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The role of prepulse inhibition in predicting new-onset postpartum depression

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Allison Eriksson[1,2], Richelle D. Björvang[1,3], Ebba Ancker[1], Fotios C. Papadopoulos[4], Inger Sundström Poromaa[1], Emma Fransson[1,5,6] ✉ & Alkistis Skalkidou[1,6]

Predictive measures for postpartum depression (PPD), which affects around 12% of childbearing women, would enable early, targeted support. Here we explore prepulse inhibition (PPI), a measure of sensorimotor processing, as a biological tool for prediction of women at risk for PPD. Using data from the longitudinal BASIC study in Uppsala, Sweden, we used PPI measures from late pregnancy and reports on depressive symptoms assessed 6 weeks postpartum with the Edinburgh Postnatal Depression Scale to determine the association between pregnancy PPI and PPD. Lower PPI was associated with PPD onset in women who were not depressed during pregnancy. Further studies are encouraged to validate these promising results suggesting PPI as a predictive marker of new-onset PPD.

Postpartum depression (PPD), a subtype of the clinical condition defined as peripartum depression, begins within the first 4 weeks after childbirth[1]; however, clinically, depressive episodes diagnosed within the first year postpartum are often included in the categorization of PPD[2]. Symptoms of PPD include depressed mood, lack of energy and reduced interest in daily activities. Women affected by PPD are a diverse group[3]; some women are at increased risk for new postpartum depressive episodes in successive pregnancies and have a higher incidence of sick leave, morbidity and suicide[4–7]. Many psychosocial risk factors for PPD are known. Studies investigating self-reported PPD have identified poor socioeconomic status, pregnancy and delivery complications, and having a history of depression to be linked to increased risk of PPD[3,8,9]. In a large register-based study, women with a history of depression were 20× more likely to suffer from clinically diagnosed PPD than those without a history of depression[10]. Previous studies have identified personality traits, such as high levels of neuroticism and anxiety and low resilience, as strong risk factors for PPD[11–13]. Poor social support also increases the risk of PPD, with a shorter relationship with a partner, poor marital relationship, and lack of social support from family and friends noted as risk factors for PPD[14–16].

Furthermore, large alterations in hormonal levels occurring during the pregnancy and postpartum periods, including those in the hypothalamus–pituitary–adrenal (HPA) axis, could put individuals sensitive to endocrinological changes at increased risk for PPD[2,14,17,18]. The hormonal and physical changes associated with pregnancy and childbirth constitute a stress test of the female body[19]. An individual's adaptation to acute or chronic stress is predictive of mental health conditions[20] and poor stress adaptation has been linked to depression[21]. Pregnancy is generally associated with a decrease in the neuroendocrine response to acute stressors, whereas increased reactivity is believed to be associated with a greater likelihood of PPD[22].

Sensorimotor gating and prepulse inhibition

The gating mechanism, a process for input filtration, has a pivotal role in stress regulation by safeguarding cortical areas from the inundation of unnecessary or irrelevant information[23,24]. One type of gating, referred to as sensorimotor gating, involves the ability to automatically inhibit a motor response to a sensory event. One paradigm that is commonly used to study sensorimotor gating involves measuring the inhibition of the startle response, which is the reflex triggered by an auditory, visual or tactile stimulus that causes heart rate acceleration and contraction of body and face muscles, thereby instinctively prompting the blink reflex[25]. The acoustic startle response (ASR) is mostly used in research and is triggered by an auditory stimulus. When a low-salience auditory stimulus immediately precedes a startle stimulus, the startle motor

[1]Department of Women's and Children's Health, Uppsala University, Uppsala, Sweden. [2]Center for Women's Mental Health During the Reproductive Lifespan (WOMHER), Uppsala University, Uppsala, Sweden. [3]Department of Clinical Science, Intervention and Technology, Karolinska Institute, Stockholm, Sweden. [4]Department of Medical Sciences, Psychiatry, Uppsala University, Uppsala, Sweden. [5]Department of Microbiology, Tumor and Cell Biology, Karolinska Institute, Stockholm, Sweden. [6]These authors contributed equally: Emma Fransson, Alkistis Skalkidou. ✉e-mail: emma.fransson@uu.se

Table 1 | Background and mental health characteristics of participants with and without PPD

Characteristic	Overall (*N*=179)	Non-PPD (*N*=151)	PPD (*N*=28)	Statistic[d]	Effect size[e]	*P* value
Age (yr), mean (s.d.)	31.6 (4.43)	31.7 (4.43)	31.2 (4.49)	0.57	0.12	0.57[f]
Education, *n* (%)						
University	142 (79.3)	125 (82.8)	17 (60.7)	5.73	−0.2	**0.02**[g]
Less	37 (20.7)	26 (17.2)	11 (39.3)			
Employment, *n* (%)						
Full- or part-time	160 (89.4)	141 (93.4)	19 (67.9)	–	–	**<0.001**[h]
Other[a]	19 (10.6)	10 (6.6)	9 (32.1)			
BMI (kg/m^2)						
Median [min–max]	22.8 [17–37.6]	22.5 [17–36.3]	24.1 [18.1–37.6]	1,690	0.13	0.09[i]
Pregnancy depression, *n* (%)[b]						
Yes	55 (30.7)	34 (22.5)	21 (75)	28.2	0.41	**<0.001**[g]
No	124 (69.3)	117 (77.5)	7 (25)			
SSRI during pregnancy, *n* (%)						
Yes	12 (6.7)	9 (6)	3 (10.7)	–	–	0.40[h]
No	167 (93.3)	142 (94)	25 (89.3)			
PMS or PMDD, *n* (%)						
Yes	15 (8.4)	8 (5.3)	7 (25)	–	–	**0.003**[h]
No	164 (91.6)	143 (94.7)	21 (75)			
Sleep before ASR measurement (h)						
Median [min–max]	7 [4–10]	7 [4–10]	6.7 [4–10]	2,325	0.06	0.40[i]
Anxiety before ASR measurement, *n* (%)[c]						
Yes	28 (15.6)	15 (9.9)	13 (46.4)	–	–	**<0.001**[h]
No	151 (84.4)	133 (90.1)	15 (53.6)			
Baseline ASR (μV)						
Median [min–max]	2,958.8 [352–7,512]	2,958.8 [352–7,512]	2,955.1 [443–5,896]	2,300	0.06	0.46[i]

PPD was defined by a score of ≥12 on the EPDS at 6 weeks postpartum. Statistical tests were two sided. Bold values indicate $P<0.05$. [a]Unemployed, studying, on sick leave or parental leave. [b]EPDS score of 12–30 at pregnancy week 32 or major depression according to MINI on test session day. [c]Based on MINI on test session day. [d]Statistic derived from the X^2 test, *W* value from the Wilcoxon rank-sum test or *t* value from the *t*-test, as appropriate. [e]Effect size represents φ coefficient for the X^2 test, *r* value for the Wilcoxon rank-sum test or Cohen's *d* for the *t*-test, as appropriate. [f]Determined by independent two-sided *t*-test. [g]Determined by X^2 test. [h]Determined by Fisher exact test. [i]Determined by Wilcoxon rank-sum test.

reaction response decreases[26]. This is referred to as prepulse inhibition (PPI) and is generally recognized as an operational measure of sensorimotor gating[27–30].

PPI in association with mental health conditions

Mounting evidence points to a role for gonadal hormones, such as progesterone, in the regulation of sensorimotor gating[31,32]. Changes in PPI are seen across the menstrual cycle[33,34] and women who are pregnant show lower levels of PPI compared with women who are postpartum[35]. An increased startle response and reduced levels of PPI have also been found in women with premenstrual dysphoric disorder (PMDD)[36–39].

Gating deficiency, indicated by reduced PPI, is observed in various psychiatric disorders[24,27,36,40,41], including schizophrenia[42,43], antisocial personality disorder[44], obsessive–compulsive disorder[45,46], bipolar disorder[40,47] and post-traumatic stress disorder[48]. Animal and human studies related to PPI and depression have been scarce and have often yielded mixed results. In animal studies, mice with separation-induced depressive symptoms showed lower PPI levels than non-isolated mice in the control group[49,50]. A study[51] investigating PPI in individuals with major depressive disorder found that these individuals only showed a non-significant tendency toward lower PPI than the healthy controls. In another study[24], individuals with only depression or only anxiety were not found to have significantly lower levels of PPI than healthy controls; individuals with comorbid depression and anxiety, however, were found to have significantly lower PPI compared with individuals with depression or anxiety alone and with healthy controls. One previous study investigating PPI in the postpartum period showed that sensorimotor gating was reduced among women with PPD[36].

Prediction of PPD

There is a growing body of knowledge suggesting that mental disorders can be predicted with the use of biomarkers[52]. Relatively high levels of sensorimotor gating have been associated with better future treatment response to cognitive behavioral therapy in patients with schizophrenia[53], and a recent study investigating PPI in individuals at clinically high risk for psychosis found that deficits in PPI occur before the onset of full-scale psychosis[54]. Previous research aimed at predicting PPD has suggested models based on self-reports and clinical health characteristics[11,55]; however, the use of physiological measures to predict PPD has remained largely unexplored.

Despite findings supporting that PPI is reduced in depression and in PPD and that alterations of PPI are seen in pregnancy, there have not been studies investigating the potential of reduced PPI in pregnancy to predict the development of postpartum depressive symptoms. Thus this study aimed to investigate whether PPI, measured in late pregnancy, could predict depressive symptom status at 6 weeks postpartum. Furthermore, we aimed to explore the predictive value of PPI among women with and without depressive symptoms during

Table 2 | Logistic-regression-derived ORs and 95% CIs for the association between PPI and PPD

	Crude, OR (95% CI); *P* value[a]	Adjusted models, aOR (95% CI); *P* value[b]				
		PPI at 72 dB	PPI at 74 dB	PPI at 78 dB	PPI at 86 dB	Global PPI
Variables						
PPI at 72 dB	0.99 (0.98–1.01); 0.24	0.99 (0.97–1.00); 0.10				
PPI at 74 dB	1.00 (0.98–1.01); 0.73		0.99 (0.96–1.01); 0.35			
PPI at 78 dB	0.99 (0.98–1.00); 0.06			0.98 (0.96–1.00); 0.11		
PPI at 86 dB	0.99 (0.98–1.00); 0.08				0.97 (0.94–1.00); **0.04**	
Global PPI	0.99 (0.97–1.00); 0.09					0.97 (0.94–1.00); 0.06
Pregnancy depression	10.3 (4.22–28.1); **0.001**	8.04 (2.56–28.5); **0.001**	4.99 (1.40–9.6); **0.02**	4.95 (1.27–20.9); **0.02**	1.87 (0.36–10.3); 0.45	3.71 (0.95–15.3); 0.06
Interactions						
PPI at 72 dB and pregnancy depression		1.01 (0.98–1.05); 0.38				
PPI at 74 dB and pregnancy depression			1.02 (0.98–1.05); 0.28			
PPI at 78 dB and pregnancy depression				1.01 (0.98–1.05); 0.37		
PPI at 86 dB and pregnancy depression					1.04 (1.00–1.08); **0.04**	
Global PPI and pregnancy depression						1.03 (0.99–1.08); 0.11

Interaction terms between PPI at different levels and pregancy depression are included. Bold values indicate $P < 0.05$. [a]Univariable logistic regression. [b]Model had interaction term between PPI and depression during pregnancy, adjusted for initial startle response value, maternal age, prepregnancy BMI, education level (university versus non-university), employment (employed full-time or part-time versus unemployed/studying/parental leave/sick leave), anxiety at time of ASR measurement, PMS or PMDD (yes versus no), SSRI use in pregnancy (yes versus no) and sleep the night before ASR measurement.

pregnancy. We hypothesized that reduced PPI in late pregnancy would be predictive of depression in the postpartum period.

Results

Sample characteristics

Data were drawn from a longitudinal study about perinatal depression from Uppsala, Sweden, named the Biology, Affect, Stress, Imaging and Cognition (BASIC) cohort[56]. In this substudy, pregnant women participating in the BASIC study were invited between January 2010 and May 2013 during gestational weeks 35–39 to measure the ASR and the PPI[57]. Depression status during pregnancy and at 6 weeks postpartum was assessed by the Edinburgh Postnatal Depression Scale (EPDS).

Out of 179 participants with complete data, 28 reported scores of 12 or more on the EPDS at 6 weeks postpartum and were categorized as having developed PPD (15.6%). Women with PPD were less likely to have attended university ($P = 0.02$), or to be working full- or part-time ($P < 0.001$) than women without PPD (Table 1). Women with PPD were also more likely to have depression during pregnancy ($P < 0.001$) and anxiety at the time of ASR measurements ($P < 0.001$) than women without PPD. Moreover, women with PPD were more likely to have had premenstrual syndrome (PMS) or PMDD when not pregnant ($P = 0.003$). No group differences were found in age, prepregnancy body mass index (BMI), selective serotonin reuptake inhibitor (SSRI) use during pregnancy, sleep the night before ASR measurement and baseline ASR (Table 1).

Results from testing the association between PPI and PPD

The associations between the PPI measures at 72 dB, 76 dB, 78 dB and 86 dB; a combined measure of global PPI; and PPD were investigated using logistic regression. In the crude models, inhibition following all prepulse decibel levels was not significantly associated with PPD.

In the adjusted models, including interaction terms for PPI and depression during pregnancy, significant negative associations were found between PPI at 86 dB and PPD. For every unit increase in PPI at 86 dB, the odds of developing PPD decreased by 3% (adjusted odds ratio (aOR), 0.97; 95% confidence interval (CI), 0.93–1.00; $P = 0.04$; Table 2). In the same model, a significant interaction was found between PPI at 86 dB and depression during pregnancy in association with PPD (aOR, 1.04; 95% CI, 1.00–1.08; $P = 0.04$; Table 2).

Analyses were then stratified according to depression during pregnancy. Among participants without depression during pregnancy ($n = 124$), baseline ASR was not significantly different between those with and those without PPD (Fig. 1a). As PPI levels were found to not be

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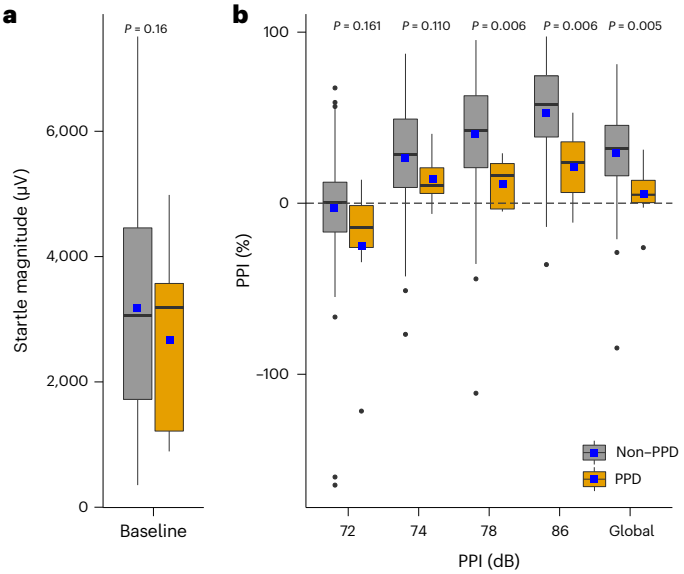

Fig. 1 | The startle magnitude and percentage PPI among women without pregnancy depression. a,**b**, Boxplots for results of two-sided Wilcoxon rank-sum tests for startle magnitude at baseline (**a**) and percentage PPI across prepulse intervals (**b**) among women without pregnancy depression ($n = 124$). Boxplots consist of the interquartile range (IQR) and the median, and whiskers are 1.5× IQR. Outliers are defined as values >1.5× IQR and are shown as dots. The blue square corresponds to the mean. Dashed line corresponds to 0% PPI.

normally distributed, non-parametric tests were conducted to assess PPD versus non-PPD group differences in startle magnitude and across prepulse intervals for women who were not depressed during pregnancy. Wilcoxon rank-sum tests revealed that PPI at 78 dB, PPI at 86 dB and global PPI were significantly different between those with and those without PPD (Fig. 1b). Using multivariable logistic regression, the odds for PPD were reduced by 3% for every unit increase in PPI at 86 dB (aOR, 0.95; 95% CI, 0.91–0.99; $P = 0.04$; Table 3 and Supplementary Table 1). This association was not found for participants with depression during pregnancy (aOR, 1.01; 95% CI, 0.98–1.03; $P = 0.62$; Table 3). Among those without pregnancy depression, ASR was not significant in any of the models (Supplementary Table 1).

Receiver operating characteristic curve analyses for prediction of PPD using PPI

We used receiver operating characteristic curve (ROC) analyses to determine the ability of PPI at 86 dB to predict PPD in women not depressed during pregnancy (Fig. 2). The area under the curve (AUC) for the crude model (only PPI at 86 dB) was 81.1%. The coordinates of the curve (sensitivity and specificity) are shown in Supplementary Table 2 along with the corresponding values of percentage reduction at each level of sensitivity and specificity. The AUC for the adjusted model (PPI at 86 dB together with covariates) was 90.5%, and the AUC for the covariates-only model (excluding PPI at 86 dB) was 87.1%. There was no significant difference in AUC between the crude and adjusted models ($P = 0.07$), the crude and covariates-only models $P = 0.46$), and the covariates-only and adjusted model ($P = 0.43$).

Discussion

This study set out to investigate if sensorimotor gating, that is, the ability to inhibit ASR following a prepulse signal, measured in late pregnancy, could predict PPD. Among women without depressive symptoms during pregnancy, we found that inhibition of the ASR following a prepulse signal at 86 dB, measured during weeks gestational weeks 35–39, was associated with PPD. Although the addition of PPI did not significantly improve predictive power for PPD in existing models

Table 3 | Association of PPI at 86 dB and PPD stratified by depression during pregnancy using multivariate logistic regression

Model	OR (95% CI)	*P* value
PPI at 86 dB among women without pregnancy depression	0.96 (0.91–0.99)	**0.04**
PPI at 86 dB among women with pregnancy depression	1.01 (0.98–1.03)	0.63

Both models were adjusted for initial startle response value, maternal age, prepregnancy BMI, education level (university versus non-university), employment (employed full-time or part-time versus unemployed/studying/parental leave/sick leave), anxiety at the time of ASR measurement, PMS or PMDD (yes versus no), SSRI use in pregnancy (yes versus no) and sleep the night before ASR measurement. Bold text indicates $P < 0.05$.

comprising self-report scales, we found that PPI at 86 dB alone had good predictive power for new-onset depression. We have shown the potential of PPI as an objective biological measure to be used in late pregnancy for predicting women at risk for new-onset depressive symptoms postpartum.

Previous studies used PPI measurement as a predictive marker for schizophrenia[54,58,59]. Our findings expand the predictive potential of PPI in psychiatric disorders to include PPD. One previous study[36] investigating PPI in the postpartum period found reduced sensorimotor gating at 78 dB and 86 dB among women with concurrent PPD. However, the presence of depressive symptoms during pregnancy was not investigated and PPI was measured only during the postpartum period. Our study showed that lower PPI was already present in late pregnancy, before the onset of depressive symptoms in the puerperium. Interestingly, this marker predicted only new-onset PPD and was not predictive of the continuation or amelioration of symptoms among those who were already depressed during pregnancy. Moreover, when we compared the AUC of the covariates-only model with that of the crude model (only PPI at 86 dB), they were not significantly different. In both models, the AUC is considered good, implying the potential of PPI as an objective measure to predict PPD. Although self-report covariates are easily obtained, they can still be subjective and vulnerable to self-report bias. Previous research also suggests that self-report measures alone may be insufficient as there is a reluctance to seek help even among women who recognize that they are suffering from poor mental health[60]. PPI measurement, although comparatively indirect, provides a method to objectively measure physiological changes. This study provides proof of concept for the use of non-invasive physiological measures to predict postpartum-onset depression.

Although the exact underlying pathophysiology is still unclear, sensitivity to stress and hormonal changes may be related to our findings. As previously discussed, gonadal hormones, such as estrogen and progesterone, dramatically increase during pregnancy, which can result in decreased activity in areas associated with stress regulation, such as the HPA axis[22]. Higher estrogen and progesterone levels have also been associated with decreased PPI in both non-pregnant[34] and pregnant women[35]. Another measure of HPA axis stress system dysregulation, the cortisol-awakening response, was shown to be positively associated with PPI at 86 dB in women who are pregnant[57]. Furthermore, the amount of perceived stress increases during pregnancy and childbirth[19]. Although all women who are pregnant are exposed to endocrine and physical challenges, there are individual differences in the capacity to regulate these stressors. Previous studies have shown that stress adaptation is predictive of mental health outcomes[20] and that PPI is impaired by stress in both animal and human models[61,62]. Future research could investigate if individuals with lower pregnancy PPI are also at an increased risk of a future diagnosis of bipolar disorder. Individuals with early postpartum onset of depression have been shown to be at increased risk of later conversion to bipolar disorder[63] and, like depression, bipolar disorder has been shown to be associated with

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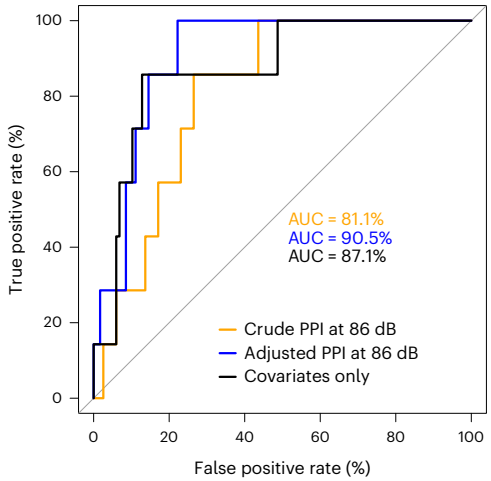

Fig. 2 | AUC for different models computed for women without pregnancy depression. The percentage AUC for the crude model (only PPI at 86 dB), adjusted model (PPI at 86 dB together with covariates) and covariate-only model (excluding PPI at 86 dB) as an estimate of the ability of PPI at 86 dB to predict PPD for participants without depression during pregnancy.

increased sensitivity to both gonadal and stress hormones[64]. At present, increased sensitivity to hormonal changes and stress during pregnancy is primarily recognized when scores on psychological self-report questionnaires meet a certain clinical threshold indicating adverse symptoms. Our results may have captured an element of identification of at-risk individuals that could otherwise be overlooked via self-report methods; some women who do not report depressive symptoms during pregnancy may be showing subtle, yet measurable, physiological markers of hormonal and stress sensitivity. As objective, predictive tools are still lacking in routine care, future studies should validate laboratory findings, such as those in this study, using feasible portable devices or mobile phone applications for use in pregnant women to improve identification and early intervention for prevention of PPD.

This study has strengths and limitations. It is among very few studies that have explored PPI as a tool to determine those at risk for developing psychiatric disorders, and no previous study has investigated risk for PPD. Given the well-characterized cohort in our study, we could adjust for several relevant variables. The sample size is modest compared with other studies using PPI as a predictive marker; further studies with larger sample sizes are, therefore, needed to confirm our findings. In this study, PPI was measured only at a single time point. Collecting PPI measurements at several time points throughout pregnancy until postpartum may give a better picture of the patterns in sensorimotor gating during this vulnerable and dynamic period and may improve prediction of women at risk for developing PPD. Furthermore, although we included a global PPI measurement to take into account all prepulse intervals, we also prioritized isolating each prepulse decibel level in independent analyses to investigate their specific contributions. However, we acknowledge that prepulse levels cannot be viewed entirely independently as they were administered within the same experimental protocol. Future studies should replicate our findings using only PPI at 86 dB to verify our results and further optimize experimental conditions for use in a clinical setting. Sleep could be an important confounder when studying PPI and it might be a limitation that the sleep variable used was a single-item measure of the sleep experienced the night before the ASR test instead of a more comprehensive measure of sleep. However, PPI was measured before birth, that is, before the major changes in sleep duration and quality that arise because of a newborn. An additional limitation was that other potential conditions, such as intellectual disability, personality disorders and substance abuse, were not taken into consideration in this study.

Conclusions

Decreased PPI during late pregnancy was predictive of new-onset depressive symptoms postpartum. Our study encourages further investigation into the potential of PPI as a non-invasive biological measure to identify women who may develop PPD, especially among women who do not display established risk factors, such as previous depression. Further studies are warranted to develop clinically feasible tools for the use of PPI measurement in routine care.

Methods

Participants and data collection

This study was conducted as a part of the BASIC study[56] in Uppsala, Sweden. Women were invited to participate in the BASIC study in association with the routine ultrasound visit between pregnancy weeks 16 and 18. Exclusion criteria included inadequate understanding of Swedish, age less than 18 years, protected identity, bloodborne illness and an unviable pregnancy as diagnosed by routine ultrasound. Women who agreed to participate filled out online questionnaires twice during pregnancy and again at 6 weeks postpartum, including the EPDS. The EPDS is a screening tool consisting of ten self-report questions to detect depression in pregnant and postpartum women[65], which has been validated in Sweden[66]. The online questionnaires also included sociodemographic information (age, education and employment status) and information related to general, mental, and pregnancy health and lifestyle (for example, smoking habits, prepregnancy weight and depression history). Premenstrual mood symptoms preceding pregnancy were also reported in the survey and classified into PMS or, if symptoms had a negative effect on social activities or relationships, PMDD. Data on SSRI use were collected at week 32. Data on gestational length were retrieved from medical records after delivery. Participants were selected for the substudy based on their reported scores on the week 32 EPDS, and women with EPDS scores of ≥13 were oversampled. The participation rate in the substudies within the whole BASIC cohort study was 48.8% for pregnancy test sessions[56]. Exclusion criteria for the substudy included pregnancy-related conditions such as preeclampsia, gestational diabetes, intrauterine growth restriction and twin pregnancy. The study was approved by the Regional Ethical Review Board at Uppsala University (number 2009/171) and the study procedure was conducted in accordance with ethical standards for human experimentation. Written informed consent was obtained from all participants. Participants in the substudy were compensated with two cinema tickets after the measurements.

Experimental procedure

At approximately gestational week 38, women included in the current substudy came to the research laboratory for measurements. The eyeblink component of the ASR was measured using electromyographic measurements of the orbicularis oculi muscle, which is innervated by the facial nerve[67], applied on the orbicularis oculi muscle of the right eye. The startle pulse was delivered in earphones in both ears (TDH-39-P; Maico) and a startle system (SR-HLAB; San Diego Instruments) was used to record the startle reflex. A Quest electronics meter was used to calibrate the sound (model 210; Quest Technologies). Two electromyographic electrodes (In Vivo Metric) were used to record the blink response; one electrode was placed below the right eye in line with the pupil and the second electrode was placed 1–2 cm laterally to the first. Furthermore, an isolated ground electrode was placed in the middle of the forehead to function as an electrically inactive site.

The participants were first exposed to 5 min of background white noise of 70 dB, followed by the experiment consisting of 3 blocks of trials. Between each trial, 70 dB of background white noise would resume. Block 1 examined the baseline startle response and had 5 startle pulse trials of 115 dB and 40 ms background white noise. Blocks 2 and 3 included 25 trials in pseudo-random order; 5 trials comprised only startle pulses and in 20 trials a prepulse noise burst lasting 20 ms

occurred 100 ms before the startle pulse. The prepulse noise bursts were 72 dB, 74 dB, 78 dB and 86 dB.

The ASR was measured as peak startle amplitudes within 20–150 ms from the onset of the startle pulse. If the peak startle occurred before 20 ms or after 150 ms, if the baseline shift was more than 40 arbitrary units (1 unit equaled 0.076 mV) or if the startle response was 25 arbitrary amplitude units or less, the participant was considered a non-responder and excluded from further analyses.

In conjunction with the ASR measurement, participants were asked to rate their sleep the night before the experiment. The Mini International Neuropsychiatric Interview (MINI) was conducted to investigate symptoms of depression and anxiety during pregnancy[68].

Study sample

Nine women in the substudy chose not to participate in the PPI measurement, three chose to cease participation because the task was challenging, two participants had technical issues in the measurements and six were found to be non-responders. This resulted in 214 women with complete PPI data, of which 207 completed the EPDS 6-weeks-postpartum outcome measure. An additional 28 participants had missing data on covariates from the questionnaires or interviews (sleep the previous night, prepregnancy BMI, presence of PMS or PMDD, education and/or employment) resulting in a final sample size of 179 women.

For categorization of pregnancy depression, women with major depression according to the MINI at the time of ASR measurement or who scored 12 or higher on the EPDS at week 32 of gestation were considered depressed during pregnancy. For categorization of PPD, participants scoring between 0 and 11 on the EPDS at 6 weeks postpartum were considered as not having depressive symptoms, whereas women scoring 12 or higher were considered to have depressive symptoms, hereafter referred to as non-PPD and PPD, respectively[69,70].

Statistical analysis

Calculation of the PPI is the percentage reduction in peak magnitude of the startle on pulse-alone trials and is calculated using the formula below[57]:

$$\%\mathrm{PPI} = 100 \times \frac{M_{\mathrm{PA}} - M_{\mathrm{PP}}}{M_{\mathrm{PA}}}$$

where M_{PA} is the mean magnitude of pulse alone in blocks 2 and 3 and M_{PP} is the mean magnitude of prepulse + pulse blocks. This was done for each prepulse level. Global PPI was also calculated using the formula below:

$$\%\text{Global PPI} = 100 \times \frac{M_{\mathrm{PA}} - ((M_{\mathrm{PP72}} + M_{\mathrm{PP74}} + M_{\mathrm{PP78}} + M_{\mathrm{PP86}})/4)}{M_{\mathrm{PA}}}$$

in which M_{PP72} is PPI at 72 dB, M_{PP74} is PPI at 74 dB, M_{PP78} is PPI at 78 dB, and M_{PP86} is PPI at 86 dB. Descriptive statistics related to background and pregnancy variables and PPI were used to determine group differences between non-PPD and PPD women. Independent t-tests, Wilcoxon rank-sum, or χ^2 tests were conducted based on whether the variables of interest were continuous (parametric versus non-parametric) or categorical. To determine the association between PPI and PPD, logistic regressions were performed for PPI at each decibel level and global PPI with PPD as the outcome. The following types of models were included in the logistic regression analyses: a crude (or univariate) model and an adjusted model. The adjusted model controlled for background and pregnancy covariates, including initial startle response value, maternal age, prepregnancy BMI, education level (university versus non-university), employment (employed full-time or part-time versus unemployed/studying/parental leave/sick leave), anxiety at the time of ASR measurement, PMS or PMDD (yes versus no), SSRI use in pregnancy (yes versus no) and sleep the night before ASR measurement. An interaction term between pregnancy depression (yes versus no) and PPI was also included in the adjusted model. Analyses were then stratified according to depression during pregnancy to further test the interaction between pregnancy depression and PPI. Background and pregnancy covariates controlled for in the adjusted model (apart from depression during pregnancy) were also controlled for in the stratified model. Differences in the PPD versus non-PPD group in startle magnitude and across prepulse intervals for women not depressed during pregnancy were assessed using Wilcoxon rank-sum tests and were visualized using boxplots.

The area under the ROC curve was calculated to estimate the ability of PPI at 86 dB to predict PPD for participants without depression during pregnancy. AUCs derived from the crude model (only PPI at 86 dB), adjusted model (PPI at 86 dB together with covariates) and an additional model with only covariates (excluding PPI at 86 dB) were compared based on the bootstrap percentile method[71,72].

Statistical analyses were conducted using the R programming language[73] through RStudio[74] with packages ggplot2[75], reshape2[76], pROC[71], cutpointr[77] and mice[72]. The significance level was set at $P < 0.05$.

Reporting summary

Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

Data availability

The data used in this study are available upon reasonable request. Owing to privacy and ethical considerations, the data are not publicly available.

Code availability

Computer code used for this project is shared at https://github.com/rdbjorvang/Eriksson_2023_prepulseinhibition_postpartumdepression.

References

1. *Diagnostic and Statistical Manual of Mental Disorders* 5th edn (American Psychiatric Organization, 2013).
2. Skalkidou, A., Hellgren, C., Comasco, E., Sylven, S. & Sundstrom Poromaa, I. Biological aspects of postpartum depression. *Womens Health* **8**, 659–672 (2012).
3. Wikman, A. et al. Characteristics of women with different perinatal depression trajectories. *J. Neurosci. Res.* **98**, 1268–1282 (2020).
4. Mehta, D. et al. Early predictive biomarkers for postpartum depression point to a role for estrogen receptor signaling. *Psychol. Med.* **44**, 2309–2322 (2014).
5. Sit, D., Seltman, H. & Wisner, K. L. Seasonal effects on depression risk and suicidal symptoms in postpartum women. *Depress. Anxiety* **28**, 400–405 (2011).
6. Iliadis, S. I. et al. Self-harm thoughts postpartum as a marker for long-term morbidity. *Front. Public Health* **6**, 34 (2018).
7. Orsolini, L. et al. Suicide during perinatal period: epidemiology, risk factors, and clinical correlates. *Front. Psychiatry* **7**, 138 (2016).
8. Eckerdal, P. et al. Delineating the association between heavy postpartum haemorrhage and postpartum depression. *PLoS ONE* **11**, e0144274 (2016).
9. Blom, E. A. et al. Perinatal complications increase the risk of postpartum depression. The Generation R Study. *BJOG* **117**, 1390–1398 (2010).
10. Silverman, M. E. et al. The risk factors for postpartum depression: a population-based study. *Depress. Anxiety* **34**, 178–187 (2017).
11. Andersson, S., Bathula, D. R., Iliadis, S. I., Walter, M. & Skalkidou, A. Predicting women with depressive symptoms postpartum with machine learning methods. *Sci. Rep.* **11**, 7877 (2021).
12. Iliadis, S. I. et al. Personality and risk for postpartum depressive symptoms. *Arch. Womens Ment. Health* **18**, 539–546 (2015).

13. Asif, S. et al. Severe obstetric lacerations associated with postpartum depression among women with low resilience-a Swedish birth cohort study. *BJOG* **127**, 1382–1390 (2020).
14. O'Hara, M. W. & Wisner, K. L. Perinatal mental illness: definition, description and aetiology. *Best Pract. Res. Clin. Obstet. Gynaecol.* **28**, 3–12 (2014).
15. Seimyr, L., Welles-Nyström, B. & Nissen, E. A history of mental health problems may predict maternal distress in women postpartum. *Midwifery* **29**, 122–131 (2013).
16. Jamshaid, S. et al. Postpartum depression and health: role of perceived social support among Pakistani women. *Diseases* **11**, 53 (2023).
17. Iliadis, S. I. et al. Mid-pregnancy corticotropin-releasing hormone levels in association with postpartum depressive symptoms. *Depress. Anxiety* **33**, 1023–1030 (2016).
18. Schweizer-Schubert, S. et al. Steroid hormone sensitivity in reproductive mood disorders: on the role of the $GABA_A$ receptor complex and stress during hormonal transitions. *Front. Med.* **7**, 479646 (2020).
19. Brislane, Á., Steinback, C. D. & Davenport, M. H. The 9-month stress test: pregnancy and exercise—similarities and interactions. *Can. J. Cardiol.* **37**, 2014–2025 (2021).
20. Arnaldo, I., Corcoran, A. W., Friston, K. J. & Ramstead, M. J. D. Stress and its sequelae: an active inference account of the etiological pathway from allostatic overload to depression. *Neurosci. Biobehav. Rev.* **135**, 104590 (2022).
21. Jacobson, L. Hypothalamic-pituitary-adrenocortical axis: neuropsychiatric aspects. *Compr Physiol.* **4**, 715-738 (2014).
22. Christian, L. M. Physiological reactivity to psychological stress in human pregnancy: current knowledge and future directions. *Prog. Neurobiol.* **99**, 106–116 (2012).
23. Adler, L. E. et al. Neurophysiological evidence for a defect in neuronal mechanisms involved in sensory gating in schizophrenia. *Biol. Psychiatry* **17**, 639–654 (1982).
24. Storozheva, Z. I. et al. Sensorimotor and sensory gating in depression, anxiety, and their comorbidity. *World J. Biol. Psychiatry* **22**, 183–193 (2021).
25. Koch, M. The neurobiology of startle. *Prog. Neurobiol.* **59**, 107–128 (1999).
26. Blumenthal, T. D., Reynolds, J. Z. & Spence, T. E. Support for the interruption and protection hypotheses of prepulse inhibition of startle: evidence from a modified Attention Network Test. *Psychophysiology* **52**, 397–406 (2015).
27. Cromwell, H. C., Mears, R. P., Wan, L. & Boutros, N. N. Sensory gating: a translational effort from basic to clinical science. *Clin. EEG Neurosci.* **39**, 69–72 (2008).
28. Gómez-Nieto, R., Hormigo, S. & López, D. E. Prepulse inhibition of the auditory startle reflex assessment as a hallmark of brainstem sensorimotor gating mechanisms. *Brain Sci.* **10**, 639 (2020).
29. Hoffman, H. S. & Searle, J. L. Acoustic and temporal factors in the evocation of startle. *J. Acoust. Soc. Am.* **43**, 269–282 (1968).
30. Graham, F. K. Presidential Address, 1974. The more or less startling effects of weak prestimulation. *Psychophysiology* **12**, 238–248 (1975).
31. Kumari, V. et al. Evidence for a role of progesterone in menstrual cycle-related variability in prepulse inhibition in healthy young women. *Neuropsychopharmacology* **35**, 929–937 (2010).
32. Bannbers, E., Kask, K., Wikström, J. & Sundström Poromaa, I. Lower levels of prepulse inhibition in luteal phase cycling women in comparison with postmenopausal women. *Psychoneuroendocrinology* **35**, 422–429 (2010).
33. Swerdlow, N. R., Hartman, P. L. & Auerbach, P. P. Changes in sensorimotor inhibition across the menstrual cycle: implications for neuropsychiatric disorders. *Biol. Psychiatry* **41**, 452–460 (1997).
34. Jovanovic, T. et al. Menstrual cycle phase effects on prepulse inhibition of acoustic startle. *Psychophysiology* **41**, 401–406 (2004).
35. Kask, K., Bäckström, T., Gulinello, M. & Sundström-Poromaa, I. Lower levels of prepulse inhibition of startle response in pregnant women compared to postpartum women. *Psychoneuroendocrinology* **33**, 100–107 (2008).
36. Comasco, E. et al. Sleep duration, depression, and oxytocinergic genotype influence prepulse inhibition of the startle reflex in postpartum women. *Eur. Neuropsychopharmacol.* **26**, 767–776 (2016).
37. Comasco, E., Hellgren, C., Olivier, J., Skalkidou, A. & Poromaa, I. S. Supraphysiological hormonal status, anxiety disorders, and COMT Val/Val genotype are associated with reduced sensorimotor gating in women. *Psychoneuroendocrinology* **60**, 217–223 (2015).
38. Hantsoo, L., Golden, C., Kornfield, S., Grillon, C. & Epperson, C. N. Startling differences: using the acoustic startle response to study sex differences and neurosteroids in affective disorders. *Curr. Psychiatry Rep.* **20**, 40 (2018).
39. Kask, K., Gulinello, M., Bäckström, T., Geyer, M. A. & Sundström-Poromaa, I. Patients with premenstrual dysphoric disorder have increased startle response across both cycle phases and lower levels of pre-pulse inhibition during the late luteal phase of the menstrual cycle. *Neuropsychopharmacology* **33**, 2283–2290 (2008).
40. Mao, Z. et al. Prepulse inhibition in patients with bipolar disorder: a systematic review and meta-analysis. *BMC Psychiatry* **19**, 282 (2019).
41. Venables, P. H. Input dysfunction in schizophrenia. *Prog. Exp. Pers. Res.* **72**, 1–47 (1964).
42. San-Martin, R. et al. Meta-analysis of sensorimotor gating deficits in patients with schizophrenia evaluated by prepulse inhibition test. *Schizophr. Bull.* **46**, 1482–1497 (2020).
43. Braff, D. et al. Prestimulus effects on human startle reflex in normals and schizophrenics. *Psychophysiology* **15**, 339–343 (1978).
44. Kumari, V. et al. Association between violent behaviour and impaired prepulse inhibition of the startle response in antisocial personality disorder and schizophrenia. *Behav. Brain Res.* **158**, 159–166 (2005).
45. Ahmari, S. E., Risbrough, V. B., Geyer, M. A. & Simpson, H. B. Impaired sensorimotor gating in unmedicated adults with obsessive-compulsive disorder. *Neuropsychopharmacology* **37**, 1216–1223 (2012).
46. Swerdlow, N. R., Benbow, C. H., Zisook, S., Geyer, M. A. & Braff, D. L. A preliminary assessment of sensorimotor gating in patients with obsessive compulsive disorder. *Biol. Psychiatry* **33**, 298–301 (1993).
47. Perry, W., Minassian, A., Feifel, D. & Braff, D. L. Sensorimotor gating deficits in bipolar disorder patients with acute psychotic mania. *Biol. Psychiatry* **50**, 418–424 (2001).
48. Pineles, S. L. et al. Prepulse inhibition deficits in women with PTSD. *Psychophysiology* **53**, 1377–1385 (2016).
49. Martin, A. L. & Brown, R. E. The lonely mouse: verification of a separation-induced model of depression in female mice. *Behav. Brain Res.* **207**, 196–207 (2010).
50. Li, N. et al. Auditory fear conditioning modulates prepulse inhibition in socially reared rats and isolation-reared rats. *Behav. Neurosci.* **122**, 107–118 (2008).
51. Perry, W., Minassian, A. & Feifel, D. Prepulse inhibition in patients with non-psychotic major depressive disorder. *J. Affect. Disord.* **81**, 179–184 (2004).
52. Chesnut, M. et al. Stress markers for mental states and biotypes of depression and anxiety: a scoping review and preliminary illustrative analysis. *Chronic Stress* **5**, 24705470211000338 (2021).
53. Kumari, V. et al. Sensorimotor gating and clinical outcome following cognitive behaviour therapy for psychosis. *Schizophr. Res.* **134**, 232–238 (2012).

54. Bo, Q. et al. Impaired sensorimotor gating using the acoustic prepulse inhibition paradigm in individuals at a clinical high risk for psychosis. *Schizophr. Bull.* **47**, 128–137 (2021).
55. Munk-Olsen, T. et al. Postpartum depression: a developed and validated model predicting individual risk in new mothers. *Transl. Psychiatry* **12**, 419 (2022).
56. Axfors, C. et al. Cohort profile: the Biology, Affect, Stress, Imaging and Cognition (BASIC) study on perinatal depression in a population-based Swedish cohort. *BMJ Open* **9**, e031514 (2019).
57. Breedh, J. et al. Hypothalamic–pituitary–adrenal axis responsiveness, startle response, and sensorimotor gating in late pregnancy. *Psychoneuroendocrinology* **106**, 1–8 (2019).
58. De Koning, M. B. et al. Pre-pulse inhibition and striatal dopamine in subjects at an ultra-high risk for psychosis. *J. Psychopharmacol.* **28**, 553–560 (2014).
59. Togay, B. et al. Lower prepulse inhibition in clinical high-risk groups but not in familial risk groups for psychosis compared with healthy controls. *Early Interv. Psychiatry* **14**, 196–202 (2020).
60. Sorsa, M. A., Kylmä, J. & Bondas, T. E. Contemplating help-seeking in perinatal psychological distress-a meta-ethnography. *Int. J. Environ. Res. Public Health* **18**, 5226 (2021).
61. Rubio, G. et al. Stress induced by the socially evaluated cold-pressor test cause equivalent deficiencies of sensory gating in male subjects with schizophrenia and healthy controls. *Psychiatry Res.* **228**, 283–288 (2015).
62. De la Casa, L. G., Mena, A. & Ruiz-Salas, J. C. Effect of stress and attention on startle response and prepulse inhibition. *Physiol. Behav.* **165**, 179–186 (2016).
63. Munk-Olsen, T. et al. Genetic liability to bipolar disorder and onset of postpartum mental disorders. *J. Ment. Health* **26**, e300835 (2023).
64. Slyepchenko, A., Minuzzi, L. & Frey, B. N. Comorbid premenstrual dysphoric disorder and bipolar disorder: a review. *Front. Psychiatry* **12**, 719241 (2021).
65. Cox, J. L., Holden, J. M. & Sagovsky, R. Detection of postnatal depression. Development of the 10-item Edinburgh Postnatal Depression Scale. *Br. J. Psychiatry* **150**, 782–786 (1987).
66. Wickberg, B. & Hwang, C. P. The Edinburgh Postnatal Depression Scale: validation on a Swedish community sample. *Acta Psychiatr. Scand.* **94**, 181–184 (1996).
67. Grillon, C. & Baas, J. A review of the modulation of the startle reflex by affective states and its application in psychiatry. *Clin. Neurophysiology* **114**, 1557–1579 (2003).
68. Sheehan, D. V. et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *J. Clin. Psychiatry* **59**, 22–33 (1998).
69. Rubertsson, C., Börjesson, K., Berglund, A., Josefsson, A. & Sydsjö, G. The Swedish validation of Edinburgh Postnatal Depression Scale (EPDS) during pregnancy. *Nord. J. Psychiatry* **65**, 414–418 (2011).
70. Levis, B., Negeri, Z., Sun, Y., Benedetti, A. & Thombs, B. D. Accuracy of the Edinburgh Postnatal Depression Scale (EPDS) for screening to detect major depression among pregnant and postpartum women: systematic review and meta-analysis of individual participant data. *BMJ* **371**, m4022 (2020).
71. Robin, X. et al. pROC: an open-source package for R and S+ to analyze and compare ROC curves. *BMC Bioinf.* **12**, 77 (2011).
72. van Buuren, S. & Groothuis-Oudshoorn, K. mice: Multivariate Imputation by Chained Equations in R. *J. Stat. Softw.* **45**, 1–67 (2011).
73. R Core Team *R: A Language and Environment for Statistical Computing*. http://www.R-project.org/ (R Foundation for Statistical Computing, 2020).
74. RStudio: Integrated Development for R. http://www.rstudio.com/ (RStudio, 2016).
75. Wickham, H. *ggplot2: Elegant Graphics for Data Analysis* (Springer, 2016).
76. Wickham, H. Reshaping data with the reshape package. *J. Stat. Softw.* **21**, 1–20 (2007).
77. Thiele, C. & Hirschfeld, G. cutpointr: Improved Estimation and Validation of Optimal Cutpoints in R. *J. Stat. Softw.* **98**, 1–27 (2021).

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Author contributions

E.F. and A.S. supervised the project. I.S.P. designed the study. A.E. and R.D.B. wrote the article and performed statistical analyses. E.F., F.C.P., I.S.P. and A.S. assisted with statistical methodology and interpretation of data. A.E., R.D.B., E.A., F.C.P., I.S.P., A.S. and E.F. critically revised and approved the final version of the article.

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Competing interests

The authors declare that they have no competing interests.

Additional information

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Correspondence and requests for materials should be addressed to Emma Fransson.

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Software and code

Policy information about availability of computer code

Data collection: The startle pulse was delivered in earphones in both ears (TDH-39-P, Maico, Minneapolis, USA) and a startle system (SR-HLAB, San Diego Instruments, San Diego, CA, USA) was used to record the startle reflex. A Quest electronics meter was used to calibrate the sound (model 210 Quest Technologies, Oconomov, WI). Two EMG electrodes (In Vivo Metric, Healdsburg, CA, USA) were used to record the blink response; one electrode was placed below the right eye in line with the pupil and the second electrode was placed 1-2 cm laterally to the first. Further, an isolated ground electrode was placed in the middle of the forehead to function as an electrically inactive site.

Data analysis	Statistical analyses were conducted using R programming language [1] through RStudio version 2023.12.0+369 [2] with packages ggplot2 version 3.4.4 [3], reshape version 1.4.4 [4], pROC version 1.18.5 [5], cutpointr version 1.1.2 [6], and mice version 3.16.0 [7]. 1 RC Team, R: A language and environment for statistical computing., 2020 2 RStudio, RStudio: integrated development environment for R. , 2016 3 Wickham. Springer-Verlag New York, 2016 4 Reshaping Data with the reshape Package Journal of Statistical Software, 2007 5 Robin et al., pROC: an open-source package for R and S+ to analyze and compare ROC curves BMC Bioinformatics, 2011 6 Thiele et al., cutpointr: Improved Estimation and Validation of Optimal Cutpoints in R Journal of Statistical Software, 2021 7 van Buuren et al., mice: Multivariate Imputation by Chained Equations in R Journal of Statistical Software, 2011 Computer code for this project is available at: https://github.com/rdbjorvang/Eriksson_2023_prepulseinhibition_postpartumdepression

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Data availability statement
The data utilized in this study are available from the corresponding author upon reasonable request. Due to privacy and ethical considerations, the data are not publicly available.

Research involving human participants, their data, or biological material

Policy information about studies with human participants or human data. See also policy information about sex, gender (identity/presentation), and sexual orientation and race, ethnicity and racism.

Reporting on sex and gender	The title and abstract indicate that this study investigates mental health in association with pregnancy and postpartum. This project includes only female participants, i.e. participants who are pregnant and or postpartum after child birth, regardless if they identify as women or not.
Reporting on race, ethnicity, or other socially relevant groupings	The study setting is Sweden and a high proportion of participants in the main cohort from where this sample was derived belong to the majority population, which is reported in more detail in a cohort description paper. Axfors C, et al.. Cohort profile: the Biology, Affect, Stress, Imaging and Cognition (BASIC) study on perinatal depression in a population-based Swedish cohort. BMJ Open. 2019 PMID: 31641004
Population characteristics	For the purpose of describing the sample (for transparency regarding generalizability) as well as to adjust for potential confounders, information about age in years (median = 31.6), pre-pregnancy BMI (median = 22.8), education (79.3% university vs 20.7% non-university), employment (89.4% working full-/part-time vs. 10.6% unemployed / studying/ sick leave/ parental leave) was reported and investigated in the study.
Recruitment	All pregnant women in the Swedish region of Uppsala was given written information about the mother study (the cohort from where the sample was taken) in association with the routine ultrasound visit between pregnancy weeks 16 – 18. Exclusion criteria included inadequate understanding of Swedish, age less than 18 years, protected identity, bloodborne illness, and an unviable pregnancy as diagnosed by routine ultrasound. Since understanding the Swedish language is a criterion, the study has a higher proportion of majority population compared with pregnant people in Sweden as a whole. The recruitment procedure also imply risk of self-selection bias. Those facts make the results less transferable to minority groups.
Ethics oversight	The study was approved by the Regional Ethical Review Board at Uppsala University (nr 2009/171) and the study procedure was conducted in accordance with ethical standards for human experimentation.

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Behavioural & social sciences study design

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Study description	Data for this sub-study were drawn from a longitudinal, quantitative study about perinatal depression from Uppsala, Sweden named the Biology, Affect, Stress, Imaging, and Cognition (BASIC) cohort.
Research sample	The research sample was comprised of pregnant women from the BASIC cohort who lived in Uppsala, Sweden or surrounding areas at the time of the study. The median age of the women who participated in this study was 31.6 years old with median BMI of 22.8 (within normal range). Participants were generally university educated (79.3%) and employed (89.4%).
Sampling strategy	Stratified random sampling was applied and participants with higher depression outcome scores were oversampled. Based on preliminary data, sufficient power (80% power, alpha = 0.05) to detect associations between neurophysiological measures and mental health symptoms would be reached with 108-136 participants. We aimed for a larger number of participants to enable sub-group analyses (women with and without a history of depression) and to compensate for dropouts.
Data collection	At approximately gestational week 38, women included in the current sub-study came to the research lab for measurements. The eye blink component of the ASR was measured using electromyographic measurements, EMG, of the orbicularis oculi muscle which is innervated by the facial nerve (Grillon & Baas, 2003), applied on the orbicularis oculi muscle of the right eye. The startle pulse was delivered in earphones in both ears (TDH-39-P, Maico, Minneapolis, USA) and a startle system (SR-HLAB, San Diego Instruments, San Diego, CA, USA) was used to record the startle reflex. A Quest electronics meter was used to calibrate the sound (model 210 Quest Technologies, Oconomov, WI). Two EMG electrodes (In Vivo Metric, Healdsburg, CA, USA) were used to record the blink response; one electrode was placed below the right eye in line with the pupil and the second electrode was placed 1-2 cm laterally to the first. Further, an isolated ground electrode was placed in the middle of the forehead to function as an electrically inactive site. The participants were first exposed to five minutes of background white noise of 70 dB, followed by the experiment consisting of three blocks of trials. Between each trial, 70 dB of background white noise would resume. Block 1 examined the baseline startle response and had five startle pulse trials of 115 dB and 40 ms broad-band white noise. Blocks 2 and 3 included 25 trials in pseudo-random order; 5 trials were comprised of only startle pulses and in 20 trials a pre-pulse noise burst lasting 20 ms occurred 100 ms prior to the startle pulse. The pre-pulse noise bursts were 72, 74, 78, and 86 decibels (dB). The ASR was measured as peak startle amplitudes within 20-150 ms from the onset of the startle pulse. If the peak startle occurred before 20 ms or after 150 ms, if the baseline shift was more than 40 arbitrary units (1 unit equaled 0.076 mV), or if the startle response was 25 arbitrary amplitude units or less, it was considered as non-response and excluded from further analyses. In conjunction with the ASR measurement, participants were asked to rate their sleep the night before the experiment. The Mini International Neuropsychiatric Interview (M.I.N.I) was conducted to investigate symptoms of depression and anxiety during pregnancy (Sheehan et al., 1998) Only the participant and researcher were present during the experiment. The researcher was not blind to the study hypotheses, but all participants were exposed to the same experimental protocol.
Timing	The data collection for this study took place between January 2010 and May 2013
Data exclusions	Nine women in the sub-study chose to not participate in the PPI measurement, three chose to cease participation because the task was challenging, two participants had technical issues in the measurements, and six were found to be non-responders. This resulted in 214 with complete PPI data of which 207 completed the EPDS 6 weeks postpartum outcome measure. An additional 28 participants had missing data on covariates from the questionnaires/interviews (sleep the previous night, pre-pregnancy BMI, presence of premenstrual syndrome (PMS) or premenstrual dysphoric disorder (PMDD), education, and/or employment) resulting in a final sample size of 179 women.
Non-participation	The participation rate in the sub-studies within the whole BASIC cohort study was 48.8 % for pregnancy test sessions.[1] 1 C Axfors et al., Cohort profile: the Biology, Affect, Stress, Imaging and Cognition (BASIC) study on perinatal depression in a population-based Swedish cohort BMJ open, 2019
Randomization	Randomization was not possible because participants were grouped by depression category postpartum.

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☒	☐ ChIP-seq
☒	☐ Flow cytometry
☒	☐ MRI-based neuroimaging

Plants

Seed stocks

Report on the source of all seed stocks or other plant material used. If applicable, state the seed stock centre and catalogue number. If plant specimens were collected from the field, describe the collection location, date and sampling procedures.

Novel plant genotypes

Describe the methods by which all novel plant genotypes were produced. This includes those generated by transgenic approaches, gene editing, chemical/radiation-based mutagenesis and hybridization. For transgenic lines, describe the transformation method, the number of independent lines analyzed and the generation upon which experiments were performed. For gene-edited lines, describe the editor used, the endogenous sequence targeted for editing, the targeting guide RNA sequence (if applicable) and how the editor was applied.

Authentication

Describe any authentication procedures for each seed stock used or novel genotype generated. Describe any experiments used to assess the effect of a mutation and, where applicable, how potential secondary effects (e.g. second site T-DNA insertions, mosiacism, off-target gene editing) were examined.