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Lifetime prevalence and risk factors for perinatal depression in a large cohort of women with depression

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Lifetime prevalence and risk factors for perinatal depression in a large cohort of women with depression

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Abstract

Objectives

Amongst women with a history of depression, this study sought to identify risk factors associated with reporting perinatal depression (PND)). Lifetime prevalence, length and severity of PND were evaluated, as well as the effect of PND onset either after previous depression episodes, or as the first episode of depression.

Setting

The Australian Genetics of Depression Study (AGDS), an online case cohort study of the etiology of depression.

Participants

In a large sample of parous women who met DSM criteria for major depressive disorder (MDD) (n=7,182), we identified two subgroups of PND cases (Edinburgh Postnatal Depression Scale score >= 13) with and without prior depression history (n=2,261; n=878 respectively). For a range of risk factors, both subgroups were compared to women with MDD who did not report depressive symptoms in the perinatal period (non-perinatal depression (NPD) cases). PND cases with prior depression history were compared to NPD cases with depression onset before their first pregnancy (n=672). PND cases without prior depression history were compared to all NPD cases (n=2,124).

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Primary and secondary outcome measures

Descriptive measures reported lifetime prevalence, length, and severity of PND. Logistic regression compared a range of characteristics of PND cases to those of the comparison group of NPD cases.

Results

Of women who experienced depression prior to first pregnancy, PND cases were significantly more likely to report more episodes of depression (OR=1.1 per additional depression episode, CI=[1.1-1.1], P=1.9e-13), non-European ancestry (OR=1.5, CI=[1.0-2.1], P=3.4e-02), severe nausea during pregnancy (OR=1.3, CI=[1.1-1.6], P=6.6e-03) and emotional abuse (OR=1.4, CI=[1.1-1.7], P=5.3e-03). Women without any depression before their first perinatal episode were significantly more likely to report emotional abuse (OR=1.3, CI=[1.1-1.6], P=1.0e-02) than women with NPD.

Conclusions

The majority of parous women in this study experienced PND, associated with more complex, severe depression. Results highlight the importance of perinatal assessments of depressive symptoms, particularly for women with a history of depression or childhood adverse experiences.

Strengths and limitations of this study

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- Largest study of its kind, comparing characteristics of women with perinatal depression to those of women with non-perinatal depression.
- Reports detailed characteristics of women with PND but with different psychiatric histories.
- An online questionnaire, with no personalized interviews or clinical reports to provide supporting evidence for self-reported data.
- Reliance on self-report information years after experiencing PND could lead to recall bias.
- The AGDS cohort is mostly young and well-educated and may not generalize to the entire population.

Funding Statement

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Competing interests

No conflict of interest has been reported

Availability of data and material

Data used in this analysis and described in this article are available to all interested researchers through collaboration. Please contact NGM.

Ethics approval and consent to participate

All study protocols were approved by the QIMR Berghofer Medical Research Institute Human Research Ethics Committee (Ref 2118). The protocol for approaching participants through the DHS, enrolling them in the study, and consenting for all phases of the study (including invitation to future related studies) and accessing MBS and PBS records was approved by the Ethics Department of the Department of Human Services.

Patient consent for participation in the study was obtained.

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Introduction

Background

Perinatal depression (PND), including both antenatal and postpartum depression, commonly classified as a subtype of major depressive disorder (MDD)[1], carries serious risk for both mother and infant. An estimated 53% of women with postpartum depression have "high suicidality"[2], whilst the rate of self-harming thoughts is three times that of the postpartum community population[3]. Estimated economic costs of PND in the UK, of which 72% are for ongoing care of the child[4] reflect findings that children of women with persistent and severe PND are at increased risk of adverse outcomes[1,5] .

The diagnostic criteria for MDD and PND are the same[6], but the strongest known PND risk factor is a previous diagnosis of any psychiatric disorder[1,7-10] , not only MDD[11]. Other risk factors may also increase PND vulnerability. Possible psychosocial factors include stress and history of abuse[12] whilst biological factors include changes that accompany pregnancy, such as hormonal fluctuations and increased inflammation[13,14].

The complexity of these risk factors contribute to ongoing debate about the heterogeneous nature of PND in relation to MDD; in particular, whether it is simply another episode of MDD that happens to coincide with the perinatal period[15]; or a subset of MDD, termed "reproductive depression", stimulated at times of hormone fluctuation such as pre-menstruation, peripartum and menopause[16,17]; or a distinct disorder, stimulated by changes occurring during pregnancy and confined to the perinatal period[13]. One suggestion is that PND is itself heterogenous[10,18], with clinical subtypes differentiated by timing and severity of symptoms, perinatal complications, and history of psychiatric disorders. However, a

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comprehensive investigation of the characteristics of women with PND, with and without a prior psychiatric history, has not been attempted.

Objectives

Using the Australian Genetics of Depression Study (AGDS), a large cohort study with over 20,000 participants self-reporting a depression diagnosis[19], we examined PND heterogeneity, based on the presence or absence of previous major depression history. We sought to address two questions:

1) What are the differences in clinical and psychosocial characteristics between women with and without PND after a depressive episode prior to their first pregnancy?

2) What are the differences in clinical and psychosocial characteristics between women whose first episode of depression was during the perinatal period and parous women who have also experienced depression, but never during any perinatal period?

Method

Study Design

Within a case cohort study of the etiology of depression, two groups of PND cases and two comparison groups of NPD cases were identified according to their history of prior depression. For both PND groups, the length and severity of their "worst case" of PND was measured. To investigate risk factors associated with PND after a previous history of psychiatric disorders, or as first onset depression, both PND groups were compared with their comparison group of NPD cases, across a range of variables.

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Setting: The Australian Genetics of Depression Study

The AGDS is a large ongoing case cohort study of the etiology of depression that recruited 20,689 participants (aged between 28 and 58 years; 75% female) during 2016-2018. The analyses conducted here are from participants enrolled prior to the initial data freeze in September 2018. Recruitment was primarily through a media campaign (86%) as well as specific invitations to women who had responded to a mobile phone app focused on PND, originally developed in the USA[20], and also ascertainment through the Pharmaceutical Benefits Scheme prescription records for antidepressants, which requested participation from anyone with a depression diagnosis from a health professional. For further details of the recruitment strategy, see Byrne, et al. [19].

AGDS participants were invited to complete an online questionnaire. A compulsory core module assessed self-reported psychiatric history, the Composite Interview Diagnostic Interview Short Form (CIDI-SF) which asseses the Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM-V) criteria for MDD[6], and experiences of using commonly prescribed antidepressants. Women reporting symptoms of depression during pregnancy or up to 6 months following childbirth were asked to complete the lifetime Edinburgh Postnatal Depression Scale (EPDS)[21], an adaptation of the standard EPDS[22] that assesses lifetime PND episodes. They were also asked whether symptoms of depression occurred during pregnancy, after giving birth, or both, the age at which they experienced their worst episode of PND, its severity and duration. For all AGDS participants, further voluntary modules assessed history of psychiatric health conditions and stressful life events.

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The AGDS protocol was approved by the Human Research Ethics Committee of QIMR Berghofer Institute for Medical Research.

Participants: PND cases and comparison groups

Participants with major depression either met DSM-V criteria for MDD, or had been previously diagnosed with depression by a health professional. PND cases were defined as women reporting at least one live birth who had been previously diagnosed with PND by a health professional, or who scored >= 13 on the lifetime EPDS, or who met criteria for major depression and reported at least one perinatal episode.

We identified two groups of cases, based on whether they had a history of MDD prior to their first PND episode. Parous participants who reported an episode of depression before their first pregnancy and met PND criteria (PND_priorDep) were compared with parous participants who reported an episode of depression before their first pregnancy, but did not experience any depression associated with childbirth (NPD_priorDep). The second group comprised participants whose first episode of depression occurred during the perinatal period (PND_firstDep), compared to participants with depression onset at other times, but never during any peripartum period (NPD_all). The NPD_priorDep that forms the comparison group for the PND_priorDep sample is a subset of the NPD_all comparison group. It was expected that, given the early onset of major depression (before first pregnancy) the NPD_priorDep would have more severe depression than the full NPD_all comparison group and might more closely match the PND_priorDep cases. Fig. 1 and

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Supplementary Table S1 illustrate sample selection. Further details are provided in Supplementary Methods.

Figure 1 about here

Variables

The outcome of interest was a PND episode for women with either a history of previous depressive episode(s), or no previous depression history. An exposure to a PND episode is defined as the period of time from conception up to six months postpartum, so that the number of reported live births represents the number of exposures. The cross-sectional nature of our study meant that no direction of causality could be assessed, but we investigated risk factors for PND using variables that have previously been associated with PND[1,23,24], including severity of depression; ancestry; comorbidity with other psychiatric disorders; adverse childhood experiences; reproductive traits and response to antidepressants.

We investigated previous history of depression as a modifier of the effect of each variable, by conducting two separate analyses of PND cases categorized as PND_priorDep or PND_firstDep, for both descriptive and comparative measures. For comparative measures each of the two PND groups was compared to an appropriate comparison group. A further effect modifier is the time of onset of PND: during pregnancy, after delivery, or both. For both samples, a sensitivity analysis was conducted to investigate the effect of PND onset both during and after pregnancy.

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Descriptive measures for cases

Clinical characteristics of PND cases included the length and severity of the worst PND episode. For both groups, the length of the PND worst episode was calculated, according to detailed occurrence before or after delivery. Length of the worst PND episode was measured using a 5 point scale: “Up to two weeks”, “2-4 weeks”, “1-3 months”, “3-6 months”, “More than 6 months”. Details of occurrence included trimester of pregnancy or length of time after delivery.

Severity of the worst PND episode was measured using the level of interference with functioning, defined as the need for any of the following: professional help, medication, and hospitalisation. More than one of the three measures could be chosen.

Comparative measures

Case and comparison groups were compared on a range of variables that have previously been identified to be associated with PND[1,23]. Demographic measures included current age, marital status, education and ancestry. A list of geographical regions from which ancestry is identified is provided in Table S2. More details are provided in Supplementary Methods. Clinical measures included the number and severity of episodes of major depression, history of childhood trauma and sexual or other physical assault, and previous diagnoses of psychiatric disorders. Eighteen psychiatric disorders were listed, of which twelve, identified by more than 3% of participants, were used in this study (Table S3). Reproductive measures included age at menarche, parity, age at first birth, presence and severity of nausea and

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vomiting during pregnancy (NVP), and previous diagnosis of gestational diabetes, endometriosis or polycystic ovarian syndrome. Antidepressant measures included the number of antidepressants that had been tried, their efficacy and any side-effects. More details of these measures are provided in Supplementary Methods, which also lists the questions used to assess each characteristic.

Potential sources of bias

Two variables, number of births and age, significantly associated with PND, were identified as exposure and confounder respectively. Each birth represents an additional exposure to PND, whilst the negative association of PND with increasing age may reflect increasing awareness and diagnosis of the disorder, or imprecise memory of past events. Reliance on self-report information years after experiencing PND could lead to recall bias, although the inclusion of age as a covariate in regression analyses may alleviate this trend and participants who provided contradictory evidence were excluded from analysis. The lifetime EPDS used to assess PND is a screening, rather than diagnostic tool and may result in overestimation of PND case status[25], although O'Connor et.al.[26] reported a sensitivity of 0.8 for the EPDS in identifying MDD with a cut-off score>=13, and a specificity of 0.9. The lifetime EPDS is a modification of this scale which has demonstrated internal consistency[21].

Statistical Analysis

For both priorDep and firstDep groups, length and severity of the worst reported episode of PND was calculated, and logistic regression measured the association of depression length

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with early onset of PND (first trimester of pregnancy or within 4 weeks of delivery). Associations between variables and PND were assessed using logistic regression, with PND the dependent variable, separately for both priorDep and firstDep groups, including age at survey time and number of births as covariates.

All modules apart from the first were optional, and some categories applied only to a limited number of participants (for example, those who had used at least one antidepressant). For these reasons, the number of participants who completed each category or variable varied. For each variable, the number of respondents is reported. Within each category, analysis employed Bonferroni correction for multiple testing (N=number of tests within each category).

Finally, to evaluate whether effect sizes were influenced by time of PND onset, we conducted a sensitivity analysis that included only women who reported experiencing PND both before and after delivery. We conducted this analysis separately for both PND_priorDep and PND_firstDep samples.

All analyses were conducted using R (version 3.6.0). Figures were generated using ggplot2[27] and Gliffy software[28].

Public and Patient Involvement

There was no public or patient involvement in the design, conduct, reporting or dissemination plans of our research.

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Results

Lifetime prevalence of depression during the peripartum period

Just over 97% of AGDS participants (n= 20,191) reported previous diagnosis of depression by a health professional, of whom 88% met DSM-V criteria for MDD. The remaining 12% either did not complete the CIDI-SF, or did not meet DSM criteria. Of these participants with major depression, 75% (n=15,198) were female with median age of 39. Among female participants, 7,182 (47%) reported at least one live birth, and, of these, 5,058 (70%) met criteria for PND.

Of the 7,182 parous women, 2,933 reported a history of major depression prior to first pregnancy. At least one episode of PND (PND_priorDep) was reported by 2,261 (77%) of these 2,933 women, whilst the remaining 672 women with no PND episodes (23%) formed their comparison group (NPD_priorDep). A total of 878 women reported that their first episode of depression occurred during pregnancy or within the first 6 months after delivery (PND_firstDep), whilst all women who met criteria for major depression, had given birth to at least one child but did not satisfy criteria for PND (NPD_all, n=2,124) formed its comparison group. Of women who met criteria for PND, 1,919 were unable to be categorized as PND_priorDep or PND_firstDep and were lost to further analysis. Fig. 1 and Supplementary Table S1 provide details of the sample selection process. Table 1 shows the reported time of onset of symptoms (for any PND episode) for both case groups (only during pregnancy, only after delivery, or both before and after delivery).

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Table 1. Reported timing of symptoms of perinatal depression among women with PND. Results are shown for all those meeting PND criteria and separately for those with a prior history of major depression (PND_priorDep) and those whose first onset of major depression was perinatal (PND_firstDep).

	During pregnancy only	After delivery only	Both during pregnancy and after delivery	Missing
All PND cases (N=5,058)	295 (6%)	1,627 (32%)	3,073 (61%)	63 (1%)
PND_priorDep (N=2,261)	144 (6%)	592 (26%)	1,507 (67%)	18 (1%)
PND_firstDep (N=878)	28 (3%)	325 (37%)	510 (58%)	15 (2%)

The reported length of the worst episode of PND is shown in Fig.2 for PND_priorDep and in Fig.3 for PND_firstDep. Full details are provided in Table S4. For both groups of cases, PND was most commonly reported to have lasted for more than six months. The most commonly reported time of PND onset for women whose episode began during pregnancy was during the first trimester, and for those whose episode began after delivery was within 0-4 weeks. Both PND_priorDep and PND_firstDep were more likely to report that their worst episode began after delivery (66% and 79% respectively), including 60% of PND_priorDep cases and 72% of PND_firstDep cases who had reported that they experienced PND both before and after delivery. This difference between the groups is significant, with PND_firstDep having

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2.0 times the odds of reporting postpartum onset of worst case symptoms (CI=[1.7-2.4], P=4.6e-13) compared to the odds of PND_priorDep. For both groups, symptom onset in the first trimester or 0-4 weeks postpartum was associated with longer duration of symptoms, significantly so for PND_priorDep (Table S4).

Figure 2 about here

Figure 3 about here

For both groups, more than 60% required some sort of professional help, although less than 45% of women reported using medication to deal with this worst episode (Fig.4, Table S4).

Figure 4 about here

Clinical and psychosocial risk factors for PND in parous women

Table S5 provides the number and percentage of participants that completed each of the risk factor variables, for both priorDep and firstDep groups.

Clinical and psychosocial risk factors for PND in parous women with a history of depression.

We investigated which risk factors are associated with PND in women with a previous history of depression. Age at enrolment (OR [PND case status]=0.97 per additional year of age, CI=[0.96-0.98], P=2.3e-17), and number of births (OR [PND case status]=1.3 per additional birth, CI=[1.2-1.4], P=4.7e-07) were significantly associated with PND. Both age and number of births were included as covariates in subsequent analyses, which were also adjusted for multiple testing. Fig. 5 illustrates nominally significant results after the inclusion of covariates, with details of all results provided in Table S6.

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Figure 5 about here

Ancestry (both non-European and Australian Indigenous) was significantly associated with PND (non-European: OR=1.5, CI=[1.0-2.1], P=2.8e-02; Australian Indigenous: OR=2.3, CI=[1.2-4.8], P=2.4e-02), although after correction for multiple testing, only Australian Indigenous remained significant. There was no association between marital status or level of education and PND. On all measures, PND_priorDep reported more severe depression than NPD_priorDep (Fig. 5), although as expected, the NPD_priorDep comparison group also experienced significantly more severe depression than the NPD_all comparison group on all measures (Table S7).

Five of twelve psychiatric disorders (premenstrual dysphoric disorder (PMDD), attention deficit hyperactive disorder (ADHD), anxiety disorder, post-traumatic stress disorder (PTSD), and social anxiety disorder) were significantly associated with PND, although none survived Bonferroni correction. There was a significant association between PND and a history of self-reported childhood emotional abuse (OR=1.4, CI=[1.1-1.7], P=5.5e-03) and neglect (OR=1.3, CI=1.0-1.6], P=3.1e-02) and physical neglect (OR=1.4, CI=[1.1-1.9], p=2.3e-02), although only emotional abuse survived Bonferroni correction.

There was no association between age at menarche and PND and no significant difference in the incidence of gestational diabetes, polycystic ovarian syndrome or endometriosis. Although there was no significant difference in the incidence of NVP for PND compared to NPD cases (P = 0.11), there was a significant difference in the severity of NVP between PND_priorDep and NPD_priorDep. For PND_priorDep, the odds that a woman with PND had experienced disruptive nausea during pregnancy, compared to NPD_priorDep, is 1.3 (CI=[1.1-1.6], P=6.6e-03), significant after Bonferroni correction.

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PND_priorDep were significantly more likely to have tried more than three antidepressants than its comparison group (OR=1.4, CI=[1.1-1.8], P=1.4e-03), were less likely to report high efficacy of any antidepressant (OR=0.7, CI=[0.5-0.8], P=5.5e-04), and were 1.5 times more likely (CI=[1.2-1.8], P=3.0e-04) to report at least one side effect for antidepressants, compared with women with NPD_priorDep (including age, number of births and the number of antidepressants tried as covariates in the model) (Fig. 4). All of the 23 side effects were more commonly reported by PND_priorDep, 15 of them significantly so, although only 2 survived Bonferroni correction.

Clinical and psychosocial risk factors associated with PND as first episode of depression.

As there may be unique risk factors associated with onset of depression perinatally, we conducted further analyses to evaluate differences between women who report their first episode occurring perinatally (PND_firstDep) and all NPD cases. Similar to priorDep findings, we found that age at enrolment and number of births were associated with increased risk of PND (Table S6). After both these variables were included as covariates, PND_firstDep was associated with emotional abuse during childhood, increased likelihood of trying at least 3 antidepressants compared with controls, and increased odds of reporting 13 of the 23 side effects, 5 of which were significant, although no side effects survived Bonferroni correction. No associations were found with other variables. FirstDep results (for variables that were nominally significant for priorDep) are illustrated in Fig.5 and full details of all results are provided in Supplementary Table S6.

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Effect of PND onset on clinical and psychosocial risk factors associated with PND.

Symptoms of PND were experienced both during pregnancy and after delivery by 67% of PND_priorDep and 58% of PND_firstDep. A sensitivity analysis using only these cases found that the odds ratios of variables already significantly associated with these groups increased. For priorDep, association of PND with three comorbidities: anxiety disorder, PTSD and social anxiety disorder remained significant after Bonferoni correction. Sexual abuse at any time became significantly associated with PND for priorDep as well as comorbidity with bipolar disorder, and PMDD became significantly associated with PND_firstDep , although none of these survived Bonferroni correction. Full details are provided in Supplementary Table S8.

Discussion

We investigated lifetime prevalence and correlates of perinatal depression in a large cross-sectional study of depression. This is to date one of the largest studies of perinatal depression among women with major depression. Although previous research highlighted heterogeneity of PND[7,10], until now detailed characteristics of women with PND but different psychiatric history have been lacking. Our study has enabled the identification of such characteristics through a comparison of two subsets of PND cases, with and without a prior history of major depression.

We found high lifetime prevalence of meeting criteria for probable PND in this sample, with the majority of women reporting symptoms both during and after pregnancy. Among those

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with prior history of major depression, PND was associated with more chronic, complicated depression, characterized by earlier onset, more reported episodes, more symptoms during the worst episode and increased likelihood of having a comorbid psychiatric disorder. They had significantly higher rates of reported emotional abuse and neglect and physical neglect during childhood, were more likely to report severe symptoms of NVP and suffer from more side effects to antidepressants. Women with no such prior history, whose first depressive episode occurred during the perinatal period, did not report more severe depression, were no more likely to be comorbid with other psychiatric disorders, apart from PMDD, and no more likely to report severe NVP than women who experienced depression outside the perinatal period. Like PND cases with a prior history of depression, women who experienced PND as their first depressive episode reported significantly more side effects to antidepressants than women with depression without a perinatal episode, and were also more likely to report childhood emotional abuse.

The main limitation of this study is that it is based on an online questionnaire, with no personalized interviews or clinical reports to provide supporting evidence for self-reported data. Answers were based on total life experience, including, but not exclusive to, the perinatal period. Furthermore, the AGDS is a cross-sectional study. Its strength lies in its sample size, but, unlike a longitudinal study, it provides no information with respect to timing of variables significantly associated with PND (with the exception of childhood adverse experiences), so no inference can be made pertaining to cause and effect. The results of the study should also be considered in the context that the AGDS cohort is mostly young and well-educated, and may not generalize to the entire population.

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Despite these limitations, the findings of this study are consistent with previous reports. PND for women with a previous history of depression seems to be more severe and complex than for women who experience PND as first depression onset, supporting the notion of PND heterogeneity according to previous psychiatric history. Prior history of psychiatric disorders, stress, and a history of abuse have emerged as strong predictive factors for PND[1,7-10,12,29]. PMDD is the severe form of premenstrual syndrome, recently identified as a risk factor for PND[30], and NVP has been recognized as the strongest obstetric predictor of PND[31]. Previous studies have also found that women suffering from both MDD and PND had more severe depression and higher incidence of anxiety disorder and childhood trauma than women suffering from MDD alone[21], and that most severe depression is suffered by women who experience PND both during pregnancy and after delivery[10].

This study found high reported rates of non-response to antidepressants in women experiencing PND for both subgroups. Studies of the efficacy of antidepressants for the treatment of PND have been inconclusive[32], and, to our knowledge, increased incidence of side effects amongst women with PND has not been previously reported. Further clinical studies of antidepressant efficacy in PND are warranted, as well as efficacy of alternative treatments.

Finally, complications of pregnancy and birth were not assessed in this study apart from NVP and gestational diabetes, so it was not possible to fully assess whether perinatal complications may contribute to PND vulnerability[7].

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Conclusions

PND is a leading cause of disease for women who give birth, adding to the overall family disease burden and potential cognitive and emotional problems for affected children. This sample of parous women with lifetime major depression found a high rate of PND, particularly for women who experienced an episode of depression before their first pregnancy. There is a compelling literature demonstrating that screening for PND should begin during pregnancy[26,33], particularly for women with prior history of depression, which is supported by the finding that the majority of cases in this study experienced PND both before and after delivery. Although women who have been previously diagnosed with major depression are, presumably, under clinical care, it is possible that women may have withdrawn from care if treatment has been ineffective. Standard prenatal care that adopts frequent assessment of depression status provides an opportunity to identify women who might otherwise "slip through the cracks" and ensure that they continue to receive support in finding a successful treatment or in the prevention of relapse[26]. Our results also support the screening of childhood adverse experiences and PMDD in pregnancy, given that all women with PND in this study had increased odds of a history of emotional abuse and neglect, as well as increased odds of PMDD. Cases were also more likely to have treatment resistant depression, with increased odds of side effects, supporting further clinical investigation of antidepressant efficacy in PND.

Authors' Contributions

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EMB, SEM, NRW, IBH and NGM designed the AGDS study. JK and EMB analysed the data. JK and EMB drafted the manuscript. SM-B, JM, EB, TM, IBH, LC-C, SEM, NGM and NRW revised the article for intellectual content. All authors have read and approve of the final version.

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Figure Legends

Fig. 1 Flow chart: Selection of cases and associated comparative group for first analysis (prior history of major depression) and second analysis (PND is first experience of major depression). Cases met criteria for major depression and had at least one live birth, plus any

2

of: EPDS score >=13; a previous diagnosis of PND; or major depression during the perinatal period. Of the comparison groups, NPD_priorDep is a subset of NPD_all. NPD_priorDep was considered to be a more appropriate comparison group for PND_priorDep since members of both these groups experienced an episode of major depression before first pregnancy.

Fig. 2 Length of worst episode of symptomatic PND for priorDep cases, for onset either during pregnancy or after delivery. Episode length is divided into 5 categories, and the Y-axis provides the number of women reporting each category, according to the timing of onset.

Fig. 3 Length of worst episode of symptomatic PND for PND_firstDep cases, for onset either during pregnancy or after delivery. Episode length is divided into 5 categories, and the Y-axis provides the number of women reporting each category, according to the timing of onset.

Fig. 4 Severity of worst episode of PND for priorDep and PND_firstDep cases, according to the time of onset of the worst episode. Severity is characterised by interference in everyday life, need for professional help, need for medication, and need to be hospitalised. The Y-axis provides the proportion of each group reporting each variable. Standard errors are included.

Fig. 5 Forest plot of odds ratios with confidence intervals of all variables nominally significantly associated with PND_priorDep cases when compared with NPD_priorDep. Odds ratios for the association of these variables with PND_firstDep cases compared with NPD_all are also included for comparison. Logistic regression, including age of participants as a covariate, was used to calculate odds ratios.

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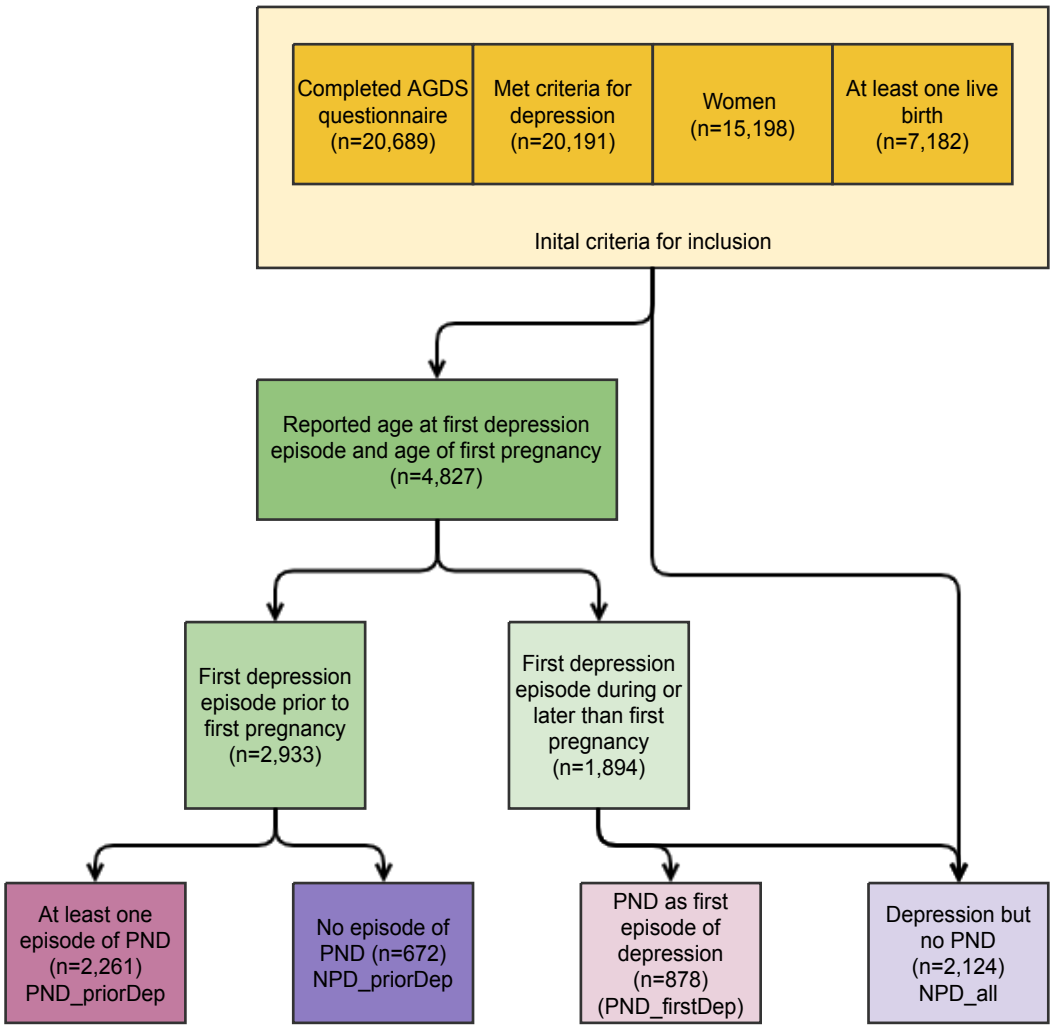
Completed AGDS questionnaire (n=20,689)
Met criteria for depression (n=20,191)
Women (n=15,198)
At least one live birth (n=7,182)
Inital criteria for inclusion
Reported age at first depression episode and age of first pregnancy (n=4,827)
First depression episode prior to first pregnancy (n=2,933)
First depression episode during or later than first pregnancy (n=1,894)
At least one episode of PND (n=2,261) PND_priorDep
No episode of PND (n=672) NPD_priorDep
PND as first episode of depression (n=878) (PND_firstDep)
Depression but no PND (n=2,124) NPD_all

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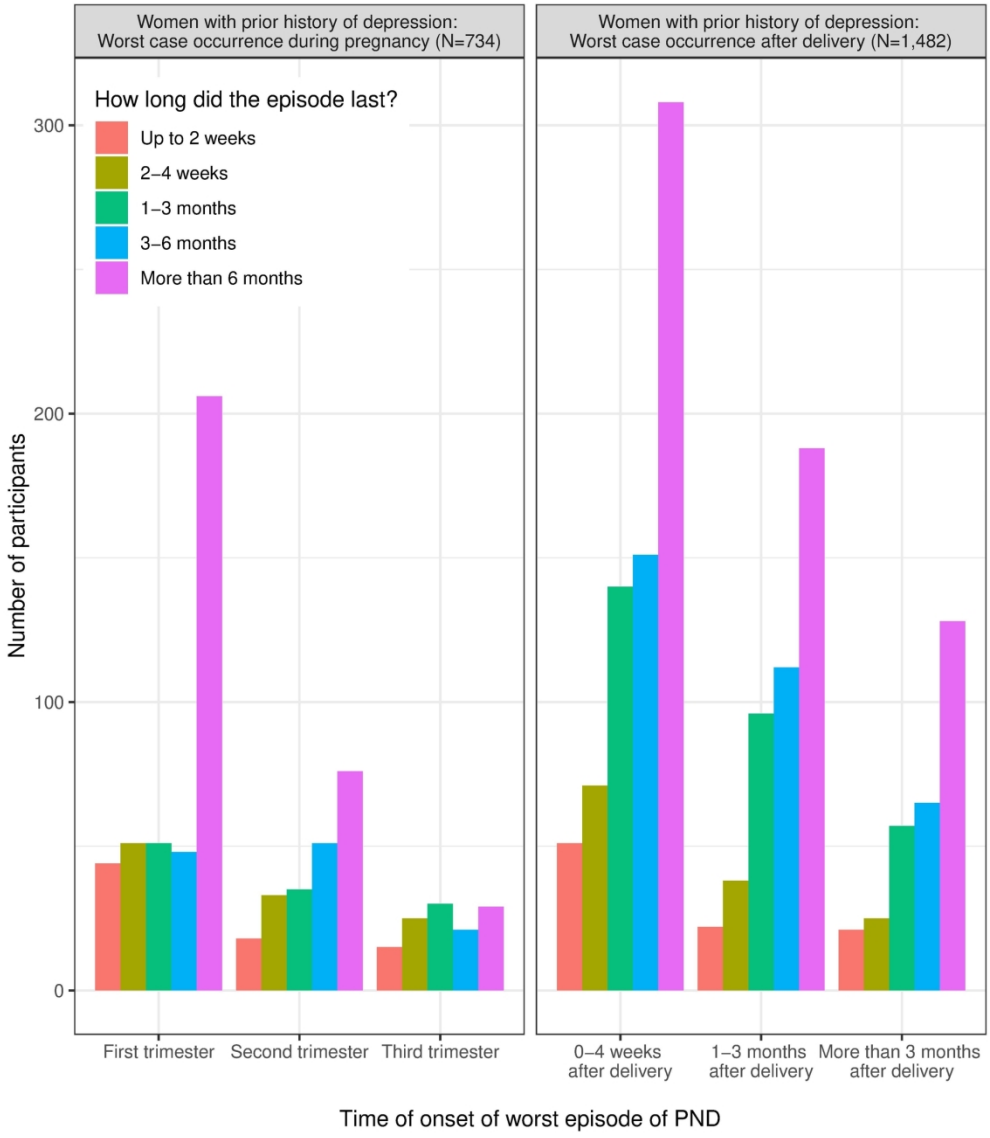

Fig. 2 Length of worst episode of symptomatic PND for priorDep cases, for onset either during pregnancy or after delivery. Episode length is divided into 5 categories, and the Y-axis provides the number of women reporting each category, according to the timing of onset.

173x199mm (300 x 300 DPI)

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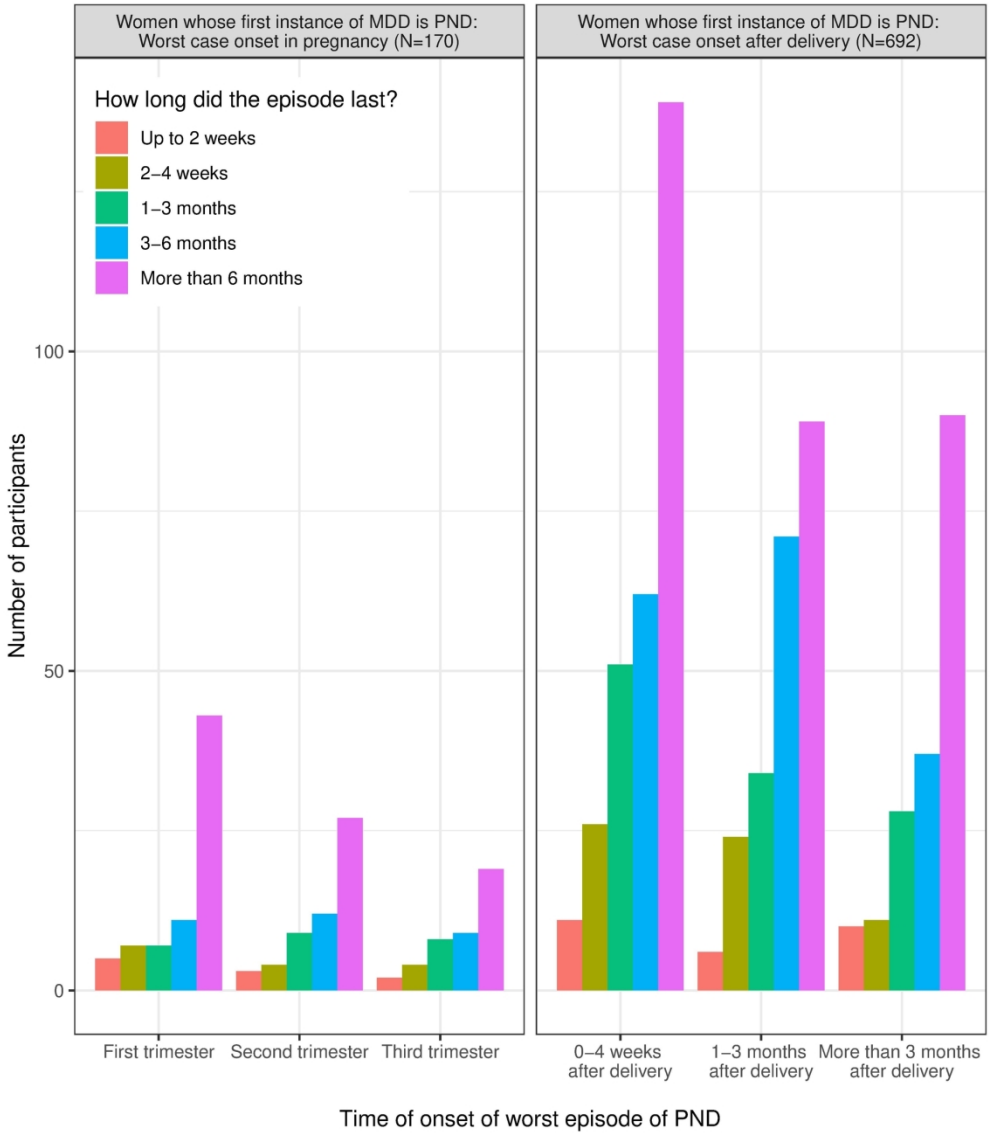

Fig. 3 Length of worst episode of symptomatic PND for PND_firstDep cases, for onset either during pregnancy or after delivery. Episode length is divided into 5 categories, and the Y-axis provides the number of women reporting each category, according to the timing of onset.

173x199mm (300 x 300 DPI)

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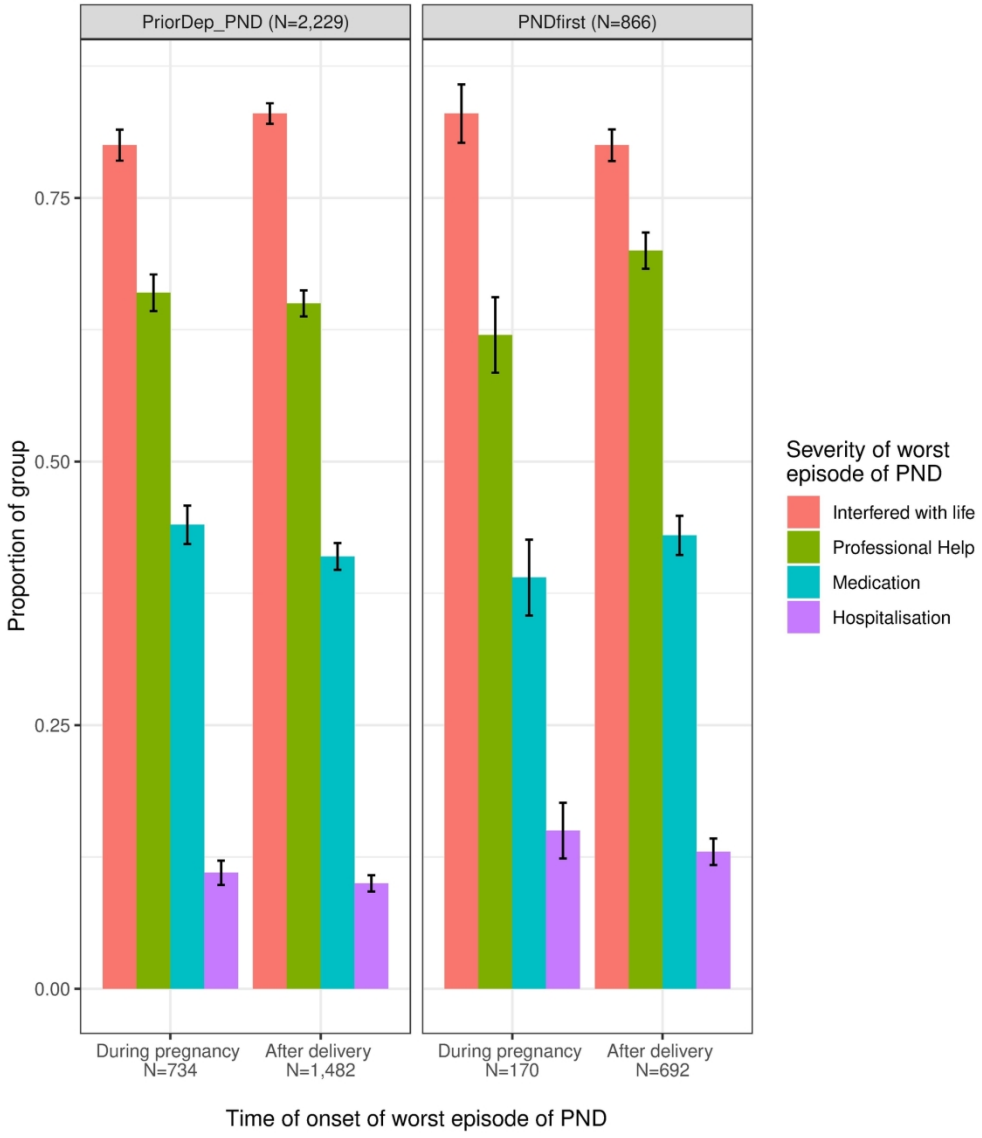

Fig. 4 Severity of worst episode of PND for priorDep and PND_firstDep cases, according to the time of onset of the worst episode. Severity is characterised by interference in everyday life, need for professional help, need for medication, and need to be hospitalised. The Y-axis provides the proportion of each group reporting each variable. Standard errors are included.

173x199mm (300 x 300 DPI)

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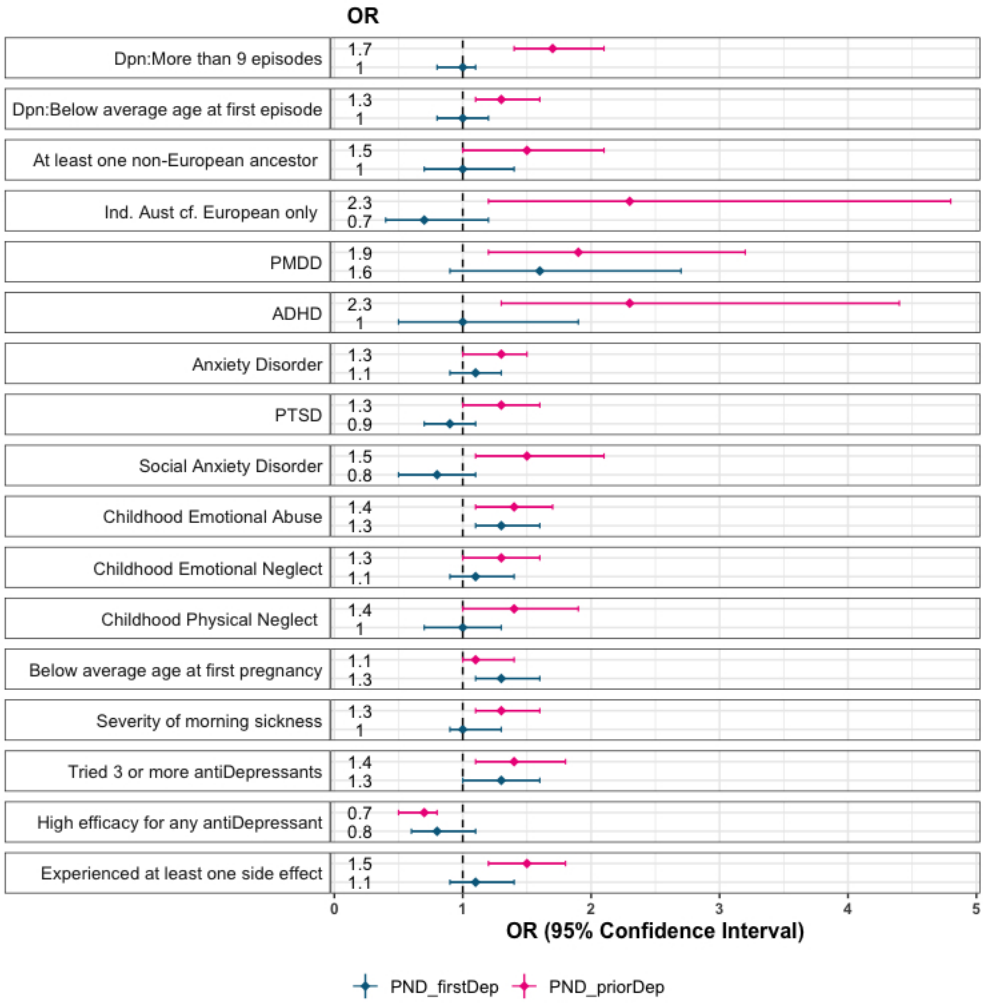

Fig. 5 Forest plot of odds ratios with confidence intervals of all variables nominally significantly associated with PND_priorDep cases when compared with NPD_priorDep. Odds ratios for the association of these variables with PND_firstDep cases compared with NPD_all are also included for comparison. Logistic regression, including age and number of live births of participants as covariates, was used to calculate odds ratios.

264x270mm (72 x 72 DPI)

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Table S1. Selection process: for PND_priorDep and PND_firstDep samples

Process	Number
Completed online survey	20,689
PriorDep cases: PND with history of major depression before first pregnancy (PND_priorDep)	2,261
PriorDep comparison group: History of major depression before first pregnancy, but no PND (NPD_priorDep)	672
PNDfirst cases: PND is first onset of major depression (PND_firstDep)	878
Uncategorized PND cases: lost to further analysis	1,919
PNDfirst comparison group: Met criteria for major depression but not associated with peripartum period (NPD_all)	2,124

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Table S2. List of geographical regions for participants to apply to great great grandparents

England, Ireland, Scotland or Wales
Australia - not of Aboriginal or Torres Strait Islander descent
Australia - of Aboriginal or Torres Strait Islander descent
New Zealand - not of Maori descent
New Zealand - of Maori descent
Northern Europe including Sweden, Norway, Finland and surrounding countries
Western Europe including France, Germany, the Netherlands and surrounding countries
Southern Europe inclding Italy, Greece, Spain, Portugal and surrounding countries
Eastern Europe including Russia, Poland, Hungary and surrounding countries
Middle East including Lebanon, Turkey and surrounding countries
Eastern Asia including China, Japan, South Korea, Taiwan and surrounding countries
South-East Asia including Thailand, Malaysia, Indonesia, Singapore and surrounding countries
South Asia including India, Pakistan, Sri Lanka and surrounding countries
Polynesia, Micronesia or Melanesia including Tonga, Fiji, Papua New Guinea and surrounding countrie
Africa
North America - not of First Nations, Native American, Inuit or Métis descent
North America - of First Nations, Native American, Inuit or Métis descent
Caribbean, Central or South America

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Table S3. List of psychiatric disorders with frequencies > 3% amongst all women with PND (N=5,058)

List of disorders	Number of cases (of all women with PND, N=5,058)	%
Bipolar Disorder	511	10.1
PMDD	195	3.8
Anorexia	178	3.5
ADHD	168	3.3
Anxiety Disorder	2680	53.0
Panic Attacks	516	10.2
Obsessive Compulsive Disorder	281	5.6
PTSD	859	17.0
Specific Phobia	635	12.6
Seasonal Affective Disorder	172	3.4
Social Anxiety Disorder	440	8.7
Personality Disorder	278	5.5

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Table S4. Length of worst episode of PND according to detailed onset information, and s

Length of worst episode	PND_p		
	Occurrence during pregnancy (n=734)		
	1st trimester (n=400)	2nd trimester (n=214)	3rd trimester (n=120)
Up to 2 weeks	44 (0.11)	18 (0.8)	15 (0.13)
2-4 weeks	51 (0.13)	33 (0.15)	25 (0.21)
1-3 months	51 (0.13)	35 (0.16)	30 (0.25)
3-6 months	48 (0.12)	51 (0.24)	21 (0.18)
More than 6 months	206 (0.52)	76 (0.36)	29 (0.24)

Regression analysis: association of length of worst episode with early onset (either first t delivery)

	PND_priorDep		
	OR	CI	P
Up to 2 weeks	1.3	0.9-1.7	1.3E-01
2-4 weeks	1.0	0.8-1.3	9.2E-01
1-3 months	0.9	0.7-1.1	1.5E-01
3-6 months	0.7	0.6-0.9	**6.0E-03**
More than 6 months	1.4	1.2-1.6	**1.7E-04**

Severity of worst episode	PND_priorDep		PND_fir
	Occurrence during pregnancy (n=734)	Occurrence after delivery (n=1,482)	Occurrence during pregnancy (n=170)
Interference	596 (0.80)	1232 (0.83)	141 (0.83)
Professional help	486 (0.66)	965 (0.65)	106 (0.62)
Medication	326 (0.44)	612 (0.41)	306 (0.43)
Hospitalisation	82 (0.11)	154 (0.10)	26 (0.15)

Note: proportions for severity measures do not add up to 1.0 since participants ticked al

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Comparison of severity measures for PND_priorDep and PND_firstDep cases for occurrences in pregnancy or after delivery: Association of each measure with PND_firstDep status.

	OR (for PND_firstDep)	CI	P
Interference	0.9	0.8-1.1	5.0E-01
Professional help	1.2	1.0-1.4	7.5E-02
Medication	1.0	0.8-1.2	8.4E-01
Hospitalisation	1.3	1.0-1.7	**2.4E-02**

Comparison of postpartum onset of worst episode for PND_priorDep and PND_firstDep cases

	PND_priorDep	PND_firstDep
Onset of worst case is postpartum	1487 (0.66)	695 (0.79)

Regression analysis: association of postpartum onset of worst case with PND_firstDep case status

OR (PND_firstDep case status)	CI	P
2.0	1.7-2.4	4.6E-13

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severity of worst episode of PND, characterised by interference in everyday life, and need for profes

priorDep (n=2,261)

Occurrence after delivery (n=1,482)			Total	Occurrence during pregnan	
0-4 weeks after delivery (n=724)	1-3 months after delivery (n=462)	More than 3 months after delivery (n=296)		1st trimester (n=73)	2nd trimester (n=55)
51 (0.07)	22 (0.05)	21 (0.07)	171	5 (0.07)	3 (0.06)
71 (0.10)	38 (0.08)	25 (0.08)	243	7 (0.10)	4 (0.07)
140 (0.19)	96 (0.21)	57 (0.19)	409	7 (0.10)	9 (0.16)
151 (0.21)	112 (0.24)	65 (0.22)	448	11 (0.15)	12 (0.22)
308 (0.43)	188 (0.41)	128 (0.43)	935	43 (0.59)	27 (0.49)

trimester of pregnancy or within 4 weeks after

PND_firstDep		
OR	CI	P
1.0	0.5-2.0	9.3E-01
1.1	0.7-1.8	7.2E-01
1.0	0.7-1.5	8.2E-01
0.7	0.5-1.0	6.1E-02
1.3	1.0-1.7	8.8E-02

rstDep

Occurrence after delivery (n=692)
559 (0.80)
488 (0.70)
67 (0.36)
91 (0.13)

ll that applied.

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sional help, medication, or hospitalisation.

	PND_firstDep (n=878)			
ıcy (n=170)	Occurrence after delivery (n=692)			Total
3rd trimester (n=42)	0-4 weeks after delivery (n=291)	1-3 months after delivery (n=225)	More than 3 months after delivery (n=176)	
2 (0.05)	11 (0.04)	6 (0.03)	10 (0.06)	37
4 (0.10)	26 (0.09)	24 (0.11)	11 (0.06)	76
8 (0.19)	51 (0.18)	34 (0.15)	28 (0.16)	137
9 (0.21)	62 (0.21)	71 (0.32)	37 (0.21)	202
19 (0.45)	139 (0.48)	89 (0.40)	90 (0.51)	407

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Table S5. priorDep and firstDep samples: Number of respondents (cases and controls) for eac

Category	Variable	priorDep sample			firs
		Number respondents	Number cases/ controls	% cases/ controls	Number respondents
Possible confounders					
	Age	2933			3002
	Number Births	2933			3002
Depression Severity					
	Number Episodes	2911			2772
	Number symptoms	2853			2698
	Age of first depressive episode	2933			2791
Eductation					
	Did not finish high school	2933	123/40	5.4/6.0	3002
	Post-secondary education	2933	1895/569	83.8/84.7	3002
Ancestry					
	At least one nonEuropean ancestor	2720	227/41	10.9/6.5	2779
	Australian Indigenous	2720	80/9	4.1/1.5	2779
Psychiatric comorbidities					
	Bipolar Disorder	2933	274/64	12.1/9.5	3002
	PMDD	2933	112/19	5.0/2.8	3002
	Anorexia	2933	97/21	4.3/3.1	3002
	ADHD	2933	97/12	4.3/1.8	3002
	Anxiety disorder	2933	1272/323	56.3/48.1	3002
	Panic attacks	2933	201/64	8.9/9.5	3002
	OCD	2933	147/32	6.5/4.8	3002
	PTSD	2933	452/103	20/15.3	3002
	Specific phobia	2933	326/78	14.4/11.6	3002
	Seasonal Affective	2933	100/25	4.4/3.7	3002
	Social anxiety disorder	2933	239/46	10.6/6.8	3002
	Personality disorder	2933	153/38	6.8/5.7	3002
	anyComorbidity	2933	1675/451	74.1/67.1	3002
Adverse experiences					
	Emotional abuse	1956	959/275	64.7/58.0	1986
	Emotional neglect	1957	839/249	56.3/53.3	1956
	Physical Abuse (anytime)	2070	642/189	40.8/38.2	2085
	Childhood Physical Abuse	1100	374/107	44.3/41.8	877
	Physical neglect	2010	267/63	17.5/13.1	2038
	Sexual abuse (anytime)	2067	1004/284	63.2/56.9	2091
Reproductive					
	Early pregnancy	2933	1143/313	50.6/46.6	2212

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	Early menarche	1880	633/184	45/41.9	1843
	Disruptive NVP	2520	1031/257	53/44.9	1913
	Polycystic ovarian syndrome	1960	195/56	13.1/11.9	1987
	Endometriosis	1969	251/67	16.8/14.1	2000
	Gestational diabetes	2933	90/18	6.7/4.2	3002
Antidepressants					
Effectiveness					
	High efficacy	2790			2792
	Moderate efficacy	2790			2792
	Low efficacy	2790			2792
Side Effects					
	Experienced at least one side effect	2832	1726/438	80/69.4	2882
	Reduced sexual desire or function	2832	1062/240	49.2/38	2882
	Weight gain	2832	968/209	44.8/33.1	2882
	Dry mouth	2832	775/179	35.9/28.4	2882
	Nausea	2832	705/140	32.7/22.2	2882
	Dizzy	2832	651/129	30.2/20.4	2882
	Drowsy	2832	599/124	27.7/19.7	2882
	Difficulty Sleeping	2832	574/129	26.6/20.4	2882
	Sweating	2832	544/116	25.2/18.4	2882
	Headache	2832	544/93	25.2/14.7	2882
	Fatigue or Weakness	2832	506/102	23.4/16.2	2882
	Agitation	2832	450/91	20.8/14.4	2882
	Increased Anxiety	2832	444/90	20.6/14.3	2882
	Suicidal Thoughts	2832	399/86	18.5/13.6	2882
	Shaking	2832	389/80	18/12.7	2882
	Constipation	2832	262/54	12.1/8.6	2882
	Diarrhoea	2832	166/34	7.7/5.4	2882
	Blurred Vision	2832	180/39	8.3/6.2	2882
	Attempted Suicide	2832	166/29	7.7/4.6	2882
	Muscle Pain	2832	142/31	6.6/4.9	2882
	Vomiting	2832	127/19	5.9/3	2882
	Weight Loss	2832	97/19	4.5/3	2882
	Runny nose	2832	73/7	3.4/1.1	2882
	Rash	2832	55/6	2.5/1	2882

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ch variable.

tDep sample

Number cases/ controls	% cases/ controls
74/209	8.4/9.8
699/1628	79.6/76.6
63/137	8/6.9
15/45	2.0/2.4
69/144	7.9/6.8
26/38	3.0/1.8
16/46	1.8/2.2
16/35	1.8/1.6
426/942	48.5/44.4
81/199	9.2/9.4
31/68	3.5/3.2
107/277	12.2/13.0
69/199	7.9/9.4
17/55	1.9/2.6
41/121	4.7/5.7
26/68	3.0/3.2
552/1274	62.9/60
323/702	56.1/49.8
281/654	49.5/47.1
195/459	32.1/31.1
96/228	36.6/37.1
72/171	12.1/11.9
321/746	52.0/49.9
405/823	59.0/53.9

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208/509	38.6/39.8
264/569	44.8/43.0
55/135	9.1/9.6
100/195	16.3/13.8
21/48	4.0/3.7
168/455	56.6/61.4
98/209	33.0/28.2
21/50	7.1/6.7
561/1222	68.3/62.0
324/629	39.5/31.9
317/631	38.6/32
247/513	30.1/26.0
192/346	23.4/17.6
160/324	19.5/16.4
188/325	22.9/16.5
162/350	19.7/17.8
162/300	19.7/15.2
159/269	19.4/13.6
141/275	17.2/14.0
125/240	15.2/12.2
131/258	16.0/13.1
75/199	9.1/10.1
97/219	11.8/11.1
73/166	8.9/8.4
54/103	6.6/5.2
39/103	4.8/5.2
34/66	4.1/3.3
40/90	4.9/4.6
32/67	3.9/3.4
34/57	4.1/2.9
13/29	1.6/1.5
16/31	1.9/1.6

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Table S6. priorDep and firstDep samples: Results of comparison of cases and controls for

priorDep sample: 2261 case
2,933 total. Significant

Characteristic	OR	CI	P
Confounders			
Age (OR per year, no covariates)	1.0	0.96-0.98	**2.3E-17**
Number Births (OR per birth, no covariates)	1.3	1.17-1.43	**4.7E-07**
Ancestry N(tests=2)			
Ancestry: At least one non-European ancestor	1.5	1.1-2.1	**2.8E-02**
Ancestry: Australian Indigenous	2.3	1.2-4.8	**2.4E-02**
Depression severity, N(tests)=6			
Odds of PND compared to NPD per symptom	1.2	1.1-1.3	**2.8E-04**
More than 7 symptoms	1.5	1.2-1.8	**4.8E-04**
Odds of PND compared to NPD per episode	1.1	1.1-1.1	**1.9E-13**
Depression severity: More than 9 episodes	1.7	1.4-2.1	**1.8E-08**
Odds of PND compared to NPD per year of age at first episode	1.0	0.96-0.99	**2.1E-03**
Depression severity: Below average age at first episode	1.3	1.1-1.6	**3.9E-03**
Education, N(tests)=3			
Did not complete high school	1.0	0.7-1.4	8.1E-01
Completed post-secondary education	0.9	0.7-1.2	6.5E-01
Comorbidity, N(tests)=12			
Having any comorbidity	1.2	1.0-1.5	**3.2E-02**
Bipolar Disorder	1.3	0.9-1.7	1.3E-01
PMDD	1.9	1.2-3.2	**1.4E-02**
Anorexia	1.3	0.8-2.2	2.4E-01
ADHD	2.3	1.3-4.4	**9.1E-03**
Anxiety Disorder	1.3	1.1-1.5	**1.2E-02**
Panic Attacks	1.0	0.7-1.4	9.4E-01
Obsessive Compulsive Disorder	1.3	0.9-1.9	2.7E-01
PTSD	1.3	1-1.6	**3.6E-02**
Specific Phobia	1.3	1-1.7	8.9E-02
Seasonal Affective Disorder	1.4	0.9-2.2	1.7E-01
Social Anxiety Disorder	1.5	1.1-2.1	**1.6E-02**
Personality Disorder	1.0	0.7-1.5	8.8E-01
Trauma, N(tests)=7			
ChildhoodEmotionalAbuse	1.4	1.1-1.7	**5.5E-03**
ChildhoodEmotionalNeglect	1.3	1-1.6	**3.1E-02**
ChildhoodPhysicalAbuse	1.0	0.8-1.4	9.4E-01
Physical abuse (any time)	1.1	0.9-1.4	3.1E-01
Physical neglect (childhood)	1.4	1.1-1.9	**2.3E-02**

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Sexual abuse (childhood)	1.0	0.7-1.3	7.9E-01
Sexual abuse (any time)	1.2	1-1.5	6.1E-02
Reproductive characteristics, N(tests)=6			
Below average age at first pregnancy	1.1	1.0-1.4	1.3E-01
Disruptive NVP	1.3	1.1-1.6	**6.6E-03**
Early menarche	1.1	0.9-1.4	3.4E-01
Endometrioses	1.2	0.9-1.6	2.1E-01
Polycystic ovarian syndrome	0.9	0.7-1.3	7.2E-01
Gestational diabetes	1.4	0.8-2.4	2.4E-01
Antidepressant use			
Tried 3 or more commonly prescribed antidepressant (as a proportion of women using antidepressants)	1.4	1.1-1.8	**1.4E-03**
Antidepressant efficacy, N(tests)=3			
High efficacy for any common antidepressant	0.7	0.5-0.8	**5.5E-04**
Moderate efficacy for any common antidepressant	1.3	1.0-1.7	6.6E-02
Low efficacy for any common antidepressant	1.2	0.9-1.6	2.5E-01
Antidepressant side effects, N(tests)=23			
Experienced at least one side effect	1.5	1.2-1.8	**3.0E-04**
Reduced sexual desire or function	1.4	1.1-1.7	**8.0E-04**
Weight gain	1.5	1.3-1.9	**1.9E-05**
Dry mouth	1.3	1.1-1.7	**4.8E-03**
Nausea	1.4	1.1-1.7	**3.8E-03**
Dizzy	1.4	1.1-1.7	**5.8E-03**
Drowsy	1.4	1.1-1.7	**7.5E-03**
Difficulty Sleeping	1.3	1-1.6	**3.7E-02**
Sweating	1.3	1-1.7	**2.3E-02**
Headache	1.7	1.3-2.1	**9.0E-05**
Fatigue or Weakness	1.4	1.1-1.8	**3.6E-03**
Agitation	1.4	1.1-1.8	**1.6E-02**
Increased Anxiety	1.4	1.1-1.8	**2.1E-02**
Suicidal Thoughts	1.2	0.9-1.6	1.3E-01
Shaking	1.2	1-1.6	1.1E-01
Constipation	1.5	1.1-2.1	**1.1E-02**
Diarrhoea	1.2	0.8-1.9	2.8E-01
Blurred Vision	1.3	0.9-2	1.2E-01
Attempt Suicide	1.3	0.8-2	2.8E-01
Muscle Pain	1.3	0.9-2	1.9E-01
Vomiting	1.4	0.9-2.4	2.0E-01
Weight Loss	1.2	0.7-2.1	4.4E-01
Runny nose	3.4	1.6-8.2	**2.5E-03**
Rash	2.5	1.1-6.8	**3.6E-02**

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· all variables, including age and number of births as convariates.

ɛs; 672 controls; t P in bold	firstDep sample: 878 cases; 2124 controls; 3002 total. Significant P in bold			
P (Bonferroni Adjustment for multiple tests)	**OR**	**CI**	**P**	P (Bonferroni Adjustment for multiple tests)
0.00	0.97	0.97-0.98	**7.44E-16**	**0.00**
0.00	1.27	1.17-1.38	**3.52E-09**	**0.00**
0.06	1.0	0.7-1.4	8.6E-01	1.00
0.05	0.7	0.4-1.2	1.9E-01	0.37
0.00	1.1	0.98-1.1	1.9E-01	0.56
0.00	1.2	0.97-1.4	9.4E-02	0.28
0.00	1.0	1.0-1.0	4.0E-01	1.00
0.00	1.0	0.8-1.1	6.4E-01	1.00
0.01	1.00	0.99-1.0	7.3E-01	1.00
0.02	1.0	0.8-1.2	8.0E-01	1.00
1.00	1.0	0.7-1.3	8.8E-01	1.00
1.00	1.1	0.9-1.4	3.1E-01	1.00
	1.1	0.9-1.2	5.3E-01	
1.00	1.2	0.9-1.6	2.7E-01	1.00
0.14	1.6	0.9-2.7	7.6E-02	0.91
1.00	0.8	0.4-1.4	4.0E-01	1.00
0.11	1.0	0.5-1.9	9.4E-01	1.00
0.17	1.1	0.9-1.3	3.0E-01	1.00
1.00	1.0	0.8-1.3	9.1E-01	1.00
1.00	1.0	0.6-1.5	9.2E-01	1.00
0.48	0.9	0.7-1.1	2.4E-01	1.00
1.00	0.8	0.6-1.1	2.2E-01	1.00
1.00	1.0	0.5-1.6	8.8E-01	1.00
0.25	0.8	0.5-1.1	1.9E-01	1.00
1.00	0.7	0.4-1.1	1.2E-01	1.00
0.04	1.3	1.1-1.6	**1.0E-02**	0.07
0.26	1.1	0.9-1.4	1.8E-01	1.00
1.00	0.9	0.7-1.3	6.1E-01	1.00
1.00	1.0	0.8-1.2	8.9E-01	1.00
0.20	1.0	0.7-1.3	9.9E-01	1.00

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1.00	0.8	0.6-1.1	2.0E-01	1.00
0.42	1.1	0.9-1.3	5.8E-01	1.00
0.78	1.3	1.1-1.6	**2.9E-03**	**0.02**
0.04	1.0	0.9-1.3	7.3E-01	1.00
1.00	0.9	0.7-1.1	2.4E-01	1.00
1.00	1.3	1.0-1.7	8.7E-02	0.52
1.00	0.8	0.6-1.1	2.4E-01	1.00
1.00	0.9	0.5-1.5	7.5E-01	1.00
	1.3	1.0-1.6	**8.0E-03**	
0.00	0.8	0.6-1.1	1.5E-01	0.60
1.00	1.3	0.9-1.7	1.5E-01	0.62
1.00	1.0	0.6-1.7	9.5E-01	1.00
	1.1	0.9-1.4	1.9E-01	
0.02	1.3	1.1-1.5	**1.1E-02**	0.25
0.00	1.2	1-1.5	**2.4E-02**	0.56
0.11	1.2	1-1.4	1.3E-01	1.00
0.09	1.3	1-1.5	**3.5E-02**	0.81
0.13	1.0	0.8-1.3	9.2E-01	1.00
0.17	1.4	1.1-1.7	**3.9E-03**	0.09
0.86	1.0	0.8-1.3	8.6E-01	1.00
0.53	1.2	1-1.5	8.5E-02	1.00
0.00	1.3	1-1.7	**1.8E-02**	0.41
0.08	1.2	0.9-1.5	1.6E-01	1.00
0.38	1.2	0.9-1.5	2.5E-01	1.00
0.47	1.2	0.9-1.5	2.4E-01	1.00
1.00	0.7	0.5-1	5.0E-02	1.00
1.00	0.9	0.7-1.2	5.5E-01	1.00
0.25	1.0	0.8-1.4	9.1E-01	1.00
1.00	1.1	0.8-1.6	5.0E-01	1.00
1.00	0.9	0.6-1.3	6.0E-01	1.00
1.00	1.0	0.6-1.5	9.6E-01	1.00
1.00	1.0	0.7-1.5	9.9E-01	1.00
1.00	1.0	0.6-1.6	9.5E-01	1.00
1.00	1.3	0.8-2	2.5E-01	1.00
0.06	1.0	0.5-2	9.1E-01	1.00
0.82	1.1	0.6-2.1	7.3E-01	1.00

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Table S7. Comparison of NPD_priorDep with NPD_all groups, using regression analysis, fo

	OR	CI	P
Depression severity: odds of priorDep compared to odds of allDep per symptom	1.1	1.0-1.2	9.80E-03
Depression severity: odds of priorDep compared to odds of allDep per episode	1.1	1.1-1.1	3.30E-09
Depression severity: odds of priorDep compared to odds of allDep per year of age at first episode	0.68	0.64-0.71	1.30E-63

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r severity of major depression, using number of symptoms and episodes and age at first episode.

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Table S8. Sensitivity analysis of women experiencing PND both before and after delivery. Analysis PriorDep sample. Significant P in I

	Cases who experienced PND both during pregnancy and 672 controls)			
Characteristic	Number of PND cases/ controls with this variable	PND cases/ controls with this variable as % of responses	OR	CI
Ancestry N(tests=2)				
Ancestry: At least one non-European ancestor	166/41	12/6.5	1.6	1.1-2.3
Ancestry: Australian Indigenous	58/9	4.5/1.5	2.2	1.1-4.9
Depression severity, N(tests)=6				
Odds of PND compared to NPD per symptom			1.3	1.2-1.4
More than 7 symptoms	1243/480	84.3/74.4	1.7	1.3-2.1
Odds of PND compared to NPD per episode			1.1	1.1-1.1
Depression severity: More than 9 episodes	804/253	54.7/39.2	2.1	1.7-2.5
Odds of PND compared to NPD per year of age at first episode			1.0	0.94-0.98
Depression severity: Below average age at first episode	933/325	63/50.1	1.5	1.2-1.8
Education, N(tests)=2				
Did not complete high school	85/40	5.6/6.0	1.0	0.6-1.5
Completed post-secondary education	1259/569	83.5/84.7	0.9	0.7-1.2
Comorbidity, N(tests)=12				
Likelihood of comorbidity	1152/451	76.4/67.1	1.3	1.1-1.7
Bipolar Disorder	196/64	13/9.5	1.4	1-1.9
PMDD	79/19	5.2/2.8	2.0	1.2-3.5
Anorexia	64/21	4.2/3.1	1.2	0.7-2.1
ADHD	70/12	4.6/1.8	2.4	1.3-4.7
Anxiety Disorder	888/323	58.9/48.1	1.4	1.1-1.7
Panic Attacks	151/64	10/9.5	1.2	0.9-1.6
Obsessive Compulsive Disorder	111/32	7.4/4.8	1.4	0.9-2.2
PTSD	336/103	22.3/15.3	1.5	1.1-1.9
Specific Phobia	242/78	16.1/11.6	1.4	1.1-1.9
Seasonal Affective Disorder	72/25	4.8/3.7	1.7	1.1-2.8
Social Anxiety Disorder	190/46	12.6/6.8	1.8	1.3-2.6

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Personality Disorder	122/38	8.1/5.7	1.2 0.8-1.8
Trauma, N(tests)=7			
ChildhoodEmotionalAbuse	657/275	68.2/58.0	1.6 1.3-2.1
ChildhoodEmotionalNeglect	585/249	60.3/53.3	1.6 1.2-2
ChildhoodPhysicalAbuse	264/107	46.4/41.8	1.0 0.8-1.4
Physical abuse (any time)	440/189	42.8/38.2	1.2 1-1.5
Physical neglect (childhood)	203/63	20.4/13.1	1.8 1.3-2.4
Sexual abuse (childhood)	430/175	74.8/77.1	0.8 0.6-1.2
Sexual abuse (any time)	675/284	65.1/56.9	1.3 1-1.6
Reproductive characteristics, N(tests)=7			
Above average number of live births	428/138	28.4/20.5	1.9 1.6-2.5
Below average age at first pregnancy	822/313	54.5/46.6	1.3 1.1-1.6
Disruptive NVP	710/257	55.1/44.9	1.4 1.1-1.7
Early menarche	422/184	46/41.9	1.2 0.9-1.5
Endometrioses	173/67	17.7/14.1	1.3 0.9-1.8
Polycystic ovarian syndrome	135/56	13.9/11.9	1.0 0.7-1.4
Gestational diabetes	66/18	7.5/4.2	1.6 0.9-2.8
Antidepressant use			
Have used common antidepressant	1442/631	95.7/93.9	
Tried 3 or more commonly prescribed antidepressant (as a proportion of women using antidepressants)	463/142	32.1/22.5	1.7 1.3-2.1
Antidepressant efficacy, N(tests)=3			
High efficacy for any common antidepressant	1444/631		0.7 0.49-0.85
Moderate efficacy for any common antidepressant	1444/631		1.4 1.0-1.8
Low efficacy for any common antidepressant	1444/631		1.0 0.7-1.5
Antidepressant side effects, N(tests)=23			
Experienced at least one side effect	1189/438	82.3/69.4	1.6 1.3-2.1
Reduced sexual desire or function	737/240	51.1/38	1.4 1.2-1.8
Weight gain	690/209	47.9/33.1	1.7 1.4-2.1
Dry mouth	565/179	39.2/28.4	1.5 1.2-1.9
Nausea	518/140	35.9/22.2	1.5 1.2-1.9
Dizzy	486/129	33.7/20.4	1.5 1.2-2
Drowsy	445/124	30.9/19.7	1.5 1.2-1.9
Difficulty Sleeping	421/129	29.2/20.4	1.4 1.1-1.8
Sweating	394/116	27.3/18.4	1.4 1.1-1.8
Headache	404/93	28/14.7	1.8 1.4-2.4
Fatigue or Weakness	370/102	25.7/16.2	1.6 1.2-2.1

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Agitation	340/91	23.6/14.4	1.6 1.2-2.1
Increased Anxiety	338/90	23.4/14.3	1.6 1.2-2.1
Suicidal Thoughts	312/86	21.6/13.6	1.4 1.1-1.9
Shaking	306/80	21.2/12.7	1.5 1.1-2
Constipation	190/54	13.2/8.6	1.6 1.2-2.3
Diarrhoea	129/34	8.9/5.4	1.4 0.9-2.1
Blurred Vision	140/39	9.7/6.2	1.6 1.1-2.4
Attempt Suicide	143/29	9.9/4.6	1.7 1.1-2.6
Muscle Pain	110/31	7.6/4.9	1.6 1-2.4
Vomiting	102/19	7.1/3	1.5 0.9-2.7
Weight Loss	68/19	4.7/3	1.2 0.7-2.1
Runny nose	58/7	4/1.1	4.0 1.9-9.9
Rash	42/6	2.9/1	2.7 1.2-7.3

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s conducted for both samples separately.

bold firstDep sample. Significant P in bold

l postpartum (1507 cases;		Cases who experienced PND both during pregnancy and postpartum (2124 controls)				
P	P (Bonferroni Adjustment for multiple tests)	Number of PND cases/ controls with this variable	PND cases/ controls with this variable as % of responses	OR	CI	P
1.9E-02	0.04	40/137	8.7/6.9	1.1	0.7-1.6	6.1E-01
3.2E-02	0.06	9/45	2.1/2.4	0.659	0.3-1.3	2.7E-01
8.6E-07	**0.00**			1.1	1.0-1.2	6.5E-02
2.0E-05	**0.00**	392/1340	78.4/72.8	1.3	1.0-1.6	6.5E-02
1.2E-17	**0.00**			1	1.0-1.0	1.3E-01
8.0E-13	**0.00**	186/630	37.2/34.3	1.3	1.0-1.5	**4.2E-02**
2.2E-05	**0.00**			1	0.99-1.0	3.3E-01
8.2E-05	**0.00**	312/1020	62.2/55.2	1.2	0.9-1.5	1.5E-01
9.9E-01	1.00	51/209	10.0/9.8	1.17	0.8-1.6	3.5E-01
6.1E-01	1.83	399/1628	78.2/76.6	1	0.8-1.3	9.0E-01
5.6E-03		334/1274	65.5/60.0	1.2	0.9-1.4	1.5E-01
4.9E-02	0.58	41/144	8.0/6.8	1.2	0.8-1.8	2.5E-01
8.1E-03	0.10	19/38	3.7/1.8	2.1	1.1-3.7	**1.3E-02**
4.3E-01	1.00	10/46	2.0/2.2	0.9	0.4-1.7	6.6E-01
7.7E-03	0.09	11/35	2.2/1.6	1.2	0.6-2.3	6.6E-01
1.6E-03	**0.02**	256/942	50.2/44.4	1.2	0.9-1.4	1.6E-01
3.2E-01	1.00	50/199	9.8/9.4	1.1	0.8-1.5	6.4E-01
1.1E-01	1.00	19/68	3.7/3.2	1.0	0.6-1.7	9.1E-01
3.0E-03	**0.04**	77/277	15.1/13	1.1	0.8-1.5	4.5E-01
2.0E-02	0.24	46/199	9.0/9.4	1.0	0.7-1.4	8.6E-01
3.3E-02	0.40	9/55	1.8/2.6	0.9	0.4-1.8	8.0E-01
7.9E-04	**0.01**	26/121	5.1/5.7	0.8	0.5-1.3	4.5E-01

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3.6E-01	1.00	21/68	4.1/3.2	0.9	0.5-1.5	7.4E-01
4.8E-05	**0.00**	200/702	58.7/49.8	1.5	1.1-1.9	**2.7E-03**
3.3E-04	**0.00**	178/654	52.8/47.1	1.3	1-1.7	**2.8E-02**
8.0E-01	1.00	61/228	38.1/37.1	1.0	0.7-1.4	8.6E-01
8.6E-02	0.60	122/459	34.2/31.1	1.1	0.9-1.4	4.5E-01
6.3E-04	**0.00**	47/171	13.3/11.9	1.1	0.8-1.6	5.6E-01
3.0E-01	1.00	118/449	73.8/75.8	0.8	0.5-1.2	3.0E-01
2.5E-02	0.17	202/746	55.6/49.9	1.2	1-1.5	1.0E-01
1.4E-08	**0.00**	201/578	39.4/27.2	2.1	1.7-2.6	**1.9E-12**
2.5E-03	**0.02**	248/823	62.6/53.9	1.6	1.3-2.0	**1.2E-04**
1.7E-03	**0.01**	166/569	48.1/43.0	1.2	0.9-1.5	1.9E-01
1.3E-01	**0.92**	126/509	39.4/39.8	0.9	0.7-1.2	4.0E-01
1.3E-01	**0.91**	60/195	16.8/13.8	1.3	0.9-1.8	9.9E-02
8.3E-01	**5.81**	135/34	9.7/9.6	0.8	0.5-1.3	4.3E-01
1.0E-01	**0.70**	13/48	4.1/3.7	0.9	0.5-1.7	7.9E-01
		475/1971	93.1/92.8			
1.2E-05		98/363	20.6/18.4	1.2	1.0-1.5	1.1E-01
1.8E-03	**0.01**	475/1971		0.96	0.7-1.3	7.4E-01
3.4E-02	0.10	475/1971		1.1	0.8-1.4	5.1E-01
8.8E-01	1.00	475/1971		0.87	0.6-1.2	4.5E-01
4.8E-05		334/1222	68.2/62.0	1.1	0.9-1.4	2.9E-01
6.7E-04	**0.02**	187/629	39.4/31.9	1.3	1-1.6	**4.7E-02**
1.3E-06	**0.00**	180/631	37.9/32.0	1.2	1-1.5	1.1E-01
2.3E-04	**0.01**	135/513	28.4/26.0	1.1	0.8-1.4	5.3E-01
2.6E-04	**0.01**	116/346	24.4/17.6	1.3	1-1.7	**2.7E-02**
3.2E-04	**0.01**	100/324	21.1/16.4	1.1	0.8-1.4	4.6E-01
9.0E-04	**0.02**	114/325	24.0/16.5	1.5	1.1-1.9	**4.1E-03**
3.1E-03	0.07	91/350	19.2/17.8	1.0	0.7-1.3	7.5E-01
4.4E-03	0.10	97/300	20.4/15.2	1.3	1-1.7	5.7E-02
4.5E-06	**0.00**	95/269	20.0/13.6	1.4	1.1-1.8	**1.8E-02**
3.0E-04	**0.01**	89/275	18.7/14	1.3	1-1.7	5.2E-02

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1.2E-03	**0.03**	82/240	17.3/12.2	1.4 1-1.8	**4.7E-02**
1.5E-03	**0.03**	79/258	16.6/13.1	1.3 0.9-1.7	1.1E-01
1.1E-02	0.25	44/199	9.3/10.1	0.7 0.5-1.1	1.2E-01
4.7E-03	0.11	58/219	12.2/11.1	0.9 0.7-1.3	7.4E-01
4.8E-03	0.11	43/166	9.1/8.4	1.1 0.7-1.5	7.4E-01
1.3E-01	1.00	31/103	6.5/5.2	1.2 0.7-1.8	5.1E-01
1.6E-02	0.37	33/103	6.9/5.2	1.4 0.9-2.2	1.0E-01
2.3E-02	0.54	18/66	3.8/3.3	0.8 0.4-1.4	4.5E-01
4.5E-02	1.00	26/90	5.7/4.6	1.1 0.7-1.8	5.8E-01
1.1E-01	1.00	19/67	4.0/3.4	1.1 0.6-1.8	8.4E-01
5.4E-01	1.00	17/57	3.6/2.9	1.1 0.6-1.9	7.4E-01
7.3E-04	**0.02**	8/29	1.7/1.5	1.1 0.4-2.3	8.5E-01
3.0E-02	0.68	7/31	1.5/1.6	0.9 0.4-2	8.1E-01

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(510 cases;	P (Bonferroni Adjustment for multiple tests)
	1.23
	0.54
	0.20
	0.19
	0.39
	0.13
	0.98
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	1.04
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Supplementary Methods

Australian Genetics of Depression Study

Selection of Cases

Prior history of depression: Participants with prior depression were selected by comparing the reported age of the first episode of depression to the reported age of first pregnancy. Where the depression onset age preceded pregnancy, participants were included amongst those with a prior history of major depression. Where the age of depression onset matched the age of first pregnancy (or age of first pregnancy +1), or the age of the worst episode of PND, participants were included amongst those who experienced their first episode of depression perinatally.

Measures

Severity of depression: DSM-V diagnostic criteria for MDD were assessed using the CIDI-SF(World Health Organization 1994). First onset age was assessed by asking participants when they had first experienced a 2-week period of depression. Severity of depression was measured using the number of symptoms reported during the worst episode, the number of episodes, and age at first episode. The total number of periods of at least 2 weeks of depression and/or anhedonia was calculated using a dropdown box where participants could select from 1 to 12 or 13+.

Demographic measures: Demographic measures included current age, marital status, and highest level of education completed or partially completed measured using an ordinal scale (primary; lower or higher secondary school; diploma; degree; or post-graduate studies).

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Ancestry analysis (self-report of ancestry of great-great-grandparents assigned to 18 geographical regions, Supplementary Table S2) considered associations between rates of endorsing PND in women with ancestors only from Europe, compared to women with at least one non-European ancestor. Further analysis compared the rate of PND in those reporting Australian Indigenous ancestry to those of only European ancestry.

Clinical measures: Participants were asked to report any previous diagnoses from a total list of 19 psychiatric disorders, of which 13, with frequencies > 3% for all women with PND, were analyzed in this study (Supplementary Table S3). History of childhood trauma was assessed using responses to three questions that asked whether participants had been emotionally abused, emotionally neglected, or physically neglected during childhood. Additionally, participants were asked whether they had experienced physical or sexual assault or unwanted sexual experience at any time in their life, as well as their age at that time. For these questions, an age less than 16 was used to designate a childhood experience.

Reproductive measures: Reproductive measures included age at menarche, parity (number of live births), age at first birth, presence and severity of nausea and vomiting during pregnancy (NVP), and diagnosis of endometriosis or polycystic ovarian syndrome. Severity of NVP was measured using a scale adapted from Zhang et al. (2011). Gestational diabetes was measured as part of a general question about experience of medical conditions, followed by a request to specify the type of diabetes (if diabetes was selected).

Effects of antidepressants: Efficacy of the top ten most commonly prescribed antidepressants in Australia was assessed by asking how well each antidepressant a participant had ever taken worked for them on a three-point scale (Not at all well,

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Moderately Well or Very Well). For each individual, the number of times each level was chosen was normalized by dividing by the number of antidepressants used by that individual: for example, if a woman had tried five antidepressants, and recorded 1 response of “very well”, 2 of “moderately well” and 2 of “not very well”, her response would be recorded as 1/5 or 0.2 for “high efficacy”, 0.4 for “moderate efficacy” and 0.4 for “low efficacy”. For each drug taken, participants were asked if they had experienced any of the 23 most reported antidepressant side-effects. Regression of each side-effect on PND case status included number of antidepressants used as a covariate.

Questions from the Australian Genetics of Depression Study Questionnaire used in phenotypic analysis (excluding Depression Scales)

Biological sex, age and marital status

Are you male or female?

How old are you now?

What is your marital status?

- Married
- Separated
- Divorced
- Widowed
- Never married
- Living with partner/defacto (for a period of six months or longer)

Education

What is your highest level of education?

- No formal education
- Completed or partially completed primary school (years 1-7)
- Completed or partially completed junior secondary school (years 8-10)
- Completed or partially completed senior secondary school (years 11-12)
- Completed or partially completed certificate or diploma
- Completed or partially completed a degree
- Completed or partially completed a Post Graduate Diploma, Masters degree, Doctorate or PhD
- Don't know

Ancestry

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Thinking about what you know of your family history, which of the following best describes the geographic regions where your ancestors (i.e. your great-great-grandparents) come from? You may select as many choices as you need

- England, Ireland, Scotland or Wales
- Australia - not of Aboriginal or Torres Strait Islander descent
- Australia - of Aboriginal or Torres Strait Islander descent
- New Zealand - not of Maori descent
- New Zealand - of Maori descent
- Northern Europe including Sweden, Norway, Finland and surrounding countries
- Western Europe including France, Germany, the Netherlands and surrounding countries
- Southern Europe including Italy, Greece, Spain, Portugal and surrounding countries
- Eastern Europe including Russia, Poland, Hungary and surrounding countries
- Middle East including Lebanon, Turkey and surrounding countries
- Eastern Asia including China, Japan, South Korea, North Korea, Taiwan and Hong Kong
- South-East Asia including Thailand, Malaysia, Indonesia, Singapore and surrounding countries
- South Asia including India, Pakistan, Sri Lanka and surrounding countries
- Polynesia, Micronesia or Melanesia including Tonga, Fiji, Papua New Guinea and surrounding countries
- Africa
- North America - not of First Nations, Native American, Inuit or Métis descent
- North America - of First Nations, Native American, Inuit or Métis descent
- Caribbean, Central or South America
- Don't know

Comorbidities

Have you ever been diagnosed with any of the following? Please select all that apply.

- Depression
- Bipolar disorder
- Premenstrual dysphoric mood disorder
- Schizophrenia
- Anorexia nervosa
- Bulimia
- Attention-deficit/hyperactivity disorder (ADD/ADHD)
- Autism spectrum disorder (Autism, Asperger's disorder)
- Tourette's disorder
- Anxiety disorder (Generalised anxiety disorder)
- Panic disorder
- Obsessive compulsive disorder
- Hoarding disorder
- Posttraumatic stress disorder (PTSD)
- Specific phobia (e.g. animals, heights, storms, blood / injection / injury, flying, enclosed spaces)
- Seasonal affective disorder (SAD)

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- Social anxiety disorder (also known as Social phobia)
- Agoraphobia
- Personality disorder
- Substance use disorder

Antidepressants

Have you ever taken any of the following antidepressants (even if it wasn't for depression or anxiety)? *Please select all that apply.*

1st List (10 most commonly prescribed antidepressants):

- Sertraline (e.g. Zoloft, Eleva, Sertra, Sertracor, Setrona, Xydep)
- Escitalopram (e.g. Lexapro, Cilopam, Escicor, Esipram, Esitalo, Lexam, LoxaLate)
- Venlafaxine (e.g. Efexor, Altven, Elaxine, Enlafax, Venla, Venlexor)
- Amitriptyline (e.g. Endep)
- Mirtazapine (e.g. Avanza, Remeron, Milivin, Axit, Aurozapine, Mirtazon)
- Desvenlafaxine (e.g. Pristiq, Desfax)
- Citalopram (e.g. Cipramil, Celapram, Celica, Ciazil, Citalo, Talam)
- Fluoxetine (e.g. Prozac, Auscap, Lovan, Zactin)
- Duloxetine (e.g. Cymbalta, Andepra, Coperin, Deotine, Depreta, Drulox)
- Paroxetine (e.g. Aropax, Paxtine, Extine, Roxet)

2nd List:

- Dothiepin (e.g. Dothep)
- Fluvoxamine (e.g. Luvox, Faverin, Movox, Voxam)
- Doxepin (e.g. Sinequan, Deptran)
- Nortriptyline (e.g. Allegron)
- Moclobemide (e.g. Amina, Clobemix, Mohexal, Aurorix)
- Clomipramine (e.g. Anafranil, Placil)
- Reboxetine (e.g. Edronax)
- Mianserin (e.g. Lumin)
- Imipramine (e.g. Tofranil, Tolerade)
- Tranylcypromine (e.g. Parnate)
- Phenelzine (e.g. Nardil)

How well does / did each antidepressant work for you?

- Not at all well
- Moderately well
- Very well
- Don't know

Side Effects

Which side effects did you experience from the following antidepressant(s). Please select all that apply.

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- Dry mouth
- Sweating
- Nausea
- Vomiting
- Diarrhoea
- Constipation
- Headache
- Dizziness
- Shaking
- Muscle pain
- Drowsiness
- Difficulty getting to sleep
- Increased anxiety
- Agitation
- Fatigue or weakness
- Weight gain
- Weight loss
- Rash
- Runny nose
- Reduced sexual desire / function
- Blurred vision
- Suicidal thoughts
- Attempted suicide

Abuse

Listed below are a number of difficult or stressful things that sometimes happen to people. For each event mark one or more of the boxes to the right to indicate that: (a) it **happened to you** personally; (b) you **witnessed it** happen to someone else; (c) you **learned about it** happening to a close family member or close friend; (d) you were exposed to it as **part of your job** (for example, paramedic, police, military or other first responder); (e) you're **not sure** if it fits; or (f) it **doesn't apply** to you. Be sure to consider your **entire life** (growing up as well as adulthood) as you go through the list of events.

(Relevant categories (only considered those marked "Happened to me"))

- Physical assault (e.g. being attacked, hit, slapped, kicked, beaten up)
- Sexual assault (rape, attempted rape, made to perform any type of sexual act through force or threat of harm)
- Other unwanted or uncomfortable sexual experience

How old were you the first and last time these things happened?

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Childhood abuse

People may experience stressful situations in childhood which may affect their future health and well-being. Please indicate if you experienced any of these situations **during your childhood**.

- Emotional abuse (e.g. often being told you were no good, yelled at in a scary way, threatened, ignored, or stopped from making friends)
- Emotional neglect (e.g. often not being shown affection, or not being given encouragement or support)
- Physical neglect (e.g. often not being given enough to eat or drink, appropriate clothing, shelter, medical care, education, supervision or a safe home environment)

Menarche

Have you begun to menstruate (started having your period)?
How old were you when you had your first menstrual period?

Parity

How many times have you been pregnant? *If you're unsure, please provide your best estimate.* How many of these pregnancies resulted in live births (including caesarean section)?

Morning sickness

While many women experience morning sickness, there are differences in how severe morning sickness is. Did you have any morning sickness, nausea or vomiting during any of your pregnancies?

Thinking back to each pregnancy, which of the following best describes your experience?

- I did not have any nausea or vomiting
- Nausea and/or vomiting for *less than 7 days*, but I didn't see a doctor about this and it didn't disrupt my daily routine.
- Nausea and/or vomiting for *more than 7 days*, but I didn't see a doctor about this. It didn't disrupt my daily routine.

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- It disrupted my daily routine, but it didn't affect my weight and I didn't need medication to manage it.
- It really disrupted my daily routine and I was prescribed medication (or was put on a drip) but it didn't lead to weight loss.
- It really disrupted my daily routine. I lost weight. I was prescribed medication or was put on a drip or feeding tube.
- I don't remember or am unsure.

Gestational diabetes

Have you ever had any of the following medical conditions? *Please select all that apply*

- Diabetes or high blood sugar

[For those selecting diabetes or high blood sugar:]

Please select the specific type of the medical condition(s) you have had.

- Type 1 diabetes
- Type 2 diabetes
- Gestational diabetes
- Other diabetes or high blood sugar

Reproductive disorders

Has a doctor ever diagnosed you with any of the following?

- Polycystic ovarian syndrome (a hormonal disorder characterised by ovarian follicles failing to ovulate and remaining as multiple cysts, distending the ovary)
- Endometriosis (the presence of tissue similar to the kind lining the uterus, at other sites in the pelvis)

Guintivano J et al. (2018) PPD ACT: an app-based genetic study of postpartum depression Transl Psychiatry 8:260 doi:10.1038/s41398-018-0305-5

World Health Organization (1994) Composite International Diagnostic Interview (CIDI) researcher's manual (Version 1.1, 1994). World Health Organisation; American Psychiatric Association,

Zhang Y, Cantor RM, MacGibbon K, Romero R, Goodwin TM, Mullin PM, Fejzo MS (2011) Familial aggregation of hyperemesis gravidarum Am J Obstet Gynecol 204:230 e231-237 doi:10.1016/j.ajog.2010.09.018

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STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2-4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-6
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6-7
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	7-8
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8-9,10-11
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	8, 9-10
Bias	9	Describe any efforts to address potential sources of bias	10-11
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	9-11
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	11-12
		(*b*) Describe any methods used to examine subgroups and interactions	11
		(*c*) Explain how missing data were addressed	11
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	12

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Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	12-14
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	12-15
		(b) Indicate number of participants with missing data for each variable of interest	15
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	15
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	15-17
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	17-18
Discussion			
Key results	18	Summarise key results with reference to study objectives	18-19
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	19
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	19-20
Generalisability	21	Discuss the generalisability (external validity) of the study results	20-21
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	4

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Lifetime prevalence and correlates of perinatal depression in the Australian Genetics of Depression Study

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1

Lifetime prevalence and correlates of perinatal depression in the Australian Genetics of Depression Study

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Abstract

Objectives

This study sought to evaluate the prevalence, timing of onset and duration of symptoms of depression or anxiety in the perinatal period (PND)) in women with depression, according to whether the perinatal episode was the first episode of depression. We further sought to identify biopsychosocial correlates ofperinatal symptoms in women with depression .

Design and Setting

The Australian Genetics of Depression Study (AGDS), an online case cohort study of the etiology of depression. For a range of variables, women with depression who report significant perinatal symptoms were compared to women with depression who did not experience perinatal symptoms.

Participants

In a large sample of parous women with major depressive disorder (MDD) (n=7,182), we identified two subgroups of PND cases) with and without prior depression history (n=2,261; n=878 respectively).

Primary and secondary outcome measures

The primary outcome measure was a positive screen for PND on the lifetime version of the Edinburgh Postnatal Depression Scale. Descriptive measures reported lifetime prevalence, timing of onset and duration of perinatal depression symptoms.

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Results

The prevalence of PND among parous women was 70%. The majority of women reported at least one perinatal episode with symptoms both antenatally and postnatally. Of women who experienced depression prior to first pregnancy, PND cases were significantly more likely to report more episodes of depression (OR=1.1 per additional depression episode, CI=[1.1-1.1], P=1.9 x 10^{13}), non-European ancestry (OR=1.5, CI=[1.0-2.1], P=0.03), severe nausea during pregnancy (OR=1.3, CI=[1.1-1.6], P=6.6 x 10^{-03}) and emotional abuse (OR=1.4, CI=[1.1-1.7], P=5.3 x 10^{-03}).

Conclusions

The majority of parous women in this study experienced PND, associated with more complex, severe depression. Results highlight the importance of perinatal assessments of depressive symptoms, particularly for women with a history of depression or childhood adverse experiences.

Strengths and limitations of this study

- Largest study of its kind, comparing characteristics of women with perinatal depression to those of women with non-perinatal depression.
- Reports detailed characteristics of women with PND but with different psychiatric histories.
- An online questionnaire, with no personalized interviews or clinical reports to provide supporting evidence for self-reported data.

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- Reliance on self-report information years after experiencing PND could lead to recall bias.
- The AGDS cohort is mostly young and well-educated and may not generalize to the entire population.

Funding Statement

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Competing interests

No conflict of interest has been reported

Availability of data and material

Data used in this analysis and described in this article are available to all interested researchers through collaboration. Please contact NGM.

Ethics approval and consent to participate

All study protocols were approved by the QIMR Berghofer Medical Research Institute Human Research Ethics Committee (Ref 2118). The protocol for approaching participants through the DHS, enrolling them in the study, and consenting for all phases of the study (including invitation to future related studies) and accessing MBS and PBS records was approved by the Ethics Department of the Department of Human Services.

Patient consent for participation in the study was obtained.

Introduction

Background

Perinatal depression (PND), including both antenatal and postpartum depression, , carries serious risk for both mother and infant. An estimated 53% of women with postpartum depression have “high suicidality”[2], whilst the rate of self-harming thoughts is three times

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that of the postpartum community population[3]. Estimated economic costs of PND in the UK, of which 72% are for ongoing care of the child[4] reflect findings that children of women with persistent and severe PND are at increased risk of adverse outcomes[1,5] .

Peripartum depression is classified diagnostically in the Diagnostic and Statistical Manual of mental disorders 5th Edition (DSM 5)[6] as a subtype of Major Depressive Disorder. The classification of the disorder as peripartum is a change from the 4th edition of the manual where the disorder was called postpartum depression. The change in nomenclature reflects the increased recognition that symptoms can begin during pregnancy.

There is ongoing debate as to whether PND is a depressive episode that happens to coincide with the perinatal period[7]; or a distinct disorder with a partially overlapping set of risk factors, stimulated by changes occurring during pregnancy and confined to the perinatal period[8].

A history of affective disorders is the strongest known risk factor for PND[9] supporting the classification of PND as a subtype of depression. However, many women with a prior history of depression do not report symptoms in the perinatal period and for others, PND is the first reported episode. This suggests the possibility that the profile of risk factors associated with depression in the perinatal period is at least partially distinct from depression outside of the perinatal period. Genetic studies have found evidence for unique genetic contributions to PND compared to MDD[10,11], suggesting heterogeneity in risk factors. One suggestion is that PND is itself heterogenous[12,13], with clinical subtypes differentiated by timing and severity of symptoms, perinatal complications, and history of psychiatric disorders. However, a comprehensive investigation of the characteristics of women with PND, with and without a prior psychiatric history, has not been attempted.

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A number of risk factors for PND have been identified including adverse childhood experiences, stress, low income and low social support . Other risk factors may also increase PND vulnerability. Possible psychosocial factors include stress and history of abuse[18] whilst biological factors include changes that accompany pregnancy, such as hormonal fluctuations and increased inflammation[8,19].

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Objectives

Using the Australian Genetics of Depression Study (AGDS), a large cohort study established in 2016 to investigate genetic risk factors and heterogeneity in depression with over 20,000 participants self-reporting a depression diagnosis[22], we first sought to evaluate the prevalence, timing and duration of symptoms of perinatal depression and anxiety symptoms in women, stratified by whether they had a history of depression prior to their pregnancy. We then sought to evaluate differences in psychosocial characteristics of women with MDD who report symptoms in the perinatal period and those who do not.

Method

Study Design

Within a case cohort study of the etiology of depression, two groups of PND cases and two comparison groups of NPD cases were identified according to their history of prior depression. For both PND groups, the length and severity of their “worst case” of PND was measured. To investigate risk factors associated with PND after a previous history of

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psychiatric disorders, or as first onset depression, both PND groups were compared with their comparison group of NPD cases, across a range of variables.

Setting: The Australian Genetics of Depression Study

The AGDS is a large ongoing case cohort study of the etiology of depression that recruited 20,689 participants (aged between 28 and 58 years; 75% female) during 2016-2018. The analyses conducted here include participants enrolled prior to the initial data freeze in September 2018. Recruitment was primarily through a media campaign (86%) which requested participation from anyone with a depression diagnosis from a health professional, as well as specific invitations to women who had responded to a mobile phone app focused on PND, originally developed in the USA[23], and also ascertainment through the Pharmaceutical Benefits Scheme prescription records for antidepressants,. For further details of the recruitment strategy, see Byrne, et al. [22].

AGDS participants were invited to complete an online questionnaire. A compulsory core module assessed self-reported psychiatric history, the Composite Interview Diagnostic Interview Short Form (CIDI-SF) which asseses the Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM 5) criteria for MDD[9], and experiences of using commonly prescribed antidepressants. Women reporting symptoms of depression during pregnancy or up to 6 months following childbirth were asked to complete the lifetime Edinburgh Postnatal Depression Scale (EPDS)[24], an adaptation of the standard EPDS[25] that assesses lifetime PND episodes. They were also asked whether symptoms of depression occurred during pregnancy, after giving birth, or both, the age at which they experienced their worst episode of PND, its severity and duration. For all AGDS participants, further

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voluntary modules assessed history of psychiatric health conditions and stressful life events. The AGDS protocol was approved by the Human Research Ethics Committee of QIMR Berghofer Institute for Medical Research.

Participants: PND cases and comparison groups

Participants with major depression either met DSM 5criteria for MDD, or had been previously diagnosed with depression by a health professional. PND cases were defined as women reporting at least one live birth who had been previously diagnosed with PND by a health professional, or who scored >= 13 on the lifetime EPDS, or who met criteria for major depression and reported at least one perinatal episode.

We identified two groups of PND cases, based on whether they had a history of MDD prior to their first PND episode. Parous participants who reported an episode of depression before their first pregnancy and met PND criteria (PND_priorDep) were compared with parous participants who reported an episode of depression before their first pregnancy, but did not experience any depression associated with childbirth (NPD_priorDep). The second group comprised participants whose first episode of depression occurred during the perinatal period (PND_firstDep) group. Fig. 1 and Supplementary Table S1 illustrate sample selection. Further details are provided in Supplementary Methods.

Figure 1 about here

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Variables

The outcome of interest was a PND episode for women with either a history of previous depressive episode(s), or no previous depression history. An exposure to a PND episode is defined as the period of time from conception up to six months postpartum, so that the number of reported live births represents the number of exposures. The cross-sectional nature of our study meant that no direction of causality could be assessed, but we investigated risk factors for PND using variables that have previously been associated with PND[1,26,27], including age at onset of depression; number of reported episodes of depression; ancestry; comorbidity with other psychiatric disorders; adverse childhood experiences; reproductive traits and response to antidepressants.

Descriptive measures for cases

The length and timing of onset of the worst PND episode were evaluated for PND cases both with and without a prior history of depression. Length of the worst PND episode was measured using a 5 point scale: “Up to two weeks”, “2-4 weeks”, “1-3 months”, “3-6 months”, “More than 6 months”. Details of occurrence included trimester of pregnancy or length of time after delivery.

Comparative measures

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The PND_priordep and NPD_priordep groups were compared on a range of variables that have previously been identified to be associated with PND[1,26]. Demographic measures included current age, marital status, education and ancestry. A list of geographical regions from which ancestry is identified is provided in Table S2. More details are provided in Supplementary Methods. Other measures included the age at onset of depression, number of episodes of depression , history of childhood trauma and sexual or other physical assault, and previous diagnoses of psychiatric disorders. Eighteen psychiatric disorders were listed, of which twelve, identified by more than 3% of participants, were evaluatedin this study (Table S3). Reproductive measures included age at menarche, parity, age at first birth, presence and severity of nausea and vomiting during pregnancy (NVP), and previous diagnosis of gestational diabetes, endometriosis or polycystic ovarian syndrome. Antidepressant measures included the number of antidepressants that had been tried and their efficacy. More details of these measures are provided in Supplementary Methods, which also lists the questions used to assess each characteristic.

Potential sources of bias

Two variables, number of births and age, significantly associated with PND, were identified as exposure and confounder respectively. Each birth represents an additional exposure to PND, whilst the negative association of PND with increasing age may reflect increasing awareness and diagnosis of the disorder, or imprecise memory of past events. Reliance on self-report information years after experiencing PND could lead to recall bias, although the inclusion of age as a covariate in regression analyses may alleviate this trend and participants who provided contradictory evidence were excluded from analysis. The lifetime EPDS used to assess PND is a screening, rather than diagnostic tool and may result in

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overestimation of PND case status[28], although O'Connor et.al.[29] reported a sensitivity of 0.8 for the EPDS in identifying MDD with a cut-off score>=13, and a specificity of 0.9. The lifetime EPDS is a modification of this scale which has demonstrated internal consistency[24].

Statistical Analysis

Associations between variables and PND were assessed using logistic regression, with PND the dependent variable, , including age at survey time and number of births as covariates.

All modules apart from the first were optional, and some categories applied only to a limited number of participants (for example, those who had used at least one antidepressant). For these reasons, the number of participants who completed each category or variable varied. For each variable, the number of respondents is reported. Within each category, analysis employed Bonferroni correction for multiple testing (N=number of tests within each category).

All analyses were conducted using R (version 3.6.0). Figures were generated using ggplot2[30] and Gliffy software[31].

Public and Patient Involvement

There was no public or patient involvement in the design, conduct, reporting or dissemination plans of our research.

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Results

Lifetime prevalence of depression during the peripartum period

A total of 15,198 female participants (median age of 39) in the Australian Genetics of Depression Study,met DSM 5 criteria for MDD. Of these, 7,182 (47%) reported at least one live birth. The prevalence of PND among parous women was 70%. A total of 2,933 women reported at least one depressive episode prior to their first pregnancy. Of these, 2,261 (77%) screened positive for PND

whilst the remaining 672 women with no PND episodes (23%) formed their comparison group (NPD_priorDep). A total of 878 out of 5,058 women reported that their first episode of depression occurred during pregnancy or within the first 6 months after delivery (PND_firstDep), Of women who met criteria for PND, 1,919 were unable to be categorized as PND_priorDep or PND_firstDep and were lost to further analysis. Fig. 1 and Supplementary Table S1 provide details of the sample selection process.

Table 1 shows the reported time of onset of symptoms (for any PND episode) for both case groups (only during pregnancy, only after delivery, or both before and after delivery). The majority of women with PND reported experiencing symptoms both ante- and postnatally. Onset of symptoms in the postnatal period was more commonly reported by women without a prior history of MDD.

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Table 1. Reported timing of symptoms of perinatal depression among women with PND. Results are shown for all those meeting PND criteria and separately for those with a prior history of major depression (PND_priorDep) and those whose first onset of major depression was perinatal (PND_firstDep).

	During pregnancy only	After delivery only	Both during pregnancy and after delivery	Missing
All PND cases (N=5,058)	295 (6%)	1,627 (32%)	3,073 (61%)	63 (1%)
PND_priorDep (N=2,261)	144 (6%)	592 (26%)	1,507 (67%)	18 (1%)
PND_firstDep (N=878)	28 (3%)	325 (37%)	510 (58%)	15 (2%)

The reported length of the worst episode of PND is shown in Table 2. Full details are provided in Table S4. For both groups of cases, PND was most commonly reported to have lasted for more than six months.

Table 2. Length of worst reported episode of PND stratified by prior history of depression.

Length of worst episode	PND_priorDep	PND_firstDep
	Total (%)	Total (%)
Up to 2 weeks	171 (7.7)	37 (4.3)
2-4 weeks	243 (11.0)	76 (8.8)
1-3 months	409 (18.5)	137 (15.9)
3-6 months	448 (20.3)	202 (23.5)
More than 6 months	935 (42.3)	407 (47.3)

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The most reported time of symptom onset during the worst episode of PND is shown in Table 3. Regardless of whether women had a prior history of depression, the most commonly reported time of onset for the worst episode was 0-4 weeks postpartum. Women with a prior history of depression were more likely to report that the worst episode began during pregnancy, specifically during the first trimester.

Table 3. Time of onset of the worst episode of perinatal depression.

	1st trimester	2nd trimester	3rd trimester	0-4 weeks after delivery	1-3 months after delivery	More than 3 months after delivery
PND_priorDep (%)	400 (18.1)	214 (9.6)	120 (5.4)	724 (32.6)	462 (20.8)	296 (13.3)
PND_firstDep (%)	73 (8.4)	55 (6.3)	42 (4.8)	291 (33.7)	225 (26.1)	176 (20.4)

Clinical and psychosocial risk factors for PND in parous women

Table S5 provides the number and percentage of participants that completed each of the risk factor variables

Clinical and psychosocial risk factors for PND in parous women with a history of depression.

We investigated which risk factors are associated with PND in women with a previous history of depression. Age (OR [PND case status]=0.97 per additional year of age, CI=[0.96-0.98], P=2.3 x 10^{-17}), and number of births (OR [PND case status]=1.3 per additional birth, CI=[1.2-1.4], P=4.7 x 10^{-07}) were significantly associated with PND. Both age and number of

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births were included as covariates in subsequent analyses, which were also adjusted for multiple testing.

Key risk factors for PND identified were age at onset of depression (OR = 0.99 per year later of onset, p = 7.6 x 10^{-06}), non-European ancestry (OR = 1.5, p = 0.03), specifically Australian Indigenous ancestry (OR = 2.5 [1.1-4.5], p = 0.02), emotional abuse in childhood (OR=1.4, [1.1-1.7], P=0.006) and severe nausea during pregnancy (OR = 1.3 [1.1-1.6], P=0.007). Being diagnosed with any psychiatric comorbidity was also associated with risk of PND (OR = 1.2 , p =0.02). The most significant individual comorbidity was ADHD (OR = 2.3 [1.3-4.4], p = 0.009). This association did not pass the Bonferroni corrected significance threshold, however this is a conservative correction given the correlation between tests. Fulldetails of all results are provided in Table S6.

Screening positive for PND was associated with an increased likelihood of reporting more than 9 episodes of depression (OR = 1.7 [1.4-2.1], p = 1.8 x 10^{-08}) and decreased likelihood of reporting high efficacy of any antidepressant (OR = 0.7 [0.5-0.8], p = 5.5 x 10^{-04}).

Discussion

We investigated lifetime prevalence and correlates of perinatal depression in a large cross-sectional study of depression. This is to date one of the largest studies of perinatal

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depression among women with major depression. We found a very high prevalence of perinatal symptoms in women with major depression, with higher likelihood of onset of symptoms during pregnancy in women with a prior history, supporting the need for screening and close monitoring of symptoms in women with a history of depression. Furthermore, our results highlight that perinatal depression is associated with a more chronic course of depression, with earlier onset, more episodes and poorer reported efficacy of antidepressants. The finding of a high prevalence of depression in women agrees with previous findings from a study in the Netherlands that found a prevalence of 40% in women with a prior history of MDD[24]. The prevalence in our study is higher and this likely reflects that this is a sample enriched for participants with severe depression[22]. While assessment of severity relies on the individual's self-report, previous analyses in the Australian Genetics of Depression Study have shown that those reporting more severe depression have higher genetic risk to depression[32], and the association between perinatal depression and more chronic course is also supported by genetic data.

Another key finding was that women without a prior history were more likely to report symptom onset in the postnatal period and were more likely to report longer duration of symptoms. This may reflect that women with a prior history may have had an ongoing episode of depression when they became pregnant and we were unable to distinguish whether symptoms had started prior to the first trimester. Furthermore, women with a prior history may have been more likely to be monitored by clinicians and have a treatment plan in place, leading to reduced length of symptoms.

Participants with a prior history of depression who report having at least one ancestor of Aboriginal or Torres Strait Islander (ATSI) descent were more likely to meet the

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criteria for PND. There have been few studies conducted on perinatal mental health among Aboriginal and Torres Strait Islanders[34]. One study conducted on a representative population sample in New South Wales did not find an increased prevalence of postnatal depressive symptoms among women of ATSI descent. However, the study did identify several risk factors that commonly affect people of ATSI descent such as placement in public housing, financial hardship, and poor self-rated health as being associated. Many other risk factors such as smoking and obstetric complications are higher in the ATSI population than non-Indigenous Australians and depression and anxiety are twice as common[35]. Results from the Australian Postnatal Screening Program found that the rate of antenatal depression in ATSI women was 18.9% compared to 8.9% in non-Indigenous Australians and 6.3% had postnatal depression compared to 2.7% in non-Indigenous women[36,37]. The findings of our study further highlight the increased risk of PND in ATSI women and the need for better screening and treatment in the Indigenous population.

Another key finding was the association between severe nausea during pregnancy and PND. Nausea and vomiting during pregnancy of varying severity affects approximately 69% of pregnant women. A meta-analysis evaluating the association between the severe form of morning sickness – hyperemesis gravidarum (HG) – and depression and anxiety found significant increased depression and anxiety scores in women with HG[38]. A recent longitudinal study in the United Kingdom found that 49% of women with HG had probable depression antenatally and 29% had probable postnatal depression. In conjunction with our findings, these results suggest that women with severe nausea during pregnancy are at high risk of depression and may need to be referred for treatment of PND[39].

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Lastly, we identified psychiatric comorbidities, particularly premenstrual dysphoric disorder and ADHD, and emotional abuse in childhood as being associated with PND. There is an extensive literature on the association between trauma and PND[40-43] and our study shows that even among those with a prior history of MDD, trauma is a risk factor for PND, consistent with previous reports[24]. Several studies have evaluated the association between ADHD in children and perinatal risk factors including PND in mothers[44-46]. However, few studies have considered that mothers with PND may also have ADHD symptoms and our results suggest that this is an important consideration. Recent studies that have attempted to account for genetic transmission from mother to child have found that much of the association between PND and ADHD in the offspring is accounted for by shared genetic risk factors between PND and ADHD[47,48].

The results of this study should be considered in the light of several limitations. The main limitation of this study is that it is based on an online questionnaire, with no personalized interviews or clinical reports to provide supporting evidence for self-reported data. Answers were based on total life experience, including, but not exclusive to, the perinatal period. Furthermore, the AGDS is a cross-sectional study. Its strength lies in its sample size, but, unlike a longitudinal study, it provides no information with respect to timing of variables significantly associated with PND (with the exception of childhood adverse experiences), so no inference can be made pertaining to cause and effect. In addition, because information only about the worst episode was ascertained, it was not possible to identify all cases where the perinatal episode was the first episode of depression which may have biased the results.

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No information on the use of mood stabilisers which would be indicative of mixed episodes was collected.

Missing data is a further limitation. Because not all women completed all parts of the questionnaire such that the sample sizes were different for each variable analysed. Previous analysis suggests that there is little bias in terms of questionnaire completion according to severity of depression. The results of the study should also be considered in the context that the AGDS cohort is mostly young and well-educated, and may not generalize to the entire population. The primary aim of the study was to identify genetic risk factors for depression and investigate heterogeneity in depression. Analyses conducted to date suggest that the sample is enriched for severe depression and the finding of a high prevalence of perinatal depression and anxiety symptoms supports this. However, this may limit the generalizability of the findings.

Finally, complications of pregnancy and birth were not assessed in this study apart from NVP and gestational diabetes, so it was not possible to fully assess whether perinatal complications may contribute to PND vulnerability[14].

Conclusions

PND is a leading cause of disease for women who give birth, adding to the overall family disease burden and potential cognitive and emotional problems for affected children. This sample of parous women with lifetime major depression found a high rate of PND, particularly for women who experienced an episode of depression before their first

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pregnancy. There is a compelling literature demonstrating that screening for PND should begin during pregnancy[29,53], particularly for women with prior history of depression, which is supported by the finding that the majority of cases in this study experienced PND both before and after delivery. Although women who have been previously diagnosed with major depression are, presumably, under clinical care, it is possible that women may have withdrawn from care if treatment has been ineffective. Standard prenatal care that adopts frequent assessment of depression status provides an opportunity to identify women who might otherwise "slip through the cracks" and ensure that they continue to receive support in finding a successful treatment or in the prevention of relapse[29]. Cases were also more likely to have treatment resistant depression, with increased odds of side effects, supporting further clinical investigation of antidepressant efficacy in PND.

Authors' Contributions

EMB, JK, NGM, NRW, designed the study. SEM, LCC, SMB, JM, EB, JG, TM, IBH provided intellectual input into the content. JK analysed the data. JK, EMB, NRW, and NGM drafted the manuscript. SEM, LCC, SMB, JM EB, JG, TM, IBH, revised the article for intellectual content. All authors have read and approve of the final version.

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Figure Legends

Fig. 1 Flow chart: Selection of cases and associated comparative group for first analysis (prior history of major depression) and second analysis (PND is first experience of major depression). Cases met criteria for major depression and had at least one live birth, plus any of: EPDS score >=13; a previous diagnosis of PND; or major depression during the perinatal period.

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596

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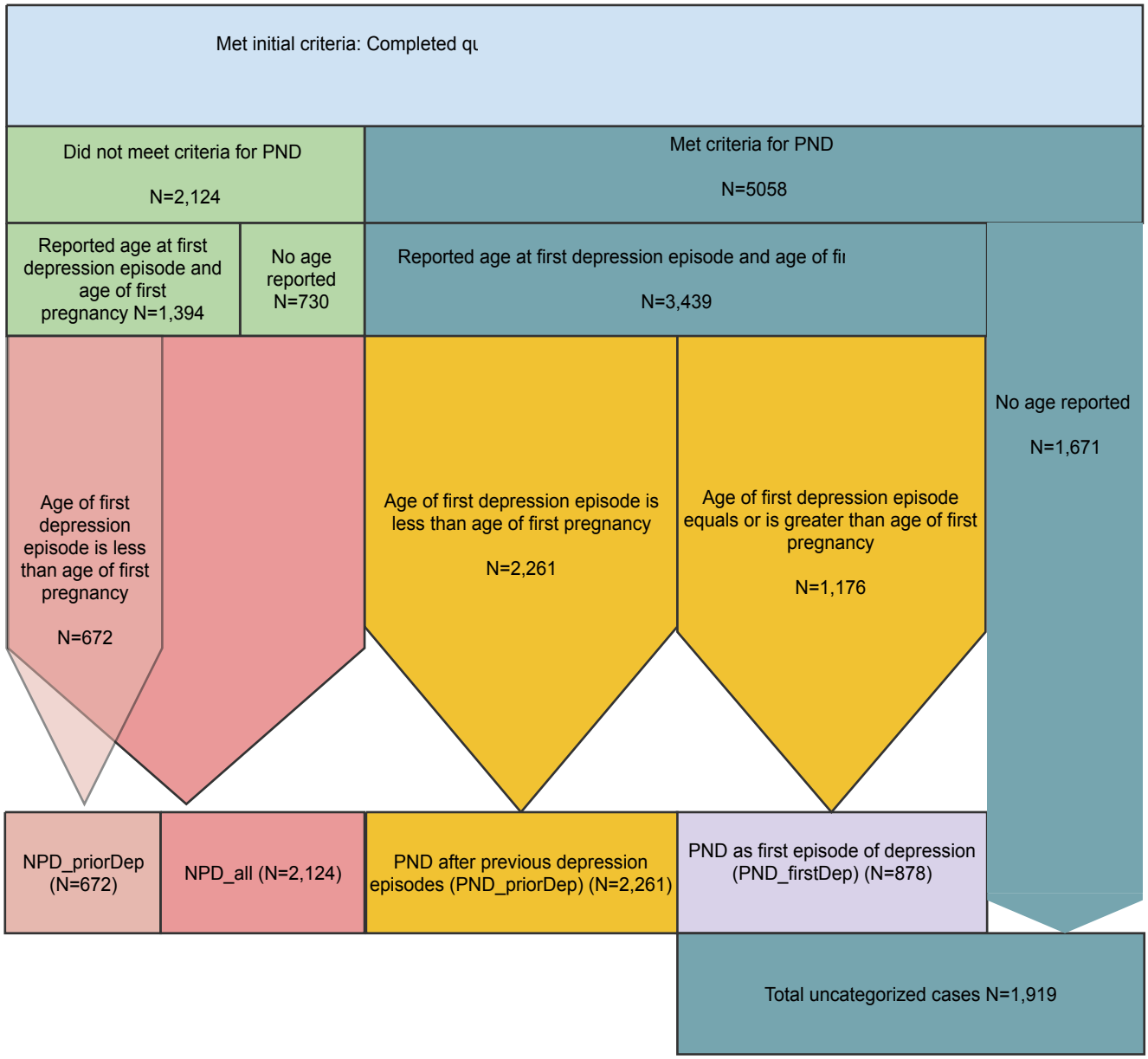
Met initial criteria: Completed qu
Did not meet criteria for PND
N=2,124
Met criteria for PND
N=5058
Reported age at first depression episode and age of first pregnancy N=1,394
No age reported N=730
Reported age at first depression episode and age of fi
N=3,439
Age of first depression episode is less than age of first pregnancy
N=672
Age of first depression episode is less than age of first pregnancy
N=2,261
Age of first depression episode equals or is greater than age of first pregnancy
N=1,176
No age reported
N=1,671
NPD_priorDep (N=672)
NPD_all (N=2,124)
PND after previous depression episodes (PND_priorDep) (N=2,261)
PND as first episode of depression (PND_firstDep) (N=878)
Total uncategorized cases N=1,919

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Supplementary Methods

Australian Genetics of Depression Study

Selection of Cases

Prior history of depression: Participants with prior depression were selected by comparing the reported age of the first episode of depression to the reported age of first pregnancy. Where the depression onset age preceded pregnancy, participants were included amongst those with a prior history of major depression. Where the age of depression onset matched the age of first pregnancy (or age of first pregnancy +1), or the age of the worst episode of PND, participants were included amongst those who experienced their first episode of depression perinatally.

Measures

Severity of depression: DSM-V diagnostic criteria for MDD were assessed using the CIDI-SF(World Health Organization 1994). First onset age was assessed by asking participants when they had first experienced a 2-week period of depression. Severity of depression was assessed using the number of lifetime episodes, and age at first episode. The total number of periods of at least 2 weeks of depression and/or anhedonia was calculated using a dropdown box where participants could select from 1 to 12 or 13+.

Demographic measures: Demographic measures included current age, marital status, and highest level of education completed or partially completed measured using an ordinal scale (primary; lower or higher secondary school; diploma; degree; or post-graduate studies). Ancestry analysis (self-report of ancestry of great-great-grandparents assigned to 18 geographical regions, Supplementary Table S2) considered associations between rates of

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endorsing PND in women with ancestors only from Europe, compared to women with at least one non-European ancestor. Further analysis compared the rate of PND in those reporting Australian Indigenous ancestry to those of only European ancestry.

Clinical measures: Participants were asked to report any previous diagnoses from a total list of 19 psychiatric disorders, of which 13, with frequencies > 3% for all women with PND, were analyzed in this study (Supplementary Table S3). History of childhood trauma was assessed using responses to three questions that asked whether participants had been emotionally abused, emotionally neglected, or physically neglected during childhood. Additionally, participants were asked whether they had experienced physical or sexual assault or unwanted sexual experience at any time in their life, as well as their age at that time. For these questions, an age less than 16 was used to designate a childhood experience.

Reproductive measures: Reproductive measures included age at menarche, parity (number of live births), age at first birth, presence and severity of nausea and vomiting during pregnancy (NVP), and diagnosis of endometriosis or polycystic ovarian syndrome. Severity of NVP was measured using a scale adapted from Zhang et al. (2011). Gestational diabetes was measured as part of a general question about experience of medical conditions, followed by a request to specify the type of diabetes (if diabetes was selected).

Effects of antidepressants: Efficacy of the top ten most commonly prescribed antidepressants in Australia was assessed by asking how well each antidepressant a participant had ever taken worked for them on a three-point scale (Not at all well, Moderately Well or Very Well).

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Questions from the Australian Genetics of Depression Study Questionnaire used in phenotypic analysis (excluding Depression Scales)

Biological sex, age and marital status

Are you male or female?

How old are you now?

What is your marital status?

- Married
- Separated
- Divorced
- Widowed
- Never married
- Living with partner/defacto (for a period of six months or longer)

Education

What is your highest level of education?

- No formal education
- Completed or partially completed primary school (years 1-7)
- Completed or partially completed junior secondary school (years 8-10)
- Completed or partially completed senior secondary school (years 11-12)
- Completed or partially completed certificate or diploma
- Completed or partially completed a degree
- Completed or partially completed a Post Graduate Diploma, Masters degree, Doctorate or PhD
- Don't know

Ancestry

Thinking about what you know of your family history, which of the following best describes the geographic regions where your ancestors (i.e. your great-great-grandparents) come from? You may select as many choices as you need

- England, Ireland, Scotland or Wales
- Australia - not of Aboriginal or Torres Strait Islander descent
- Australia - of Aboriginal or Torres Strait Islander descent
- New Zealand - not of Maori descent
- New Zealand - of Maori descent
- Northern Europe including Sweden, Norway, Finland and surrounding countries
- Western Europe including France, Germany, the Netherlands and surrounding countries
- Southern Europe including Italy, Greece, Spain, Portugal and surrounding countries
- Eastern Europe including Russia, Poland, Hungary and surrounding countries
- Middle East including Lebanon, Turkey and surrounding countries
- Eastern Asia including China, Japan, South Korea, North Korea, Taiwan and Hong Kong

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- South-East Asia including Thailand, Malaysia, Indonesia, Singapore and surrounding countries
- South Asia including India, Pakistan, Sri Lanka and surrounding countries
- Polynesia, Micronesia or Melanesia including Tonga, Fiji, Papua New Guinea and surrounding countries
- Africa
- North America - not of First Nations, Native American, Inuit or Métis descent
- North America - of First Nations, Native American, Inuit or Métis descent
- Caribbean, Central or South America
- Don't know

Comorbidities

Have you ever been diagnosed with any of the following? Please select all that apply.

- Depression
- Bipolar disorder
- Premenstrual dysphoric mood disorder
- Schizophrenia
- Anorexia nervosa
- Bulimia
- Attention-deficit/hyperactivity disorder (ADD/ADHD)
- Autism spectrum disorder (Autism, Asperger's disorder)
- Tourette's disorder
- Anxiety disorder (Generalised anxiety disorder)
- Panic disorder
- Obsessive compulsive disorder
- Hoarding disorder
- Posttraumatic stress disorder (PTSD)
- Specific phobia (e.g. animals, heights, storms, blood / injection / injury, flying, enclosed spaces)
- Seasonal affective disorder (SAD)
- Social anxiety disorder (also known as Social phobia)
- Agoraphobia
- Personality disorder
- Substance use disorder

Antidepressants

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Have you ever taken any of the following antidepressants (even if it wasn't for depression or anxiety)? *Please select all that apply.*

1st List (10 most commonly prescribed antidepressants):

- Sertraline (e.g. Zoloft, Eleva, Sertra, Sertracor, Setrona, Xydep)
- Escitalopram (e.g. Lexapro, Cilopam, Escicor, Esipram, Esitalo, Lexam, LoxaLate)
- Venlafaxine (e.g. Efexor, Altven, Elaxine, Enlafax, Venla, Venlexor)
- Amitriptyline (e.g. Endep)
- Mirtazapine (e.g. Avanza, Remeron, Milivin, Axit, Aurozapine, Mirtazon)
- Desvenlafaxine (e.g. Pristiq, Desfax)
- Citalopram (e.g. Cipramil, Celapram, Celica, Ciazil, Citalo, Talam)
- Fluoxetine (e.g. Prozac, Auscap, Lovan, Zactin)
- Duloxetine (e.g. Cymbalta, Andepra, Coperin, Deotine, Depreta, Drulox)
- Paroxetine (e.g. Aropax, Paxtine, Extine, Roxet)

2nd List:

- Dothiepin (e.g. Dothep)
- Fluvoxamine (e.g. Luvox, Faverin, Movox, Voxam)
- Doxepin (e.g. Sinequan, Deptran)
- Nortriptyline (e.g. Allegron)
- Moclobemide (e.g. Amina, Clobemix, Mohexal, Aurorix)
- Clomipramine (e.g. Anafranil, Placil)
- Reboxetine (e.g. Edronax)
- Mianserin (e.g. Lumin)
- Imipramine (e.g. Tofranil, Tolerade)
- Tranylcypromine (e.g. Parnate)
- Phenelzine (e.g. Nardil)

How well does / did each antidepressant work for you?

- Not at all well
- Moderately well
- Very well
- Don't know

Abuse

Listed below are a number of difficult or stressful things that sometimes happen to people. For each event mark one or more of the boxes to the right to indicate that: (a) it **happened to you** personally; (b) you **witnessed it** happen to someone else; (c) you **learned about it** happening to a close family member or close friend; (d) you were exposed to it as **part of your job** (for example, paramedic, police, military or other first responder);

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(e) you're **not sure** if it fits; or (f) it **doesn't apply** to you. Be sure to consider your **entire life** (growing up as well as adulthood) as you go through the list of events.

(Relevant categories (only considered those marked "Happened to me"))

- Physical assault (e.g. being attacked, hit, slapped, kicked, beaten up)
- Sexual assault (rape, attempted rape, made to perform any type of sexual act through force or threat of harm)
- Other unwanted or uncomfortable sexual experience

How old were you the first and last time these things happened?

Childhood abuse

People may experience stressful situations in childhood which may affect their future health and well-being. Please indicate if you experienced any of these situations **during your childhood**.

- Emotional abuse (e.g. often being told you were no good, yelled at in a scary way, threatened, ignored, or stopped from making friends)
- Emotional neglect (e.g. often not being shown affection, or not being given encouragement or support)
- Physical neglect (e.g. often not being given enough to eat or drink, appropriate clothing, shelter, medical care, education, supervision or a safe home environment)

Menarche

Have you begun to menstruate (started having your period)?
How old were you when you had your first menstrual period?

Parity

How many times have you been pregnant? *If you're unsure, please provide your best estimate.* How many of these pregnancies resulted in live births (including caesarean section)?

Morning sickness

While many women experience morning sickness, there are differences in how severe morning sickness is. Did you have any morning sickness, nausea or vomiting during any of your pregnancies?

Thinking back to each pregnancy, which of the following best describes your experience?

- I did not have any nausea or vomiting
- Nausea and/or vomiting for *less than 7 days*, but I didn't see a doctor about this and it didn't disrupt my daily routine.
- Nausea and/or vomiting for *more than 7 days*, but I didn't see a doctor about this. It didn't disrupt my daily routine.

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- It disrupted my daily routine, but it didn't affect my weight and I didn't need medication to manage it.
- It really disrupted my daily routine and I was prescribed medication (or was put on a drip) but it didn't lead to weight loss.
- It really disrupted my daily routine. I lost weight. I was prescribed medication or was put on a drip or feeding tube.
- I don't remember or am unsure.

Gestational diabetes

Have you ever had any of the following medical conditions? *Please select all that apply*

- Diabetes or high blood sugar

[For those selecting diabetes or high blood sugar:]

Please select the specific type of the medical condition(s) you have had.

- Type 1 diabetes
- Type 2 diabetes
- Gestational diabetes
- Other diabetes or high blood sugar

Reproductive disorders

Has a doctor ever diagnosed you with any of the following?

- Polycystic ovarian syndrome (a hormonal disorder characterised by ovarian follicles failing to ovulate and remaining as multiple cysts, distending the ovary)
- Endometriosis (the presence of tissue similar to the kind lining the uterus, at other sites in the pelvis)

Guintivano J et al. (2018) PPD ACT: an app-based genetic study of postpartum depression Transl Psychiatry 8:260 doi:10.1038/s41398-018-0305-5

World Health Organization (1994) Composite International Diagnostic Interview (CIDI) researcher's manual (Version 1.1, 1994). World Health Organisation; American Psychiatric Association,

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Table S1. Selection process: for PND_priorDep and PND_firstDep samples

Process	Number
Completed online survey	20,689
PriorDep cases: PND with history of major depression before first pregnancy (PND_priorDep)	2,261
PriorDep comparison group: History of major depression before first pregnancy, but no PND (NPD_priorDep)	672
PNDfirst cases: PND is first onset of major depression (PND_firstDep)	878
Uncategorized PND cases: lost to further analysis	1,919
PNDfirst comparison group: Met criteria for major depression but not associated with peripartum period (NPD_all)	2,124

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Table S2. List of geographical regions for participants to apply to great great grandparents

England, Ireland, Scotland or Wales
Australia - not of Aboriginal or Torres Strait Islander descent
Australia - of Aboriginal or Torres Strait Islander descent
New Zealand - not of Maori descent
New Zealand - of Maori descent
Northern Europe including Sweden, Norway, Finland and surrounding countries
Western Europe including France, Germany, the Netherlands and surrounding countries
Southern Europe inclding Italy, Greece, Spain, Portugal and surrounding countries
Eastern Europe including Russia, Poland, Hungary and surrounding countries
Middle East including Lebanon, Turkey and surrounding countries
Eastern Asia including China, Japan, South Korea, Taiwan and surrounding countries
South-East Asia including Thailand, Malaysia, Indonesia, Singapore and surrounding countries
South Asia including India, Pakistan, Sri Lanka and surrounding countries
Polynesia, Micronesia or Melanesia including Tonga, Fiji, Papua New Guinea and surrounding countrie
Africa
North America - not of First Nations, Native American, Inuit or Métis descent
North America - of First Nations, Native American, Inuit or Métis descent
Caribbean, Central or South America

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Table S3. List of psychiatric disorders with frequencies > 3% amongst all women with PND (N=5,058)

List of disorders	Number of cases (of all women with PND, N=5,058)	%
Bipolar Disorder	511	10.1
PMDD	195	3.8
Anorexia	178	3.5
ADHD	168	3.3
Anxiety Disorder	2680	53.0
Panic Attacks	516	10.2
Obsessive Compulsive Disorder	281	5.6
PTSD	859	17.0
Specific Phobia	635	12.6
Seasonal Affective Disorder	172	3.4
Social Anxiety Disorder	440	8.7
Personality Disorder	278	5.5

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Table S4. Length of worst episode of PND according to detailed onset information, and s

Length of worst episode	PND_p		
	Occurrence during pregnancy (n=734)		
	1st trimester (n=400)	2nd trimester (n=214)	3rd trimester (n=120)
Up to 2 weeks	44 (0.11)	18 (0.8)	15 (0.13)
2-4 weeks	51 (0.13)	33 (0.15)	25 (0.21)
1-3 months	51 (0.13)	35 (0.16)	30 (0.25)
3-6 months	48 (0.12)	51 (0.24)	21 (0.18)
More than 6 months	206 (0.52)	76 (0.36)	29 (0.24)

Regression analysis: association of length of worst episode with early onset (either first t delivery)	PND_priorDep		
	OR	CI	P
Up to 2 weeks	1.3	0.9-1.7	1.3E-01
2-4 weeks	1.0	0.8-1.3	9.2E-01
1-3 months	0.9	0.7-1.1	1.5E-01
3-6 months	0.7	0.6-0.9	**6.0E-03**
More than 6 months	1.4	1.2-1.6	**1.7E-04**

Severity of worst episode	PND_priorDep		PND_fir
	Occurrence during pregnancy (n=734)	Occurrence after delivery (n=1,482)	Occurrence during pregnancy (n=170)
Interference	596 (0.80)	1232 (0.83)	141 (0.83)
Professional help	486 (0.66)	965 (0.65)	106 (0.62)
Medication	326 (0.44)	612 (0.41)	306 (0.43)
Hospitalisation	82 (0.11)	154 (0.10)	26 (0.15)
Note: proportions for severity measures do not add up to 1.0 since participants ticked al			

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Comparison of severity measures for PND_priorDep and PND_firstDep cases for occurrences in pregnancy or after delivery: Association of each measure with PND_firstDep status.

	OR (for PND_firstDep)	CI	P
Interference	0.9	0.8-1.1	5.0E-01
Professional help	1.2	1.0-1.4	7.5E-02
Medication	1.0	0.8-1.2	8.4E-01
Hospitalisation	1.3	1.0-1.7	**2.4E-02**

Comparison of postpartum onset of worst episode for PND_priorDep and PND_firstDep cases

	PND_priorDep	PND_firstDep
Onset of worst case is postpartum	1487 (0.66)	695 (0.79)

Regression analysis: association of postpartum onset of worst case with PND_firstDep case status

OR (PND_firstDep case status)	CI	P
2.0	1.7-2.4	4.6E-13

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severity of worst episode of PND, characterised by interference in everyday life, and need for profes

priorDep (n=2,261)

Occurrence after delivery (n=1,482)			Total	Occurrence during pregnan	
0-4 weeks after delivery (n=724)	1-3 months after delivery (n=462)	More than 3 months after delivery (n=296)		1st trimester (n=73)	2nd trimester (n=55)
51 (0.07)	22 (0.05)	21 (0.07)	171	5 (0.07)	3 (0.06)
71 (0.10)	38 (0.08)	25 (0.08)	243	7 (0.10)	4 (0.07)
140 (0.19)	96 (0.21)	57 (0.19)	409	7 (0.10)	9 (0.16)
151 (0.21)	112 (0.24)	65 (0.22)	448	11 (0.15)	12 (0.22)
308 (0.43)	188 (0.41)	128 (0.43)	935	43 (0.59)	27 (0.49)

trimester of pregnancy or within 4 weeks after

PND_firstDep		
OR	CI	P
1.0	0.5-2.0	9.3E-01
1.1	0.7-1.8	7.2E-01
1.0	0.7-1.5	8.2E-01
0.7	0.5-1.0	6.1E-02
1.3	1.0-1.7	8.8E-02

rstDep

Occurrence after delivery (n=692)
559 (0.80)
488 (0.70)
67 (0.36)
91 (0.13)

ll that applied.

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sional help, medication, or hospitalisation.

	PND_firstDep (n=878)			
ıcy (n=170)	Occurrence after delivery (n=692)			Total
3rd trimester (n=42)	0-4 weeks after delivery (n=291)	1-3 months after delivery (n=225)	More than 3 months after delivery (n=176)	
2 (0.05)	11 (0.04)	6 (0.03)	10 (0.06)	37
4 (0.10)	26 (0.09)	24 (0.11)	11 (0.06)	76
8 (0.19)	51 (0.18)	34 (0.15)	28 (0.16)	137
9 (0.21)	62 (0.21)	71 (0.32)	37 (0.21)	202
19 (0.45)	139 (0.48)	89 (0.40)	90 (0.51)	407

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Table S5. priorDep samples: Number of respondents (cases and controls) for each variable.

Category	Variable	priorDep sample		
		Number respondents	Number cases/ controls	% cases/ controls
Possible confounders				
	Age	2933		
	Number Births	2933		
Depression				
	Number Episodes	2911		
	Age of first depressive episode	2933		
Eductation				
	Did not finish high school	2933	123/40	5.4/6.0
	Post-secondary education	2933	1895/569	83.8/84.7
Ancestry				
	At least one nonEuropean ancestor	2720	227/41	10.9/6.5
	Australian Indigenous	2720	80/9	4.1/1.5
Psychiatric comorbidities				
	Bipolar Disorder	2933	274/64	12.1/9.5
	PMDD	2933	112/19	5.0/2.8
	Anorexia	2933	97/21	4.3/3.1
	ADHD	2933	97/12	4.3/1.8
	Anxiety disorder	2933	1272/323	56.3/48.1
	Panic attacks	2933	201/64	8.9/9.5
	OCD	2933	147/32	6.5/4.8
	PTSD	2933	452/103	20/15.3
	Specific phobia	2933	326/78	14.4/11.6
	Seasonal Affective	2933	100/25	4.4/3.7
	Social anxiety disorder	2933	239/46	10.6/6.8
	Personality disorder	2933	153/38	6.8/5.7
	anyComorbidity	2933	1675/451	74.1/67.1
Adverse experiences				
	Emotional abuse	1956	959/275	64.7/58.0
	Emotional neglect	1957	839/249	56.3/53.3
	Physical Abuse (anytime)	2070	642/189	40.8/38.2
	Childhood Physical Abuse	1100	374/107	44.3/41.8
	Physical neglect	2010	267/63	17.5/13.1
	Sexual abuse (anytime)	2067	1004/284	63.2/56.9
Reproductive				
	Early pregnancy	2933	1143/313	50.6/46.6
	Early menarche	1880	633/184	45/41.9
	Disruptive NVP	2520	1031/257	53/44.9

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	Polycystic ovarian syndrome	1960	195/56	13.1/11.9
	Endometriosis	1969	251/67	16.8/14.1
	Gestational diabetes	2933	90/18	6.7/4.2
Antidepressants				
Effectiveness				
	High efficacy	2790		

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Table S6. priorDep and firstDep samples: Results of comparison of cases and controls for al

priorDep sample: 2261 cases;

Significant P

Characteristic	OR	CI	P
Confounders			
Age (OR per year, no covariates)	1.0	0.96-0.98	**2.3E-17**
Number Births (OR per birth, no covariates)	1.3	1.17-1.43	**4.7E-07**
Depression onset/severity N(tests=2)			
Depression severity: More than 9 episodes	1.7	1.4-2.1	**1.8E-08**
Odds of PND compared to NPD per year of age at first episode	1.0	0.96-0.99	**2.1E-03**
Ancestry N(tests=2)			
Ancestry: At least one non-European ancestor	1.5	1.1-2.1	**2.8E-02**
Ancestry: Australian Indigenous	2.3	1.2-4.8	**2.4E-02**
Education, N(tests)=3			
Did not complete high school	1.0	0.7-1.4	8.1E-01
Completed post-secondary education	0.9	0.7-1.2	6.5E-01
Comorbidity, N(tests)=12			
Having any comorbidity	1.2	1.0-1.5	**3.2E-02**
Bipolar Disorder	1.3	0.9-1.7	1.3E-01
PMDD	1.9	1.2-3.2	**1.4E-02**
Anorexia	1.3	0.8-2.2	2.4E-01
ADHD	2.3	1.3-4.4	**9.1E-03**
Anxiety Disorder	1.3	1.1-1.5	**1.2E-02**
Panic Attacks	1.0	0.7-1.4	9.4E-01
Obsessive Compulsive Disorder	1.3	0.9-1.9	2.7E-01
PTSD	1.3	1-1.6	**3.6E-02**
Specific Phobia	1.3	1-1.7	8.9E-02
Seasonal Affective Disorder	1.4	0.9-2.2	1.7E-01
Social Anxiety Disorder	1.5	1.1-2.1	**1.6E-02**
Personality Disorder	1.0	0.7-1.5	8.8E-01
Trauma, N(tests)=7			
ChildhoodEmotionalAbuse	1.4	1.1-1.7	**5.5E-03**
ChildhoodEmotionalNeglect	1.3	1-1.6	**3.1E-02**
ChildhoodPhysicalAbuse	1.0	0.8-1.4	9.4E-01
Physical abuse (any time)	1.1	0.9-1.4	3.1E-01
Physical neglect (childhood)	1.4	1.1-1.9	**2.3E-02**
Sexual abuse (childhood)	1.0	0.7-1.3	7.9E-01
Sexual abuse (any time)	1.2	1-1.5	6.1E-02
Reproductive characteristics, N(tests)=5			
Disruptive NVP	1.3	1.1-1.6	**6.6E-03**
Early menarche	1.1	0.9-1.4	3.4E-01
Endometrioses	1.2	0.9-1.6	2.1E-01
Polycystic ovarian syndrome	0.9	0.7-1.3	7.2E-01
Gestational diabetes	1.4	0.8-2.4	2.4E-01

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Antidepressant use			
Tried 3 or more commonly prescribed antidepressant (as a proportion of women using antidepressants)	1.4	1.1-1.8	**1.4E-03**
Antidepressant efficacy, N(tests)=3			
High efficacy for any common antidepressant	0.7	0.5-0.8	**5.5E-04**

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ll variables, including age and number of births as convariates.

672 controls; 2,933 total.
in bold

P (Bonferroni Adjustment for multiple tests)
0.000
0.000
0.000
0.004
0.056
0.047
1.000
1.000
1.000
0.140
1.000
0.114
0.173
1.000
1.000
0.479
1.000
1.000
0.247
1.000
0.037
0.262
1.000
1.000
0.199
1.000
0.422
0.039
1.000
1.000
1.000
1.000

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Table S7. Comparison of NPD_priorDep with NPD_all groups, using regression analysis, for severity o

	OR	CI	P
Depression severity: odds of priorDep compared to odds of allDep per symptom	1.1	1.0-1.2	9.80E-03
Depression severity: odds of priorDep compared to odds of allDep per episode	1.1	1.1-1.1	3.30E-09
Depression severity: odds of priorDep compared to odds of allDep per year of age at first episode	0.68	0.64-0.71	1.30E-63

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of major depression, using number of symptoms and episodes and age at first episode.

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Table S8. Sensitivity analysis of women experiencing PND both before and after delivery. Analy
PriorDep sample. Significant P in

	Cases who experienced PND both during pregnancy a cases; 672 controls)			
Characteristic	Number of PND cases/ controls with this variable	PND cases/ controls with this variable as % of responses	OR	CI
Ancestry N(tests=2)				
Ancestry: At least one non-European ancestor	166/41	12/6.5	1.6	1.1-2.3
Ancestry: Australian Indigenous	58/9	4.5/1.5	2.2	1.1-4.9
Depression severity, N(tests)=6				
Odds of PND compared to NPD per symptom			1.3	1.2-1.4
More than 7 symptoms	1243/480	84.3/74.4	1.7	1.3-2.1
Odds of PND compared to NPD per episode			1.1	1.1-1.1
Depression severity: More than 9 episodes	804/253	54.7/39.2	2.1	1.7-2.5
Odds of PND compared to NPD per year of age at first episode			1.0	0.94-0.98
Depression severity: Below average age at first episode	933/325	63/50.1	1.5	1.2-1.8
Education, N(tests)=2				
Did not complete high school	85/40	5.6/6.0	1.0	0.6-1.5
Completed post-secondary education	1259/569	83.5/84.7	0.9	0.7-1.2
Comorbidity, N(tests)=12				
Likelihood of comorbidity	1152/451	76.4/67.1	1.3	1.1-1.7
Bipolar Disorder	196/64	13/9.5	1.4	1-1.9
PMDD	79/19	5.2/2.8	2.0	1.2-3.5
Anorexia	64/21	4.2/3.1	1.2	0.7-2.1
ADHD	70/12	4.6/1.8	2.4	1.3-4.7
Anxiety Disorder	888/323	58.9/48.1	1.4	1.1-1.7
Panic Attacks	151/64	10/9.5	1.2	0.9-1.6
Obsessive Compulsive Disorder	111/32	7.4/4.8	1.4	0.9-2.2
PTSD	336/103	22.3/15.3	1.5	1.1-1.9
Specific Phobia	242/78	16.1/11.6	1.4	1.1-1.9
Seasonal Affective Disorder	72/25	4.8/3.7	1.7	1.1-2.8
Social Anxiety Disorder	190/46	12.6/6.8	1.8	1.3-2.6
Personality Disorder	122/38	8.1/5.7	1.2	0.8-1.8
Trauma, N(tests)=7				
ChildhoodEmotionalAbuse	657/275	68.2/58.0	1.6	1.3-2.1

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ChildhoodEmotionalNeglect	585/249	60.3/53.3	1.6 1.2-2
ChildhoodPhysicalAbuse	264/107	46.4/41.8	1.0 0.8-1.4
Physical abuse (any time)	440/189	42.8/38.2	1.2 1-1.5
Physical neglect (childhood)	203/63	20.4/13.1	1.8 1.3-2.4
Sexual abuse (childhood)	430/175	74.8/77.1	0.8 0.6-1.2
Sexual abuse (any time)	675/284	65.1/56.9	1.3 1-1.6
Reproductive characteristics, N(tests)=7			
Above average number of live births	428/138	28.4/20.5	1.9 1.6-2.5
Below average age at first pregnancy	822/313	54.5/46.6	1.3 1.1-1.6
Disruptive NVP	710/257	55.1/44.9	1.4 1.1-1.7
Early menarche	422/184	46/41.9	1.2 0.9-1.5
Endometrioses	173/67	17.7/14.1	1.3 0.9-1.8
Polycystic ovarian syndrome	135/56	13.9/11.9	1.0 0.7-1.4
Gestational diabetes	66/18	7.5/4.2	1.6 0.9-2.8
Antidepressant use			
Have used common antidepressant	1442/631	95.7/93.9	
Tried 3 or more commonly prescribed antidepressant (as a proportion of women using antidepressants)	463/142	32.1/22.5	1.7 1.3-2.1
Antidepressant efficacy, N(tests)=3			
High efficacy for any common antidepressant	1444/631		0.7 0.49-0.85
Moderate efficacy for any common antidepressant	1444/631		1.4 1.0-1.8
Low efficacy for any common antidepressant	1444/631		1.0 0.7-1.5
Antidepressant side effects, N(tests)=23			
Experienced at least one side effect	1189/438	82.3/69.4	1.6 1.3-2.1
Reduced sexual desire or function	737/240	51.1/38	1.4 1.2-1.8
Weight gain	690/209	47.9/33.1	1.7 1.4-2.1
Dry mouth	565/179	39.2/28.4	1.5 1.2-1.9
Nausea	518/140	35.9/22.2	1.5 1.2-1.9
Dizzy	486/129	33.7/20.4	1.5 1.2-2
Drowsy	445/124	30.9/19.7	1.5 1.2-1.9
Difficulty Sleeping	421/129	29.2/20.4	1.4 1.1-1.8
Sweating	394/116	27.3/18.4	1.4 1.1-1.8
Headache	404/93	28/14.7	1.8 1.4-2.4
Fatigue or Weakness	370/102	25.7/16.2	1.6 1.2-2.1
Agitation	340/91	23.6/14.4	1.6 1.2-2.1
Increased Anxiety	338/90	23.4/14.3	1.6 1.2-2.1
Suicidal Thoughts	312/86	21.6/13.6	1.4 1.1-1.9
Shaking	306/80	21.2/12.7	1.5 1.1-2
Constipation	190/54	13.2/8.6	1.6 1.2-2.3
Diarrhoea	129/34	8.9/5.4	1.4 0.9-2.1
Blurred Vision	140/39	9.7/6.2	1.6 1.1-2.4

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Attempt Suicide	143/29	9.9/4.6	1.7 1.1-2.6
Muscle Pain	110/31	7.6/4.9	1.6 1-2.4
Vomiting	102/19	7.1/3	1.5 0.9-2.7
Weight Loss	68/19	4.7/3	1.2 0.7-2.1
Runny nose	58/7	4/1.1	4.0 1.9-9.9
Rash	42/6	2.9/1	2.7 1.2-7.3

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ysis conducted for both samples separately.

n bold

firstDep sample. Significant P in bold

nd postpartum (1507		Cases who experienced PND both during pregnancy and postpartur 2124 controls)				
P	P (Bonferroni Adjustment for multiple tests)	Number of PND cases/ controls with this variable	PND cases/ controls with this variable as % of responses	OR	CI	P
1.9E-02	0.04	40/137	8.7/6.9	1.1	0.7-1.6	6.1E-01
3.2E-02	0.06	9/45	2.1/2.4	0.659	0.3-1.3	2.7E-01
8.6E-07	**0.00**			1.1	1.0-1.2	6.5E-02
2.0E-05	**0.00**	392/1340	78.4/72.8	1.3	1.0-1.6	6.5E-02
1.2E-17	**0.00**			1	1.0-1.0	1.3E-01
8.0E-13	**0.00**	186/630	37.2/34.3	1.3	1.0-1.5	**4.2E-02**
2.2E-05	**0.00**			1	0.99-1.0	3.3E-01
8.2E-05	**0.00**	312/1020	62.2/55.2	1.2	0.9-1.5	1.5E-01
9.9E-01	1.00	51/209	10.0/9.8	1.17	0.8-1.6	3.5E-01
6.1E-01	1.83	399/1628	78.2/76.6	1	0.8-1.3	9.0E-01
5.6E-03		334/1274	65.5/60.0	1.2	0.9-1.4	1.5E-01
4.9E-02	0.58	41/144	8.0/6.8	1.2	0.8-1.8	2.5E-01
8.1E-03	0.10	19/38	3.7/1.8	2.1	1.1-3.7	**1.3E-02**
4.3E-01	1.00	10/46	2.0/2.2	0.9	0.4-1.7	6.6E-01
7.7E-03	0.09	11/35	2.2/1.6	1.2	0.6-2.3	6.6E-01
1.6E-03	**0.02**	256/942	50.2/44.4	1.2	0.9-1.4	1.6E-01
3.2E-01	1.00	50/199	9.8/9.4	1.1	0.8-1.5	6.4E-01
1.1E-01	1.00	19/68	3.7/3.2	1.0	0.6-1.7	9.1E-01
3.0E-03	**0.04**	77/277	15.1/13	1.1	0.8-1.5	4.5E-01
2.0E-02	0.24	46/199	9.0/9.4	1.0	0.7-1.4	8.6E-01
3.3E-02	0.40	9/55	1.8/2.6	0.9	0.4-1.8	8.0E-01
7.9E-04	**0.01**	26/121	5.1/5.7	0.8	0.5-1.3	4.5E-01
3.6E-01	1.00	21/68	4.1/3.2	0.9	0.5-1.5	7.4E-01
4.8E-05	**0.00**	200/702	58.7/49.8	1.5	1.1-1.9	**2.7E-03**

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3.3E-04	**0.00**	178/654	52.8/47.1	1.3 1-1.7	**2.8E-02**
8.0E-01	1.00	61/228	38.1/37.1	1.0 0.7-1.4	8.6E-01
8.6E-02	0.60	122/459	34.2/31.1	1.1 0.9-1.4	4.5E-01
6.3E-04	**0.00**	47/171	13.3/11.9	1.1 0.8-1.6	5.6E-01
3.0E-01	1.00	118/449	73.8/75.8	0.8 0.5-1.2	3.0E-01
2.5E-02	0.17	202/746	55.6/49.9	1.2 1-1.5	1.0E-01
1.4E-08	**0.00**	201/578	39.4/27.2	2.1 1.7-2.6	**1.9E-12**
2.5E-03	**0.02**	248/823	62.6/53.9	1.6 1.3-2.0	**1.2E-04**
1.7E-03	**0.01**	166/569	48.1/43.0	1.2 0.9-1.5	1.9E-01
1.3E-01	**0.92**	126/509	39.4/39.8	0.9 0.7-1.2	4.0E-01
1.3E-01	**0.91**	60/195	16.8/13.8	1.3 0.9-1.8	9.9E-02
8.3E-01	**5.81**	135/34	9.7/9.6	0.8 0.5-1.3	4.3E-01
1.0E-01	**0.70**	13/48	4.1/3.7	0.9 0.5-1.7	7.9E-01
		475/1971	93.1/92.8		
1.2E-05		98/363	20.6/18.4	1.2 1.0-1.5	1.1E-01
1.8E-03	**0.01**	475/1971		0.96 0.7-1.3	7.4E-01
3.4E-02	0.10	475/1971		1.1 0.8-1.4	5.1E-01
8.8E-01	1.00	475/1971		0.87 0.6-1.2	4.5E-01
4.8E-05		334/1222	68.2/62.0	1.1 0.9-1.4	2.9E-01
6.7E-04	**0.02**	187/629	39.4/31.9	1.3 1-1.6	**4.7E-02**
1.3E-06	**0.00**	180/631	37.9/32.0	1.2 1-1.5	1.1E-01
2.3E-04	**0.01**	135/513	28.4/26.0	1.1 0.8-1.4	5.3E-01
2.6E-04	**0.01**	116/346	24.4/17.6	1.3 1-1.7	**2.7E-02**
3.2E-04	**0.01**	100/324	21.1/16.4	1.1 0.8-1.4	4.6E-01
9.0E-04	**0.02**	114/325	24.0/16.5	1.5 1.1-1.9	**4.1E-03**
3.1E-03	0.07	91/350	19.2/17.8	1.0 0.7-1.3	7.5E-01
4.4E-03	0.10	97/300	20.4/15.2	1.3 1-1.7	5.7E-02
4.5E-06	**0.00**	95/269	20.0/13.6	1.4 1.1-1.8	**1.8E-02**
3.0E-04	**0.01**	89/275	18.7/14	1.3 1-1.7	5.2E-02
1.2E-03	**0.03**	82/240	17.3/12.2	1.4 1-1.8	**4.7E-02**
1.5E-03	**0.03**	79/258	16.6/13.1	1.3 0.9-1.7	1.1E-01
1.1E-02	0.25	44/199	9.3/10.1	0.7 0.5-1.1	1.2E-01
4.7E-03	0.11	58/219	12.2/11.1	0.9 0.7-1.3	7.4E-01
4.8E-03	0.11	43/166	9.1/8.4	1.1 0.7-1.5	7.4E-01
1.3E-01	1.00	31/103	6.5/5.2	1.2 0.7-1.8	5.1E-01
1.6E-02	0.37	33/103	6.9/5.2	1.4 0.9-2.2	1.0E-01

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2.3E-02	0.54	18/66	3.8/3.3	0.8	0.4-1.4	4.5E-01
4.5E-02	1.00	26/90	5.7/4.6	1.1	0.7-1.8	5.8E-01
1.1E-01	1.00	19/67	4.0/3.4	1.1	0.6-1.8	8.4E-01
5.4E-01	1.00	17/57	3.6/2.9	1.1	0.6-1.9	7.4E-01
7.3E-04	**0.02**	8/29	1.7/1.5	1.1	0.4-2.3	8.5E-01
3.0E-02	0.68	7/31	1.5/1.6	0.9	0.4-2	8.1E-01

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ɱ (510 cases;	P (Bonferroni Adjustment for multiple tests)
	1.23
	0.54
	0.20
	0.19
	0.39
	0.13
	0.98
	1.00
	1.04
	1.00
	1.00
	0.16
	1.00
	1.00
	1.00
	1.00
	1.00
	1.00
	1.00
	1.00
	1.00
	0.02

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0.19
1.00
1.00
1.00
1.00
0.71
0.00
0.00
1.00
1.00
0.69
1.00
1.00
2.96
1.00
1.00
1.00
1.00
1.00
0.62
1.00
0.09
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1.00
0.41
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1.00
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STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2-4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-6
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6-7
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	7-8
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8-9,10-11
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	8, 9-10
Bias	9	Describe any efforts to address potential sources of bias	10-11
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	9-11
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	11-12
		(*b*) Describe any methods used to examine subgroups and interactions	11
		(*c*) Explain how missing data were addressed	11
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	12

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Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	12-14
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	12-15
		(b) Indicate number of participants with missing data for each variable of interest	15
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	15
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	15-17
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	17-18
Discussion			
Key results	18	Summarise key results with reference to study objectives	18-19
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	19
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	19-20
Generalisability	21	Discuss the generalisability (external validity) of the study results	20-21
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	4

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Lifetime prevalence and correlates of perinatal depression in a case-cohort study of depression

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Lifetime prevalence and correlates of perinatal depression in a case-cohort study of depression

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Abstract

Objectives

This study sought to evaluate the prevalence, timing of onset and duration of symptoms of depression in the perinatal period (PND)) in women with depression, according to whether they had a history of depression prior to their first perinatal period. We further sought to identify biopsychosocial correlates of perinatal symptoms in women with depression.

Design and Setting

The Australian Genetics of Depression Study (AGDS) is an online case cohort study of the etiology of depression. For a range of variables, women with depression who report significant perinatal depressive symptoms were compared to women with lifetime depression who did not experience perinatal symptoms.

Participants

In a large sample of parous women with major depressive disorder (MDD) (n=7,182), we identified two subgroups of PND cases with and without prior depression history (n=2,261; n=878 respectively).

Primary and secondary outcome measures

The primary outcome measure was a positive screen for PND on the lifetime version of the Edinburgh Postnatal Depression Scale. Descriptive measures reported lifetime prevalence, timing of onset and duration of perinatal depression symptoms. There were no secondary outcome measures.

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Results

The prevalence of PND among parous women was 70%. The majority of women reported at least one perinatal episode with symptoms both antenatally and postnatally. Of women who experienced depression prior to first pregnancy, PND cases were significantly more likely to report more episodes of depression (OR=1.15 per additional depression episode, CI=[1.13-1.17], P < 0.001), non-European ancestry (OR=1.5, CI=[1.0-2.1], P=0.03), severe nausea during pregnancy (OR=1.3, CI=[1.1-1.6], P=0.006) and emotional abuse (OR=1.4, CI=[1.1-1.7], P=0.005).

Conclusions

The majority of parous women with lifetime depression in this study experienced PND, associated with more complex, severe depression. Results highlight the importance of perinatal assessments of depressive symptoms, particularly for women with a history of depression or childhood adverse experiences.

Strengths and limitations of this study

- Largest study of its kind, comparing characteristics of women with perinatal depression to those of women with non-perinatal depression.
- Reports detailed characteristics of women with PND but with different psychiatric histories.
- An online questionnaire, with no personalized interviews or clinical reports to provide supporting evidence for self-reported data.

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- Reliance on self-report information years after experiencing PND could lead to recall bias.
- The AGDS cohort is mostly young and well-educated and may not generalize to the entire population.

Funding Statement

This work was primarily funded by National Health and Medical Research Council (NHMRC) of Australia grant 1086683, and further supported by NHMRC grants 1145645, 1078901 and 1087889. JK is supported by a UQ Research Training Program scholarship. LC-C is supported by a QIMR Berghofer Institute fellowship.

Competing interests

No conflict of interest has been reported

Availability of data and material

Data used in this analysis and described in this article are available to all interested researchers through collaboration. Please contact NGM.

Ethics approval and consent to participate

All study protocols were approved by the QIMR Berghofer Medical Research Institute Human Research Ethics Committee (Ref 2118). The protocol for approaching participants through the DHS, enrolling them in the study, and consenting for all phases of the study (including invitation to future related studies) and accessing MBS and PBS records was approved by the Ethics Department of the Department of Human Services.

Patient consent for participation in the study was obtained.

Introduction

Background

Perinatal depression (PND), including both antenatal and postpartum depression, carries serious risk for both mother and infant. An estimated 53% of women with postpartum depression have “high suicidality” [1], whilst the rate of self-harming thoughts is three times

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that of the postpartum community population [2]. Estimated economic costs of PND in the UK, of which 72% are for ongoing care of the child [3] reflect findings that children of women with persistent and severe PND are at increased risk of adverse outcomes [4, 5] .

Peripartum depression is classified diagnostically in the Diagnostic and Statistical Manual of mental disorders 5th Edition (DSM 5) [6] as a subtype of Major Depressive Disorder. The classification of the disorder as peripartum is a change from the 4th edition of the manual where the disorder was called postpartum depression. The change in nomenclature reflects the increased recognition that symptoms can begin during pregnancy.

There is ongoing debate as to whether PND is a depressive episode that happens to coincide with the perinatal period [7]; or a distinct disorder with a partially overlapping set of risk factors, stimulated by changes occurring during pregnancy and confined to the perinatal period [8].

The strongest known risk factor for PND is a previous diagnosis of a psychiatric disorder [5, 9-12]. Women with a history of depression are at greatly increased risk of experiencing depressive symptoms during and after pregnancy. However, many women with a prior history of depression do not report symptoms in the perinatal period and for others, PND is the first reported episode. This suggests the possibility that the profile of risk factors associated with depression in the perinatal period is at least partially distinct from depression outside of the perinatal period. One suggestion is that PND is itself heterogenous [12, 13], with clinical subtypes differentiated by timing and severity of symptoms, perinatal complications, and history of psychiatric disorders. A number of studies have found evidence for heterogeneity in symptom profiles across the perinatal period [14-16]. Most studies have found evidence for groups of women with persistent high or low levels of

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depression symptoms through the perinatal period, and some have found evidence of transient symptom profiles with changes from the antenatal to postnatal period [17] Differences in symptom trajectories have been linked to risk factors including a previous history of depression [18], history of abuse [19], low social support [19], low income [18], lower levels of education [20, 21] and ethnicity [21].

Objectives

Using the Australian Genetics of Depression Study (AGDS), a large cohort study established in 2016 to investigate genetic risk factors and heterogeneity in depression with over 20,000 participants self-reporting a depression diagnosis [22], we first sought to evaluate the prevalence, timing and duration of symptoms of perinatal depression symptoms in women, stratified by whether they had a history of depression prior to their pregnancy. We then sought to evaluate differences in psychosocial characteristics of women with MDD who report symptoms in the perinatal period and those who do not. Table S1 summarizes the selection process of cases according to their history of depression, as well as their comparison groups.

Method

Setting: The Australian Genetics of Depression Study

The AGDS is a large ongoing case cohort study of the etiology of depression that recruited 20,689 participants (aged between 28 and 58 years; 75% female) during 2016-2018. The

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analyses conducted here include participants enrolled prior to the initial data freeze in September 2018. Recruitment was primarily through a media campaign (86%) which requested participation from anyone with a depression diagnosis from a health professional, as well as specific invitations to women who had responded to a mobile phone app focused on PND, originally developed in the USA [23], and also ascertainment through the Pharmaceutical Benefits Scheme prescription records for antidepressants. For further details of the recruitment strategy, see Byrne, et al. [22]. The AGDS protocol was approved by the Human Research Ethics Committee of QIMR Berghofer Institute for Medical Research.

Study Design

Within the cross-sectional case cohort, we investigated the prevalence of PND, and the timing of onset and duration of perinatal depression symptoms in two groups of PND cases who were identified according to whether or not they reported having experienced an episode of depression prior to becoming pregnant for the first time. Women with a prior history of depression who met the study criteria for PND were compared to a corresponding control group of women who met criteria for lifetime depression but did not report significant depressive symptoms during the perinatal period – non-perinatal depression cases (NPD) (Table S1).

Variables

AGDS participants were invited to complete an online questionnaire. A compulsory core module assessed self-reported psychiatric history, the Composite Interview Diagnostic

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Interview Short Form (CIDI-SF) which assesses the Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM 5) criteria for MDD [24], and experiences of using commonly prescribed antidepressants. Women reporting symptoms of depression during pregnancy or up to 6 months following childbirth were asked to complete the lifetime Edinburgh Postnatal Depression Scale (EPDS) [25], an adaptation of the standard EPDS [26] that assesses lifetime PND episodes. They were also asked whether symptoms of depression occurred during pregnancy, after giving birth, or both, the age at which they experienced their worst episode of PND, its severity and duration. Furthermore, participants were asked if they had ever been diagnosed with any of 18 psychiatric disorders. For all AGDS participants, further voluntary modules assessed history of psychiatric health conditions and stressful life events.

The outcome of interest was a positive screen for PND for women with either a history of previous depressive episode(s), or no previous depression history. An exposure to a PND episode is defined as the period of time from conception up to six months postpartum, so that the number of reported live births represents the number of exposures. PND cases were defined as women reporting at least one live birth who had been previously diagnosed with PND by a health professional, or who scored >= 13 on the lifetime EPDS, or who met criteria for major depression and reported at least one perinatal episode. The length and timing of onset of the worst PND episode were evaluated for PND cases both with and without a prior history of depression. Length of the worst PND episode was assessed using a 5 point scale: “Up to two weeks”, “2-4 weeks”, “1-3 months”, “3-6 months”, “More than 6 months”. Timing of onset was assessed by participants reporting which trimester of pregnancy or how long after delivery their symptoms began.

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The cross-sectional nature of our study meant that no direction of causality could be assessed, but we investigated differences between PND cases with a prior history of depression (PND_priordep) and NPD (NPD_priordep) cases across a range of clinical and psychosocial variables that have previously been identified to be associated with PND [5, 27, 28]. Demographic measures included current age, marital status, education and ancestry. A list of geographical regions from which ancestry is identified is provided in Table S2. More details are provided in Supplementary Methods. Other measures included the self-reported age at onset of depression, number of episodes of depression, history of childhood trauma and sexual or other physical assault, and self-reported previous diagnoses of psychiatric disorders. Eighteen psychiatric disorders were listed, of which twelve, identified by more than 3% of participants, were evaluated in this study (Table S3). Reproductive measures included age at menarche, parity, age at first birth, presence and severity of nausea and vomiting during pregnancy (NVP), and previous diagnosis of gestational diabetes, endometriosis or polycystic ovarian syndrome. Antidepressant measures included the number of antidepressants that had been tried and their efficacy. More details of these measures are provided in Supplementary Methods, which also lists the questions used to assess each characteristic.

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Participants: PND cases and non-perinatal comparison group

Participants with major depression either met DSM-5 criteria for MDD, or reported having been previously diagnosed with depression by a health professional.

We identified two groups of PND cases, based on whether they had a history of MDD prior to their first PND episode – PND_priorDep and PND_firstDep respectively. Parous participants who reported an episode of depression before their first pregnancy and met PND criteria (PND_priorDep) were compared with parous participants who reported an episode of depression before their first pregnancy, but did not experience any depression associated with childbirth (NPD_priorDep). Fig. 1 and Supplementary Table S1 illustrate sample selection. Further details are provided in Supplementary Methods.

Figure 1 about here

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Statistical Analysis

Associations between variables and PND were assessed using logistic regression, with PND the dependent variable, including age at survey time and number of births as covariates.

All modules apart from the first were optional, and some categories applied only to a limited number of participants (for example, those who had used at least one antidepressant). For these reasons, the number of participants who completed each category or variable varied. For each variable, the number of respondents is reported. Within each category, analysis employed Bonferroni correction for multiple testing (N=number of tests within each category).

All analyses were conducted using R (version 3.6.0). Figures were generated using ggplot2 [29] and Gliffy software [30].

Public and Patient Involvement

There was no public or patient involvement in the design, conduct, reporting or dissemination plans of our research.

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Results

Lifetime prevalence of depression during the peripartum period

A total of 15,198 female participants (median age of 39) in the Australian Genetics of Depression Study, met DSM 5 criteria for MDD. Of these, 7,182 (47%) reported at least one live birth. The prevalence of PND among parous women was 70.4%. A total of 2,933 women reported at least one depressive episode prior to their first pregnancy. Of these, 2,261 (77%) screened positive for PND, whilst the remaining 672 women with no PND episodes (23%) formed their comparison group (NPD_priorDep). A total of 878 out of 5,058 women reported that their first episode of depression occurred during pregnancy or within the first 6 months after delivery (PND_firstDep), Of women who met criteria for PND, 1,919 were unable to be categorized as PND_priorDep or PND_firstDep and were lost to further analysis. Fig. 1 and Supplementary Table S1 provide details of the sample selection process.

Table 1 shows the reported time of onset of symptoms (for any PND episode) for both case groups (only during pregnancy, only after delivery, or both before and after delivery). The majority of women with PND reported experiencing symptoms both ante- and postnatally.

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Onset of symptoms in the postnatal period was more commonly reported by women without a prior history of MDD.

Table 1. Reported timing of symptoms of perinatal depression among women with PND. Results are shown for all those meeting PND criteria and separately for those with a prior history of major depression (PND_priorDep) and those whose first onset of major depression was perinatal (PND_firstDep).

	During pregnancy only	After delivery only	Both during pregnancy and after delivery	Missing
All PND cases (N=5,058)	295 (6%)	1,627 (32%)	3,073 (61%)	63 (1%)
PND_priorDep (N=2,261)	144 (6%)	592 (26%)	1,507 (67%)	18 (1%)
PND_firstDep (N=878)	28 (3%)	325 (37%)	510 (58%)	15 (2%)

The reported length of the worst episode of PND is shown in Table 2. Full details are provided in Table S4. For both groups of cases, PND was most commonly reported to have lasted for more than six months.

Table 2. Length of worst reported episode of PND stratified by prior history of depression.

Length of worst episode	PND_priorDep	PND_firstDep
	Total (%)	Total (%)
Up to 2 weeks	171 (7.7)	37 (4.3)
2-4 weeks	243 (11.0)	76 (8.8)

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1-3 months	409 (18.5)	137 (15.9)
3-6 months	448 (20.3)	202 (23.5)
More than 6 months	935 (42.3)	407 (47.3)

The most reported time of symptom onset during the worst episode of PND is shown in Table 3. Regardless of whether women had a prior history of depression, the most commonly reported time of onset for the worst episode was 0-4 weeks postpartum. However, women with a prior history of depression were more likely to report that the worst episode began during pregnancy than women with no reported prior history, specifically during the first trimester.

Table 3. Time of onset of the worst episode of perinatal depression.

	1st trimester	2nd trimester	3rd trimester	0-4 weeks after delivery	1-3 months after delivery	More than 3 months after delivery
PND_priorDep (%)	400 (18.1)	214 (9.6)	120 (5.4)	724 (32.6)	462 (20.8)	296 (13.3)
PND_firstDep (%)	73 (8.4)	55 (6.3)	42 (4.8)	291 (33.7)	225 (26.1)	176 (20.4)

Clinical and psychosocial risk factors for PND in parous women

Table S5 provides the number and percentage of participants that completed each of the risk factor variables

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Clinical and psychosocial risk factors for PND in parous women with a history of depression.

We investigated which risk factors are associated with PND in women with a previous history of depression. Age (OR [PND case status]=0.97 per additional year of age, CI=[0.96-0.98], p < 0.001), and number of births (OR [PND case status]=1.3 per additional birth, CI=[1.2-1.4], p < 0.001) were significantly associated with PND. Both age and number of births were included as covariates in subsequent analyses, which were also adjusted for multiple testing.

Key risk factors for PND among parous women with a prior history of depression were age at onset of depression (OR = 0.99 per year later of onset, p < 0.001), non-European ancestry (OR = 1.5, p = 0.03), specifically Australian Indigenous ancestry (OR = 2.5 [1.1-4.5], p = 0.02), emotional abuse in childhood (OR=1.4 [1.1-1.7], P=0.006) and severe nausea during pregnancy (OR = 1.3 [1.1-1.6], P=0.007). Being diagnosed with any psychiatric comorbidity was also associated with risk of PND (OR = 1.2 [1.0-1.5], p =0.02). The most significant individual comorbidity was ADHD (OR = 2.3 [1.3-4.4], p = 0.009). This association did not pass the Bonferroni corrected significance threshold; however, this is a conservative correction given the correlation between tests. Full details of all results are provided in Table S6.

Screening positive for PND among parous women with a history of depression was associated with an overall increased number of reported episodes (OR per episode = 1.15 [1.13 – 1.17], p < 0.001) and decreased likelihood of reporting high efficacy of any antidepressant (OR = 0.7 [0.5-0.8], p< 0.001).

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Discussion

We investigated lifetime prevalence and correlates of perinatal depression among women in a large cross-sectional study of depression. This is to date one of the largest studies of perinatal depression among women with major depression. We found a very high prevalence of perinatal depressive symptoms in women with lifetime depression, with higher likelihood of onset of symptoms during pregnancy in women with a prior history, supporting the need for screening and close monitoring of symptoms in women with a history of depression. Furthermore, our results highlight that perinatal depression is associated with a more chronic course of depression, with earlier onset, more episodes and poorer reported efficacy of antidepressants. The finding of a high prevalence of perinatal depression in women agrees with previous findings from a study in the Netherlands that found a prevalence of 40% in women with a prior history of MDD [25]. The prevalence in our study is higher and this likely reflects that this is a sample enriched for participants with severe depression [22]. While assessment of severity relies on the individual's self-report, previous analyses in the Australian Genetics of Depression Study have shown that those reporting more severe depression have higher genetic risk to depression [31], and the association between perinatal depression and more chronic course is also supported by genetic data [32].

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Another key finding was that women without a prior history were more likely to report symptom onset in the postnatal period and were more likely to report longer duration of symptoms. This may reflect that women with a prior history may have had an ongoing episode of depression when they became pregnant, and we were unable to distinguish whether symptoms had started prior to the first trimester. Furthermore, women with a prior history may have been more likely to be monitored by clinicians and have a treatment plan in place, leading to reduced length of symptoms.

Participants with a prior history of depression who report having at least one ancestor of Aboriginal or Torres Strait Islander (ATSI) descent were more likely to report significant perinatal depressive symptoms. There have been few studies conducted on perinatal mental health among Aboriginal and Torres Strait Islanders [33]. One study conducted on a representative population sample in New South Wales did not find an increased prevalence of postnatal depressive symptoms among women of ATSI descent. However, the study did identify several associated risk factors that commonly affect people of ATSI descent such as placement in public housing, financial hardship, and poor self-rated health. Many other risk factors such as smoking and obstetric complications are higher in the ATSI population than in non-Indigenous Australians and depression and anxiety are twice as common [34]. Results from the Australian Postnatal Screening Program found that the rate of antenatal depression in ATSI women was 18.9% compared to 8.9% in non-Indigenous Australians and 6.3% had postnatal depression compared to 2.7% in non-Indigenous women [35, 36]. The findings of our study further highlight the increased risk of PND in ATSI women and the need for better screening and treatment in the Indigenous population.

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Another key finding was the association between severe nausea during pregnancy and PND. Nausea and vomiting during pregnancy of varying severity affects approximately 69% of pregnant women. A meta-analysis evaluating the association between the severe form of morning sickness – hyperemesis gravidarum (HG) – and depression and anxiety found significant increased depression and anxiety scores in women with HG [37]. A recent longitudinal study in the United Kingdom found that 49% of women with HG had probable depression antenatally and 29% had probable postnatal depression. In conjunction with our findings, these results suggest that women with severe nausea during pregnancy are at high risk of depression and may need to be referred for treatment of PND [38].

Lastly, we identified psychiatric comorbidities, particularly premenstrual dysphoric disorder and ADHD, and emotional abuse in childhood as being associated with perinatal depressive symptoms. There is an extensive literature on the association between trauma and PND [39-42] and our study shows that even among those with a prior history of MDD, trauma is a risk factor for PND, consistent with previous reports [25]. Several studies have evaluated the association between ADHD in children and perinatal risk factors including PND in mothers [43-45]. However, few studies have considered that mothers with PND may also have ADHD symptoms and our results suggest that this is an important consideration. Recent studies that have attempted to account for genetic transmission from mother to child have found that much of the association between PND and ADHD in the offspring is accounted for by shared genetic risk factors between PND and ADHD [46, 47].

The results of this study should be considered in the light of several limitations. The main limitation of this study is that it is based on an online questionnaire, with no personalized

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interviews or clinical reports to provide supporting evidence for self-reported data. Answers were based on total life experience, including, but not exclusive to, the perinatal period. Furthermore, the AGDS is a cross-sectional study. Its strength lies in its sample size, but, unlike a longitudinal study, it provides no information with respect to timing of variables significantly associated with PND (with the exception of childhood adverse experiences), so no inference can be made pertaining to cause and effect. In addition, because information only about the worst episode was ascertained, it was not possible to identify all cases where the perinatal episode was the first episode of depression, which may have biased the results. No information on the use of mood stabilisers which would be indicative of mixed episodes was collected.

Furthermore, the lifetime EPDS used to assess PND is a screening, rather than diagnostic tool and may result in overestimation of PND case status [48], although O'Connor et.al. [49] reported a sensitivity of 0.8 for the EPDS in identifying MDD with a cut-off score>=13, and a specificity of 0.9. The lifetime EPDS is a modification of this scale which has demonstrated internal consistency [25].

Missing data is a further limitation. Because not all women completed all parts of the questionnaire, the sample sizes were different for each variable analyzed. The results of the study should also be considered in the context that the AGDS cohort is mostly young and well-educated and may not generalize to the entire population. The primary aim of the study was to identify genetic risk factors for depression and investigate heterogeneity in depression. Analyses conducted to date suggest that the sample is enriched for severe

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depression and the finding of a high prevalence of perinatal depression symptoms supports this. However, this may limit the generalizability of the findings.

Finally, complications of pregnancy and birth were not assessed in this study apart from NVP and gestational diabetes, so it was not possible to fully assess whether perinatal complications may contribute to PND vulnerability [9].

Conclusions

PND is a leading cause of disease for women who give birth, adding to the overall family disease burden and potential cognitive and emotional problems for affected children. This sample of parous women with lifetime major depression found a high rate of perinatal depressive symptoms, particularly for women who experienced an episode of depression before their first pregnancy. There is a compelling literature demonstrating that screening for PND should begin during pregnancy [49, 50], particularly for women with prior history of depression, which is supported by the finding that the majority of cases in this study experienced PND both before and after delivery. Although women who have been previously diagnosed with major depression are, presumably, under clinical care, it is possible that women may have withdrawn from care if treatment has been ineffective. Standard prenatal care that adopts frequent assessment of depression status provides an opportunity to identify women who might otherwise “slip through the cracks” and ensure that they continue to receive support in finding a successful treatment or in the prevention

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of relapse [49]. Cases were also more likely to have treatment resistant depression, supporting further clinical investigation of antidepressant efficacy in PND.

Authors' Contributions

EMB, JK, NGM, NRW, designed the study. SEM, LCC, SMB, JM, EB, JG, TM, IBH provided intellectual input into the content. JK analysed the data. JK, EMB, NRW, and NGM drafted the manuscript. SEM, LCC, SMB, JM EB, JG, TM, IBH, revised the article for intellectual content. All authors have read and approve of the final version.

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Figure Legends

Fig. 1 Flow chart: Selection of cases and associated comparative group for first analysis (prior history of major depression) and second analysis (PND is first experience of major

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depression). Cases met criteria for major depression and had at least one live birth, plus any of: EPDS score >=13; a previous diagnosis of PND; or major depression during the perinatal period.

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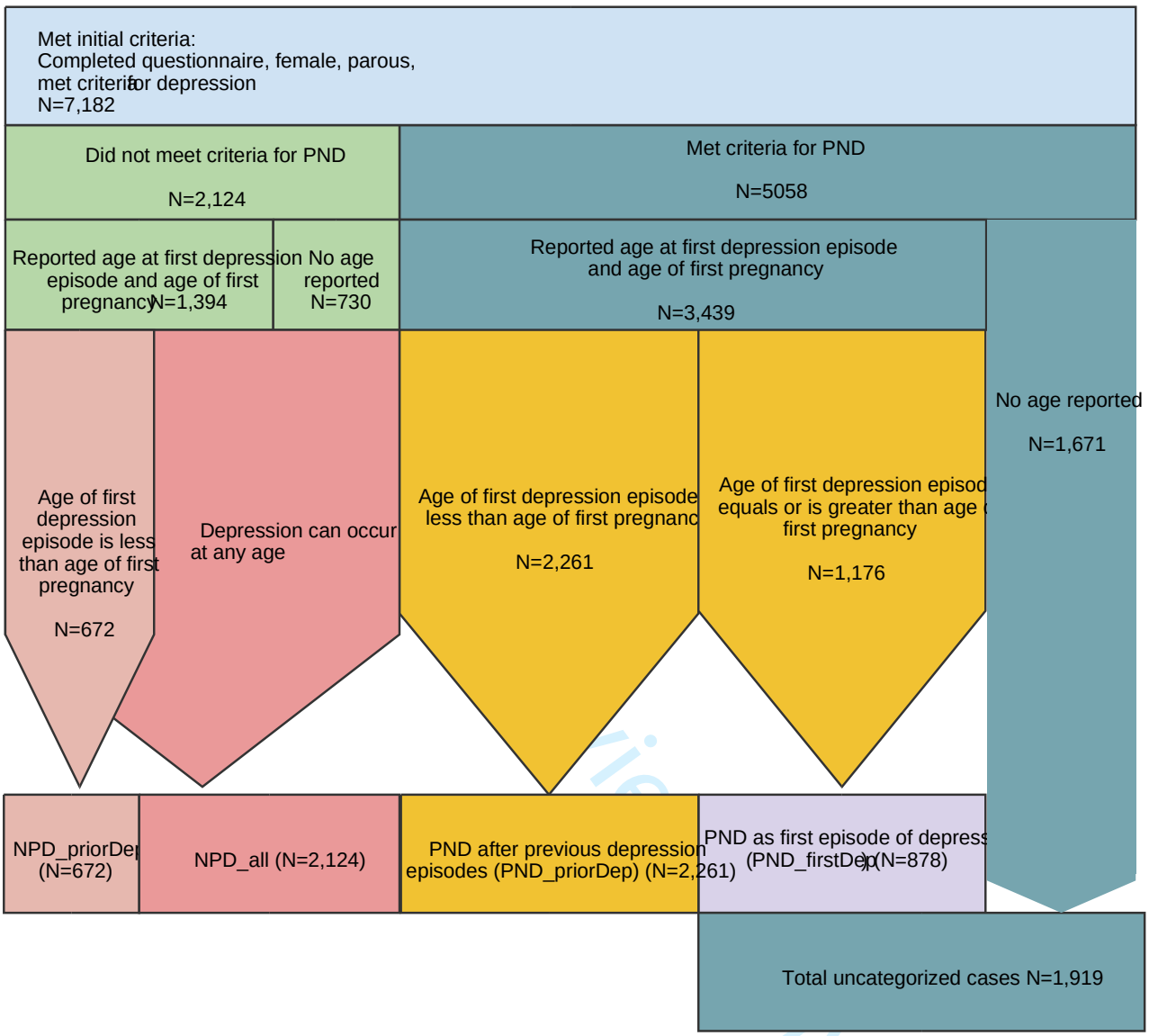
Met initial criteria:
Completed questionnaire, female, parous,
met criteria for depression
N=7,182
Did not meet criteria for PND
N=2,124
Met criteria for PND
N=5058
Reported age at first depression episode and age of first pregnancy N=1,394
No age reported N=730
Reported age at first depression episode and age of first pregnancy
N=3,439
Age of first depression episode is less than age of first pregnancy
N=672
Depression can occur at any age
Age of first depression episode less than age of first pregnanc
N=2,261
Age of first depression episod equals or is greater than age first pregnancy
N=1,176
No age reported
N=1,671
NPD_priorDep (N=672)
NPD_all (N=2,124)
PND after previous depression episodes (PND_priorDep) (N=2,261)
PND as first episode of depress (PND_firstDep) (N=878)
Total uncategorized cases N=1,919

Supplementary Methods

Australian Genetics of Depression Study

Selection of Cases

Prior history of depression: Participants with prior depression were selected by comparing the reported age of the first episode of depression to the reported age of first pregnancy. Where the depression onset age preceded pregnancy, participants were included amongst those with a prior history of major depression. Where the age of depression onset matched the age of first pregnancy (or age of first pregnancy +1), or the age of the worst episode of PND, participants were included amongst those who experienced their first episode of depression perinatally.

Measures

Severity of depression: DSM-V diagnostic criteria for MDD were assessed using the CIDI-SF(World Health Organization 1994). First onset age was assessed by asking participants when they had first experienced a 2-week period of depression. Severity of depression was assessed using the number of lifetime episodes, and age at first episode. The total number of periods of at least 2 weeks of depression and/or anhedonia was calculated using a dropdown box where participants could select from 1 to 12 or 13+.

Demographic measures: Demographic measures included current age, marital status, and highest level of education completed or partially completed measured using an ordinal scale (primary; lower or higher secondary school; diploma; degree; or post-graduate studies). Ancestry analysis (self-report of ancestry of great-great-grandparents assigned to 18 geographical regions, Supplementary Table S2) considered associations between rates of

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endorsing PND in women with ancestors only from Europe, compared to women with at least one non-European ancestor. Further analysis compared the rate of PND in those reporting Australian Indigenous ancestry to those of only European ancestry.

Clinical measures: Participants were asked to report any previous diagnoses from a total list of 19 psychiatric disorders, of which 13, with frequencies > 3% for all women with PND, were analyzed in this study (Supplementary Table S3). History of childhood trauma was assessed using responses to three questions that asked whether participants had been emotionally abused, emotionally neglected, or physically neglected during childhood. Additionally, participants were asked whether they had experienced physical or sexual assault or unwanted sexual experience at any time in their life, as well as their age at that time. For these questions, an age less than 16 was used to designate a childhood experience.

Reproductive measures: Reproductive measures included age at menarche, parity (number of live births), age at first birth, presence and severity of nausea and vomiting during pregnancy (NVP), and diagnosis of endometriosis or polycystic ovarian syndrome. Severity of NVP was measured using a scale adapted from Zhang et al. (2011). Gestational diabetes was measured as part of a general question about experience of medical conditions, followed by a request to specify the type of diabetes (if diabetes was selected).

Effects of antidepressants: Efficacy of the top ten most commonly prescribed antidepressants in Australia was assessed by asking how well each antidepressant a participant had ever taken worked for them on a three-point scale (Not at all well, Moderately Well or Very Well).

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Questions from the Australian Genetics of Depression Study Questionnaire used in phenotypic analysis (excluding Depression Scales)

Biological sex, age and marital status

Are you male or female?

How old are you now?

What is your marital status?

- Married
- Separated
- Divorced
- Widowed
- Never married
- Living with partner/defacto (for a period of six months or longer)

Education

What is your highest level of education?

- No formal education
- Completed or partially completed primary school (years 1-7)
- Completed or partially completed junior secondary school (years 8-10)
- Completed or partially completed senior secondary school (years 11-12)
- Completed or partially completed certificate or diploma
- Completed or partially completed a degree
- Completed or partially completed a Post Graduate Diploma, Masters degree, Doctorate or PhD
- Don't know

Ancestry

Thinking about what you know of your family history, which of the following best describes the geographic regions where your ancestors (i.e. your great-great-grandparents) come from? You may select as many choices as you need

- England, Ireland, Scotland or Wales
- Australia - not of Aboriginal or Torres Strait Islander descent
- Australia - of Aboriginal or Torres Strait Islander descent
- New Zealand - not of Maori descent
- New Zealand - of Maori descent
- Northern Europe including Sweden, Norway, Finland and surrounding countries
- Western Europe including France, Germany, the Netherlands and surrounding countries
- Southern Europe including Italy, Greece, Spain, Portugal and surrounding countries
- Eastern Europe including Russia, Poland, Hungary and surrounding countries
- Middle East including Lebanon, Turkey and surrounding countries
- Eastern Asia including China, Japan, South Korea, North Korea, Taiwan and Hong Kong

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- South-East Asia including Thailand, Malaysia, Indonesia, Singapore and surrounding countries
- South Asia including India, Pakistan, Sri Lanka and surrounding countries
- Polynesia, Micronesia or Melanesia including Tonga, Fiji, Papua New Guinea and surrounding countries
- Africa
- North America - not of First Nations, Native American, Inuit or Métis descent
- North America - of First Nations, Native American, Inuit or Métis descent
- Caribbean, Central or South America
- Don't know

Comorbidities

Have you ever been diagnosed with any of the following? Please select all that apply.

- Depression
- Bipolar disorder
- Premenstrual dysphoric mood disorder
- Schizophrenia
- Anorexia nervosa
- Bulimia
- Attention-deficit/hyperactivity disorder (ADD/ADHD)
- Autism spectrum disorder (Autism, Asperger's disorder)
- Tourette's disorder
- Anxiety disorder (Generalised anxiety disorder)
- Panic disorder
- Obsessive compulsive disorder
- Hoarding disorder
- Posttraumatic stress disorder (PTSD)
- Specific phobia (e.g. animals, heights, storms, blood / injection / injury, flying, enclosed spaces)
- Seasonal affective disorder (SAD)
- Social anxiety disorder (also known as Social phobia)
- Agoraphobia
- Personality disorder
- Substance use disorder

Antidepressants

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Have you ever taken any of the following antidepressants (even if it wasn't for depression or anxiety)? *Please select all that apply.*

1st List (10 most commonly prescribed antidepressants):

- Sertraline (e.g. Zoloft, Eleva, Sertra, Sertracor, Setrona, Xydep)
- Escitalopram (e.g. Lexapro, Cilopam, Escicor, Esipram, Esitalo, Lexam, LoxaLate)
- Venlafaxine (e.g. Efexor, Altven, Elaxine, Enlafax, Venla, Venlexor)
- Amitriptyline (e.g. Endep)
- Mirtazapine (e.g. Avanza, Remeron, Milivin, Axit, Aurozapine, Mirtazon)
- Desvenlafaxine (e.g. Pristiq, Desfax)
- Citalopram (e.g. Cipramil, Celapram, Celica, Ciazil, Citalo, Talam)
- Fluoxetine (e.g. Prozac, Auscap, Lovan, Zactin)
- Duloxetine (e.g. Cymbalta, Andepra, Coperin, Deotine, Depreta, Drulox)
- Paroxetine (e.g. Aropax, Paxtine, Extine, Roxet)

2nd List:

- Dothiepin (e.g. Dothep)
- Fluvoxamine (e.g. Luvox, Faverin, Movox, Voxam)
- Doxepin (e.g. Sinequan, Deptran)
- Nortriptyline (e.g. Allegron)
- Moclobemide (e.g. Amina, Clobemix, Mohexal, Aurorix)
- Clomipramine (e.g. Anafranil, Placil)
- Reboxetine (e.g. Edronax)
- Mianserin (e.g. Lumin)
- Imipramine (e.g. Tofranil, Tolerade)
- Tranylcypromine (e.g. Parnate)
- Phenelzine (e.g. Nardil)

How well does / did each antidepressant work for you?

- Not at all well
- Moderately well
- Very well
- Don't know

Abuse

Listed below are a number of difficult or stressful things that sometimes happen to people. For each event mark one or more of the boxes to the right to indicate that: (a) it **happened to you** personally; (b) you **witnessed it** happen to someone else; (c) you **learned about it** happening to a close family member or close friend; (d) you were exposed to it as **part of your job** (for example, paramedic, police, military or other first responder);

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(e) you're **not sure** if it fits; or (f) it **doesn't apply** to you. Be sure to consider your **entire life** (growing up as well as adulthood) as you go through the list of events.

(Relevant categories (only considered those marked "Happened to me"))

- Physical assault (e.g. being attacked, hit, slapped, kicked, beaten up)
- Sexual assault (rape, attempted rape, made to perform any type of sexual act through force or threat of harm)
- Other unwanted or uncomfortable sexual experience

How old were you the first and last time these things happened?

Childhood abuse

People may experience stressful situations in childhood which may affect their future health and well-being. Please indicate if you experienced any of these situations **during your childhood**.

- Emotional abuse (e.g. often being told you were no good, yelled at in a scary way, threatened, ignored, or stopped from making friends)
- Emotional neglect (e.g. often not being shown affection, or not being given encouragement or support)
- Physical neglect (e.g. often not being given enough to eat or drink, appropriate clothing, shelter, medical care, education, supervision or a safe home environment)

Menarche

Have you begun to menstruate (started having your period)?
How old were you when you had your first menstrual period?

Parity

How many times have you been pregnant? *If you're unsure, please provide your best estimate.* How many of these pregnancies resulted in live births (including caesarean section)?

Morning sickness

While many women experience morning sickness, there are differences in how severe morning sickness is. Did you have any morning sickness, nausea or vomiting during any of your pregnancies?

Thinking back to each pregnancy, which of the following best describes your experience?

- I did not have any nausea or vomiting
- Nausea and/or vomiting for *less than 7 days*, but I didn't see a doctor about this and it didn't disrupt my daily routine.
- Nausea and/or vomiting for *more than 7 days*, but I didn't see a doctor about this. It didn't disrupt my daily routine.

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- It disrupted my daily routine, but it didn't affect my weight and I didn't need medication to manage it.
- It really disrupted my daily routine and I was prescribed medication (or was put on a drip) but it didn't lead to weight loss.
- It really disrupted my daily routine. I lost weight. I was prescribed medication or was put on a drip or feeding tube.
- I don't remember or am unsure.

Gestational diabetes

Have you ever had any of the following medical conditions? *Please select all that apply*

- Diabetes or high blood sugar

[For those selecting diabetes or high blood sugar:]

Please select the specific type of the medical condition(s) you have had.

- Type 1 diabetes
- Type 2 diabetes
- Gestational diabetes
- Other diabetes or high blood sugar

Reproductive disorders

Has a doctor ever diagnosed you with any of the following?

- Polycystic ovarian syndrome (a hormonal disorder characterised by ovarian follicles failing to ovulate and remaining as multiple cysts, distending the ovary)
- Endometriosis (the presence of tissue similar to the kind lining the uterus, at other sites in the pelvis)

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Table S1. Selection process: for PND_priorDep and PND_firstDep samples

Process	Number
Completed online survey	20,689
PriorDep cases: PND with history of major depression before first pregnancy (PND_priorDep)	2,261
PriorDep comparison group: History of major depression before first pregnancy, but no PND (NPD_priorDep)	672
PNDfirst cases: PND is first onset of major depression (PND_firstDep)	878
Uncategorized PND cases: lost to further analysis	1,919
PNDfirst comparison group: Met criteria for major depression but not associated with peripartum period (NPD_all)	2,124

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Table S2. List of geographical regions for participants to apply to great great grandparents

England, Ireland, Scotland or Wales
Australia - not of Aboriginal or Torres Strait Islander descent
Australia - of Aboriginal or Torres Strait Islander descent
New Zealand - not of Maori descent
New Zealand - of Maori descent
Northern Europe including Sweden, Norway, Finland and surrounding countries
Western Europe including France, Germany, the Netherlands and surrounding countries
Southern Europe inclding Italy, Greece, Spain, Portugal and surrounding countries
Eastern Europe including Russia, Poland, Hungary and surrounding countries
Middle East including Lebanon, Turkey and surrounding countries
Eastern Asia including China, Japan, South Korea, Taiwan and surrounding countries
South-East Asia including Thailand, Malaysia, Indonesia, Singapore and surrounding countries
South Asia including India, Pakistan, Sri Lanka and surrounding countries
Polynesia, Micronesia or Melanesia including Tonga, Fiji, Papua New Guinea and surrounding countrie
Africa
North America - not of First Nations, Native American, Inuit or Métis descent
North America - of First Nations, Native American, Inuit or Métis descent
Caribbean, Central or South America

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Table S3. List of psychiatric disorders with frequencies > 3% amongst all women with PND (N=5,058)

List of disorders	Number of cases (of all women with PND, N=5,058)	%
Bipolar Disorder	511	10.1
PMDD	195	3.8
Anorexia	178	3.5
ADHD	168	3.3
Anxiety Disorder	2680	53.0
Panic Attacks	516	10.2
Obsessive Compulsive Disorder	281	5.6
PTSD	859	17.0
Specific Phobia	635	12.6
Seasonal Affective Disorder	172	3.4
Social Anxiety Disorder	440	8.7
Personality Disorder	278	5.5

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Table S4. Length of worst episode of PND according to detailed onset information, and s

Length of worst episode	PND_p		
	Occurrence during pregnancy (n=734)		
	1st trimester (n=400)	2nd trimester (n=214)	3rd trimester (n=120)
Up to 2 weeks	44 (0.11)	18 (0.8)	15 (0.13)
2-4 weeks	51 (0.13)	33 (0.15)	25 (0.21)
1-3 months	51 (0.13)	35 (0.16)	30 (0.25)
3-6 months	48 (0.12)	51 (0.24)	21 (0.18)
More than 6 months	206 (0.52)	76 (0.36)	29 (0.24)

Regression analysis: association of length of worst episode with early onset (either first t delivery)	PND_priorDep		
	OR	CI	P
Up to 2 weeks	1.3	0.9-1.7	1.3E-01
2-4 weeks	1.0	0.8-1.3	9.2E-01
1-3 months	0.9	0.7-1.1	1.5E-01
3-6 months	0.7	0.6-0.9	**6.0E-03**
More than 6 months	1.4	1.2-1.6	**1.7E-04**

Severity of worst episode	PND_priorDep		PND_fir
	Occurrence during pregnancy (n=734)	Occurrence after delivery (n=1,482)	Occurrence during pregnancy (n=170)
Interference	596 (0.80)	1232 (0.83)	141 (0.83)
Professional help	486 (0.66)	965 (0.65)	106 (0.62)
Medication	326 (0.44)	612 (0.41)	306 (0.43)
Hospitalisation	82 (0.11)	154 (0.10)	26 (0.15)

Note: proportions for severity measures do not add up to 1.0 since participants ticked al

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Comparison of severity measures for PND_priorDep and PND_firstDep cases for occurrences in pregnancy or after delivery: Association of each measure with PND_firstDep status.

	OR (for PND_firstDep)	CI	P
Interference	0.9	0.8-1.1	5.0E-01
Professional help	1.2	1.0-1.4	7.5E-02
Medication	1.0	0.8-1.2	8.4E-01
Hospitalisation	1.3	1.0-1.7	**2.4E-02**

Comparison of postpartum onset of worst episode for PND_priorDep and PND_firstDep cases

	PND_priorDep	PND_firstDep
Onset of worst case is postpartum	1487 (0.66)	695 (0.79)

Regression analysis: association of postpartum onset of worst case with PND_firstDep case status

OR (PND_firstDep case status)	CI	P
2.0	1.7-2.4	4.6E-13

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severity of worst episode of PND, characterised by interference in everyday life, and need for profes

priorDep (n=2,261)

Occurrence after delivery (n=1,482)			Total	Occurrence during pregnan	
0-4 weeks after delivery (n=724)	1-3 months after delivery (n=462)	More than 3 months after delivery (n=296)		1st trimester (n=73)	2nd trimester (n=55)
51 (0.07)	22 (0.05)	21 (0.07)	171	5 (0.07)	3 (0.06)
71 (0.10)	38 (0.08)	25 (0.08)	243	7 (0.10)	4 (0.07)
140 (0.19)	96 (0.21)	57 (0.19)	409	7 (0.10)	9 (0.16)
151 (0.21)	112 (0.24)	65 (0.22)	448	11 (0.15)	12 (0.22)
308 (0.43)	188 (0.41)	128 (0.43)	935	43 (0.59)	27 (0.49)

trimester of pregnancy or within 4 weeks after

PND_firstDep		
OR	CI	P
1.0	0.5-2.0	9.3E-01
1.1	0.7-1.8	7.2E-01
1.0	0.7-1.5	8.2E-01
0.7	0.5-1.0	6.1E-02
1.3	1.0-1.7	8.8E-02

rstDep

Occurrence after delivery (n=692)
559 (0.80)
488 (0.70)
67 (0.36)
91 (0.13)

ll that applied.

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sional help, medication, or hospitalisation.

	PND_firstDep (n=878)			
ıcy (n=170)	Occurrence after delivery (n=692)			Total
3rd trimester (n=42)	0-4 weeks after delivery (n=291)	1-3 months after delivery (n=225)	More than 3 months after delivery (n=176)	
2 (0.05)	11 (0.04)	6 (0.03)	10 (0.06)	37
4 (0.10)	26 (0.09)	24 (0.11)	11 (0.06)	76
8 (0.19)	51 (0.18)	34 (0.15)	28 (0.16)	137
9 (0.21)	62 (0.21)	71 (0.32)	37 (0.21)	202
19 (0.45)	139 (0.48)	89 (0.40)	90 (0.51)	407

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Table S5. priorDep samples: Number of respondents (cases and controls) for each variable.

Category	Variable	priorDep sample		
		Number respondents	Number cases/ controls	% cases/ controls
Possible confounders				
	Age	2933		
	Number Births	2933		
Depression				
	Number Episodes	2911		
	Age of first depressive episode	2933		
Eductation				
	Did not finish high school	2933	123/40	5.4/6.0
	Post-secondary education	2933	1895/569	83.8/84.7
Ancestry				
	At least one nonEuropean ancestor	2720	227/41	10.9/6.5
	Australian Indigenous	2720	80/9	4.1/1.5
Psychiatric comorbidities				
	Bipolar Disorder	2933	274/64	12.1/9.5
	PMDD	2933	112/19	5.0/2.8
	Anorexia	2933	97/21	4.3/3.1
	ADHD	2933	97/12	4.3/1.8
	Anxiety disorder	2933	1272/323	56.3/48.1
	Panic attacks	2933	201/64	8.9/9.5
	OCD	2933	147/32	6.5/4.8
	PTSD	2933	452/103	20/15.3
	Specific phobia	2933	326/78	14.4/11.6
	Seasonal Affective	2933	100/25	4.4/3.7
	Social anxiety disorder	2933	239/46	10.6/6.8
	Personality disorder	2933	153/38	6.8/5.7
	anyComorbidity	2933	1675/451	74.1/67.1
Adverse experiences				
	Emotional abuse	1956	959/275	64.7/58.0
	Emotional neglect	1957	839/249	56.3/53.3
	Physical Abuse (anytime)	2070	642/189	40.8/38.2
	Childhood Physical Abuse	1100	374/107	44.3/41.8
	Physical neglect	2010	267/63	17.5/13.1
	Sexual abuse (anytime)	2067	1004/284	63.2/56.9
Reproductive				
	Early pregnancy	2933	1143/313	50.6/46.6
	Early menarche	1880	633/184	45/41.9

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	Disruptive NVP	2520	1031/257	53/44.9
	Polycystic ovarian syndrome	1960	195/56	13.1/11.9
	Endometriosis	1969	251/67	16.8/14.1
	Gestational diabetes	2933	90/18	6.7/4.2
Antidepressants				
Effectiveness				
	High efficacy	2790		

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Table S6. Results of comparison of PND_priorDep and NPD_priorDep for all variables, includin

priorDep sample: 2261 cases; 6

Significant P i

Characteristic	OR	CI	P
Confounders			
Age (OR per year, no covariates)	1.0	0.96-0.98	**2.3E-17**
Number Births (OR per birth, no covariates)	1.3	1.17-1.43	**4.7E-07**
Depression onset/severity N(tests=2)			
Odds of PND compared to NPD per episode	1.1	1.1-1.1	**1.2E-17**
Odds of PND compared to NPD per year of age at first episode	0.97	0.96-0.99	**2.1E-03**
Ancestry N(tests=2)			
Ancestry: At least one non-European ancestor	1.5	1.1-2.1	**2.8E-02**
Ancestry: Australian Indigenous	2.3	1.2-4.8	**2.4E-02**
Education, N(tests)=3			
Did not complete high school	1.0	0.7-1.4	8.1E-01
Completed post-secondary education	0.9	0.7-1.2	6.5E-01
Comorbidity, N(tests)=12			
Having any comorbidity	1.2	1.0-1.5	**3.2E-02**
Bipolar Disorder	1.3	0.9-1.7	1.3E-01
PMDD	1.9	1.2-3.2	**1.4E-02**
Anorexia	1.3	0.8-2.2	2.4E-01
ADHD	2.3	1.3-4.4	**9.1E-03**
Anxiety Disorder	1.3	1.1-1.5	**1.2E-02**
Panic Attacks	1.0	0.7-1.4	9.4E-01
Obsessive Compulsive Disorder	1.3	0.9-1.9	2.7E-01
PTSD	1.3	1-1.6	**3.6E-02**
Specific Phobia	1.3	1-1.7	8.9E-02
Seasonal Affective Disorder	1.4	0.9-2.2	1.7E-01
Social Anxiety Disorder	1.5	1.1-2.1	**1.6E-02**
Personality Disorder	1.0	0.7-1.5	8.8E-01
Trauma, N(tests)=7			
ChildhoodEmotionalAbuse	1.4	1.1-1.7	**5.5E-03**
ChildhoodEmotionalNeglect	1.3	1-1.6	**3.1E-02**
ChildhoodPhysicalAbuse	1.0	0.8-1.4	9.4E-01
Physical abuse (any time)	1.1	0.9-1.4	3.1E-01
Physical neglect (childhood)	1.4	1.1-1.9	**2.3E-02**
Sexual abuse (childhood)	1.0	0.7-1.3	7.9E-01
Sexual abuse (any time)	1.2	1-1.5	6.1E-02
Reproductive characteristics, N(tests)=5			
Disruptive NVP	1.3	1.1-1.6	**6.6E-03**

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Early menarche	1.1	0.9-1.4	3.4E-01
Endometrioses	1.2	0.9-1.6	2.1E-01
Polycystic ovarian syndrome	0.9	0.7-1.3	7.2E-01
Gestational diabetes	1.4	0.8-2.4	2.4E-01
Antidepressant use			
Tried 3 or more commonly prescribed antidepressant (as a proportion of women using antidepressants)	1.4	1.1-1.8	**1.4E-03**
Antidepressant efficacy, N(tests)=3			
High efficacy for any common antidepressant	0.7	0.5-0.8	**5.5E-04**

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g age and number of births as convariates.

72 controls; 2,933 total.
n bold

P (Bonferroni Adjustment for multiple tests)
0.000
0.000
0.000
0.004
0.056
0.047
1.000
1.000
1.000
0.140
1.000
0.114
0.173
1.000
1.000
0.479
1.000
1.000
0.247
1.000
0.037
0.262
1.000
1.000
0.199
1.000
0.422
0.039

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1.000
1.000
1.000
1.000

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STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2-4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-6
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6-7
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	7-8
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8-9,10-11
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	8, 9-10
Bias	9	Describe any efforts to address potential sources of bias	10-11
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	9-11
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	11-12
		(*b*) Describe any methods used to examine subgroups and interactions	11
		(*c*) Explain how missing data were addressed	11
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	12

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Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	12-14
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	12-15
		(b) Indicate number of participants with missing data for each variable of interest	15
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	15
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	15-17
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	17-18
Discussion			
Key results	18	Summarise key results with reference to study objectives	18-19
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	19
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	19-20
Generalisability	21	Discuss the generalisability (external validity) of the study results	20-21
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	4

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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