetic correlations between psychiatric disorders and reproductive behavior, we further adjusted for PGS for age at first birth (Ni et al., 2019). This was done based on documented differences in mental health in mothers *v.* non-mothers (Agerbo, Mortensen, & Munk-Olsen, 2013; Johannsen et al., 2016; Munk-Olsen, Laursen, Pedersen, Mors, & Mortensen, 2006). PGS for age at first birth was calculated using LDpred2-auto in the external GWAS summary statistics (Watanabe et al., 2019) and the HapMap 3 (HM3) subset of SNPs. Finally, we adjusted the analyses for the MDD PGS.

To investigate whether any associations were driven by fertility, we conducted a sensitivity analysis among women with at least one child at the time of first depression diagnosis and matched each PPD case to one MDD case on age at first onset, calendar year at birth, and the recruitment year (iPSYCH2012 or iPSYCH2015i). In adittion, we conducted a sensitivity analysis stratifying on timing of depression onset following childbirth (0–3, 3–6, 6–12 months).

A principal component analysis was performed on the iPSYCH2015 sample, using the bigsnpr R package (Privé, Luu, Blum, McGrath, & Vilhjálmsson, 2020) and following their proposed guidelines.

Data processing and analyses were conducted in Stata version 15.0 (StataCorp, College Station, TX, USA).

Results

The sample consisted of 333 PPD cases, 999 female controls from the background population, and additional 993 matched MDD cases (non-PPD cases), see Table 1 for further characteristics of the study population. All women with PPD had at least one child at diagnosis, whereas around 20% of women from MDD and controls had a child at the time of matching. Women from the PPD and MDD groups were more likely to have a maternal and paternal psychiatric history than the controls from the background population.

Does genetic vulnerability to PTSD increase risk of PPD? (aim 1)

PTSD PGS was significantly associated with an increased risk of PPD (aOR 1.25, 95% CI 1.05–1.49 for per standard deviation increase in PTSD PGS. When exploring the ORs by PTSD PGS in quintiles, the risk of PPD was significantly increased for PTSD PGS in the second quintile and above, except that the associations were not statistically significant for the third and fourth quintiles, with the aORs ranging from 1.25 to 2.01, in comparison to the lowest quintile of PTSD PGS (Fig. 2). The distribution of the standardized PTSD PGS in the three groups is shown in Fig. 3. For MDD and PPD cases, the distribution is slightly shifted to the right compared to controls, meaning a higher density of a higher PTSD score for these two groups.

When compared to controls, the PTSD PGS was significantly associated with an increased risk of MDD (aOR 1.17, 95% CI 1.02–1.33 for per standard deviation increase in PTSD PGS). Exploring the ORs by PTSD PGS in quintiles, the risk of MDD was significantly increased for PTSD PGS in the second quintile and above, with the aOR ranging from 1.44 to 1.51, in comparison to the lowest quintile of PTSD PGS (Fig. 2).

To which extent does a genetic predisposition to PTSD exceed that of depression outside the postpartum period? (aim 2)

The odds of PPD *v.* MDD was not associated with an increase in PTSD PGS (per standard deviation aOR 1.08, 95% CI 0.92–1.28). When dividing the samples into quintiles, the aOR did not differ between women with higher PTSD PGS and those with the lowest quintile in terms of PPDs *v.* MDD, and the aOR did additionally not differ by second, third, or fourth quintile compared to the lowest quintile (Fig. 4).

In the sensitivity analysis restricting to women who had given birth at the time of depression diagnosis, 320 PPD cases were matched to 320 MDD cases. The results from the sensitivity analysis (aOR 1.05, 95% CI 0.84–1.30 per standard deviation) did not differ substantially from the primary analysis (aOR 1.08, 95% CI 0.92–1.28 per standard deviation). Neither did the aOR differ between women with higher PTSD PGS and those with the lowest quintile, when dividing the samples into quintiles (online Supplementary Fig. S1).

Stratifying on timing of depression onset, we found 116 cases during 0–3 months, 81 cases during 3–6 months, and 136 cases during 6–12 months postpartum. The adjusted ORs of PPD *v.* MDD were 1.02 (95% CI 0.80–1.31), 1.07 (95% CI 0.78–1.47), and 1.15 (95% CI 0.91–1.46) per S.D. increase in PTSD PRS for PPD diagnosed at 0–3, 3–6, and 6–12 months.

Discussion

Using a matched set-up comparing PPD cases to both healthy and MDD controls, we found genetic vulnerability to PTSD was significantly associated with an increased risk of PPD compared to healthy female controls. However, the PTSD PGS was not associated with PPD when compared with MDD outside the postpartum, meaning a predisposition for PTSD in PPD cases does not exceed that of depression outside the postpartum.

While some women have a specific biological vulnerability to the postpartum (sensitivity to the drastic decrease in gonadal hormones following birth) (Bloch et al., 2000; Schiller, Meltzer-Brody, & Rubinow, 2015), others may have a general vulnerability to traumatic life events, which increases their risk of developing PPD if birth is experienced as traumatic (Batt et al., 2020). Söderquist et al. found that PTSD and depression occurring postpartum were positively related and were predicted by mainly the same factors (Söderquist et al., 2009). Also, prior depression has been reported to be a strong vulnerability factor for developing childbirth-related PTSD (Söderquist et al., 2009), and prior PTSD to render vulnerability to PPD (Johansen, Stenhaug, Robakis, Williams, & Cullen, 2020; Oh et al., 2016). Dekel and et al. found 90% of women who experienced postpartum PTSD also had postpartum depressive symptoms, while among those with depressive symptoms postpartum, one-third experienced postpartum PTSD symptoms (Dekel, Ein-Dor, Dishy, & Mayopoulos, 2020). Jointly these results indicate a bidirectional association between PTSD and PPD. Further, their results suggested that PPD alone *v.* PTSD and PPD co-occurrence had

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Table 1. Characteristics of the study population at the time of first depression diagnosis

Characteristics	Postpartum depression ($n = 333$)	Control women ($n = 999$)	Non-postpartum depression ($n = 993$)
Age at first psychiatric onset (years), mean ± S.D.	24.9 ± 3.1	–	24.8 ± 3.1
Parental country of origin			
Denmark	300 (90.1)	911 (91.2)	907 (91.3)
At least one parent outside Denmark	33 (9.9)	88 (8.8)	86 (8.7)
Maternal psychiatric history	40 (12.0)	57 (5.7)	121 (12.2)
Paternal psychiatric history	37 (11.1)	51 (5.1)	106 (10.7)
Having at least one child at the time of diagnosis[a]	333 (100.0)	214 (21.4)	220 (22.2)
The selection of cohort			
iPSYCH2012	310 (93.1)	930 (93.1)	925 (93.2)
iPSYCH2015i	23 (6.9)	69 (6.9)	68 (6.8)
Calendar year at birth			
1981–1984	174 (52.3)	522 (52.3)	521 (52.5)
1985–1989	131 (39.3)	393 (39.3)	389 (39.2)
1990–1997	28 (8.4)	84 (8.4)	83 (8.4)

[a]For the controls, having at least one child at the time of diagnosis refers to the status when their matched PPD cases had the first depression episode.

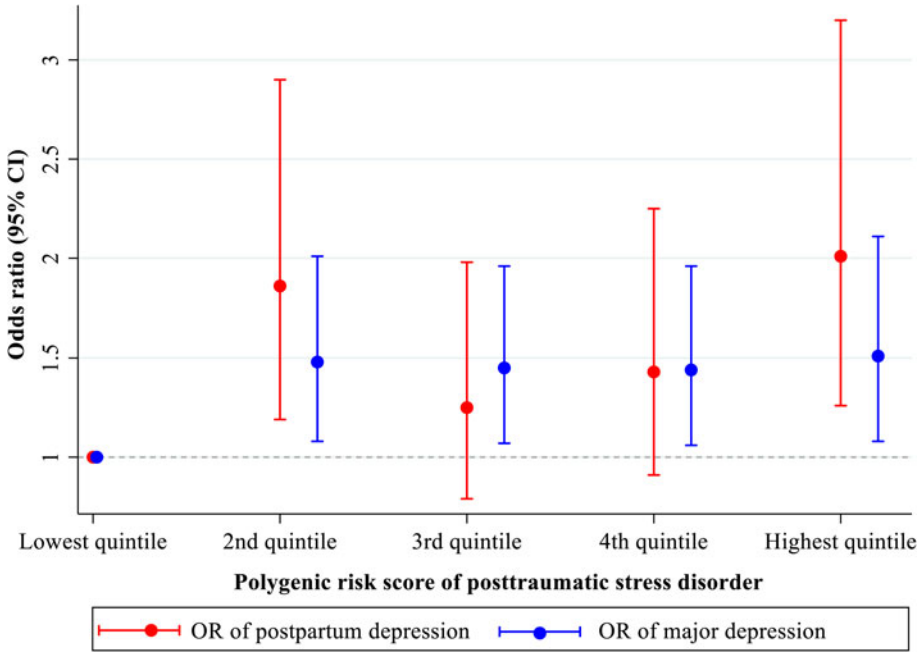

Fig. 2. aORs of postpartum depression and major depression *v.* controls binned by PTSD PGS after adjusting for the first 10 principal components, PGS for age at first birth, MDD PGS, maternal and paternal psychiatric history, and parental country of origin. ORs represent comparisons against the lowest quintile.

different combinations of risk factors. Unlike PPD alone, stressors concerning the childbirth event (preterm delivery, medical complications, and admission of the newborn) were predictive of the comorbid PTSD-PPD expression (Dekel et al., 2020).

PPD and PTSD constitute separate diagnostic and conceptual entities, with PTSD classified as a trauma and stress-related disorder and PPD as a mood disorder (American Psychiatric Association & American Psychiatric Association, 2013). However, PPD and PTSD share several common diagnostic features, including diminished interest in activities, feelings of detachment from others, a restricted range of affect, difficulty falling or staying asleep, and difficulty in concentrating (American Psychiatric Association & American Psychiatric Association, 2013), and the disorders are highly comorbid (Ayers, Bond, Bertullies, & Wijma, 2016). Also, genetic variation associated with PTSD has been shown to positively correlate with PGS from other psychiatric traits, including depressive symptoms (Nievergelt et al., 2019).

We found genetic vulnerability to PTSD in PPD cases did not exceed that in matched MDD female controls. In itself, this may not be surprising as psychiatric disorders are highly polygenic and

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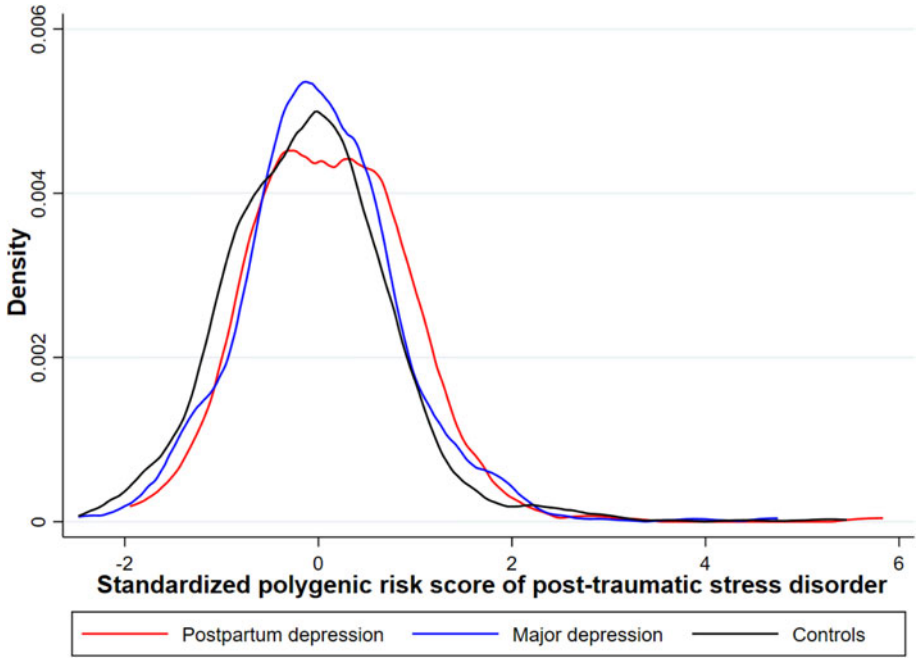

Fig. 3. Kernel density distribution of PGS of post-traumatic disorders in postpartum depression cases, major depression cases, and controls.

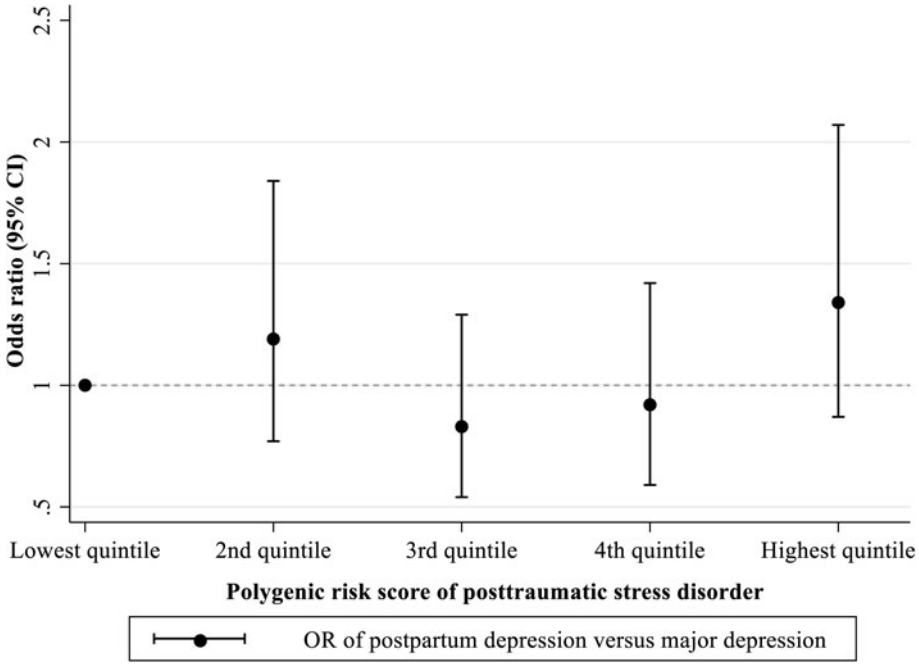

Fig. 4. aORs of PPD *v.* MDD binned by PTSD PGS after adjusting for first 10 principal components, PGS for age at first birth, MDD PGS, maternal and paternal psychiatric history, and parental country of origin. aORs represent comparisons against the lowest quintile.

PTSD is significantly (genetically) correlated with major depression (Nievergelt et al., 2019). However, these observations feed into a PPD-related discussion, centered around an overall question if PPD is a distinct diagnostic entity or a depression subtype (Batt et al., 2020; Di Florio & Meltzer-Brody, 2015). Considering this specific discussion, our results do not indicate PPD is a distinct disorder from MDD, although only when comparing PTSD vulnerability in the two groups. Regardless, we eagerly await the arrival of a PPD PGS which will contribute to a discussion related to PPD diagnostic heterogeneity, and elucidate the genetic basis of PPD and thereby provide data on the genetic overlap with both PTSD and MDD (Guintivano, Putnam, Sullivan, & Meltzer-Brody, 2019).

Strengths and limitations

To our knowledge, this is the first study to examine PTSD vulnerability in PPD cases using genetic information. We based our study on data from the iPSYCH2015 study sample, one of the largest data sources combining genetic and environmental information on psychiatric disorders (Bybjerg-Grauholm et al., 2020). The iPSYCH study sample is selected from a national representative sample strengthening the generalizability of our results. Information of high validity on all individuals in the study sample was ensured using data from the national registers. The validity of the ICD-10 diagnosis of single depressive episode as recorded in

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the Danish Psychiatric Central Register has been reported to be reasonably good (Bock, Bukh, Vinberg, Gether, & Kessing, 2009).

In contrast, methodological limitations include a small study sample with inherent limited statistical power. Also, the iPSYCH sample is a young cohort (born between 1981 and 2008), which means that it is a selected population of women who have given birth at a young age. Thus, we do not know their complete reproductive and psychiatric history. For generalizability, we included women at different ages, and therefore we chose to control for the PGS for age at first birth to take into account the inbuilt selection into motherhood and correlation between psychiatric disorders and reproductive behavior. The results from our sensitivity analysis restricting to women who had given birth at time of depression diagnosis did not differ from our primary analysis.

We defined PPD as depression onset up to 12 months postpartum. Applying this definition may show a higher overlap of PPD with MDD. However, our sensitivity analysis stratifying on timing of PPD onset did not show any differences.

We note that the PTSD GWAS included about 5% of the entire iPSYCH sample, corresponding to about 2% of samples used in the GWAS. This suggests that there is a small sample overlap (likely less than 100) between the training sample and the testing sample, which could potentially lead to overfitting of the PTSD PRS.

Finally, we report associations with no opportunity to make any claims regarding causality, and rely on PGS genetic measures which only partly captures a genetic disease vulnerability.

Conclusion

Applying a matched study design and relying on PGS data on PSTD, we found that a high genetic vulnerability to PTSD was associated with an increased risk of PPD. However, the genetic vulnerability to PTSD in PPD cases did not exceed that in matched MDD female controls.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S0033291722002045

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Conflict of interest. None.

Ethical standards. The study was approved by the Danish Scientific Ethics Committee (Project ID: 1-10-72-287-12), the Danish Data Protection Agency (Project ID: 2012-41-0110), and the Danish Neonatal Screening Biobank Steering Committee. No informed consent is needed for register-based studies in Denmark.

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