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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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2

28 Abstract

29 Objectives

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

34 Setting

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

37 Participants

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

3

46 Primary and secondary outcome measures

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

50 Results

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

58 Conclusions

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

64 Strengths and limitations of this study

65

4

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

77 **Funding Statement**

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79 of Australia grant 1086683, and further supported by NHMRC grants 1145645, 1078901 and
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81 by a QIMR Berghofer Institute fellowship.

82 **Competing interests**

83 No conflict of interest has been reported

84 **Availability of data and material**

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

87 **Ethics approval and consent to participate**

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

93 Patient consent for participation in the study was obtained.

94 Introduction

95

96 Background

97 Perinatal depression (PND), including both antenatal and postpartum depression, commonly
98 classified as a subtype of major depressive disorder (MDD)¹, carries serious risk for both
99 mother and infant. An estimated 53% of women with postpartum depression have “high
100 suicidality”², whilst the rate of self-harming thoughts is three times that of the postpartum
101 community population³. Estimated economic costs of PND in the UK, of which 72% are for
102 ongoing care of the child⁴ reflect findings that children of women with persistent and severe
103 PND are at increased risk of adverse outcomes^{1,5}.

104 The diagnostic criteria for MDD and PND are the same⁶, but the strongest known PND risk
105 factor is a previous diagnosis of any psychiatric disorder^{1,7-10}, not only MDD¹¹. Other risk
106 factors may also increase PND vulnerability. Possible psychosocial factors include stress and
107 history of abuse¹² whilst biological factors include changes that accompany pregnancy, such
108 as hormonal fluctuations and increased inflammation^{13,14}.

109 The complexity of these risk factors contribute to ongoing debate about the heterogeneous
110 nature of PND in relation to MDD; in particular, whether it is simply another episode of
111 MDD that happens to coincide with the perinatal period¹⁵; or a subset of MDD, termed
112 “reproductive depression”, stimulated at times of hormone fluctuation such as pre-
113 menstruation, peripartum and menopause^{16,17}; or a distinct disorder, stimulated by changes
114 occurring during pregnancy and confined to the perinatal period¹³. One suggestion is that
115 PND is itself heterogeneous^{10,18}, with clinical subtypes differentiated by timing and severity of
116 symptoms, perinatal complications, and history of psychiatric disorders. However, a

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3 117 comprehensive investigation of the characteristics of women with PND, with and without a
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6 118 prior psychiatric history, has not been attempted.
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9 119 Objectives

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12 120 Using the Australian Genetics of Depression Study (AGDS), a large cohort study with over

13
14 121 20,000 participants self-reporting a depression diagnosis¹⁹, we examined PND

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17 122 heterogeneity, based on the presence or absence of previous major depression history. We

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19 123 sought to address two questions:
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23 124 1) What are the differences in clinical and psychosocial characteristics between women with

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25 125 and without PND after a depressive episode prior to their first pregnancy?
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29 126 2) What are the differences in clinical and psychosocial characteristics between women

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31 127 whose first episode of depression was during the perinatal period and parous women who

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33 128 have also experienced depression, but never during any perinatal period?
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36 37 129 Method

38 39 40 41 42 130 Study Design

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45 131 Within a case cohort study of the etiology of depression, two groups of PND cases and two

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47 132 comparison groups of NPD cases were identified according to their history of prior

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49 133 depression. For both PND groups, the length and severity of their “worst case” of PND was

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51 134 measured. To investigate risk factors associated with PND after a previous history of

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53 135 psychiatric disorders, or as first onset depression, both PND groups were compared with

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55 136 their comparison group of NPD cases, across a range of variables.
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138 Setting: The Australian Genetics of Depression Study

139 The AGDS is a large ongoing case cohort study of the etiology of depression that recruited
140 20,689 participants (aged between 28 and 58 years; 75% female) during 2016-2018. The
141 analyses conducted here are from participants enrolled prior to the initial data freeze in
142 September 2018. Recruitment was primarily through a media campaign (86%) as well as
143 specific invitations to women who had responded to a mobile phone app focused on PND,
144 originally developed in the USA²⁰, and also ascertainment through the Pharmaceutical
145 Benefits Scheme prescription records for antidepressants, which requested participation
146 from anyone with a depression diagnosis from a health professional. For further details of
147 the recruitment strategy, see Byrne, et al.¹⁹.

148 AGDS participants were invited to complete an online questionnaire. A compulsory core
149 module assessed self-reported psychiatric history, the Composite Interview Diagnostic
150 Interview Short Form (CIDI-SF) which assesses the Diagnostic and Statistical Manual of
151 Mental Disorders Fifth Edition (DSM-V) criteria for MDD⁶, and experiences of using
152 commonly prescribed antidepressants. Women reporting symptoms of depression during
153 pregnancy or up to 6 months following childbirth were asked to complete the lifetime
154 Edinburgh Postnatal Depression Scale (EPDS)²¹, an adaptation of the standard EPDS²² that
155 assesses lifetime PND episodes. They were also asked whether symptoms of depression
156 occurred during pregnancy, after giving birth, or both, the age at which they experienced
157 their worst episode of PND, its severity and duration. For all AGDS participants, further
158 voluntary modules assessed history of psychiatric health conditions and stressful life events.

8

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

161

162 Participants: PND cases and comparison groups

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

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

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3 180 Supplementary Table S1 illustrate sample selection. Further details are provided in
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6 181 Supplementary Methods.

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9 182 Figure 1 about here
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16 17 184 Variables

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21 185 The outcome of interest was a PND episode for women with either a history of previous
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23 186 depressive episode(s), or no previous depression history. An exposure to a PND episode is
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26 187 defined as the period of time from conception up to six months postpartum, so that the
27
28 188 number of reported live births represents the number of exposures. The cross-sectional
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31 189 nature of our study meant that no direction of causality could be assessed, but we
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33 190 investigated risk factors for PND using variables that have previously been associated with
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36 191 PND^{1,23,24}, including severity of depression; ancestry; comorbidity with other psychiatric
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38 192 disorders; adverse childhood experiences; reproductive traits and response to
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41 193 antidepressants.

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44 194 We investigated previous history of depression as a modifier of the effect of each variable,
45
46 195 by conducting two separate analyses of PND cases categorized as PND_priorDep or
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49 196 PND_firstDep, for both descriptive and comparative measures. For comparative measures
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51 197 each of the two PND groups was compared to an appropriate comparison group. A further
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53 198 effect modifier is the time of onset of PND: during pregnancy, after delivery, or both. For
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56 199 both samples, a sensitivity analysis was conducted to investigate the effect of PND onset
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59 200 both during and after pregnancy.
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202 Descriptive measures for cases

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

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

212

213 Comparative measures

214 Case and comparison groups were compared on a range of variables that have previously
215 been identified to be associated with PND^{1,23}. Demographic measures included current age,
216 marital status, education and ancestry. A list of geographical regions from which ancestry is
217 identified is provided in Table S2. More details are provided in Supplementary Methods.

218 Clinical measures included the number and severity of episodes of major depression, history
219 of childhood trauma and sexual or other physical assault, and previous diagnoses of
220 psychiatric disorders. Eighteen psychiatric disorders were listed, of which twelve, identified
221 by more than 3% of participants, were used in this study (Table S3). Reproductive measures
222 included age at menarche, parity, age at first birth, presence and severity of nausea and

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3 223 vomiting during pregnancy (NVP), and previous diagnosis of gestational diabetes,
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5 224 endometriosis or polycystic ovarian syndrome. Antidepressant measures included the
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8 225 number of antidepressants that had been tried, their efficacy and any side-effects. More
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10 226 details of these measures are provided in Supplementary Methods, which also lists the
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13 227 questions used to assess each characteristic.

16 228 **Potential sources of bias**

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20 229 Two variables, number of births and age, significantly associated with PND, were identified
21
22 230 as exposure and confounder respectively. Each birth represents an additional exposure to
23
24 231 PND, whilst the negative association of PND with increasing age may reflect increasing
25
26 232 awareness and diagnosis of the disorder, or imprecise memory of past events. Reliance on
27
28 233 self-report information years after experiencing PND could lead to recall bias, although the
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30 234 inclusion of age as a covariate in regression analyses may alleviate this trend and
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32 235 participants who provided contradictory evidence were excluded from analysis. The lifetime
33
34 236 EPDS used to assess PND is a screening, rather than diagnostic tool and may result in
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36 237 overestimation of PND case status²⁵, although O'Connor et.al.²⁶ reported a sensitivity of 0.8
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38 238 for the EPDS in identifying MDD with a cut-off score ≥ 13 , and a specificity of 0.9. The
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40 239 lifetime EPDS is a modification of this scale which has demonstrated internal consistency²¹.

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51 241 **Statistical Analysis**

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56 242 For both priorDep and firstDep groups, length and severity of the worst reported episode of
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58 243 PND was calculated, and logistic regression measured the association of depression length
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3 244 with early onset of PND (first trimester of pregnancy or within 4 weeks of delivery).
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5 245 Associations between variables and PND were assessed using logistic regression, with PND
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8 246 the dependent variable, separately for both priorDep and firstDep groups, including age at
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10 247 survey time and number of births as covariates.

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14 248 All modules apart from the first were optional, and some categories applied only to a
15
16 249 limited number of participants (for example, those who had used at least one
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18 250 antidepressant). For these reasons, the number of participants who completed each
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21 251 category or variable varied. For each variable, the number of respondents is reported.
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24 252 Within each category, analysis employed Bonferroni correction for multiple testing
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26 253 (N=number of tests within each category).

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30 254 Finally, to evaluate whether effect sizes were influenced by time of PND onset, we
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32 255 conducted a sensitivity analysis that included only women who reported experiencing PND
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34 256 both before and after delivery. We conducted this analysis separately for both
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37 257 PND_priorDep and PND_firstDep samples.

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40 258 All analyses were conducted using R (version 3.6.0). Figures were generated using ggplot2²⁷
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42 259 and Gliffy software²⁸.

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261 Public and Patient Involvement

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

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265 Results

266

267 Lifetime prevalence of depression during the peripartum period

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

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

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286

287 Table 1. Reported timing of symptoms of perinatal depression among women with PND.

288 Results are shown for all those meeting PND criteria and separately for those with a prior

289 history of major depression (PND_priorDep) and those whose first onset of major

290 depression was perinatal (PND_firstDep).

291

	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%)

292

293

294 The reported length of the worst episode of PND is shown in Fig.2 for PND_priorDep and in

295 Fig.3 for PND_firstDep. Full details are provided in Table S4. For both groups of cases, PND

296 was most commonly reported to have lasted for more than six months. The most commonly

297 reported time of PND onset for women whose episode began during pregnancy was during

298 the first trimester, and for those whose episode began after delivery was within 0-4 weeks.

299 Both PND_priorDep and PND_firstDep were more likely to report that their worst episode

300 began after delivery (66% and 79% respectively), including 60% of PND_priorDep cases and

301 72% of PND_firstDep cases who had reported that they experienced PND both before and

302 after delivery. This difference between the groups is significant, with PND_firstDep having

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3 303 2.0 times the odds of reporting postpartum onset of worst case symptoms (CI=[1.7-2.4],
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5 304 P=4.6e-13) compared to the odds of PND_priorDep. For both groups, symptom onset in the
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8 305 first trimester or 0-4 weeks postpartum was associated with longer duration of symptoms,
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10 306 significantly so for PND_priorDep (Table S4).

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14 307 Figure 2 about here

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22 310 For both groups, more than 60% required some sort of professional help, although less than
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24 311 45% of women reported using medication to deal with this worst episode (Fig.4, Table S4).

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27 312 Figure 4 about here

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31 314 **Clinical and psychosocial risk factors for PND in parous women**

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35 315 Table S5 provides the number and percentage of participants that completed each of the
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37 316 risk factor variables, for both priorDep and firstDep groups.

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41 318 **Clinical and psychosocial risk factors for PND in parous women with a history of** 42 319 **depression.**

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45 320 We investigated which risk factors are associated with PND in women with a previous
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47 321 history of depression. Age at enrolment (OR [PND case status]=0.97 per additional year of
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49 322 age, CI=[0.96-0.98], P=2.3e-17), and number of births (OR [PND case status]=1.3 per
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51 323 additional birth, CI=[1.2-1.4], P=4.7e-07) were significantly associated with PND. Both age
52
53 324 and number of births were included as covariates in subsequent analyses, which were also
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55 325 adjusted for multiple testing. Fig. 5 illustrates nominally significant results after the inclusion
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57 326 of covariates, with details of all results provided in Table S6.

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3 327 Figure 5 about here
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6 328 Ancestry (both non-European and Australian Indigenous) was significantly associated with
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9 329 PND (non-European: OR=1.5, CI=[1.0-2.1], P=2.8e-02; Australian Indigenous: OR=2.3,
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11 330 CI=[1.2-4.8], P=2.4e-02), although after correction for multiple testing, only Australian
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13 331 Indigenous remained significant. There was no association between marital status or level of
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15 332 education and PND. On all measures, PND_priorDep reported more severe depression than
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17 333 NPD_priorDep (Fig. 5), although as expected, the NPD_priorDep comparison group also
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19 334 experienced significantly more severe depression than the NPD_all comparison group on all
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21 335 measures (Table S7).
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27 336 Five of twelve psychiatric disorders (premenstrual dysphoric disorder (PMDD), attention
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29 337 deficit hyperactive disorder (ADHD), anxiety disorder, post-traumatic stress disorder (PTSD),
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31 338 and social anxiety disorder) were significantly associated with PND, although none survived
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33 339 Bonferroni correction. There was a significant association between PND and a history of
34
35 340 self-reported childhood emotional abuse (OR=1.4, CI=[1.1-1.7], P=5.5e-03) and neglect
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37 341 (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),
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39 342 although only emotional abuse survived Bonferroni correction.
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45 343 There was no association between age at menarche and PND and no significant difference
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47 344 in the incidence of gestational diabetes, polycystic ovarian syndrome or endometriosis.

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49 345 Although there was no significant difference in the incidence of NVP for PND compared to
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51 346 NPD cases (P = 0.11), there was a significant difference in the severity of NVP between
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53 347 PND_priorDep and NPD_priorDep. For PND_priorDep, the odds that a woman with PND had
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55 348 experienced disruptive nausea during pregnancy, compared to NPD_priorDep, is 1.3
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57 349 (CI=[1.1-1.6], P=6.6e-03), significant after Bonferroni correction.
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3 350 PND_priorDep were significantly more likely to have tried more than three antidepressants
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6 351 than its comparison group (OR=1.4, CI=[1.1-1.8], P=1.4e-03), were less likely to report high
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8 352 efficacy of any antidepressant (OR=0.7, CI=[0.5-0.8], P=5.5e-04), and were 1.5 times more
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10 353 likely (CI=[1.2-1.8], P=3.0e-04) to report at least one side effect for antidepressants,
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13 354 compared with women with NPD_priorDep (including age, number of births and the
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15 355 number of antidepressants tried as covariates in the model) (Fig. 4). All of the 23 side effects
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17 356 were more commonly reported by PND_priorDep, 15 of them significantly so, although only
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19 357 2 survived Bonferroni correction.
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27 359 **Clinical and psychosocial risk factors associated with PND as first episode of depression.**

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29 360 As there may be unique risk factors associated with onset of depression perinatally, we
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31 361 conducted further analyses to evaluate differences between women who report their first
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33 362 episode occurring perinatally (PND_firstDep) and all NPD cases. Similar to priorDep findings,
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35 363 we found that age at enrolment and number of births were associated with increased risk of
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37 364 PND (Table S6). After both these variables were included as covariates, PND_firstDep was
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39 365 associated with emotional abuse during childhood, increased likelihood of trying at least 3
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41 366 antidepressants compared with controls, and increased odds of reporting 13 of the 23 side
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43 367 effects, 5 of which were significant, although no side effects survived Bonferroni correction.
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46 368 No associations were found with other variables. FirstDep results (for variables that were
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48 369 nominally significant for priorDep) are illustrated in Fig.5 and full details of all results are
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50 370 provided in Supplementary Table S6.
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372 Effect of PND onset on clinical and psychosocial risk factors associated with PND.

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

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383 Discussion

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

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

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

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

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3 415 Despite these limitations, the findings of this study are consistent with previous reports.
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6 416 PND for women with a previous history of depression seems to be more severe and complex
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8 417 than for women who experience PND as first depression onset, supporting the notion of
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10 418 PND heterogeneity according to previous psychiatric history. Prior history of psychiatric
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13 419 disorders, stress, and a history of abuse have emerged as strong predictive factors for
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15 420 PND^{1,7-10,12,29}. PMDD is the severe form of premenstrual syndrome, recently identified as a
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17 421 risk factor for PND³⁰, and NVP has been recognized as the strongest obstetric predictor of
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19 422 PND³¹. Previous studies have also found that women suffering from both MDD and PND had
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21 423 more severe depression and higher incidence of anxiety disorder and childhood trauma
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23 424 than women suffering from MDD alone²¹, and that most severe depression is suffered by
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25 425 women who experience PND both during pregnancy and after delivery¹⁰.
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31 426 This study found high reported rates of non-response to antidepressants in women
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33 427 experiencing PND for both subgroups. Studies of the efficacy of antidepressants for the
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35 428 treatment of PND have been inconclusive³², and, to our knowledge, increased incidence of
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37 429 side effects amongst women with PND has not been previously reported. Further clinical
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39 430 studies of antidepressant efficacy in PND are warranted, as well as efficacy of alternative
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41 431 treatments.
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46 432 Finally, complications of pregnancy and birth were not assessed in this study apart from
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48 433 NVP and gestational diabetes, so it was not possible to fully assess whether perinatal
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50 434 complications may contribute to PND vulnerability⁷.
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436 Conclusions

437 PND is a leading cause of disease for women who give birth, adding to the overall family
438 disease burden and potential cognitive and emotional problems for affected children. This
439 sample of parous women with lifetime major depression found a high rate of PND,
440 particularly for women who experienced an episode of depression before their first
441 pregnancy. There is a compelling literature demonstrating that screening for PND should
442 begin during pregnancy^{26,33}, particularly for women with prior history of depression, which
443 is supported by the finding that the majority of cases in this study experienced PND both
444 before and after delivery. Although women who have been previously diagnosed with major
445 depression are, presumably, under clinical care, it is possible that women may have
446 withdrawn from care if treatment has been ineffective. Standard prenatal care that adopts
447 frequent assessment of depression status provides an opportunity to identify women who
448 might otherwise “slip through the cracks” and ensure that they continue to receive support
449 in finding a successful treatment or in the prevention of relapse²⁶. Our results also support
450 the screening of childhood adverse experiences and PMDD in pregnancy, given that all
451 women with PND in this study had increased odds of a history of emotional abuse and
452 neglect, as well as increased odds of PMDD. Cases were also more likely to have treatment
453 resistant depression, with increased odds of side effects, supporting further clinical
454 investigation of antidepressant efficacy in PND.

455 456 Authors' Contributions

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

460

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473

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51 566 Figure Legends

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54 569 **Fig. 1** Flow chart: Selection of cases and associated comparative group for first analysis

55 570 (prior history of major depression) and second analysis (PND is first experience of major

56 571 depression). Cases met criteria for major depression and had at least one live birth, plus any

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3 572 of: EPDS score ≥ 13 ; a previous diagnosis of PND; or major depression during the perinatal
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5 573 period. Of the comparison groups, NPD_priorDep is a subset of NPD_all. NPD_priorDep was
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7 574 considered to be a more appropriate comparison group for PND_priorDep since members of
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9 575 both these groups experienced an episode of major depression before first pregnancy.

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13 577 **Fig. 2** Length of worst episode of symptomatic PND for priorDep cases, for onset either
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15 578 during pregnancy or after delivery. Episode length is divided into 5 categories, and the Y-axis
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17 579 provides the number of women reporting each category, according to the timing of onset.

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23 581 **Fig. 3** Length of worst episode of symptomatic PND for PND_firstDep cases, for onset either
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25 582 during pregnancy or after delivery. Episode length is divided into 5 categories, and the Y-axis
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27 583 provides the number of women reporting each category, according to the timing of onset.

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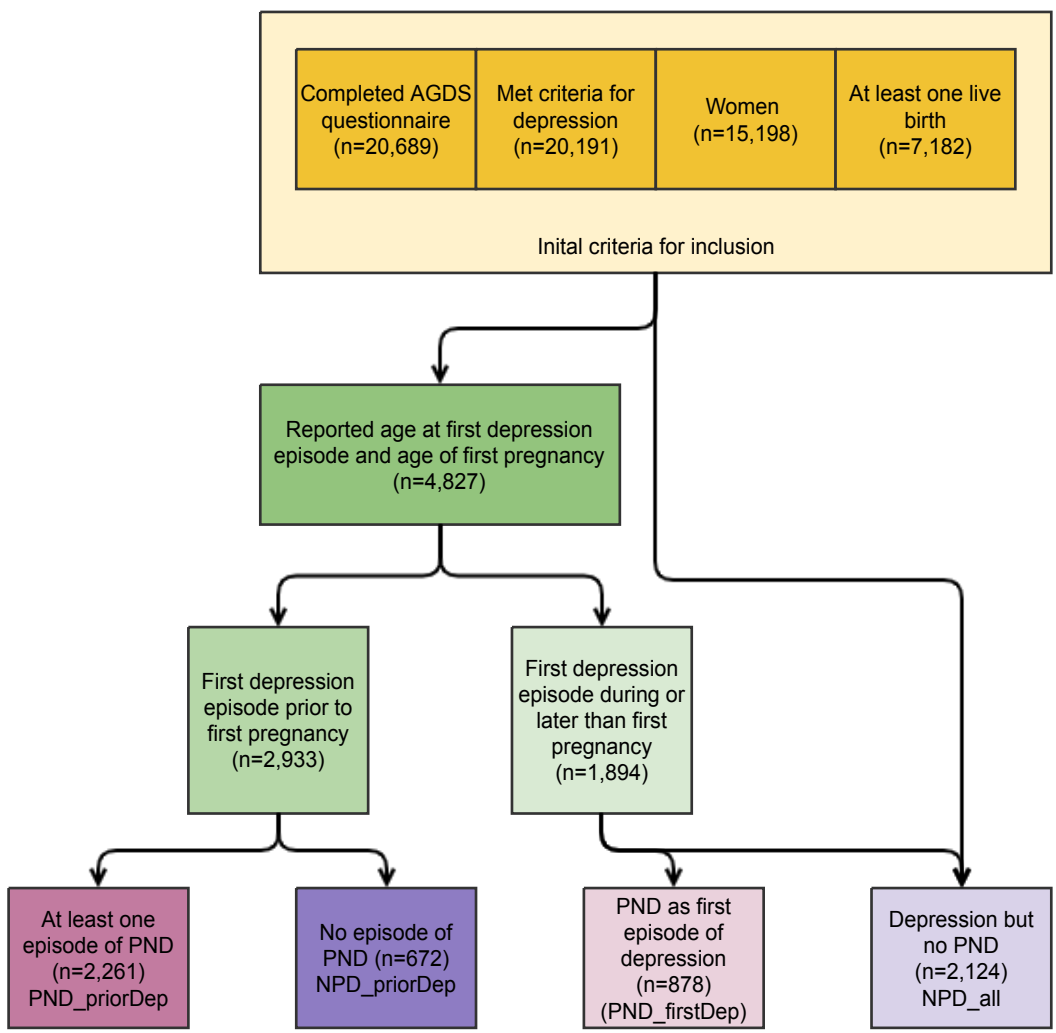
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33 585 **Fig. 4** Severity of worst episode of PND for priorDep and PND_firstDep cases, according to
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35 586 the time of onset of the worst episode. Severity is characterised by interference in everyday
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37 587 life, need for professional help, need for medication, and need to be hospitalised. The Y-axis
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39 588 provides the proportion of each group reporting each variable. Standard errors are included.

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45 590 **Fig. 5** Forest plot of odds ratios with confidence intervals of all variables nominally
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47 591 significantly associated with PND_priorDep cases when compared with NPD_priorDep. Odds
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49 592 ratios for the association of these variables with PND_firstDep cases compared with NPD_all
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52 593 are also included for comparison. Logistic regression, including age of participants as a
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54 594 covariate, was used to calculate odds ratios.

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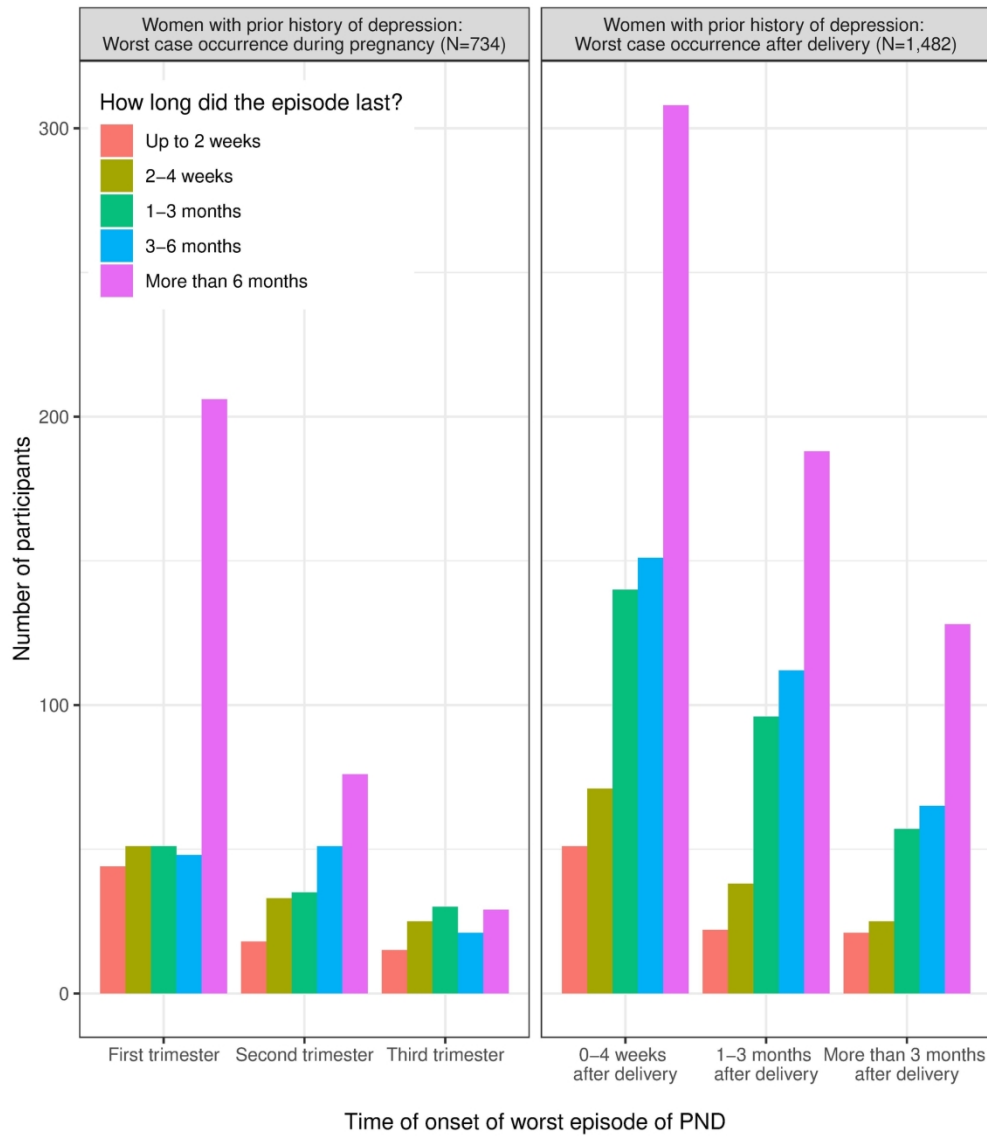


Fig. 2 Length of worst episode of symptomatic PND for priorDep cases, for onset either during pregnancy or after delivery. Episode length is divided into 5 categories, and the Y-axis provides the number of women reporting each category, according to the timing of onset.

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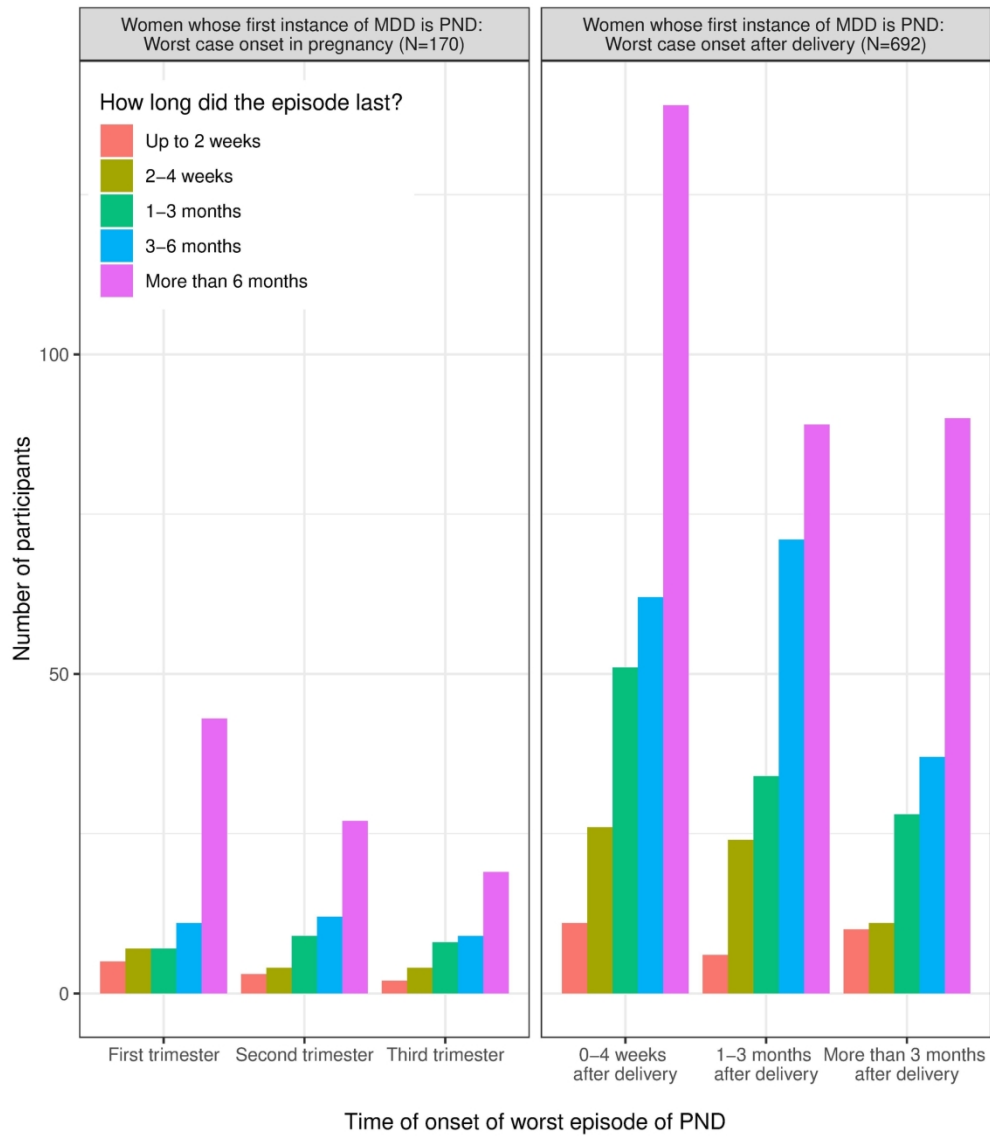


Fig. 3 Length of worst episode of symptomatic PND for PND_firstDep cases, for onset either during pregnancy or after delivery. Episode length is divided into 5 categories, and the Y-axis provides the number of women reporting each category, according to the timing of onset.

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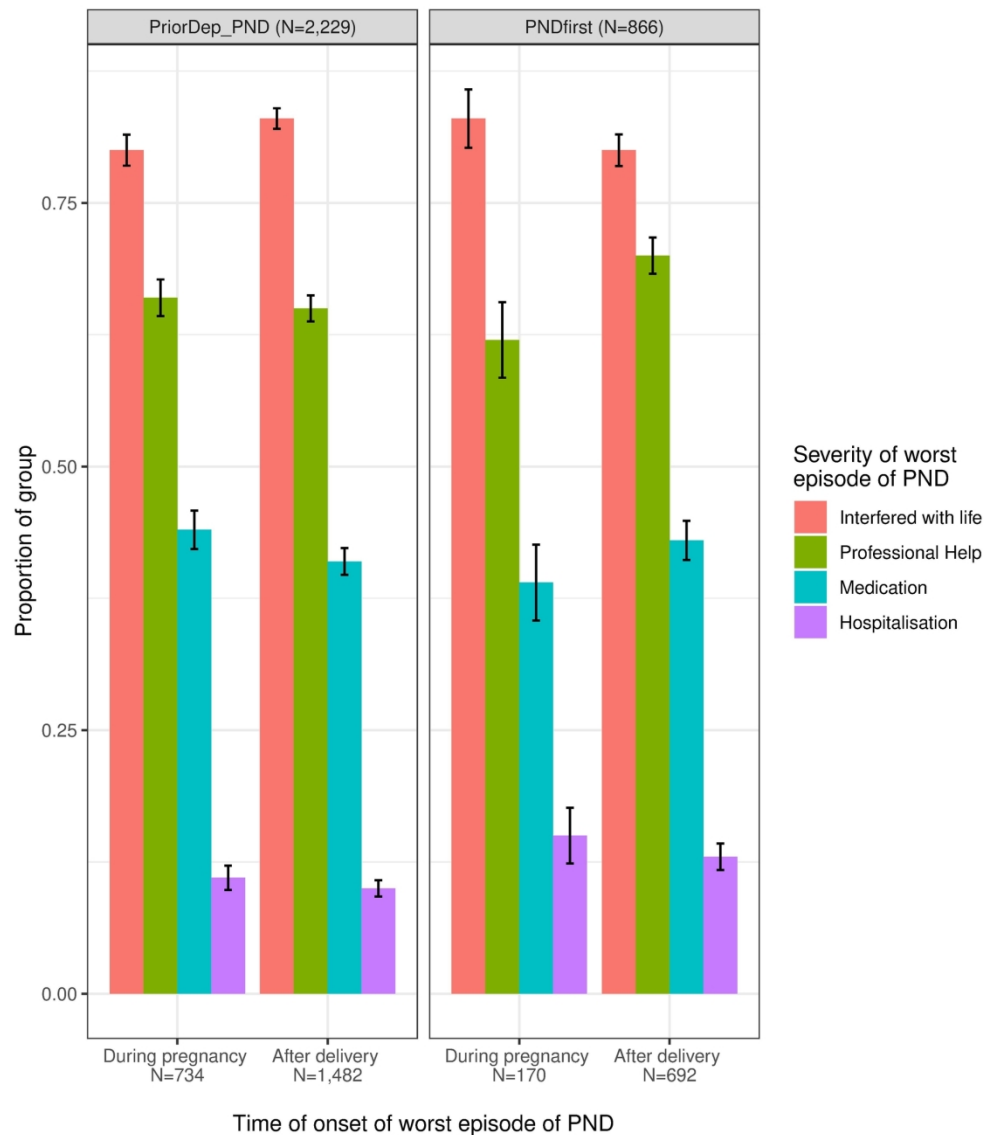


Fig. 4 Severity of worst episode of PND for priorDep and PND_firstDep cases, according to the time of onset of the worst episode. Severity is characterised by interference in everyday life, need for professional help, need for medication, and need to be hospitalised. The Y-axis provides the proportion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

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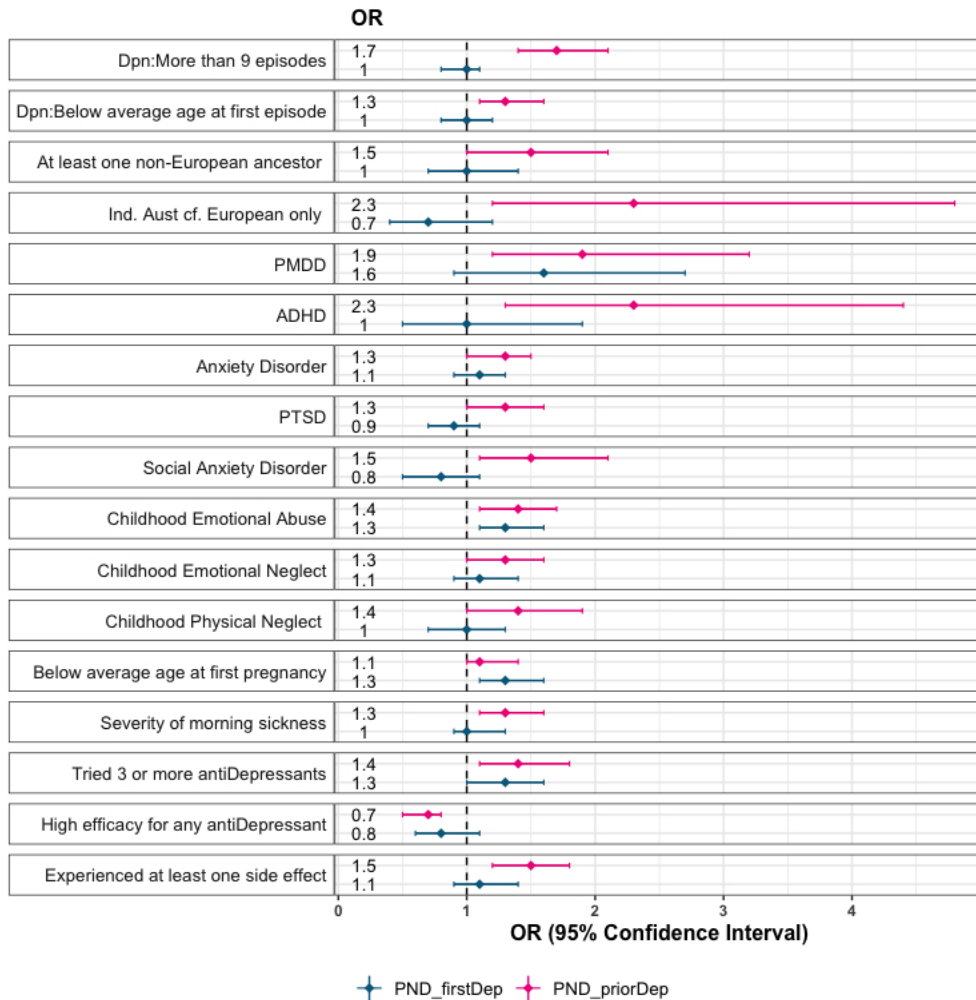


Fig. 5 Forest plot of odds ratios with confidence intervals of all variables nominally significantly associated with PND_priorDep cases when compared with NPD_priorDep. Odds ratios for the association of these variables with PND_firstDep cases compared with NPD_all are also included for comparison. Logistic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

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

3 England, Ireland, Scotland or Wales

4 Australia - not of Aboriginal or Torres Strait Islander descent

5 Australia - of Aboriginal or Torres Strait Islander descent

6 New Zealand - not of Maori descent

7 New Zealand - of Maori descent

8 Northern Europe including Sweden, Norway, Finland and surrounding countries

9 Western Europe including France, Germany, the Netherlands and surrounding countries

10 Southern Europe including Italy, Greece, Spain, Portugal and surrounding countries

11 Eastern Europe including Russia, Poland, Hungary and surrounding countries

12 Middle East including Lebanon, Turkey and surrounding countries

13 Eastern Asia including China, Japan, South Korea, Taiwan and surrounding countries

14 South-East Asia including Thailand, Malaysia, Indonesia, Singapore and surrounding countries

15 South Asia including India, Pakistan, Sri Lanka and surrounding countries

16 Polynesia, Micronesia or Melanesia including Tonga, Fiji, Papua New Guinea and surrounding countries

17 Africa

18 North America - not of First Nations, Native American, Inuit or Métis descent

19 North America - of First Nations, Native American, Inuit or Métis descent

20 Caribbean, Central or South America

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

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

Length of worst episode	PND_r		
	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

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

severity of worst episode of PND, characterised by interference in everyday life, and need for professional help. Occurrence of PND prior to delivery (priorDep) (n=2,261)

Occurrence after delivery (n=1,482)			Total	Occurrence during pregnancy	
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

firstDep

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

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sional help, medication, or hospitalisation.

PND_firstDep (n=878)

icy (n=170)	Occurrence after delivery (n=692)			Total
	0-4 weeks after delivery (n=291)	1-3 months after delivery (n=225)	More than 3 months after delivery (n=176)	
3rd trimester (n=42)				
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

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

Category	Variable	priorDep sample			firstDep sample
		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
Education	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

1				
2	Early menarche	1880	633/184	45/41.9
3	Disruptive NVP	2520	1031/257	53/44.9
4				
5	Polycystic ovarian			
6	syndrome	1960	195/56	13.1/11.9
7	Endometriosis	1969	251/67	16.8/14.1
8	Gestational diabetes	2933	90/18	6.7/4.2
9				
10	Antidepressants			
11	Effectiveness			
12				
13	High efficacy	2790		2792
14	Moderate efficacy	2790		2792
15	Low efficacy	2790		2792
16				
17	Side Effects			
18				
19	Experienced at least one			
20	side effect	2832	1726/438	80/69.4
21				
22	Reduced sexual desire or			
23	function	2832	1062/240	49.2/38
24	Weight gain	2832	968/209	44.8/33.1
25	Dry mouth	2832	775/179	35.9/28.4
26	Nausea	2832	705/140	32.7/22.2
27	Dizzy	2832	651/129	30.2/20.4
28	Drowsy	2832	599/124	27.7/19.7
29	Difficulty Sleeping	2832	574/129	26.6/20.4
30	Sweating	2832	544/116	25.2/18.4
31	Headache	2832	544/93	25.2/14.7
32	Fatigue or Weakness	2832	506/102	23.4/16.2
33	Agitation	2832	450/91	20.8/14.4
34	Increased Anxiety	2832	444/90	20.6/14.3
35	Suicidal Thoughts	2832	399/86	18.5/13.6
36	Shaking	2832	389/80	18/12.7
37	Constipation	2832	262/54	12.1/8.6
38	Diarrhoea	2832	166/34	7.7/5.4
39	Blurred Vision	2832	180/39	8.3/6.2
40	Attempted Suicide	2832	166/29	7.7/4.6
41	Muscle Pain	2832	142/31	6.6/4.9
42	Vomiting	2832	127/19	5.9/3
43	Weight Loss	2832	97/19	4.5/3
44	Runny nose	2832	73/7	3.4/1.1
45	Rash	2832	55/6	2.5/1
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ch variable.

Dep sample

Number

cases/ % cases/
controls 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

1		
2	208/509	38.6/39.8
3	264/569	44.8/43.0
4		
5		
6	55/135	9.1/9.6
7	100/195	16.3/13.8
8	21/48	4.0/3.7
9		
10		
11		
12		
13	168/455	56.6/61.4
14	98/209	33.0/28.2
15	21/50	7.1/6.7
16		
17		
18		
19	561/1222	68.3/62.0
20		
21		
22	324/629	39.5/31.9
23	317/631	38.6/32
24		
25	247/513	30.1/26.0
26	192/346	23.4/17.6
27		
28	160/324	19.5/16.4
29	188/325	22.9/16.5
30		
31	162/350	19.7/17.8
32	162/300	19.7/15.2
33	159/269	19.4/13.6
34		
35	141/275	17.2/14.0
36	125/240	15.2/12.2
37	131/258	16.0/13.1
38		
39	75/199	9.1/10.1
40	97/219	11.8/11.1
41	73/166	8.9/8.4
42		
43	54/103	6.6/5.2
44	39/103	4.8/5.2
45	34/66	4.1/3.3
46	40/90	4.9/4.6
47		
48	32/67	3.9/3.4
49	34/57	4.1/2.9
50		
51	13/29	1.6/1.5
52	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

1				
2	Sexual abuse (childhood)	1.0	0.7-1.3	7.9E-01
3	Sexual abuse (any time)	1.2	1-1.5	6.1E-02
4				
5	Reproductive characteristics, N(tests)=6			
6	Below average age at first pregnancy	1.1	1.0-1.4	1.3E-01
7	Disruptive NVP	1.3	1.1-1.6	6.6E-03
8	Early menarche	1.1	0.9-1.4	3.4E-01
9	Endometrioses	1.2	0.9-1.6	2.1E-01
10	Polycystic ovarian syndrome	0.9	0.7-1.3	7.2E-01
11	Gestational diabetes	1.4	0.8-2.4	2.4E-01
12				
13	Antidepressant use			
14				
15	Tried 3 or more commonly prescribed antidepressant (as a			
16	proportion of women using antidepressants)	1.4	1.1-1.8	1.4E-03
17				
18	Antidepressant efficacy, N(tests)=3			
19				
20	High efficacy for any common antidepressant	0.7	0.5-0.8	5.5E-04
21	Moderate efficacy for any common antidepressant	1.3	1.0-1.7	6.6E-02
22	Low efficacy for any common antidepressant	1.2	0.9-1.6	2.5E-01
23				
24	Antidepressant side effects, N(tests)=23			
25				
26	Experienced at least one side effect	1.5	1.2-1.8	3.0E-04
27	Reduced sexual desire or function	1.4	1.1-1.7	8.0E-04
28	Weight gain	1.5	1.3-1.9	1.9E-05
29	Dry mouth	1.3	1.1-1.7	4.8E-03
30	Nausea	1.4	1.1-1.7	3.8E-03
31	Dizzy	1.4	1.1-1.7	5.8E-03
32	Drowsy	1.4	1.1-1.7	7.5E-03
33	Difficulty Sleeping	1.3	1-1.6	3.7E-02
34	Sweating	1.3	1-1.7	2.3E-02
35	Headache	1.7	1.3-2.1	9.0E-05
36	Fatigue or Weakness	1.4	1.1-1.8	3.6E-03
37	Agitation	1.4	1.1-1.8	1.6E-02
38	Increased Anxiety	1.4	1.1-1.8	2.1E-02
39	Suicidal Thoughts	1.2	0.9-1.6	1.3E-01
40	Shaking	1.2	1-1.6	1.1E-01
41	Constipation	1.5	1.1-2.1	1.1E-02
42	Diarrhoea	1.2	0.8-1.9	2.8E-01
43	Blurred Vision	1.3	0.9-2	1.2E-01
44	Attempt Suicide	1.3	0.8-2	2.8E-01
45	Muscle Pain	1.3	0.9-2	1.9E-01
46	Vomiting	1.4	0.9-2.4	2.0E-01
47	Weight Loss	1.2	0.7-2.1	4.4E-01
48	Runny nose	3.4	1.6-8.2	2.5E-03
49	Rash	2.5	1.1-6.8	3.6E-02
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all variables, including age and number of births as covariates.

n; 672 controls; firstDep sample: 878 cases; 2124 controls; t P in bold		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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2	1.00	0.8	0.6-1.1	2.0E-01	1.00
3	0.42	1.1	0.9-1.3	5.8E-01	1.00
4					
5					
6	0.78	1.3	1.1-1.6	2.9E-03	0.02
7	0.04	1.0	0.9-1.3	7.3E-01	1.00
8					
9	1.00	0.9	0.7-1.1	2.4E-01	1.00
10	1.00	1.3	1.0-1.7	8.7E-02	0.52
11					
12	1.00	0.8	0.6-1.1	2.4E-01	1.00
13	1.00	0.9	0.5-1.5	7.5E-01	1.00
14					
15					
16					
17		1.3	1.0-1.6	8.0E-03	
18					
19					
20	0.00	0.8	0.6-1.1	1.5E-01	0.60
21	1.00	1.3	0.9-1.7	1.5E-01	0.62
22	1.00	1.0	0.6-1.7	9.5E-01	1.00
23					
24					
25					
26		1.1	0.9-1.4	1.9E-01	
27	0.02	1.3	1.1-1.5	1.1E-02	0.25
28					
29	0.00	1.2	1-1.5	2.4E-02	0.56
30	0.11	1.2	1-1.4	1.3E-01	1.00
31	0.09	1.3	1-1.5	3.5E-02	0.81
32	0.13	1.0	0.8-1.3	9.2E-01	1.00
33	0.17	1.4	1.1-1.7	3.9E-03	0.09
34	0.86	1.0	0.8-1.3	8.6E-01	1.00
35	0.53	1.2	1-1.5	8.5E-02	1.00
36	0.00	1.3	1-1.7	1.8E-02	0.41
37	0.08	1.2	0.9-1.5	1.6E-01	1.00
38	0.38	1.2	0.9-1.5	2.5E-01	1.00
39	0.47	1.2	0.9-1.5	2.4E-01	1.00
40	1.00	0.7	0.5-1	5.0E-02	1.00
41	1.00	0.9	0.7-1.2	5.5E-01	1.00
42	0.25	1.0	0.8-1.4	9.1E-01	1.00
43	1.00	1.1	0.8-1.6	5.0E-01	1.00
44	1.00	0.9	0.6-1.3	6.0E-01	1.00
45	1.00	1.0	0.6-1.5	9.6E-01	1.00
46	1.00	1.0	0.7-1.5	9.9E-01	1.00
47	1.00	1.0	0.6-1.6	9.5E-01	1.00
48	1.00	1.3	0.8-2	2.5E-01	1.00
49	0.06	1.0	0.5-2	9.1E-01	1.00
50	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, for

	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

For peer review only

1
2
3 r severity of major depression, using number of symptoms and episodes and age at first episode.
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For peer review only

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

1	Personality Disorder	122/38	8.1/5.7	1.2 0.8-1.8
2				
3	Trauma, N(tests)=7			
4	ChildhoodEmotionalAbuse	657/275	68.2/58.0	1.6 1.3-2.1
5	ChildhoodEmotionalNeglect	585/249	60.3/53.3	1.6 1.2-2
6	ChildhoodPhysicalAbuse	264/107	46.4/41.8	1.0 0.8-1.4
7	Physical abuse (any time)	440/189	42.8/38.2	1.2 1-1.5
8	Physical neglect (childhood)	203/63	20.4/13.1	1.8 1.3-2.4
9	Sexual abuse (childhood)	430/175	74.8/77.1	0.8 0.6-1.2
10	Sexual abuse (any time)	675/284	65.1/56.9	1.3 1-1.6
11				
12	Reproductive characteristics,			
13	N(tests)=7			
14	Above average number of live births	428/138	28.4/20.5	1.9 1.6-2.5
15	Below average age at first pregnancy	822/313	54.5/46.6	1.3 1.1-1.6
16	Disruptive NVP	710/257	55.1/44.9	1.4 1.1-1.7
17	Early menarche	422/184	46/41.9	1.2 0.9-1.5
18	Endometrioses	173/67	17.7/14.1	1.3 0.9-1.8
19	Polycystic ovarian syndrome	135/56	13.9/11.9	1.0 0.7-1.4
20	Gestational diabetes	66/18	7.5/4.2	1.6 0.9-2.8
21				
22	Antidepressant use			
23	Have used common antidepressant	1442/631	95.7/93.9	
24	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
25				
26	Antidepressant efficacy, N(tests)=3			
27	High efficacy for any common antidepressant	1444/631		0.7 0.49-0.85
28	Moderate efficacy for any common antidepressant	1444/631		1.4 1.0-1.8
29	Low efficacy for any common antidepressant	1444/631		1.0 0.7-1.5
30				
31	Antidepressant side effects,			
32	N(tests)=23			
33	Experienced at least one side effect	1189/438	82.3/69.4	1.6 1.3-2.1
34	Reduced sexual desire or function	737/240	51.1/38	1.4 1.2-1.8
35	Weight gain	690/209	47.9/33.1	1.7 1.4-2.1
36	Dry mouth	565/179	39.2/28.4	1.5 1.2-1.9
37	Nausea	518/140	35.9/22.2	1.5 1.2-1.9
38	Dizzy	486/129	33.7/20.4	1.5 1.2-2
39	Drowsy	445/124	30.9/19.7	1.5 1.2-1.9
40	Difficulty Sleeping	421/129	29.2/20.4	1.4 1.1-1.8
41	Sweating	394/116	27.3/18.4	1.4 1.1-1.8
42	Headache	404/93	28/14.7	1.8 1.4-2.4
43	Fatigue or Weakness	370/102	25.7/16.2	1.6 1.2-2.1

1				
2	Agitation	340/91	23.6/14.4	1.6 1.2-2.1
3	Increased Anxiety	338/90	23.4/14.3	1.6 1.2-2.1
4	Suicidal Thoughts	312/86	21.6/13.6	1.4 1.1-1.9
5	Shaking	306/80	21.2/12.7	1.5 1.1-2
6	Constipation	190/54	13.2/8.6	1.6 1.2-2.3
7	Diarrhoea	129/34	8.9/5.4	1.4 0.9-2.1
8	Blurred Vision	140/39	9.7/6.2	1.6 1.1-2.4
9	Attempt Suicide	143/29	9.9/4.6	1.7 1.1-2.6
10	Muscle Pain	110/31	7.6/4.9	1.6 1-2.4
11	Vomiting	102/19	7.1/3	1.5 0.9-2.7
12	Weight Loss	68/19	4.7/3	1.2 0.7-2.1
13	Runny nose	58/7	4/1.1	4.0 1.9-9.9
14	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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2	3.6E-01	1.00	21/68	4.1/3.2	0.9 0.5-1.5	7.4E-01
3						
4	4.8E-05	0.00	200/702	58.7/49.8	1.5 1.1-1.9	2.7E-03
5	3.3E-04	0.00	178/654	52.8/47.1	1.3 1-1.7	2.8E-02
6	8.0E-01	1.00	61/228	38.1/37.1	1.0 0.7-1.4	8.6E-01
7	8.6E-02	0.60	122/459	34.2/31.1	1.1 0.9-1.4	4.5E-01
8	6.3E-04	0.00	47/171	13.3/11.9	1.1 0.8-1.6	5.6E-01
9	3.0E-01	1.00	118/449	73.8/75.8	0.8 0.5-1.2	3.0E-01
10	2.5E-02	0.17	202/746	55.6/49.9	1.2 1-1.5	1.0E-01
11						
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17	1.4E-08	0.00	201/578	39.4/27.2	2.1 1.7-2.6	1.9E-12
18	2.5E-03	0.02	248/823	62.6/53.9	1.6 1.3-2.0	1.2E-04
19	1.7E-03	0.01	166/569	48.1/43.0	1.2 0.9-1.5	1.9E-01
20	1.3E-01	0.92	126/509	39.4/39.8	0.9 0.7-1.2	4.0E-01
21	1.3E-01	0.91	60/195	16.8/13.8	1.3 0.9-1.8	9.9E-02
22	8.3E-01	5.81	135/34	9.7/9.6	0.8 0.5-1.3	4.3E-01
23	1.0E-01	0.70	13/48	4.1/3.7	0.9 0.5-1.7	7.9E-01
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32	1.2E-05		98/363	20.6/18.4	1.2 1.0-1.5	1.1E-01
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36	1.8E-03	0.01	475/1971		0.96 0.7-1.3	7.4E-01
37						
38	3.4E-02	0.10	475/1971		1.1 0.8-1.4	5.1E-01
39						
40	8.8E-01	1.00	475/1971		0.87 0.6-1.2	4.5E-01
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46	4.8E-05		334/1222	68.2/62.0	1.1 0.9-1.4	2.9E-01
47	6.7E-04	0.02	187/629	39.4/31.9	1.3 1-1.6	4.7E-02
48	1.3E-06	0.00	180/631	37.9/32.0	1.2 1-1.5	1.1E-01
49	2.3E-04	0.01	135/513	28.4/26.0	1.1 0.8-1.4	5.3E-01
50	2.6E-04	0.01	116/346	24.4/17.6	1.3 1-1.7	2.7E-02
51	3.2E-04	0.01	100/324	21.1/16.4	1.1 0.8-1.4	4.6E-01
52	9.0E-04	0.02	114/325	24.0/16.5	1.5 1.1-1.9	4.1E-03
53	3.1E-03	0.07	91/350	19.2/17.8	1.0 0.7-1.3	7.5E-01
54	4.4E-03	0.10	97/300	20.4/15.2	1.3 1-1.7	5.7E-02
55	4.5E-06	0.00	95/269	20.0/13.6	1.4 1.1-1.8	1.8E-02
56	3.0E-04	0.01	89/275	18.7/14	1.3 1-1.7	5.2E-02
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2	1.2E-03	0.03	82/240	17.3/12.2	1.4 1-1.8	4.7E-02
3	1.5E-03	0.03	79/258	16.6/13.1	1.3 0.9-1.7	1.1E-01
4	1.1E-02	0.25	44/199	9.3/10.1	0.7 0.5-1.1	1.2E-01
5	4.7E-03	0.11	58/219	12.2/11.1	0.9 0.7-1.3	7.4E-01
6	4.8E-03	0.11	43/166	9.1/8.4	1.1 0.7-1.5	7.4E-01
7	1.3E-01	1.00	31/103	6.5/5.2	1.2 0.7-1.8	5.1E-01
8	1.6E-02	0.37	33/103	6.9/5.2	1.4 0.9-2.2	1.0E-01
9	2.3E-02	0.54	18/66	3.8/3.3	0.8 0.4-1.4	4.5E-01
10	4.5E-02	1.00	26/90	5.7/4.6	1.1 0.7-1.8	5.8E-01
11	1.1E-01	1.00	19/67	4.0/3.4	1.1 0.6-1.8	8.4E-01
12	5.4E-01	1.00	17/57	3.6/2.9	1.1 0.6-1.9	7.4E-01
13	7.3E-04	0.02	8/29	1.7/1.5	1.1 0.4-2.3	8.5E-01
14	3.0E-02	0.68	7/31	1.5/1.6	0.9 0.4-2	8.1E-01
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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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3 Ancestry analysis (self-report of ancestry of great-great-grandparents assigned to 18
4 geographical regions, Supplementary Table S2) considered associations between rates of
5 endorsing PND in women with ancestors only from Europe, compared to women with at
6 least one non-European ancestor. Further analysis compared the rate of PND in those
7 reporting Australian Indigenous ancestry to those of only European ancestry.
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16 Clinical measures: Participants were asked to report any previous diagnoses from a total list
17 of 19 psychiatric disorders, of which 13, with frequencies > 3% for all women with PND,
18 were analyzed in this study (Supplementary Table S3). History of childhood trauma was
19 assessed using responses to three questions that asked whether participants had been
20 emotionally abused, emotionally neglected, or physically neglected during childhood.
21 Additionally, participants were asked whether they had experienced physical or sexual
22 assault or unwanted sexual experience at any time in their life, as well as their age at that
23 time. For these questions, an age less than 16 was used to designate a childhood
24 experience.
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40 Reproductive measures: Reproductive measures included age at menarche, parity (number
41 of live births), age at first birth, presence and severity of nausea and vomiting during
42 pregnancy (NVP), and diagnosis of endometriosis or polycystic ovarian syndrome. Severity
43 of NVP was measured using a scale adapted from Zhang et al. (2011). Gestational diabetes
44 was measured as part of a general question about experience of medical conditions,
45 followed by a request to specify the type of diabetes (if diabetes was selected).
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55 Effects of antidepressants: Efficacy of the top ten most commonly prescribed
56 antidepressants in Australia was assessed by asking how well each antidepressant a
57 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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4 Thinking about what you know of your family history, which of the following best describes
5 the geographic regions where your ancestors (i.e. your great-great-grandparents) come
6 from? You may select as many choices as you need

- 7 • England, Ireland, Scotland or Wales
- 8 • Australia - not of Aboriginal or Torres Strait Islander descent
- 9 • Australia - of Aboriginal or Torres Strait Islander descent
- 10 • New Zealand - not of Maori descent
- 11 • New Zealand - of Maori descent
- 12 • Northern Europe including Sweden, Norway, Finland and surrounding countries
- 13 • Western Europe including France, Germany, the Netherlands and surrounding
- 14 countries
- 15 • Southern Europe including Italy, Greece, Spain, Portugal and surrounding countries
- 16 • Eastern Europe including Russia, Poland, Hungary and surrounding countries
- 17 • Middle East including Lebanon, Turkey and surrounding countries
- 18 • Eastern Asia including China, Japan, South Korea, North Korea, Taiwan and Hong
- 19 Kong
- 20 • South-East Asia including Thailand, Malaysia, Indonesia, Singapore and surrounding
- 21 countries
- 22 • South Asia including India, Pakistan, Sri Lanka and surrounding countries
- 23 • Polynesia, Micronesia or Melanesia including Tonga, Fiji, Papua New Guinea and
- 24 surrounding countries
- 25 • Africa
- 26 • North America - not of First Nations, Native American, Inuit or Métis descent
- 27 • North America - of First Nations, Native American, Inuit or Métis descent
- 28 • Caribbean, Central or South America
- 29 • Don't know

36 37 *Comorbidities*

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

- 39 • Depression
 - 40 • Bipolar disorder
 - 41 • Premenstrual dysphoric mood disorder
 - 42 • Schizophrenia
 - 43 • Anorexia nervosa
 - 44 • Bulimia
 - 45 • Attention-deficit/hyperactivity disorder (ADD/ADHD)
 - 46 • Autism spectrum disorder (Autism, Asperger's disorder)
 - 47 • Tourette's disorder
 - 48 • Anxiety disorder (Generalised anxiety disorder)
 - 49 • Panic disorder
 - 50 • Obsessive compulsive disorder
 - 51 • Hoarding disorder
 - 52 • Posttraumatic stress disorder (PTSD)
 - 53 • Specific phobia (e.g. animals, heights, storms, blood / injection / injury, flying,
 - 54 enclosed spaces)
 - 55 • 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.

- 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?

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.

- 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

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) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i> —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 <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants	7-8
		(b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> —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) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed <i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed <i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy	
		(e) Describe any sensitivity analyses	12

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Continued on next page

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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 (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	12-14
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	12-15
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time <i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure <i>Cross-sectional study</i> —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 (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	15-17
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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Lifetime prevalence and correlates of perinatal depression in the Australian Genetics of Depression Study

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2

28 Abstract

29 Objectives

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

34 Design and Setting

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

39 Participants

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

43 Primary and secondary outcome measures

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

3

47 Results

48 The prevalence of PND among parous women was 70%. The majority of women reported at
49 least one perinatal episode with symptoms both antenatally and postnatally. Of women
50 who experienced depression prior to first pregnancy, PND cases were significantly more
51 likely to report more episodes of depression (OR=1.1 per additional depression episode,
52 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
53 nausea during pregnancy (OR=1.3, CI=[1.1-1.6], P=6.6 x 10⁻⁰³) and emotional abuse (OR=1.4,
54 CI=[1.1-1.7], P=5.3 x 10⁻⁰³).

55 Conclusions

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

61 Strengths and limitations of this study

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

4

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

73

74 **Funding Statement**

75 This work was primarily funded by National Health and Medical Research Council (NHMRC)
76 of Australia grant 1086683, and further supported by NHMRC grants 1145645, 1078901 and
77 1087889. JK is supported by a UQ Research Training Program scholarship. LC-C is supported
78 by a QIMR Berghofer Institute fellowship.

79 **Competing interests**

80 No conflict of interest has been reported

81 **Availability of data and material**

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

84 **Ethics approval and consent to participate**

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

90 Patient consent for participation in the study was obtained.

91 **Introduction**

92

93 **Background**

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

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3 97 that of the postpartum community population³. Estimated economic costs of PND in the UK,
4
5 98 of which 72% are for ongoing care of the child⁴ reflect findings that children of women with
6
7
8 99 persistent and severe PND are at increased risk of adverse outcomes^{1,5} .
9

10
11 100 Peripartum depression is classified diagnostically in the Diagnostic and Statistical Manual of
12
13
14 101 mental disorders 5th Edition (DSM 5)⁶ as a subtype of Major Depressive Disorder. The
15
16 102 classification of the disorder as peripartum is a change from the 4th edition of the manual
17
18 103 where the disorder was called postpartum depression. The change in nomenclature reflects
19
20 104 the increased recognition that symptoms can begin during pregnancy.
21
22

23
24 105 There is ongoing debate as to whether PND is a depressive episode that happens to coincide
25
26 106 with the perinatal period⁷; or a distinct disorder with a partially overlapping set of risk
27
28 107 factors, stimulated by changes occurring during pregnancy and confined to the perinatal
29
30 108 period⁸.
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35 109 A history of affective disorders is the strongest known risk factor for PND⁹ supporting the
36
37 110 classification of PND as a subtype of depression. However, many women with a prior history
38
39 111 of depression do not report symptoms in the perinatal period and for others, PND is the first
40
41 112 reported episode. This suggests the possibility that the profile of risk factors associated with
42
43 113 depression in the perinatal period is at least partially distinct from depression outside of the
44
45 114 perinatal period. Genetic studies have found evidence for unique genetic contributions to
46
47 115 PND compared to MDD^{10,11}, suggesting heterogeneity in risk factors. One suggestion is that
48
49 116 PND is itself heterogenous^{12,13}, with clinical subtypes differentiated by timing and severity of
50
51 117 symptoms, perinatal complications, and history of psychiatric disorders. However, a
52
53 118 comprehensive investigation of the characteristics of women with PND, with and without a
54
55 119 prior psychiatric history, has not been attempted.
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3 120 A number of risk factors for PND have been identified including adverse childhood
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5 121 experiences, stress, low income and low social support . Other risk factors may also increase
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7
8 122 PND vulnerability. Possible psychosocial factors include stress and history of abuse¹⁸ whilst
9
10 123 biological factors include changes that accompany pregnancy, such as hormonal fluctuations
11
12
13 124 and increased inflammation^{8,19}.

125 .

126 Objectives

127 Using the Australian Genetics of Depression Study (AGDS), a large cohort study established
128 in 2016 to investigate genetic risk factors and heterogeneity in depression with over 20,000
129 participants self-reporting a depression diagnosis²², we first sought to evaluate the
130 prevalence, timing and duration of symptoms of perinatal depression and anxiety symptoms
131 in women, stratified by whether they had a history of depression prior to their pregnancy.
132 We then sought to evaluate differences in psychosocial characteristics of women with MDD
133 who report symptoms in the perinatal period and those who do not.

134 Method

135 Study Design

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

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3 140 psychiatric disorders, or as first onset depression, both PND groups were compared with
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6 141 their comparison group of NPD cases, across a range of variables.
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12 143 **Setting: The Australian Genetics of Depression Study**

15 144 The AGDS is a large ongoing case cohort study of the etiology of depression that recruited
16
17 145 20,689 participants (aged between 28 and 58 years; 75% female) during 2016-2018. The
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20 146 analyses conducted here include participants enrolled prior to the initial data freeze in
21
22 147 September 2018. Recruitment was primarily through a media campaign (86%) which
23
24
25 148 requested participation from anyone with a depression diagnosis from a health
26
27 149 professional, as well as specific invitations to women who had responded to a mobile phone
28
29
30 150 app focused on PND, originally developed in the USA²³, and also ascertainment through the
31
32 151 Pharmaceutical Benefits Scheme prescription records for antidepressants,. For further
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34
35 152 details of the recruitment strategy, see Byrne, et al.²².

36
37
38 153 AGDS participants were invited to complete an online questionnaire. A compulsory core
39
40 154 module assessed self-reported psychiatric history, the Composite Interview Diagnostic
41
42
43 155 Interview Short Form (CIDI-SF) which assesses the Diagnostic and Statistical Manual of
44
45 156 Mental Disorders Fifth Edition (DSM 5) criteria for MDD⁹, and experiences of using
46
47
48 157 commonly prescribed antidepressants. Women reporting symptoms of depression during
49
50 158 pregnancy or up to 6 months following childbirth were asked to complete the lifetime
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52
53 159 Edinburgh Postnatal Depression Scale (EPDS)²⁴, an adaptation of the standard EPDS²⁵ that
54
55 160 assesses lifetime PND episodes. They were also asked whether symptoms of depression
56
57
58 161 occurred during pregnancy, after giving birth, or both, the age at which they experienced
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60 162 their worst episode of PND, its severity and duration. For all AGDS participants, further

8

163 voluntary modules assessed history of psychiatric health conditions and stressful life events.

164 The AGDS protocol was approved by the Human Research Ethics Committee of QIMR

165 Berghofer Institute for Medical Research.

166

167 Participants: PND cases and comparison groups

168 Participants with major depression either met DSM 5 criteria for MDD, or had been

169 previously diagnosed with depression by a health professional. PND cases were defined as

170 women reporting at least one live birth who had been previously diagnosed with PND by a

171 health professional, or who scored ≥ 13 on the lifetime EPDS, or who met criteria for major

172 depression and reported at least one perinatal episode.

173 We identified two groups of PND cases, based on whether they had a history of MDD prior

174 to their first PND episode. Parous participants who reported an episode of depression

175 before their first pregnancy and met PND criteria (PND_priorDep) were compared with

176 parous participants who reported an episode of depression before their first pregnancy, but

177 did not experience any depression associated with childbirth (NPD_priorDep). The second

178 group comprised participants whose first episode of depression occurred during the

179 perinatal period (PND_firstDep) group. Fig. 1 and Supplementary Table S1 illustrate sample

180 selection. Further details are provided in Supplementary Methods.

181 Figure 1 about here

182

183 Variables

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

193

194 Descriptive measures for cases

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

200

201 Comparative measures

1¹

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

216 **Potential sources of bias**

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

1

225 overestimation of PND case status²⁸, although O'Connor et.al.²⁹ reported a sensitivity of 0.8
226 for the EPDS in identifying MDD with a cut-off score ≥ 13 , and a specificity of 0.9. The
227 lifetime EPDS is a modification of this scale which has demonstrated internal consistency²⁴.

228

229 Statistical Analysis

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

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

238 All analyses were conducted using R (version 3.6.0). Figures were generated using ggplot2³⁰
239 and Gliffy software³¹.

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241 Public and Patient Involvement

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

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4 245 **Results**5
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11 247 **Lifetime prevalence of depression during the peripartum period**

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15 248 A total of 15,198 female participants (median age of 39) in the Australian Genetics of
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17 249 Depression Study, met DSM 5 criteria for MDD. Of these, 7,182 (47%) reported at least one
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20 250 live birth. The prevalence of PND among parous women was 70%. A total of 2,933 women
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22 251 reported at least one depressive episode prior to their first pregnancy. Of these, 2,261 (77%)
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24 252 screened positive for PND
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28 253 whilst the remaining 672 women with no PND episodes (23%) formed their comparison
29
30 254 group (NPD_priorDep). A total of 878 out of 5,058 women reported that their first episode
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32 255 of depression occurred during pregnancy or within the first 6 months after delivery
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34 256 (PND_firstDep), Of women who met criteria for PND, 1,919 were unable to be categorized
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36 257 as PND_priorDep or PND_firstDep and were lost to further analysis. Fig. 1 and
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40 258 Supplementary Table S1 provide details of the sample selection process.
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42
43
44 259 Table 1 shows the reported time of onset of symptoms (for any PND episode) for both case
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46 260 groups (only during pregnancy, only after delivery, or both before and after delivery). The
47
48 261 majority of women with PND reported experiencing symptoms both ante- and postnatally.
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51 262 Onset of symptoms in the postnatal period was more commonly reported by women
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54 263 without a prior history of MDD.
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265 Table 1. Reported timing of symptoms of perinatal depression among women with PND.

266 Results are shown for all those meeting PND criteria and separately for those with a prior
 267 history of major depression (PND_priorDep) and those whose first onset of major
 268 depression was perinatal (PND_firstDep).

269

	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%)

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

275 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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277 The most reported time of symptom onset during the worst episode of PND is shown in
 278 Table 3. Regardless of whether women had a prior history of depression, the most
 279 commonly reported time of onset for the worst episode was 0-4 weeks postpartum.
 280 Women with a prior history of depression were more likely to report that the worst episode
 281 began during pregnancy, specifically during the first trimester.

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283

284 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)

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287 Clinical and psychosocial risk factors for PND in parous women

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

290

291 **Clinical and psychosocial risk factors for PND in parous women with a history of** 292 **depression.**

293 We investigated which risk factors are associated with PND in women with a previous
 294 history of depression. Age (OR [PND case status]=0.97 per additional year of age, CI=[0.96-
 295 0.98], $P=2.3 \times 10^{-17}$), and number of births (OR [PND case status]=1.3 per additional birth,
 296 CI=[1.2-1.4], $P=4.7 \times 10^{-07}$) were significantly associated with PND. Both age and number of

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3 297 births were included as covariates in subsequent analyses, which were also adjusted for
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6 298 multiple testing.

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9 299 Key risk factors for PND identified were age at onset of depression (OR = 0.99 per year later
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11 300 of onset, $p = 7.6 \times 10^{-06}$), non-European ancestry (OR = 1.5, $p = 0.03$), specifically Australian
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13 301 Indigenous ancestry (OR = 2.5 [1.1-4.5], $p = 0.02$), emotional abuse in childhood (OR=1.4,
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16 302 [1.1-1.7], $P=0.006$) and severe nausea during pregnancy (OR = 1.3 [1.1-1.6], $P=0.007$). Being
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18 303 diagnosed with any psychiatric comorbidity was also associated with risk of PND (OR = 1.2 ,
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21 304 $p = 0.02$). The most significant individual comorbidity was ADHD (OR = 2.3 [1.3-4.4], $p =$
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23 305 0.009). This association did not pass the Bonferroni corrected significance threshold,
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25 306 however this is a conservative correction given the correlation between tests. Full details of
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27
28 307 all results are provided in Table S6.

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32 308 Screening positive for PND was associated with an increased likelihood of reporting more
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34 309 than 9 episodes of depression (OR = 1.7 [1.4-2.1], $p = 1.8 \times 10^{-08}$) and decreased likelihood of
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36 310 reporting high efficacy of any antidepressant (OR = 0.7 [0.5-0.8], $p = 5.5 \times 10^{-04}$).

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314 Discussion

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

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3 317 depression among women with major depression. We found a very high prevalence of
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5 318 perinatal symptoms in women with major depression, with higher likelihood of onset of
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8 319 symptoms during pregnancy in women with a prior history, supporting the need for
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10 320 screening and close monitoring of symptoms in women with a history of depression.
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13 321 Furthermore, our results highlight that perinatal depression is associated with a more
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15 322 chronic course of depression, with earlier onset, more episodes and poorer reported
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18 323 efficacy of antidepressants. The finding of a high prevalence of depression in women agrees
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20 324 with previous findings from a study in the Netherlands that found a prevalence of 40% in
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23 325 women with a prior history of MDD²⁴. The prevalence in our study is higher and this likely
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25 326 reflects that this is a sample enriched for participants with severe depression²². While
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28 327 assessment of severity relies on the individual's self-report, previous analyses in the
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30 328 Australian Genetics of Depression Study have shown that those reporting more severe
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33 329 depression have higher genetic risk to depression³², and the association between perinatal
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35 330 depression and more chronic course is also supported by genetic data.

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38 331 Another key finding was that women without a prior history were more likely to
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41 332 report symptom onset in the postnatal period and were more likely to report longer
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44 333 duration of symptoms. This may reflect that women with a prior history may have had an
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46 334 ongoing episode of depression when they became pregnant and we were unable to
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49 335 distinguish whether symptoms had started prior to the first trimester. Furthermore, women
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51 336 with a prior history may have been more likely to be monitored by clinicians and have a
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53 337 treatment plan in place, leading to reduced length of symptoms.

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56 338 Participants with a prior history of depression who report having at least one
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59 339 ancestor of Aboriginal or Torres Strait Islander (ATSI) descent were more likely to meet the
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3 340 criteria for PND. There have been few studies conducted on perinatal mental health among
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5 341 Aboriginal and Torres Strait Islanders³⁴. One study conducted on a representative
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7 342 population sample in New South Wales did not find an increased prevalence of postnatal
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9 343 depressive symptoms among women of ATSI descent. However, the study did identify
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11 344 several risk factors that commonly affect people of ATSI descent such as placement in public
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13 345 housing, financial hardship, and poor self-rated health as being associated. Many other risk
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15 346 factors such as smoking and obstetric complications are higher in the ATSI population than
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17 347 non-Indigenous Australians and depression and anxiety are twice as common³⁵. Results
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19 348 from the Australian Postnatal Screening Program found that the rate of antenatal
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21 349 depression in ATSI women was 18.9% compared to 8.9% in non-Indigenous Australians and
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23 350 6.3% had postnatal depression compared to 2.7% in non-Indigenous women^{36,37}. The
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25 351 findings of our study further highlight the increased risk of PND in ATSI women and the need
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27 352 for better screening and treatment in the Indigenous population.
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36 353 Another key finding was the association between severe nausea during pregnancy
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38 354 and PND. Nausea and vomiting during pregnancy of varying severity affects approximately
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40 355 69% of pregnant women. A meta-analysis evaluating the association between the severe
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42 356 form of morning sickness – hyperemesis gravidarum (HG) – and depression and anxiety
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44 357 found significant increased depression and anxiety scores in women with HG³⁸. A recent
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46 358 longitudinal study in the United Kingdom found that 49% of women with HG had probable
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48 359 depression antenatally and 29% had probable postnatal depression. In conjunction with our
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50 360 findings, these results suggest that women with severe nausea during pregnancy are at high
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52 361 risk of depression and may need to be referred for treatment of PND³⁹.
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3 362 Lastly, we identified psychiatric comorbidities, particularly premenstrual dysphoric
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6 363 disorder and ADHD, and emotional abuse in childhood as being associated with PND. There
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8 364 is an extensive literature on the association between trauma and PND⁴⁰⁻⁴³ and our study
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10 365 shows that even among those with a prior history of MDD, trauma is a risk factor for PND,
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13 366 consistent with previous reports²⁴. Several studies have evaluated the association between
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15 367 ADHD in children and perinatal risk factors including PND in mothers⁴⁴⁻⁴⁶. However, few
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17 368 studies have considered that mothers with PND may also have ADHD symptoms and our
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19 369 results suggest that this is an important consideration. Recent studies that have attempted
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21 370 to account for genetic transmission from mother to child have found that much of the
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23 371 association between PND and ADHD in the offspring is accounted for by shared genetic risk
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25 372 factors between PND and ADHD^{47,48}.

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34 374 The results of this study should be considered in the light of several limitations. The main
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36 375 limitation of this study is that it is based on an online questionnaire, with no personalized
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38 376 interviews or clinical reports to provide supporting evidence for self-reported data. Answers
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40 377 were based on total life experience, including, but not exclusive to, the perinatal period.
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42 378 Furthermore, the AGDS is a cross-sectional study. Its strength lies in its sample size, but,
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44 379 unlike a longitudinal study, it provides no information with respect to timing of variables
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46 380 significantly associated with PND (with the exception of childhood adverse experiences), so
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48 381 no inference can be made pertaining to cause and effect. In addition, because information
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50 382 only about the worst episode was ascertained, it was not possible to identify all cases where
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52 383 the perinatal episode was the first episode of depression which may have biased the results.
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384 No information on the use of mood stabilisers which would be indicative of mixed episodes
385 was collected.

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

396 Finally, complications of pregnancy and birth were not assessed in this study apart from
397 NVP and gestational diabetes, so it was not possible to fully assess whether perinatal
398 complications may contribute to PND vulnerability¹⁴.

399

400 Conclusions

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

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3 405 pregnancy. There is a compelling literature demonstrating that screening for PND should
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5 406 begin during pregnancy^{29,53}, particularly for women with prior history of depression, which
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8 407 is supported by the finding that the majority of cases in this study experienced PND both
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10 408 before and after delivery. Although women who have been previously diagnosed with major
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13 409 depression are, presumably, under clinical care, it is possible that women may have
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15 410 withdrawn from care if treatment has been ineffective. Standard prenatal care that adopts
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18 411 frequent assessment of depression status provides an opportunity to identify women who
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20 412 might otherwise “slip through the cracks” and ensure that they continue to receive support
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23 413 in finding a successful treatment or in the prevention of relapse²⁹. Cases were also more
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25 414 likely to have treatment resistant depression, with increased odds of side effects,
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27
28 415 supporting further clinical investigation of antidepressant efficacy in PND.

416

417 **Authors' Contributions**

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36 418 EMB, JK, NGM, NRW, designed the study. SEM, LCC, SMB, JM, EB, JG, TM, IBH provided
37
38 419 intellectual input into the content. JK analysed the data. JK, EMB, NRW, and NGM drafted
39
40
41 420 the manuscript. SEM, LCC, SMB, JM EB, JG, TM, IBH, revised the article for intellectual
42
43 421 content. All authors have read and approve of the final version.

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47
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2

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14
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587 Figure Legends

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589
590 **Fig. 1** Flow chart: Selection of cases and associated comparative group for first analysis
591 (prior history of major depression) and second analysis (PND is first experience of major
592 depression). Cases met criteria for major depression and had at least one live birth, plus any
593 of: EPDS score ≥ 13 ; a previous diagnosis of PND; or major depression during the perinatal
594 period.
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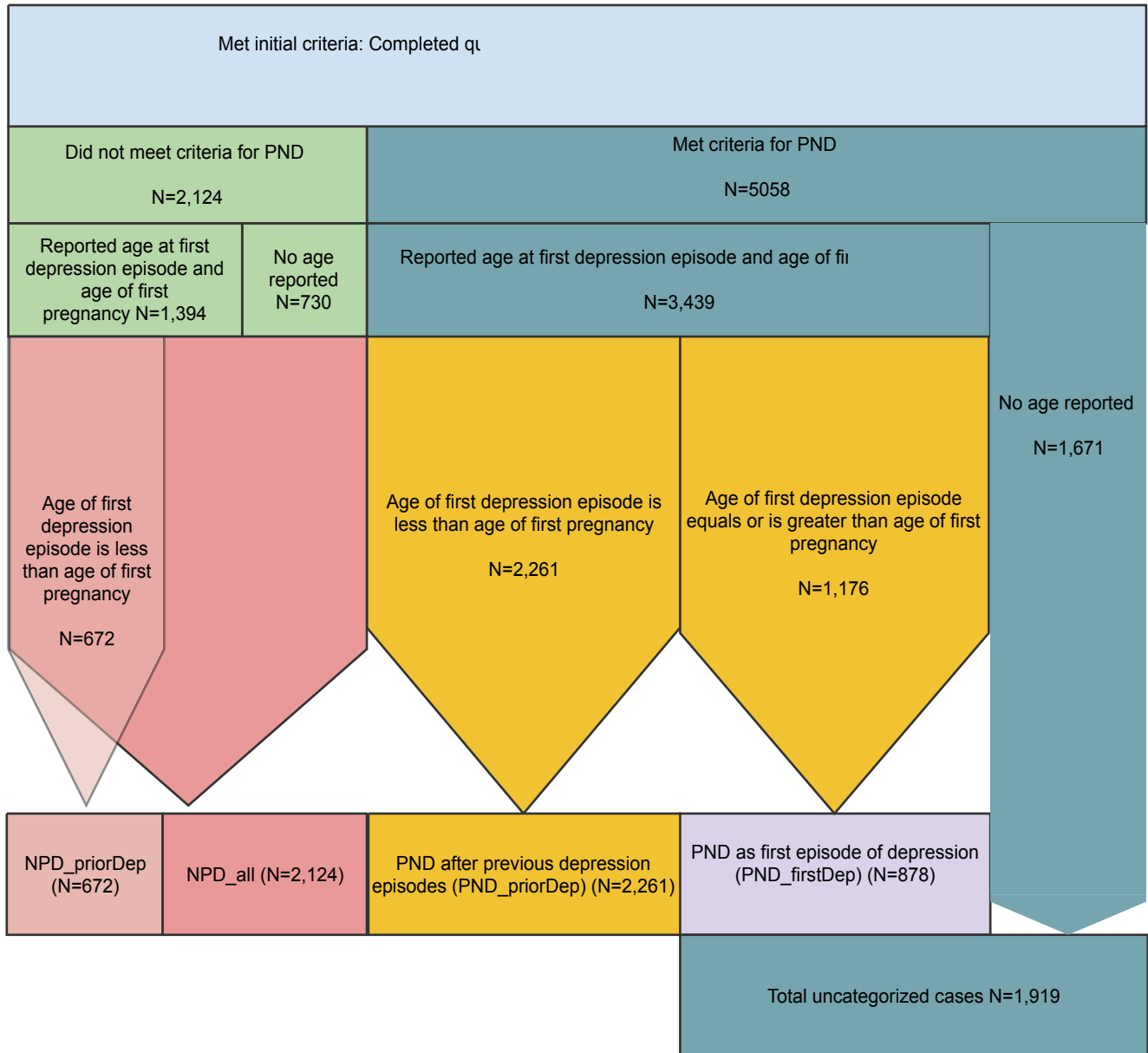
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Supplementary Methods

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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2
3 endorsing PND in women with ancestors only from Europe, compared to women with at
4
5 least one non-European ancestor. Further analysis compared the rate of PND in those
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7 reporting Australian Indigenous ancestry to those of only European ancestry.
8
9

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11 Clinical measures: Participants were asked to report any previous diagnoses from a total list
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13 of 19 psychiatric disorders, of which 13, with frequencies > 3% for all women with PND,
14
15 were analyzed in this study (Supplementary Table S3). History of childhood trauma was
16
17 assessed using responses to three questions that asked whether participants had been
18
19 emotionally abused, emotionally neglected, or physically neglected during childhood.
20
21 Additionally, participants were asked whether they had experienced physical or sexual
22
23 assault or unwanted sexual experience at any time in their life, as well as their age at that
24
25 time. For these questions, an age less than 16 was used to designate a childhood
26
27 experience.
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35 Reproductive measures: Reproductive measures included age at menarche, parity (number
36
37 of live births), age at first birth, presence and severity of nausea and vomiting during
38
39 pregnancy (NVP), and diagnosis of endometriosis or polycystic ovarian syndrome. Severity
40
41 of NVP was measured using a scale adapted from Zhang et al. (2011). Gestational diabetes
42
43 was measured as part of a general question about experience of medical conditions,
44
45 followed by a request to specify the type of diabetes (if diabetes was selected).
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50
51 Effects of antidepressants: Efficacy of the top ten most commonly prescribed
52
53 antidepressants in Australia was assessed by asking how well each antidepressant a
54
55 participant had ever taken worked for them on a three-point scale (Not at all well,
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57 Moderately Well or Very Well).
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4 Questions from the Australian Genetics of Depression Study Questionnaire used in
5 phenotypic analysis (excluding Depression Scales)
6
7

8 *Biological sex, age and marital status*

9 Are you male or female?

10 How old are you now?

11 What is your marital status?

- 12 • Married
- 13 • Separated
- 14 • Divorced
- 15 • Widowed
- 16 • Never married
- 17 • Living with partner/defacto (for a period of six months or longer)

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23 *Education*

24 What is your highest level of education?

- 25 • No formal education
- 26 • Completed or partially completed primary school (years 1-7)
- 27 • Completed or partially completed junior secondary school (years 8-10)
- 28 • Completed or partially completed senior secondary school (years 11-12)
- 29 • Completed or partially completed certificate or diploma
- 30 • Completed or partially completed a degree
- 31 • Completed or partially completed a Post Graduate Diploma, Masters degree,
- 32 • Doctorate or PhD
- 33 • Don't know

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39 *Ancestry*

40 Thinking about what you know of your family history, which of the following best describes
41 the geographic regions where your ancestors (i.e. your great-great-grandparents) come
42 from? You may select as many choices as you need
43

- 44 • England, Ireland, Scotland or Wales
 - 45 • Australia - not of Aboriginal or Torres Strait Islander descent
 - 46 • Australia - of Aboriginal or Torres Strait Islander descent
 - 47 • New Zealand - not of Maori descent
 - 48 • New Zealand - of Maori descent
 - 49 • Northern Europe including Sweden, Norway, Finland and surrounding countries
 - 50 • Western Europe including France, Germany, the Netherlands and surrounding
51 countries
 - 52 • Southern Europe including Italy, Greece, Spain, Portugal and surrounding countries
 - 53 • Eastern Europe including Russia, Poland, Hungary and surrounding countries
 - 54 • Middle East including Lebanon, Turkey and surrounding countries
 - 55 • Eastern Asia including China, Japan, South Korea, North Korea, Taiwan and Hong
56 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

1
2
3 Have you ever taken any of the following antidepressants (even if it wasn't for depression or
4 anxiety)? *Please select all that apply.*

5
6 1st List (10 most commonly prescribed antidepressants):

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

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21 2nd List:

- 22 • Dothiepin (e.g. Dothep)
- 23 • Fluvoxamine (e.g. Luvox, Faverin, Movox, Voxam)
- 24 • Doxepin (e.g. Sinequan, Deptran)
- 25 • Nortriptyline (e.g. Allegron)
- 26 • Moclobemide (e.g. Amina, Clobemix, Mohexal, Aurorix)
- 27 • Clomipramine (e.g. Anafranil, Placil)
- 28 • Reboxetine (e.g. Edronax)
- 29 • Mianserin (e.g. Lumin)
- 30 • Imipramine (e.g. Tofranil, Tolerade)
- 31 • Tranylcypromine (e.g. Parnate)
- 32 • Phenelzine (e.g. Nardil)

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41 How well does / did each antidepressant work for you?

- 42 • Not at all well
- 43 • Moderately well
- 44 • Very well
- 45 • Don't know

46 47 48 49 50 51 *Abuse*

52 Listed below are a number of difficult or stressful things that sometimes happen to
53 people. For each event mark one or more of the boxes to the right to indicate that: (a) it
54 **happened to you** personally; (b) you **witnessed it** happen to someone else; (c) you
55 **learned about it** happening to a close family member or close friend; (d) you were exposed
56 to it as **part of your job** (for example, paramedic, police, military or other first responder);
57
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3 (e) you're **not sure** if it fits; or (f) it **doesn't apply** to you. Be sure to consider your **entire**
4 **life** (growing up as well as adulthood) as you go through the list of events.
5
6

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

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

12
13
14 How old were you the first and last time these things happened?
15

16 *Childhood abuse*

17 People may experience stressful situations in childhood which may affect their future health
18 and well-being. Please indicate if you experienced any of these situations **during your**
19 **childhood**.
20

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

27 *Menarche*

28 Have you begun to menstruate (started having your period)?

29 How old were you when you had your first menstrual period?
30

31 *Parity*

32 How many times have you been pregnant? *If you're unsure, please provide your best*
33 *estimate*. How many of these pregnancies resulted in live births (including caesarean
34 section)?
35

36 *Morning sickness*

37 While many women experience morning sickness, there are differences in how severe
38 morning sickness is. Did you have any morning sickness, nausea or vomiting during any of
39 your pregnancies?
40

41 Thinking back to each pregnancy, which of the following best describes your experience?
42

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

- 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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researcher's manual (Version 1.1, 1994). World Health Organisation; American
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237 doi:10.1016/j.ajog.2010.09.018

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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1 Table S2. List of geographical regions for participants to apply to great great grandparents
2 England, Ireland, Scotland or Wales
3 Australia - not of Aboriginal or Torres Strait Islander descent
4 Australia - of Aboriginal or Torres Strait Islander descent
5 New Zealand - not of Maori descent
6 New Zealand - of Maori descent
7 Northern Europe including Sweden, Norway, Finland and surrounding countries
8 Western Europe including France, Germany, the Netherlands and surrounding countries
9 Southern Europe including Italy, Greece, Spain, Portugal and surrounding countries
10 Eastern Europe including Russia, Poland, Hungary and surrounding countries
11 Middle East including Lebanon, Turkey and surrounding countries
12 Eastern Asia including China, Japan, South Korea, Taiwan and surrounding countries
13 South-East Asia including Thailand, Malaysia, Indonesia, Singapore and surrounding countries
14 South Asia including India, Pakistan, Sri Lanka and surrounding countries
15 Polynesia, Micronesia or Melanesia including Tonga, Fiji, Papua New Guinea and surrounding countries
16 Africa
17 North America - not of First Nations, Native American, Inuit or Métis descent
18 North America - of First Nations, Native American, Inuit or Métis descent
19 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

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

Length of worst episode	PND_r		
	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

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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 2.0 1.7-2.4	P 4.6E-13

severity of worst episode of PND, characterised by interference in everyday life, and need for professional help. Occurrence of PND was defined as moderate or severe PND, or priorDep (n=2,261)

Occurrence after delivery (n=1,482)			Total	Occurrence during pregnancy	
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

firstDep

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

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sional help, medication, or hospitalisation.

PND_firstDep (n=878)

icy (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)	
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

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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2	Polycystic ovarian		
3	syndrome	1960 195/56	13.1/11.9
4	Endometriosis	1969 251/67	16.8/14.1
5	Gestational diabetes	2933 90/18	6.7/4.2
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7	Antidepressants		
8	Effectiveness		
9	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

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.

p in bold

P (Bonferroni Adjustment for multiple tests)
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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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3 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				
Childhood Emotional Abuse	657/275	68.2/58.0	1.6	1.3-2.1

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

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

ind 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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2	3.3E-04	0.00	178/654	52.8/47.1	1.3 1-1.7	2.8E-02
3	8.0E-01	1.00	61/228	38.1/37.1	1.0 0.7-1.4	8.6E-01
4	8.6E-02	0.60	122/459	34.2/31.1	1.1 0.9-1.4	4.5E-01
5	6.3E-04	0.00	47/171	13.3/11.9	1.1 0.8-1.6	5.6E-01
6	3.0E-01	1.00	118/449	73.8/75.8	0.8 0.5-1.2	3.0E-01
7	2.5E-02	0.17	202/746	55.6/49.9	1.2 1-1.5	1.0E-01
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12	1.4E-08	0.00	201/578	39.4/27.2	2.1 1.7-2.6	1.9E-12
13	2.5E-03	0.02	248/823	62.6/53.9	1.6 1.3-2.0	1.2E-04
14	1.7E-03	0.01	166/569	48.1/43.0	1.2 0.9-1.5	1.9E-01
15	1.3E-01	0.92	126/509	39.4/39.8	0.9 0.7-1.2	4.0E-01
16	1.3E-01	0.91	60/195	16.8/13.8	1.3 0.9-1.8	9.9E-02
17	8.3E-01	5.81	135/34	9.7/9.6	0.8 0.5-1.3	4.3E-01
18	1.0E-01	0.70	13/48	4.1/3.7	0.9 0.5-1.7	7.9E-01
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22			475/1971	93.1/92.8		
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26	1.2E-05		98/363	20.6/18.4	1.2 1.0-1.5	1.1E-01
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30	1.8E-03	0.01	475/1971		0.96 0.7-1.3	7.4E-01
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32	3.4E-02	0.10	475/1971		1.1 0.8-1.4	5.1E-01
33						
34						
35	8.8E-01	1.00	475/1971		0.87 0.6-1.2	4.5E-01
36						
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39	4.8E-05		334/1222	68.2/62.0	1.1 0.9-1.4	2.9E-01
40	6.7E-04	0.02	187/629	39.4/31.9	1.3 1-1.6	4.7E-02
41	1.3E-06	0.00	180/631	37.9/32.0	1.2 1-1.5	1.1E-01
42	2.3E-04	0.01	135/513	28.4/26.0	1.1 0.8-1.4	5.3E-01
43	2.6E-04	0.01	116/346	24.4/17.6	1.3 1-1.7	2.7E-02
44	3.2E-04	0.01	100/324	21.1/16.4	1.1 0.8-1.4	4.6E-01
45	9.0E-04	0.02	114/325	24.0/16.5	1.5 1.1-1.9	4.1E-03
46	3.1E-03	0.07	91/350	19.2/17.8	1.0 0.7-1.3	7.5E-01
47	4.4E-03	0.10	97/300	20.4/15.2	1.3 1-1.7	5.7E-02
48	4.5E-06	0.00	95/269	20.0/13.6	1.4 1.1-1.8	1.8E-02
49	3.0E-04	0.01	89/275	18.7/14	1.3 1-1.7	5.2E-02
50	1.2E-03	0.03	82/240	17.3/12.2	1.4 1-1.8	4.7E-02
51	1.5E-03	0.03	79/258	16.6/13.1	1.3 0.9-1.7	1.1E-01
52	1.1E-02	0.25	44/199	9.3/10.1	0.7 0.5-1.1	1.2E-01
53	4.7E-03	0.11	58/219	12.2/11.1	0.9 0.7-1.3	7.4E-01
54	4.8E-03	0.11	43/166	9.1/8.4	1.1 0.7-1.5	7.4E-01
55	1.3E-01	1.00	31/103	6.5/5.2	1.2 0.7-1.8	5.1E-01
56	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	2.3E-02	0.54	18/66	3.8/3.3	0.8 0.4-1.4	4.5E-01
3	4.5E-02	1.00	26/90	5.7/4.6	1.1 0.7-1.8	5.8E-01
4	1.1E-01	1.00	19/67	4.0/3.4	1.1 0.6-1.8	8.4E-01
5	5.4E-01	1.00	17/57	3.6/2.9	1.1 0.6-1.9	7.4E-01
6						
7	7.3E-04	0.02	8/29	1.7/1.5	1.1 0.4-2.3	8.5E-01
8	3.0E-02	0.68	7/31	1.5/1.6	0.9 0.4-2	8.1E-01
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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) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i> —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 <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants	7-8
		(b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> —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) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed <i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed <i>Cross-sectional study</i> —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 (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	12-14
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	12-15
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time <i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure <i>Cross-sectional study</i> —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 (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	15-17
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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2

28 Abstract

29 Objectives

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

34 Design and Setting

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

39 Participants

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

43 Primary and secondary outcome measures

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

48 Results

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

56 Conclusions

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

62 Strengths and limitations of this study

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

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3 70 • Reliance on self-report information years after experiencing PND could lead to recall
4 bias.
5 71
6
7 72 • The AGDS cohort is mostly young and well-educated and may not generalize to the
8 entire population.
9 73
10 74

75 **Funding Statement**

14 76 This work was primarily funded by National Health and Medical Research Council (NHMRC)
15 of Australia grant 1086683, and further supported by NHMRC grants 1145645, 1078901 and
16 77 1087889. JK is supported by a UQ Research Training Program scholarship. LC-C is supported
17 78 by a QIMR Berghofer Institute fellowship.
18 79

80 **Competing interests**

24 81 No conflict of interest has been reported

82 **Availability of data and material**

29 83 Data used in this analysis and described in this article are available to all interested
30 84 researchers through collaboration. Please contact NGM.

85 **Ethics approval and consent to participate**

35 86 All study protocols were approved by the QIMR Berghofer Medical Research Institute
36 87 Human Research Ethics Committee (Ref 2118). The protocol for approaching participants
37 88 through the DHS, enrolling them in the study, and consenting for all phases of the study
38 89 (including invitation to future related studies) and accessing MBS and PBS records was
39 90 approved by the Ethics Department of the Department of Human Services.

45 91 Patient consent for participation in the study was obtained.

92 **Introduction**

93

94 **Background**

54 95 Perinatal depression (PND), including both antenatal and postpartum depression, carries
55 96 serious risk for both mother and infant. An estimated 53% of women with postpartum
56 97 depression have “high suicidality” [1], whilst the rate of self-harming thoughts is three times

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3 98 that of the postpartum community population [2]. Estimated economic costs of PND in the
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5 99 UK, of which 72% are for ongoing care of the child [3] reflect findings that children of
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8 100 women with persistent and severe PND are at increased risk of adverse outcomes [4, 5] .
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11 101 Peripartum depression is classified diagnostically in the Diagnostic and Statistical Manual of
12
13 102 mental disorders 5th Edition (DSM 5) [6] as a subtype of Major Depressive Disorder. The
14
15 103 classification of the disorder as peripartum is a change from the 4th edition of the manual
16
17 104 where the disorder was called postpartum depression. The change in nomenclature reflects
18
19 105 the increased recognition that symptoms can begin during pregnancy.
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24 106 There is ongoing debate as to whether PND is a depressive episode that happens to coincide
25
26 107 with the perinatal period [7]; or a distinct disorder with a partially overlapping set of risk
27
28 108 factors, stimulated by changes occurring during pregnancy and confined to the perinatal
29
30 109 period [8].
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35 110 The strongest known risk factor for PND is a previous diagnosis of a psychiatric disorder [5,
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37 111 9-12]. Women with a history of depression are at greatly increased risk of experiencing
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39 112 depressive symptoms during and after pregnancy. However, many women with a prior
40
41 113 history of depression do not report symptoms in the perinatal period and for others, PND is
42
43 114 the first reported episode. This suggests the possibility that the profile of risk factors
44
45 115 associated with depression in the perinatal period is at least partially distinct from
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47 116 depression outside of the perinatal period. One suggestion is that PND is itself heterogenous
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49 117 [12, 13], with clinical subtypes differentiated by timing and severity of symptoms, perinatal
50
51 118 complications, and history of psychiatric disorders. A number of studies have found
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53 119 evidence for heterogeneity in symptom profiles across the perinatal period [14-16]. Most
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55 120 studies have found evidence for groups of women with persistent high or low levels of
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3 121 depression symptoms through the perinatal period, and some have found evidence of
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6 122 transient symptom profiles with changes from the antenatal to postnatal period [17]
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8 123 Differences in symptom trajectories have been linked to risk factors including a previous
9
10 124 history of depression [18], history of abuse [19], low social support [19], low income [18],
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13 125 lower levels of education [20, 21] and ethnicity [21].
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127 Objectives

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

137 Method

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139 Setting: The Australian Genetics of Depression Study

140 The AGDS is a large ongoing case cohort study of the etiology of depression that recruited
141 20,689 participants (aged between 28 and 58 years; 75% female) during 2016-2018. The

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3 142 analyses conducted here include participants enrolled prior to the initial data freeze in
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6 143 September 2018. Recruitment was primarily through a media campaign (86%) which
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8 144 requested participation from anyone with a depression diagnosis from a health
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10 145 professional, as well as specific invitations to women who had responded to a mobile phone
11
12 146 app focused on PND, originally developed in the USA [23], and also ascertainment through
13
14 147 the Pharmaceutical Benefits Scheme prescription records for antidepressants. For further
15
16 148 details of the recruitment strategy, see Byrne, et al. [22]. The AGDS protocol was approved
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18 149 by the Human Research Ethics Committee of QIMR Berghofer Institute for Medical
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23 150 Research.

26 151 Study Design

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31 152 Within the cross-sectional case cohort, we investigated the prevalence of PND, and the
32
33 153 timing of onset and duration of perinatal depression symptoms in two groups of PND cases
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35 154 who were identified according to whether or not they reported having experienced an
36
37 155 episode of depression prior to becoming pregnant for the first time. Women with a prior
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39 156 history of depression who met the study criteria for PND were compared to a corresponding
40
41 157 control group of women who met criteria for lifetime depression but did not report
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43 158 significant depressive symptoms during the perinatal period – non-perinatal depression
44
45 159 cases (NPD) (Table S1).

52 160 Variables

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56 161 AGDS participants were invited to complete an online questionnaire. A compulsory core
57
58 162 module assessed self-reported psychiatric history, the Composite Interview Diagnostic
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3 163 Interview Short Form (CIDI-SF) which assesses the Diagnostic and Statistical Manual of
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6 164 Mental Disorders Fifth Edition (DSM 5) criteria for MDD [24], and experiences of using
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8 165 commonly prescribed antidepressants. Women reporting symptoms of depression during
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10 166 pregnancy or up to 6 months following childbirth were asked to complete the lifetime
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13 167 Edinburgh Postnatal Depression Scale (EPDS) [25], an adaptation of the standard EPDS [26]
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15 168 that assesses lifetime PND episodes. They were also asked whether symptoms of depression
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18 169 occurred during pregnancy, after giving birth, or both, the age at which they experienced
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20 170 their worst episode of PND, its severity and duration. Furthermore, participants were asked
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23 171 if they had ever been diagnosed with any of 18 psychiatric disorders. For all AGDS
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25 172 participants, further voluntary modules assessed history of psychiatric health conditions and
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28 173 stressful life events.

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31 174
32 175 The outcome of interest was a positive screen for PND for women with either a history of
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34 176 previous depressive episode(s), or no previous depression history. An exposure to a PND
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37 177 episode is defined as the period of time from conception up to six months postpartum, so
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40 178 that the number of reported live births represents the number of exposures. PND cases
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42 179 were defined as women reporting at least one live birth who had been previously diagnosed
43
44 180 with PND by a health professional, or who scored ≥ 13 on the lifetime EPDS, or who met
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46
47 181 criteria for major depression and reported at least one perinatal episode. The length and
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49
50 182 timing of onset of the worst PND episode were evaluated for PND cases both with and
51
52 183 without a prior history of depression. Length of the worst PND episode was assessed using a
53
54 184 5 point scale: "Up to two weeks", "2-4 weeks", "1-3 months", "3-6 months", "More than 6
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56
57 185 months". Timing of onset was assessed by participants reporting which trimester of
58
59 186 pregnancy or how long after delivery their symptoms began.
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187

188 The cross-sectional nature of our study meant that no direction of causality could be
189 assessed, but we investigated differences between PND cases with a prior history of
190 depression (PND_priordep) and NPD (NPD_priordep) cases across a range of clinical and
191 psychosocial variables that have previously been identified to be associated with PND [5, 27,
192 28]. Demographic measures included current age, marital status, education and ancestry. A
193 list of geographical regions from which ancestry is identified is provided in Table S2. More
194 details are provided in Supplementary Methods. Other measures included the self-reported
195 age at onset of depression, number of episodes of depression, history of childhood trauma
196 and sexual or other physical assault, and self-reported previous diagnoses of psychiatric
197 disorders. Eighteen psychiatric disorders were listed, of which twelve, identified by more
198 than 3% of participants, were evaluated in this study (Table S3). Reproductive measures
199 included age at menarche, parity, age at first birth, presence and severity of nausea and
200 vomiting during pregnancy (NVP), and previous diagnosis of gestational diabetes,
201 endometriosis or polycystic ovarian syndrome. Antidepressant measures included the
202 number of antidepressants that had been tried and their efficacy. More details of these
203 measures are provided in Supplementary Methods, which also lists the questions used to
204 assess each characteristic.

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207 Participants: PND cases and non-perinatal comparison group

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

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

217 Figure 1 about here

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223 Statistical Analysis

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

226 All modules apart from the first were optional, and some categories applied only to a

227 limited number of participants (for example, those who had used at least one

228 antidepressant). For these reasons, the number of participants who completed each

229 category or variable varied. For each variable, the number of respondents is reported.

230 Within each category, analysis employed Bonferroni correction for multiple testing

231 (N=number of tests within each category).

232 All analyses were conducted using R (version 3.6.0). Figures were generated using ggplot2

233 [29] and Glify software [30].

234

235 Public and Patient Involvement

236 There was no public or patient involvement in the design, conduct, reporting or

237 dissemination plans of our research.

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241 Results

242

243 Lifetime prevalence of depression during the peripartum period

244 A total of 15,198 female participants (median age of 39) in the Australian Genetics of
245 Depression Study, met DSM 5 criteria for MDD. Of these, 7,182 (47%) reported at least one
246 live birth. The prevalence of PND among parous women was 70.4%. A total of 2,933 women
247 reported at least one depressive episode prior to their first pregnancy. Of these, 2,261 (77%)
248 screened positive for PND, whilst the remaining 672 women with no PND episodes (23%)
249 formed their comparison group (NPD_priorDep). A total of 878 out of 5,058 women
250 reported that their first episode of depression occurred during pregnancy or within the first
251 6 months after delivery (PND_firstDep), Of women who met criteria for PND, 1,919 were
252 unable to be categorized as PND_priorDep or PND_firstDep and were lost to further
253 analysis. Fig. 1 and Supplementary Table S1 provide details of the sample selection process.

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

1

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

259

260 Table 1. Reported timing of symptoms of perinatal depression among women with PND.

261 Results are shown for all those meeting PND criteria and separately for those with a prior
 262 history of major depression (PND_priorDep) and those whose first onset of major
 263 depression was perinatal (PND_firstDep).

264

	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%)

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

270 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)

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272 The most reported time of symptom onset during the worst episode of PND is shown in

273 Table 3. Regardless of whether women had a prior history of depression, the most

274 commonly reported time of onset for the worst episode was 0-4 weeks postpartum.

275 However, women with a prior history of depression were more likely to report that the

276 worst episode began during pregnancy than women with no reported prior history,

277 specifically during the first trimester.

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280 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)

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283 Clinical and psychosocial risk factors for PND in parous women

284 Table S5 provides the number and percentage of participants that completed each of the

285 risk factor variables

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

289 We investigated which risk factors are associated with PND in women with a previous
290 history of depression. Age (OR [PND case status]=0.97 per additional year of age, CI=[0.96-
291 0.98], $p < 0.001$), and number of births (OR [PND case status]=1.3 per additional birth,
292 CI=[1.2-1.4], $p < 0.001$) were significantly associated with PND. Both age and number of
293 births were included as covariates in subsequent analyses, which were also adjusted for
294 multiple testing.

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

305 Screening positive for PND among parous women with a history of depression was
306 associated with an overall increased number of reported episodes (OR per episode = 1.15
307 [1.13 – 1.17], $p < 0.001$) and decreased likelihood of reporting high efficacy of any
308 antidepressant (OR = 0.7 [0.5-0.8], $p < 0.001$).

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312 Discussion

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

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3 330 Another key finding was that women without a prior history were more likely to report
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5 331 symptom onset in the postnatal period and were more likely to report longer duration of
6
7 332 symptoms. This may reflect that women with a prior history may have had an ongoing
8
9 333 episode of depression when they became pregnant, and we were unable to distinguish
10
11 334 whether symptoms had started prior to the first trimester. Furthermore, women with a
12
13 335 prior history may have been more likely to be monitored by clinicians and have a treatment
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15 336 plan in place, leading to reduced length of symptoms.

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18 337 Participants with a prior history of depression who report having at least one ancestor of
19
20 338 Aboriginal or Torres Strait Islander (ATSI) descent were more likely to report significant
21
22 339 perinatal depressive symptoms. There have been few studies conducted on perinatal
23
24 340 mental health among Aboriginal and Torres Strait Islanders [33]. One study conducted on a
25
26 341 representative population sample in New South Wales did not find an increased prevalence
27
28 342 of postnatal depressive symptoms among women of ATSI descent. However, the study did
29
30 343 identify several associated risk factors that commonly affect people of ATSI descent such as
31
32 344 placement in public housing, financial hardship, and poor self-rated health. Many other risk
33
34 345 factors such as smoking and obstetric complications are higher in the ATSI population than
35
36 346 in non-Indigenous Australians and depression and anxiety are twice as common [34].
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38 347 Results from the Australian Postnatal Screening Program found that the rate of antenatal
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40 348 depression in ATSI women was 18.9% compared to 8.9% in non-Indigenous Australians and
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42 349 6.3% had postnatal depression compared to 2.7% in non-Indigenous women [35, 36]. The
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44 350 findings of our study further highlight the increased risk of PND in ATSI women and the need
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46 351 for better screening and treatment in the Indigenous population.
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3 352 Another key finding was the association between severe nausea during pregnancy and PND.
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5 353 Nausea and vomiting during pregnancy of varying severity affects approximately 69% of
6
7 354 pregnant women. A meta-analysis evaluating the association between the severe form of
8
9 355 morning sickness – hyperemesis gravidarum (HG) – and depression and anxiety found
10
11 356 significant increased depression and anxiety scores in women with HG [37]. A recent
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13 357 longitudinal study in the United Kingdom found that 49% of women with HG had probable
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15 358 depression antenatally and 29% had probable postnatal depression. In conjunction with our
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17 359 findings, these results suggest that women with severe nausea during pregnancy are at high
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19 360 risk of depression and may need to be referred for treatment of PND [38].
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26 361 Lastly, we identified psychiatric comorbidities, particularly premenstrual dysphoric disorder
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28 362 and ADHD, and emotional abuse in childhood as being associated with perinatal depressive
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30 363 symptoms. There is an extensive literature on the association between trauma and PND [39-
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32 364 42] and our study shows that even among those with a prior history of MDD, trauma is a risk
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34 365 factor for PND, consistent with previous reports [25]. Several studies have evaluated the
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36 366 association between ADHD in children and perinatal risk factors including PND in mothers
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38 367 [43-45]. However, few studies have considered that mothers with PND may also have ADHD
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40 368 symptoms and our results suggest that this is an important consideration. Recent studies
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42 369 that have attempted to account for genetic transmission from mother to child have found
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44 370 that much of the association between PND and ADHD in the offspring is accounted for by
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46 371 shared genetic risk factors between PND and ADHD [46, 47].
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57 373 The results of this study should be considered in the light of several limitations. The main
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59 374 limitation of this study is that it is based on an online questionnaire, with no personalized

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3 375 interviews or clinical reports to provide supporting evidence for self-reported data. Answers
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6 376 were based on total life experience, including, but not exclusive to, the perinatal period.
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8 377 Furthermore, the AGDS is a cross-sectional study. Its strength lies in its sample size, but,
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10 378 unlike a longitudinal study, it provides no information with respect to timing of variables
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12 379 significantly associated with PND (with the exception of childhood adverse experiences), so
13
14 380 no inference can be made pertaining to cause and effect. In addition, because information
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16 381 only about the worst episode was ascertained, it was not possible to identify all cases where
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18 382 the perinatal episode was the first episode of depression, which may have biased the
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20 383 results. No information on the use of mood stabilisers which would be indicative of mixed
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22 384 episodes was collected.

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28 385 Furthermore, the lifetime EPDS used to assess PND is a screening, rather than diagnostic
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30 386 tool and may result in overestimation of PND case status [48], although O'Connor et.al. [49]
31
32 387 reported a sensitivity of 0.8 for the EPDS in identifying MDD with a cut-off score ≥ 13 , and a
33
34 388 specificity of 0.9. The lifetime EPDS is a modification of this scale which has demonstrated
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36 389 internal consistency [25].

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

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

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

402

403 Conclusions

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

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3 417 of relapse [49]. Cases were also more likely to have treatment resistant depression,
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5 418 supporting further clinical investigation of antidepressant efficacy in PND.
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10 11 420 **Authors' Contributions**

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14 421 EMB, JK, NGM, NRW, designed the study. SEM, LCC, SMB, JM, EB, JG, TM, IBH provided
15
16 422 intellectual input into the content. JK analysed the data. JK, EMB, NRW, and NGM drafted
17
18 423 the manuscript. SEM, LCC, SMB, JM, EB, JG, TM, IBH, revised the article for intellectual
19
20 424 content. All authors have read and approve of the final version.
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22

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41 611

612 Figure Legends

613
614
615 **Fig. 1** Flow chart: Selection of cases and associated comparative group for first analysis
616 (prior history of major depression) and second analysis (PND is first experience of major

2

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

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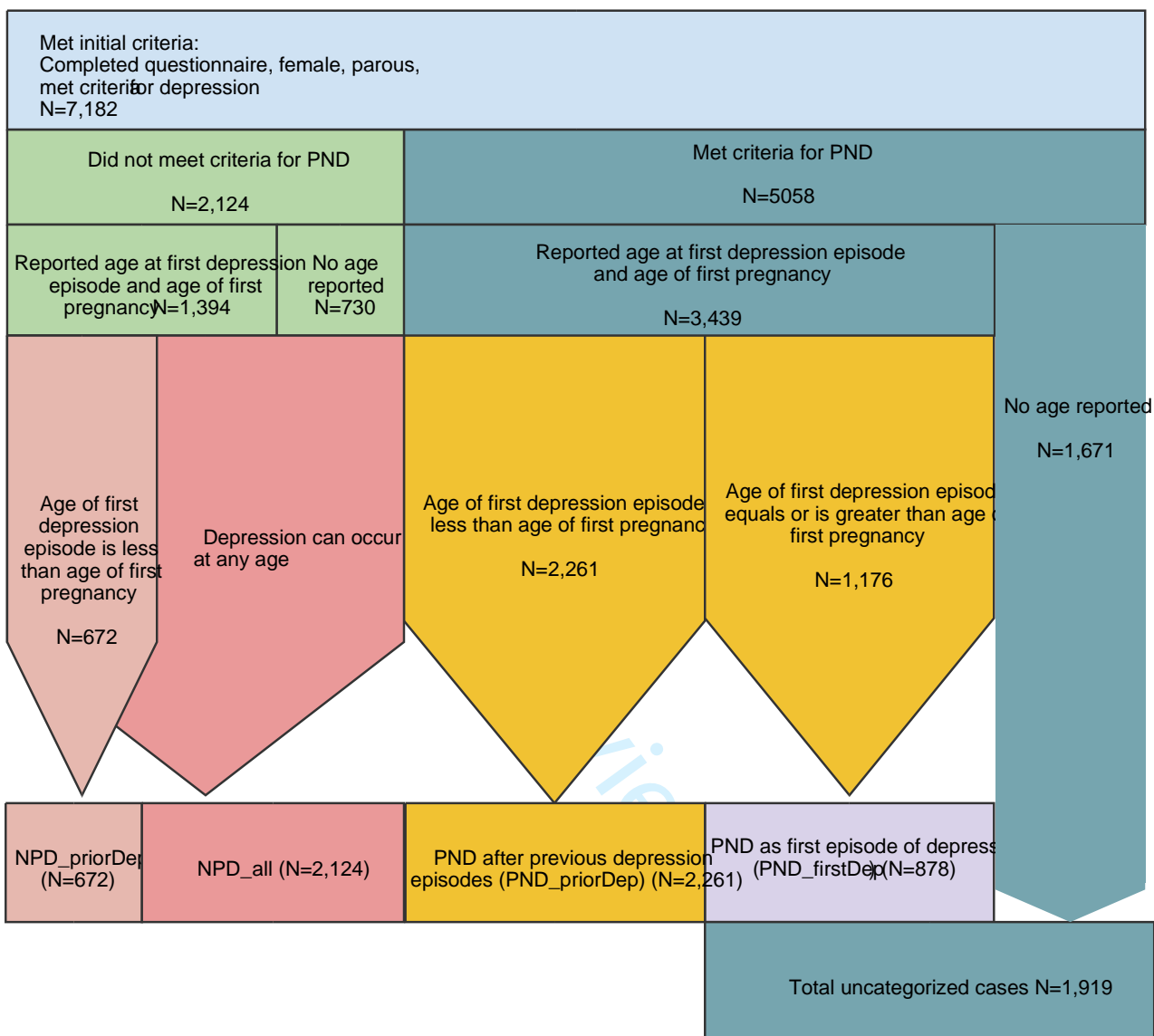
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Supplementary Methods

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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2
3 endorsing PND in women with ancestors only from Europe, compared to women with at
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5 least one non-European ancestor. Further analysis compared the rate of PND in those
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7 reporting Australian Indigenous ancestry to those of only European ancestry.
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11 Clinical measures: Participants were asked to report any previous diagnoses from a total list
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13 of 19 psychiatric disorders, of which 13, with frequencies > 3% for all women with PND,
14
15 were analyzed in this study (Supplementary Table S3). History of childhood trauma was
16
17 assessed using responses to three questions that asked whether participants had been
18
19 emotionally abused, emotionally neglected, or physically neglected during childhood.
20
21 Additionally, participants were asked whether they had experienced physical or sexual
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23 assault or unwanted sexual experience at any time in their life, as well as their age at that
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25 time. For these questions, an age less than 16 was used to designate a childhood
26
27 experience.
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34 Reproductive measures: Reproductive measures included age at menarche, parity (number
35
36 of live births), age at first birth, presence and severity of nausea and vomiting during
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38 pregnancy (NVP), and diagnosis of endometriosis or polycystic ovarian syndrome. Severity
39
40 of NVP was measured using a scale adapted from Zhang et al. (2011). Gestational diabetes
41
42 was measured as part of a general question about experience of medical conditions,
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44 followed by a request to specify the type of diabetes (if diabetes was selected).
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50 Effects of antidepressants: Efficacy of the top ten most commonly prescribed
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52 antidepressants in Australia was assessed by asking how well each antidepressant a
53
54 participant had ever taken worked for them on a three-point scale (Not at all well,
55
56 Moderately Well or Very Well).
57
58
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3
4 Questions from the Australian Genetics of Depression Study Questionnaire used in
5 phenotypic analysis (excluding Depression Scales)
6
7

8 *Biological sex, age and marital status*

9 Are you male or female?

10 How old are you now?

11 What is your marital status?

- 12 • Married
- 13 • Separated
- 14 • Divorced
- 15 • Widowed
- 16 • Never married
- 17 • Living with partner/defacto (for a period of six months or longer)

18
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21
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23 *Education*

24 What is your highest level of education?

- 25 • No formal education
- 26 • Completed or partially completed primary school (years 1-7)
- 27 • Completed or partially completed junior secondary school (years 8-10)
- 28 • Completed or partially completed senior secondary school (years 11-12)
- 29 • Completed or partially completed certificate or diploma
- 30 • Completed or partially completed a degree
- 31 • Completed or partially completed a Post Graduate Diploma, Masters degree,
- 32 • Doctorate or PhD
- 33 • Don't know

34
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37
38
39 *Ancestry*

40 Thinking about what you know of your family history, which of the following best describes
41 the geographic regions where your ancestors (i.e. your great-great-grandparents) come
42 from? You may select as many choices as you need
43

- 44 • England, Ireland, Scotland or Wales
- 45 • Australia - not of Aboriginal or Torres Strait Islander descent
- 46 • Australia - of Aboriginal or Torres Strait Islander descent
- 47 • New Zealand - not of Maori descent
- 48 • New Zealand - of Maori descent
- 49 • Northern Europe including Sweden, Norway, Finland and surrounding countries
- 50 • Western Europe including France, Germany, the Netherlands and surrounding
51 countries
- 52 • Southern Europe including Italy, Greece, Spain, Portugal and surrounding countries
- 53 • Eastern Europe including Russia, Poland, Hungary and surrounding countries
- 54 • Middle East including Lebanon, Turkey and surrounding countries
- 55 • Eastern Asia including China, Japan, South Korea, North Korea, Taiwan and Hong
56 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)
- Social anxiety disorder (also known as Social phobia)
- Agoraphobia
- Personality disorder
- Substance use disorder

Antidepressants

1
2
3 Have you ever taken any of the following antidepressants (even if it wasn't for depression or
4 anxiety)? *Please select all that apply.*

5
6 1st List (10 most commonly prescribed antidepressants):

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

17
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21 2nd List:

- 22 • Dothiepin (e.g. Dothep)
- 23 • Fluvoxamine (e.g. Luvox, Faverin, Movox, Voxam)
- 24 • Doxepin (e.g. Sinequan, Deptran)
- 25 • Nortriptyline (e.g. Allegron)
- 26 • Moclobemide (e.g. Amina, Clobemix, Mohexal, Aurorix)
- 27 • Clomipramine (e.g. Anafranil, Placil)
- 28 • Reboxetine (e.g. Edronax)
- 29 • Mianserin (e.g. Lumin)
- 30 • Imipramine (e.g. Tofranil, Tolerade)
- 31 • Tranylcypromine (e.g. Parnate)
- 32 • Phenelzine (e.g. Nardil)

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41 How well does / did each antidepressant work for you?

- 42 • Not at all well
- 43 • Moderately well
- 44 • Very well
- 45 • Don't know

46 47 48 49 50 51 *Abuse*

52 Listed below are a number of difficult or stressful things that sometimes happen to
53 people. For each event mark one or more of the boxes to the right to indicate that: (a) it
54 **happened to you** personally; (b) you **witnessed it** happen to someone else; (c) you
55 **learned about it** happening to a close family member or close friend; (d) you were exposed
56 to it as **part of your job** (for example, paramedic, police, military or other first responder);
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3 (e) you're **not sure** if it fits; or (f) it **doesn't apply** to you. Be sure to consider your **entire**
4 **life** (growing up as well as adulthood) as you go through the list of events.
5
6

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

- 8 • Physical assault (e.g. being attacked, hit, slapped, kicked, beaten up)
- 9 • Sexual assault (rape, attempted rape, made to perform any type of sexual act
10 through force or threat of harm)
- 11 • Other unwanted or uncomfortable sexual experience
- 12
- 13

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

15 *Childhood abuse*

16 People may experience stressful situations in childhood which may affect their future health
17 and well-being. Please indicate if you experienced any of these situations **during your**
18 **childhood**.
19

- 20 • Emotional abuse (e.g. often being told you were no good, yelled at in a scary way,
21 threatened, ignored, or stopped from making friends)
- 22 • Emotional neglect (e.g. often not being shown affection, or not being given
23 encouragement or support)
- 24 • Physical neglect (e.g. often not being given enough to eat or drink, appropriate
25 clothing, shelter, medical care, education, supervision or a safe home environment)
- 26
- 27
- 28
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30 *Menarche*

31 Have you begun to menstruate (started having your period)?

32 How old were you when you had your first menstrual period?

33 *Parity*

34 How many times have you been pregnant? *If you're unsure, please provide your best*
35 *estimate*. How many of these pregnancies resulted in live births (including caesarean
36 section)?
37

38 *Morning sickness*

39 While many women experience morning sickness, there are differences in how severe
40 morning sickness is. Did you have any morning sickness, nausea or vomiting during any of
41 your pregnancies?
42

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

- 44 • I did not have any nausea or vomiting
- 45 • Nausea and/or vomiting for *less than 7 days*, but I didn't see a doctor about this and
46 it didn't disrupt my daily routine.
- 47 • Nausea and/or vomiting for *more than 7 days*, but I didn't see a doctor about this. It
48 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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Zhang Y, Cantor RM, MacGibbon K, Romero R, Goodwin TM, Mullin PM, Fejzo MS (2011)
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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

1
2 Table S2. List of geographical regions for participants to apply to great great grandparents
3 England, Ireland, Scotland or Wales
4 Australia - not of Aboriginal or Torres Strait Islander descent
5 Australia - of Aboriginal or Torres Strait Islander descent
6 New Zealand - not of Maori descent
7 New Zealand - of Maori descent
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9 Northern Europe including Sweden, Norway, Finland and surrounding countries
10 Western Europe including France, Germany, the Netherlands and surrounding countries
11 Southern Europe including Italy, Greece, Spain, Portugal and surrounding countries
12 Eastern Europe including Russia, Poland, Hungary and surrounding countries
13 Middle East including Lebanon, Turkey and surrounding countries
14 Eastern Asia including China, Japan, South Korea, Taiwan and surrounding countries
15 South-East Asia including Thailand, Malaysia, Indonesia, Singapore and surrounding countries
16 South Asia including India, Pakistan, Sri Lanka and surrounding countries
17 Polynesia, Micronesia or Melanesia including Tonga, Fiji, Papua New Guinea and surrounding countries
18 Africa
19 North America - not of First Nations, Native American, Inuit or Métis descent
20 North America - of First Nations, Native American, Inuit or Métis descent
21 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

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

Length of worst episode	PND_r		
	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

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

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)

icy (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)	
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

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		
Education	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, including

priorDep sample: 2261 cases; 6

Significant P values

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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2	Early menarche	1.1	0.9-1.4	3.4E-01
3	Endometrioses	1.2	0.9-1.6	2.1E-01
4	Polycystic ovarian syndrome	0.9	0.7-1.3	7.2E-01
5	Gestational diabetes	1.4	0.8-2.4	2.4E-01
6				
7	Antidepressant use			
8				
9	Tried 3 or more commonly prescribed antidepressant (as a			
10	proportion of women using antidepressants)	1.4	1.1-1.8	1.4E-03
11				
12	Antidepressant efficacy, N(tests)=3			
13	High efficacy for any common antidepressant	0.7	0.5-0.8	5.5E-04
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4 i72 controls; 2,933 total.

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8	P (Bonferroni Adjustment
9	for multiple tests)

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36	0.114
37	0.173
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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) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i> —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 <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants	7-8
		(b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> —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) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed <i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed <i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy	
		(e) Describe any sensitivity analyses	12

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60**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 (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	12-14
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	12-15
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time <i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure <i>Cross-sectional study</i> —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 (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	15-17
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
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*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.