

Familial risk of postpartum depression

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Abstract

Objective: Many psychiatric diseases have a strong familial aggregation, but it is unknown whether postpartum depression (PPD) without prior psychiatric history aggregates in families.

Methods: Based on Danish national registers, we constructed a cohort with information on 848,544 singleton deliveries (1996–2017). Women with an episode of PPD were defined as having used antidepressant medication and/or had a hospital contact for depression within 6 months after delivery. Those with psychiatric history prior to the delivery were excluded. We estimated relative risk (RR) of PPD, comparing women with female relatives with and without PPD history, respectively.

Results: Overall, women with a PPD history in female blood relatives had themselves a higher risk of PPD (RR = 1.64, 95% CI 1.16–2.34). Having the first-degree female relative with PPD history was associated with a more than 2.5 times (RR = 2.65, 95% CI 1.79–3.91) increased risk of PPD. However, having the second/third-degree female relative and/or a female non-blood relative with PPD history did not increase the woman's own risk of PPD (RR = 0.58, 95% CI 0.26–1.28, RR = 1.09, 95% CI 0.83–1.44).

Conclusion: Postpartum depression aggregates in families with no other psychiatric history, but the findings do not support a strong genetic trait as a major cause. Other possible mechanisms are shared environment and/or health-seeking behavior in close relationships.

KEYWORDS

epidemiology, family study, genetics, postpartum depression, register-based cohort study

1 | INTRODUCTION

About 5–15% of all women giving birth experience a postpartum depression (PPD).^{1–4} Many psychiatric diseases have a strong familial aggregation as well as co-aggregation. Diseases such as major depression,^{5,6} generalized anxiety,⁷

attention deficit disorder, autism spectrum disorder, and schizophrenia^{8,9} have all been shown to aggregate in families,^{5–10} and linked with potential genetic traits in studies of genetics variants.^{11–15} However, familial aggregation of postpartum depression (PPD) is less well studied. In a large Swedish population-based cohort, the authors

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investigated the heritability of perinatal depression (the prenatal and antenatal period combined) among twins and sisters. They found a moderate heritability of perinatal depression, 44% and 54%, respectively, depending on the type of study design employed.¹⁶ Largely all previous investigations of familial aggregation of perinatal or postpartum depression have been limited in numbers and only included twin or sibling pairs, however, based on their findings there seem to be a small yet noticeable aggregation among sisters.^{17–19}

Postpartum depression is a phenotype encompassing a number of different sub-types.^{20,21} In general, studies on the etiology and pathogenesis of PPD are challenged by the heterogeneity of the disorder. In a large study using self-reported questionnaire data, 9853 women completed questions on antenatal risk factors such as the previous psychiatric conditions and filled a postnatal EPDS questionnaire.²² A total of 372 women with reported PPD had no psychiatric history, whereas 389 women had a psychiatric history (data from Table 3, Milgrom et al.).²² Thus, almost half the PPD cases, 49%, occurred among women without psychiatric history. A Danish study, also using self-reported questionnaire data, found that 19.6% of women who reported depression at 4 months postpartum had a psychiatric history.² Thus, women with PPD without previous psychiatric history constitutes a relatively large proportion of PPD cases overall. However, the literature is relatively sparse when it comes to characterizing women with PPD without previous psychiatric history. A Danish family study from 2018²³ investigated whether family history of a general psychopathology was associated with postpartum psychiatric disorders in proband first-time mothers with and without psychiatric history, respectively. They found that risk of postpartum psychiatric disorders was higher for women with first-degree relatives with psychiatric disorder. Interestingly, this increased risk of postpartum psychiatric disorders was more pronounced among women with no previous psychiatric history themselves (no psychiatric history, hazard ratio [HR] = 1.76, 95% CI 1.47–2.11, psychiatric history, HR = 1.27, 95% CI 1.06–1.52). This points to a possible genetic link between general familial psychopathology and the risk of postpartum psychiatric disorders, and that this link is dependent on the women's own psychiatric history.

1.1 | Aims of the study

The aim of the study was to investigate the familial aggregation of PPD in women with no previous psychiatric history, in a nationwide cohort design that enabled us to investigate how history of PPD in both female blood and

Significant Outcomes

- The risk of a PPD episode was significantly higher among women with a female first-degree relative with a PPD history, compared to women with a female first-degree relative with no PPD history.
- Having a female second- or third-degree relative, as well as a female non-blood relative with a PPD history was not associated with a higher PPD risk.
- The findings do not support a strong genetic trait as a major cause of PPD in women with no psychiatric history.

Limitations

- This study is a nationwide-cohort study based on national health registers. Thus, only the presumed most severe cases of PPD are included in the study, that is, only women with a hospital contact and/or prescribed antidepressants in the postpartum period.
- This study investigates the heritability of PPD in women with no psychiatric history. The results of this study cannot without further investigation be extrapolated to include women with psychiatric history.

non-blood family members (i.e., female relatives with shared environment, but no genetic relation) was associated with the risk of PPD in index women according to the type of family relation.

2 | METHOD

2.1 | Study population

Based on the Danish Civil Registration System (CRS), we established a nationwide cohort comprising all deliveries between January 1, 1996 and December 7, 2017, excluding stillbirths and deliveries by women not born in Denmark (see Figure 1). The Danish personal identification number permits complete follow-up of all persons living in Denmark and accurate linkage of individual-level information from Denmark's many mandatory national population-based registers. Based on information from national registers, we excluded (1) deliveries by women with prior PPD episodes, (2) deliveries by women

with psychiatric history prior to the delivery, and (3) deliveries by women with no link to any type of female relatives (all further defined below). Thus, a total of 848,544 eligible index deliveries were included in the cohort. Complete nationwide data on prescriptions were available in the DNPR starting in 1995, so cohort inclusion began January 1, 1996 in order to have information on antidepressant use in the year before delivery in those delivering in early 1996. The follow-up period ended June 7 2018 to include 6 months follow-up on all deliveries, also in the last part of the inclusion period.

2.2 | Identification postpartum depression

Women with an episode of PPD were defined as women with the use of an antidepressant medication and/or a hospital contact for depression within 6 months after delivery. These episodes were identified based on information in the National Patient Registry (NPR), the Psychiatric Central Research Register (PCRR), and the Danish National Prescription Register (DNPR). Episodes in the DNPR were identified as women filling at least one prescription for antidepressant medication (ATC: N06A). Episodes in the NPR and PCRR were identified as women having an in- or outpatient contact for a depressive episode, using main diagnoses only (ICD-8: 296.0, 296.2, 296.8, 296.9, 298.0, 300.4, and 301.1; ICD-10:

F320-F329). Information from NPR and PCRR was available in all 6 months after delivery except if the women died or emigrated. In these deliveries, PPD was defined according to the available information.

2.3 | Identification of psychiatric history

Psychiatric history was defined as use of antipsychotics or psychoanaleptics (ATC: N05 and N06) registered in the DNPR, and/or a registration in the PCRR or the NPR with mental illnesses (ICD-8: 29*, 30*; ICD-10: F0-F9) any time prior to childbirth. Thus, a woman might give birth in 2002, have a psychiatric episode in 2004, and give birth again in 2006. Only the delivery from 2002 will be included in this study. This pertains to index women and female relatives alike.

2.4 | Identification of female relatives

Female relatives were identified in the Danish Family Relations Database (FRD). The Danish FRD is based on parental links as registered in the CRS. Most individuals born in Denmark since 1950 have parental links reflecting the biologic or adoptive parents. Therefore, the FRD provides identity of the parents, siblings and half-siblings residing in Denmark for nearly all persons born in Denmark since 1950. Through parental links of parents,

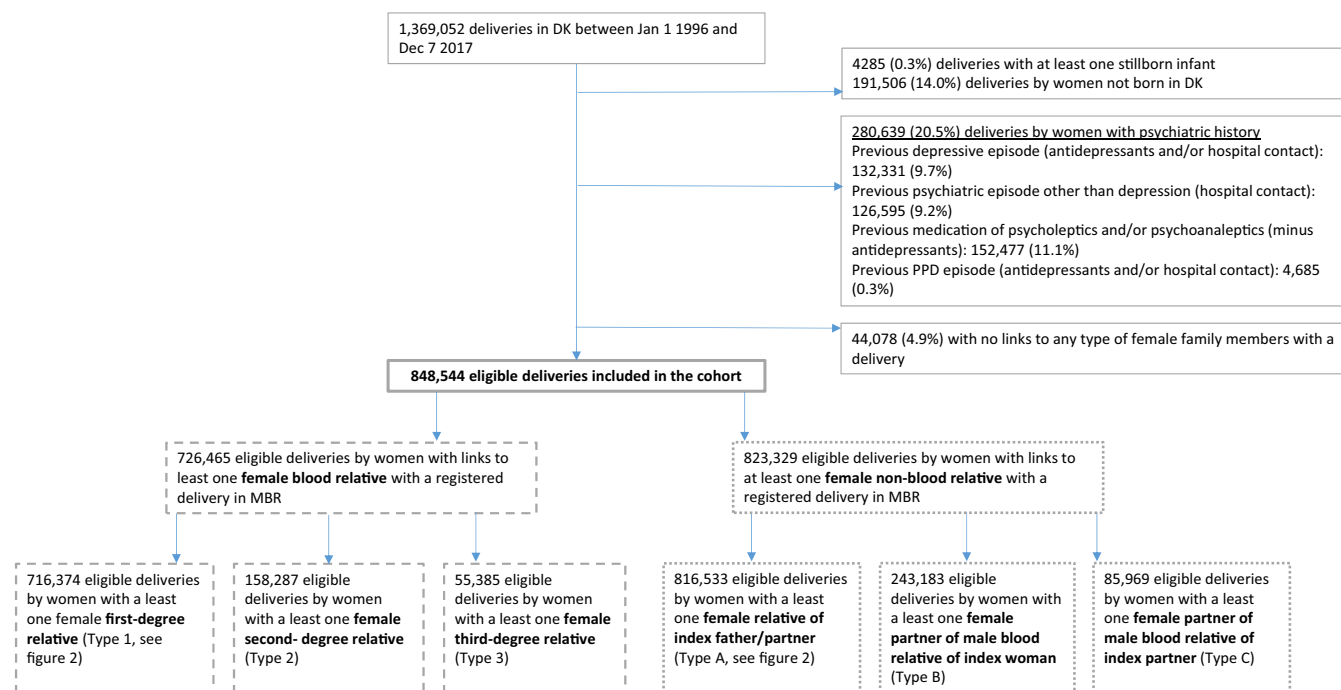


FIGURE 1 Flow chart of study population

it is also possible to identify grandparents and, thereby, aunts, uncles and cousins in later birth cohorts. Figure 2 shows the connection between the different types of relatives of the index woman. In the main analysis of this study, and because of the sparse number of exposed cases, we only discriminated between any degree of female relative, first-, and second/third-degree female relatives. Female first-degree relatives included mother, full sisters, and daughters (Type 1 in Figure 2); female second-degree relatives included grandmothers, half-sisters, nieces, and aunts (Type 2); female third-degree relatives included paternal or maternal female cousins, half nieces, and half aunts (Type 3). In order to investigate the genetic component of PPD further, we also included female relatives of the index women that were not genetically related—referred to as non-blood relatives. These were either female relative of the index partners (Type A); female partners of male blood relatives of the index woman (Type B); or female partners of the index partners' male blood relatives (Type C).

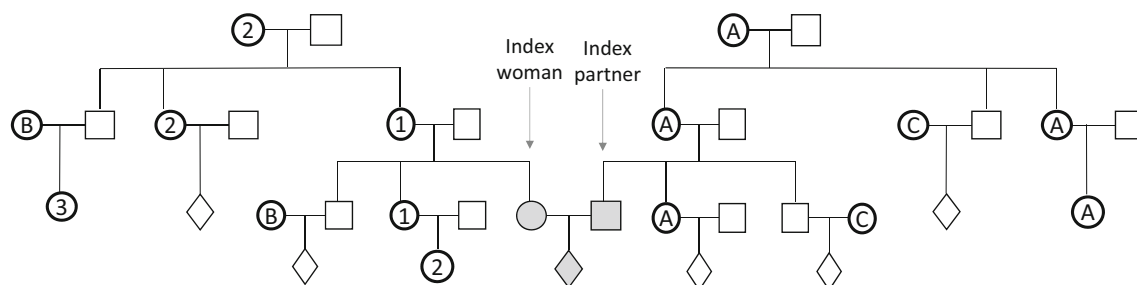
When comparing index women with a female relative with and without PPD history, only female relatives with a live birth at least 6 months prior to the index delivery were included. Furthermore, only index women with that specific type of female relative were included in the analysis. Finally, as for index women, only births of female relatives with no psychiatric history at time of own childbirth were included in the analysis (see “Psychiatric history”). For example, when estimating the relative risk of a PPD in index women with a female first-degree relative with and without a PPD history, only index women with a female first-degree relative with no psychiatric history at time of childbirth, with a live birth, and 6 months

follow-up time, were included in the analyses. In case of death or emigration, the status was defined according to the available information.

2.5 | Statistical analysis

Using binomial log-linear regression, we estimated the relative risk of PPD in index women with female relatives with and without PPD history according to degree and type of relation. The main analysis presents the relative risks given two different adjustment models. The first model includes the following adjustment covariates; year of delivery (in categories, see Table 1), parity, and an interaction term between maternal age (linear) and year of delivery (in categories). The second model includes the before mentioned adjustment covariates and an additional covariate indicating if the index women have the first-degree female blood relative with a psychiatric history, see definition below.

We constructed a covariate that encompasses whether or not the index women had the first-degree female relative with psychiatric history. Especially, when looking at the second- and third-degree female relatives, as well as female non-blood relatives in general, psychiatric history in the immediate relations (i.e., mother and sister) might be a confounder of the relation between PPD in more distant relatives and own risk of PPD, or at least a strong independent risk factor for PPD in index women. The covariate of psychiatric history in the first-degree female relatives is defined more narrow and specific than the exclusion criteria “no psychiatric history,” as defined in Identification of psychiatric history. For the covariate, we



Female blood and non-blood relatives, and their connection to the index woman:

- Type 1 – Female first-degree relatives
- Type 2 – Female second-degree relatives
- Type 3 – Female third-degree relatives
- Type A – Female relatives of the index partner
- Type B – Female partners of male blood relative of index woman
- Type C – Female partners of male blood relative of the index partner

FIGURE 2 Female blood and non-blood relatives, and their connection to the index woman

TABLE 1 Number and proportion of index deliveries with family history of PPD (link to at least one relative or partner of relative with at least one episode of PPD and no prior psychiatric history) by selected characteristics at index delivery

Characteristics at index delivery	PPD Family history			
	Number of index deliveries with female blood relatives	Index deliveries with PPD in female blood relatives	Number of index deliveries with female non-blood relatives	Index deliveries with PPD in female non-blood relatives
Total	726,465	2888 (0.4%)	823,329	8087 (1.0%)
Year of index delivery				
1996–1999	125,884	149 (0.1%)	169,152	470 (0.3%)
2000–2004	173,878	375 (0.2%)	208,528	1138 (0.5%)
2005–2009	182,558	650 (0.4%)	196,205	1832 (0.9%)
2010–2014	155,156	961 (0.6%)	159,155	2629 (1.7%)
2015–2017	88,989	753 (0.8%)	90,289	2018 (2.2%)
Age of index woman				
< 20 years	11,034	115 (1.0%)	11,237	225 (2.0%)
20–24 years	92,081	563 (0.6%)	94,387	1268 (1.3%)
25–29 years	272,482	1090 (0.4%)	296,328	2966 (1.0%)
30–34 years	251,317	797 (0.3%)	294,671	2488 (0.8%)
35–39 years	87,791	281 (0.3%)	110,586	986 (0.9%)
40+	11,760	42 (0.4%)	16,120	154 (1.0%)
Parity of index delivery				
0 prev. Deliveries	343,812	1380 (0.4%)	378,720	3757 (1.0%)
1 prev. Delivery	273,756	1034 (0.4%)	314,735	2926 (0.9%)
2+ prev. Deliveries	108,897	474 (0.4%)	129,874	1404 (1.1%)
Education of index woman ^a				
Short	110,553	652 (0.6%)	121,523	1450 (1.2%)
Intermediate	338,417	1333 (0.4%)	387,277	3747 (1.0%)
Long	272,757	885 (0.3%)	308,688	2855 (0.9%)
Psychiatric history in the first-degree female blood relatives of index women				
No	505,695	1369 (0.3%)	604,700	5285 (0.9%)
Yes	220,770	1519 (0.7%)	218,629	2802 (1.3%)

^aInformation on education was missing for 0.7% of the index women with female blood relatives with PPD and 0.7% for index women with female non-blood relatives with PPD, respectively.

only included psychiatric disorders in the family that might be associated with an increased risk of PPD in the index woman. In contrast, our exclusion criteria aimed at excluding women with any psychiatric history to solely understand PPD risk and not more broad psychiatric phenotypes. Hence, the covariate used in the main models, was defined as the first-degree female relatives with a hospital episode for a mental or behavioral disorder (ICD-8: 295–301, 306 or ICD-10: F20-F69, F80-F99, excluding organic mental disorders, substance abuse and mental retardation), or having two or more prescriptions within a year within the same ATC group of psycholeptics and psychoanaleptics medicine (N05A, N05B, N05C, N06A, N06B, N06D), excluding PPD episodes.

2.6 | Supplementary analyses

In a supplementary analysis, women were allowed to enter with more than one PPD episode. This analysis accounted for repeated observations on the same woman by generalized estimating equations (GEE) using an exchangeable working correlation structure.

3 | RESULTS

A total of 848,544 singleton deliveries from women with at least one relative, and by women born in Denmark with no history of psychiatric illness were included in the cohort

TABLE 2 Relative risk of PPD in index women with female relatives with PPD history compared to index women with female relatives with no PPD history, according to the type and degree of relation (cf. Figure 2). Only index women and female relatives with no psychiatric history at time of own birth

	PPD family history		No PPD family history		PPD history vs. no history	
	Total no. of deliveries	No. of cases (%)	Total no. of deliveries	No. of cases (%)	RR (95% CI) ^a	RR (95% CI) ^b
<i>Female blood relative of the index woman</i>						
All	2888	31 (1.07%)	723,577	3784 (0.52%)	1.77 (1.25, 2.52)	1.64 (1.16, 2.34)
First-degree relative (relative type 1)	1456	25 (1.72%)	714,918	3738 (0.52%)	3.04 (2.06, 4.49)	2.65 (1.79, 3.91)
Second-/third-degree relative (relative types 2 and 3)	1432	6 (0.42%)	170,539	1155 (0.68%)	0.59 (0.26, 1.30)	0.58 (0.26, 1.28)
<i>Female non-blood relatives of index woman</i>						
All	8087	51 (0.63%)	815,242	4146 (0.51%)	1.11 (0.84, 1.46)	1.09 (0.83, 1.44)
Relatives of index father/partner (relative type A)	4612	34 (0.69%)	811,921	4136 (0.51%)	1.31 (0.92, 1.85)	1.29 (0.91, 1.83)
Partner of male blood relative of index woman/ Partner of male blood relative of index father/partner (relative types B and C)	3510	21 (0.60%)	255,911	1618 (0.63%)	0.90 (0.58, 1.38)	0.89 (0.58, 1.37)

^aAdjusted for year of delivery, interaction term by maternal age and year of delivery, parity.

^bAdjusted for year of delivery, interaction term by maternal age and year of delivery, parity and psychiatric history in female first-degree relatives.

(Figure 1). Table 1 shows the number of index deliveries with a female relative (blood or non-blood) with a history of PPD, by selected index characteristics. When dividing the index deliveries by female relatives that are blood and non-blood related to the index woman, 2888 (0.4%) and 8087 (1.0%) of the index deliveries, respectively, had a family female relative with a prior episode of PPD.

Table 2 shows the relative risk of PPD in index women given the family history of PPD in female relatives and according to the degree and type of female relative. Overall, we found an association between having a female blood relative with a PPD history and the index women's risk of a PPD episode (RR = 1.64, 95% CI 1.16–2.34). Especially, for women with a female first-degree blood relative (mother or sister) with PPD history, the risk of own PPD was more than 2.5 times higher (RR = 2.65, 95% CI 1.79–3.91), when compared to index women with no first-degree blood relatives with PPD history. In contrast, we found no higher risk of PPD among women with second- or third-degree female blood relatives with PPD history (RR = 0.58, 95% CI 0.26–1.28). Also, having a female non-blood relative with a PPD history was not associated with an increased risk of PPD in the index women (RR = 1.09, 95% CI 0.83–1.44).

Further analysis showed that accounting for psychiatric history in the immediate female blood relatives of the index women, did not affect the associations markedly (Table 2).

3.1 | Supplementary analyses

In supplementary analyses, we investigated the robustness of the findings in the main analyses. Firstly, Supplementary Table 1 shows the relative risk of PPD in index women given family history of PPD and according to the degree and type of female relative, comparable to estimates in Table 2 of the main analyses, however in a cohort of women that includes previous isolated PPD episodes in index women and their female relatives. We used a GEE model for repeated measures to estimate the RRs. In general, we found that the estimates in Supplementary Table 1 mirror those of Table 2. Lastly, Supplementary Table 2 in the supplementary analyses shows the means, standard deviations and correlation coefficient for time to PPD diagnoses in affected female first-degree relatives, that is, exposed cases of index women. The correlation coefficient ($r = 0.005$, $p = 0.98$) indicates no correlation between time of PPD (diagnosis or first prescription of antidepressants) for index women and their relatives.

4 | DISCUSSION

Using a nationwide population-based cohort design, only including index women and female relatives with no

psychiatric history prior to own delivery, we found that having a female first-degree relative with PPD was significantly associated with a more than 2.5 fold higher risk of PPD in the index woman. In contrast, having a female second- or third degree blood relative with a similar history was not associated with a higher risk of PPD in the index women. For index women with a female non-blood relative with history of PPD we found no higher risk of PPD, when compared to index women with female non-blood relatives without a PPD history.

The existing family studies on PPD have mainly focused on female sibling/twin pairs^{16–19} and the outcome measures have varied substantially, from self-reported questionnaires,¹⁷ clinical diagnoses¹⁹ using DSM-IV and ICD-10 criteria,¹⁸ to register-based treatment data.¹⁶ However overall, our finding that PPD history in female first-degree blood relatives of the index woman increase the risk of PPD, is in line with the previous investigations, that have found that PPD, and especially PPD narrowly defined within the first 4 weeks after childbirth, appears to cluster in sisters. In a Danish cohort study from 2018, Bauer et al found that the risk of a postpartum psychiatric episode increased significantly in women, with no psychiatric history, that had a first-degree relative with a unipolar disorder (hazard ratio = 1.85, 95%CI 1.39–2.45).²³

To our knowledge, our study is the first register-based nationwide study of familial aggregation of PPD. The design enabled us to investigate whether PPD cluster within not only first-degree relatives, but also second- and third-degree relatives. We observed that having an affected female second- and/or third-degree relative was not associated with the index women's risk of PPD. Thus, while our and others findings from female first-degree relatives showed a familial aggregation of PPD, which could be due to a shared genetic trait, our results concerning second- and third-degree relatives did not seem to support this interpretation. Previously, two studies have pointed to the modest to medium heritability of PPD (Treloar et al., 25%, 95%CI 13%–42%,¹⁷ and Viktorin et al., 40%, 95%CI 31%–49%¹⁶). The twin study by Treloar and colleagues assessed PPD based on self-reported questionnaire information, and the sibling part of the study by Viktorin and colleagues used retrospective data from Swedish health register data, however, none of them accounted for psychiatric history. Also, genetic studies on PPD are growing in numbers. The candidate genes investigated are mainly inspired by genes implicated in MDD, for example, tryptophan hydroxylase-2 (TPH2),²⁴ fatty acid desaturases (FADS),²⁵ monoamine oxidase (MAO),²⁶ the serotonin transporter (5-HTT),²⁶ corticotrophin releasing hormone receptor type 1 (CRHR1),²⁷ catecholomethyl transferase (COMT),^{26,28} and brain-derived

neurotrophic factor (BDNF)^{29,30} and also by genes mediating reproductive and lactogenic hormones, for example, the estrogen receptor alpha (ESR1),³¹ and the oxytocin receptor (OXTR).³² All of the above polymorphisms were significantly associated with PPD. However, the timing of the PPD period is of importance, as many of the gene associations pertained to specific time-periods of the postpartum period. Evidence points to the late pregnancy and the immediate period after parturition to be of greater genetic vulnerability, when compared to the beginning of the pregnancy and late postpartum period.^{33,34} A recently published study on gene expression profiles during pregnancy and the risk of PPD suggests that an altered immunological profile during pregnancy and estrogen signaling plays a³⁵ role in PPD pathogenesis.³⁶ However, PPD is a complex phenotype, likely encompassing several disorders with different disease pathways, and further research is required to understand the heritability of PPD. The results of our study suggest that, for PPD in women with no prior psychiatric history, heritability seem to play a small role in the disease pathway.

The design of our study also allowed us to include female non-blood relatives in our analyses. To our knowledge, this group of female relatives has not been included in previous studies before. We found that having an affected female non-blood relative did not increase the risk of a PPD in the index women. The results supplement the observed associations in blood relatives, with an increased risk only among female first-degree relatives, and underline the effect of very close kinship.

Several studies point to a specific period, during which women might be susceptible to genetic factors or epigenetic modifications.³³ In our cohort, among cases with a female first-degree blood relative with a PPD history, we found no correlation between time of diagnosis for relatives and index women, see Supplementary Table S2. However, this finding is based on few observations.

Possible limitations should be considered. First, focus was on clustering of PPD in family members with no psychiatric history. General psychiatric history is therefore a potential confounder. However, great effort has been made to exclude and adjust for such history in index women and their families. Using antidepressants to identify cases of PPD in our study means that the women characterized as PPD women in our study do not necessarily fulfill the ICD-10 diagnostic criteria for depression, as antidepressants are also used for other indications, e.g. anxiety,³⁷ and for a number of off-label indications. This may introduce misclassification of PPD cases. A Canadian study from 2017 found that 29% of antidepressants prescribed in primary care were used off-label.³⁸ However, in our study, the use of antidepressants is first-time and in the postpartum period, where one must

assume the proportion of off-label use is lower and depression one of the most frequent psychiatric disorder. On the other hand, excluding antidepressant medication from our case definition would significantly underestimate the number of cases, as the majority of cases of depression in Denmark are treated in primary care, and are therefore not registered in the hospital registries. Furthermore, as another potential source of misclassification, PPD is a disease with a substantial number of unregistered and untreated incidents. If the misclassification of the PPD status in the index women is unrelated to the PPD status of the female relatives (i.e., non-differential misclassification), then this bias will only attenuate our risk estimates toward one. However, the inclination to be treated, may be family related, especially pronounced in close family relations. This may be due to a similar health-seeking behavior and/or attention to signs of the disease, and awareness of treatment possibilities. Thus, this differential information-bias, described as health-seeking behavior or PPD disease and treatment awareness within affected families may explain some of the, in this study, observed increased risk of PPD of having an affected mother and/or sister. This may also be true for other studies based on the first-degree relatives including studies on twins. Further, in the main analyses we only included women with no PPD episodes after prior deliveries due to the focus on women without psychiatric history. However, the aim of the study was to investigate the heritability of PPD as a distinct phenotype, thus one might alternatively argue that previous episodes of only PPD could be included. In a sensitivity analysis, we included women with the previous isolated PPD episode in the cohort, analyzed in a GEE model, and found that the estimates did not change significantly, see Supplementary Table S1. Also, although this study is a nationwide population-based study, the Danish population is a homogenous population, with little ethnic diversity. In addition, in this study, only women born in Denmark are included. This is done purposely to ensure that information on psychiatric history is complete, however the result cannot necessarily be generalized to other ethnic groups. Lastly, despite the nationwide cohort design, we did not have enough cases, only 6 exposed cases in all, to analyze the second- and third-degree female relatives' separately, which could have provided us with further insight into the genetics of PPD.

Our study also had strengths. First of all, we used a nationwide and population-based cohort design that included all residents in Denmark eligible for study. Therefore, selection bias is considered to be minimal. Furthermore, pedigree information, pharmacological treatment, and psychiatric diagnoses, including PPD, was all information obtained in mandatorily reportable

national registries. Also, the national cohort design enabled us to examine different degrees of female relatives as well as in female blood and non-blood relatives. Another strength was our focus and ability to construct a cohort of women and female relatives with no psychiatric history, as we are interested in heredity of PPD as a distinctive entity that do not include a more general psychopathology. Thus, this study addresses the specific subtypes of depression that is restricted to pregnancy, and thereby makes a stronger and more relevant conclusion on a subset comprising almost half of the total number, of women with PPD. In our study, PPD was defined by treatment-based methods only, most likely identifying the most severe cases, however, this is also a strength as it enables us to focus our investigation and more likely target the same type of PPD in index women and relatives alike.

The findings of this study do not support a genetic trait as a major cause of isolated PPD. Other possible mechanisms that could explain this and previous observed associations among close family include effects of shared environmental and/or health-seeking behavior in very close relationships. More research is needed on this subtype of PPD, in women with no previous psychiatric history.

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CONFLICT OF INTEREST

Mads Melbye is a cofounder of Mirvie Inc. that creates precise, actionable, non-invasive tests for maternal-fetal health. The other authors report no competing interests.

PEER REVIEW

The peer review history for this article is available at <https://publons.com/publon/10.1111/acps.13465>.

DATA AVAILABILITY STATEMENT

Our study is based on Danish national register data. These data belong not to us but to the Danish Ministry of Health, and we are not permitted to release them, except in aggregate (as, for example, in a publication). However, interested parties can obtain the data on which our study was based by submitting a research protocol to the Danish Data Protection Agency (Datatilsynet:www.datatilsynet.dk/blanketter/om-anmeldelsessystemet/) and then, once Data Protection Agency permission has been received,

applying to the Ministry of Health's Research Service (Forskertjeneste) at forskertjeneste@ssi.dk.

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