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Male infants and birth complications are associated with increased incidence of postnatal depression

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Abstract

Rationale: A growing body of literature links both depressive symptoms generally, and those specifically in the postnatal period, with an inflammatory immune response. Evolutionary medical approaches, such as the Pathogen Host Defence Theory of Depression, have likened depression to sickness behaviour in other mammals, and propose that the characteristics associated with depression are protective when an individual is experiencing pathogenic threat. Many known risk factors for depressive symptoms are associated with activation of inflammatory pathways, opening up the potential for identifying novel risk factors based on their inflammation causing effects.

Objective: Both the gestation of male foetuses and the experience of birth complications have documented associations with increased inflammation, yet their relationships with postnatal depression (PND) are currently unclear.

Method: Here we use the complete reproductive histories of 296 women from contemporary, low fertility populations gathered by retrospective survey to assess whether the odds of PND increased when mothers gave birth to male infants or experienced birth complications, using generalised estimating equation models controlling for individual effects of the mother and other known PND risk factors.

Results: We found the odds of PND increased by 71-79% when male infants were born compared to female infants. The occurrence of birth complications increased the odds of PND by 174% compared to having no complications. Testing for interaction effects found that, while always at increased risk of PND, women with a tendency towards symptoms of depression, anxiety, and stress at other points in the life course had reduced odds of PND when experiencing birth complications, suggesting such women may elicit greater support.

Conclusions: These results highlight two novel PND risk factors, male infants and birth complications, which can be easily assessed by health professionals.

Keywords

Postnatal depression; Infant sex; Birth complications; Inflammation; Evolutionary medicine

Introduction

Postnatal/postpartum depression (PND/PPD) is the label given to Major Depressive Disorder when the onset is in the peripartum (either during pregnancy or within four weeks of giving birth) (APA, 2013). PND is both chronically underdiagnosed (Paulden et al., 2009) and associated with a range of detrimental outcomes for mothers and their children. PND predisposes women to future bouts of both PND *and* depression at other points in time (Solomon et al., 2000), leaving them at risk of a range of inflammation related health issues (Keicolt-Glaser and Glaser, 2002; Mykletun et al., 2009). It is also linked to compromised social, emotional, physical, and cognitive development of their infants (Avan et al., 2010; Beck, 1995; Cogill et al., 1986; Gelfand and Teti, 1990; Halligan et al., 2007; Murray and Cooper, 1997; O'Hara and McCabe, 2013; Wright et al., 2006), poorer mother-child relations across the life course (Myers and Johns 2018), lower emotional closeness to resultant grandchildren (Myers and Johns 2018a), and reductions in future childbearing (Myers et al., 2016). Maternal mental health issues also place a considerable burden on healthcare systems: it was recently estimated that the long-term cost to UK society was £8.1 billion per one-year cohort of births (Bauer et al., 2014). Therefore, identifying key risk factors for PND is of substantial importance.

Major depressive disorder is increasingly accepted as being a neuroprogressive and inflammatory process (Rahola 2012), with a growing literature linking both psychosocial and genetic risk factors for depression to innate immune inflammatory responses (Cole et al., 2007; Cole 2008; Cole 2009; Slavich et al., 2010a; Slavich et al., 2010b; Raison and Miller, 2013; Raison and Miller, 2017). A link further supported by the findings that most antidepressant drugs have anti-inflammatory effects (Maes et al., 2009), that depressive symptoms positively correlate with inflammatory markers and pathogen load in a high pathogen-bearing population (Stieglitz et al., 2015), and inflammation precedes rather than follows emotional distress (Das, 2016). Such findings have led to the suggestion that depressive symptoms are an evolutionary adaptation to both prevent and fight infection (Anders et al., 2013; Kinney and Tanaka, 2009; Slavich et al., 2010a; Raison and Miller, 2013; Slavich and Irwin, 2014). If inflammation is predictive of, or causal to, depression then possibility is open to identify novel risk factors on the basis of their known role in inflammatory immune activation.

While less is known about the aetiology of PND, compared to depression at other points in the life course (Skalkidou et al., 2012), there is a burgeoning body of work also supporting the role of inflammation in the perinatal period–indeed, a recent review heralded it as one of the most exciting areas of investigation (Yim et al., 2015). For instance, a broad-spectrum approach employing 74 inflammatory markers found inflammation to be the second best predictor of PND after prior depressive history (Bränn et al., 2017). Women in the perinatal period are potentially at heightened risk of inflammatory activation (Luppi, 2003; Skalkidou et al., 2012; Yim et al., 2015). Pro-inflammatory cytokine release triggers a systematic inflammatory reaction characterized by activity reduction, decreased appetite, fever, fatigue, hypersomnia, and depressed mood (Skalkidou et al., 2012; Raison and Miller, 2013)–all characteristics of depression. While it has been proposed that, in some women, PND may denote a psycho-neuro-immunological disorder, due to an excessive inflammatory response combined with inadequate suppression of the hypothalamic-pituitary-adrenal (HPA) axis (Raison et al., 2006), there are likely to be multiple causal pathways leading to inflammation and associated depressive symptoms. Variation in both the expression of genes linked to the immune system and in markers of inflammation have been found in association with social isolation, chronic threat of social loss, shame, social evaluative threat, and acute social stress (Cole et al., 2007; Cole, 2009; Slavich et al., 2010a; Slavich et al., 2010b). Newly adopting mothers also show similar levels of depression to postnatal women, indicating the importance of psychosocial stressors, in addition to biological factors, relating to early maternal experience (Mott et al., 2011; Senecky et al., 2009). For instance, it has been noted that a number of risk factors for PND–past or current psychological trauma, sleep disturbance, postpartum pain, and stress–trigger the release of pro-inflammatory cytokines (Kendall-Tackett, 2007). Low socioeconomic status (SES) and poor social support (Beck, 2001), two prominent psychosocial stressors conferring increased likelihood of PND occurring, are also associated with increased levels of inflammation (SES–Steptoe et al., 2002; Jousilahti et al., 2003; Pollitt et al., 2007; social support–Hughes et al., 2014; Loucks et al., 2006).

Significant ethical justification is rightly required before conducting biomedical tests on perinatal women, and while understanding causal pathways in depression aetiology is important, they are not necessarily needed to identify new risk factors. The knowledge that inflammation predicts or

correlates with many, if not all, cases of PND (Yim et al., 2015) highlights a new avenue for identifying novel risk factors for PND on the basis of their known role in inflammatory activation. Here we focus on two such potential risk factors, intrinsically entwined with pregnancy and associated with inflammatory responses, yet currently underexplored in relation to PND: *foetal sex* and the act of *childbirth* itself.

Research indicates the maternal immune milieu differs by foetal sex, with women carrying male foetuses showing increased pro-inflammatory markers relative to those bearing female foetuses (Enninga et al., 2015). Maternal inflammatory profiles, according to multiple markers, are found to differ by the sex of the foetus as early as six weeks' post-conception and remain differentiated throughout pregnancy (Enninga et al., 2015; Mitchell et al., 2017), before returning to an undifferentiated state after the infant's birth (Enninga et al., 2015). Analysis of placental tissue also indicates that mothers produce a stronger inflammatory response to male foetuses (Ghidini and Salafia, 2005; Goldenberg et al., 2006; Cyitic et al., 2013). However, little attention has been paid to whether carrying a male foetus increases the risk of PND. To our knowledge, only one study has reported an association between the birth of male infants and higher rates of PND (de Tychey et al., 2007). This study of 181 contemporary French women, conducted on the premise that mothers may hold undocumented gender preferences, was cross-sectional and lacked controls for potential confounding factors. Here, we test the hypothesis that the birth of male infants increases the risk of PND using data from the complete reproductive histories of 296 women from Western, educated, industrialised, rich, and democratic (WEIRD) contexts (Henrich et al., 2010), who between them had 651 births. This approach allows us to conduct a multilevel analysis of the relationship between giving birth to a male infant and PND, while controlling for individual effects of the mothers and other known PND risk factors.

A further underexplored factor in the aetiology of PND is the experience of obstetric complications. Complications during childbirth typically lead to medical interventions, surgical or otherwise, which are likely to result in the activation of inflammatory pathways due to the physical nature of the intervention. For instance, caesarean section (the surgical delivery of an infant via the abdomen) and episiotomy (a surgical incision made to the opening of the vagina to aid delivery) entail

wounds to which the immune system will respond and also carry a risk of post-operative infections. Surgical site infections occur after 3-15% of caesareans worldwide (Zuarez-Easton et al., 2017), and caesareans are also associated with uterine infections (Lydon-Rochelle et al., 2000). Assisted vaginal deliveries also increase the risk of postnatal infection (Kabiru et al., 2001; Lydon-Rochelle et al., 2000). Perineal wound infections were found to be present 21 days after 15% of episiotomies, 17% of instrumental deliveries, and 25% of labours involving prolonged rupture of membranes in postpartum UK women with perineal tearing (Johnson et al., 2012). Obstetrical interventions and emergencies are also associated with psychological trauma (Andersen et al., 2012; Creedy et al., 2001; Montmasson et al., 2012) and such emotional stress is related to increased inflammation (Gola et al., 2013; O'Donovan et al., 2012).

While the occurrence of birth complications seems a likely candidate for increasing a woman's likelihood of developing PND, evidence from the existing literature is mixed. For instance, a detailed study of 490 Australian women found that while various obstetric variables – caesarean section, forceps use, antepartum haemorrhage, epidural anaesthetic, artificial membrane rupture – marginally increased the odds of PND, all the effects were statistically nonsignificant (Johnstone et al., 2001). The occurrence of birth complications was noted as a "weak to moderate risk factor" for PND in a meta-analysis published in 1996 (O'Hara and Swain, 1996), yet two recent papers reviewing the risk factors of PND did not note birth complications (Skalkidou et al., 2012; Yim et al., 2015). Psychological trauma in the postnatal period has been positively associated with PND (Beck et al., 2011); though the cause of the trauma was not documented. Thus, further research into the role of birth complications in PND aetiology is warranted.

A lack of consensus regarding the role of birth complications in PND can perhaps be explained by the magnitude of the inflammatory 'hit' required for depression to manifest. Models of depression, such as PATHOS-D (Raison and Miller, 2013) and the psychobiological model of social rejection and depression (Slavich et al., 2010a), are often conceived of as additive or threshold models. For instance, most people will encounter various risk factors for depression over their lives without becoming depressed; it is only when multiple risks coincide that the threshold for depression is crossed – with the thresholds of individuals being determined by their genetic and epigenetic profiles

(Slavich and Cole, 2013). In addition to assessing if the experience of birth complications predicts PND incidence in our sample, we assess whether birth complications only become risk factors when experienced in conjunction with other inflammation increasing factors. We test for an interaction effect between birth complications and infant sex, as well as testing for interactions between birth complications and a variety of other known risk factors for both PND and inflammation: a mother's general tendency towards depression, stress, and anxiety (DAS), indicating her propensity for mental health issues at other times in the life course (Beck, 2001; Raison and Miller, 2017), socioeconomic status, and social support in the infant's first year.

Hypotheses

1) Women will be at increased risk of PND when giving birth to a male infant.

2) Women will be at increased risk of PND when a birth is associated with complications.

3) The experience of birth complications will interact with other known PND risk factors to increase the risk of PND.

Method

Data Collection

Complete reproductive histories of post-menopausal women were collected by retrospective survey. Respondents reported details about every birth they had experienced and were assessed on a number of demographic and psychological measures. Valid responses from 306 women were received; women who experienced the death of an infant (n = 9), or who gave an infant up for adoption (n = 1), were excluded from the analysis. The survey was conducted online using the SurveyGizmo platform and, to minimise inaccurate reporting due to the sensitive nature of information requested, participants were anonymous with the exception of their IP address (used to prevent multiple responses from the same address). Participants were engaged via advertising in newsletters and social media channels of UK-wide branches of the Women's Institute (whose membership largely met our age restrictions (The Women's Institute, 2012)), the alumni networks of two UK universities, and social media appealing to older women. Approval for the study was granted by the Research and Ethics Committee of the School of Anthropology and Conservation at the

University of Kent. All participants read a statement regarding the aims and content of the survey, namely to "gain a greater understanding of how women experience early motherhood and the long-term effects these experiences have on women" and highlighting our interest in PND. However, the underlying hypotheses guiding the survey design were not disclosed. The potentially sensitive nature of the questions surrounding postnatal emotional experience was emphasised, and by proceeding participants were deemed to have given written informed consent. Participants were told that they could withdraw from the study at any time and that their responses prior to withdrawal would not be retained. They were also provided with details of where they could seek help regarding mental health issues.

Measures

Postnatal depression. Participants were requested to self-report whether they had received a clinical diagnosis of PND in association with each of their births. Additionally, the Bromley Postnatal Depression Scale (BPDS) (Stein and van den Akker, 1992) was used to assess PND incidence. The BPDS was specifically designed to assess PND symptoms retrospectively and consists of a statement regarding depressive symptoms and a question regarding whether such symptoms were experienced; if the answer is yes, then the symptom duration is recorded. When symptoms lasted for a month or more, PND is considered to have occurred at a given birth, providing a binary categorical measure of whether or not PND was experienced. The average time elapsed since birth (calculated approximately as year of survey completion [2013-2014] minus year of birth) was 28.7 years (range 7 – 58, *SD* = 9.8) – this is comparable to previous studies utilising the BPDS (McLaren et al., 2007; Séjourné et al., 2011). We chose to use this screening measure alongside actual diagnostic history, due to the estimation that as many as 50% of cases of PND in the UK go undiagnosed (Paulden et al., 2009).

Infant sex. Participants were requested to report the sex of infants born at a given birth.

Birth complications. Participants were requested to select a response to question 'Which of the following best describes the physical experience of this labour and birth?' from the following options: 'no complications', 'minor complications – no extended recovery time', 'minor complications – extended recover time', 'major complications – no extended recovery time', and 'major complications

– extended recovery time.' Due to sample size constraints it was necessary to condense the response options when complications were experienced – we did this in two ways and performed separate analyses on each: 1) a binary categorical *occurrence of birth complications* variable was created with the response categories 'no complications' versus 'complications'; 2) a multi-categorical *recovery time from birth complications* variable was created with the response categories 'no complications', 'complications with no extended recovery', and 'complications with extended recovery'.

History of depression. History of depression and prenatal anxiety are known to increase the risk of PND (Beck, 2001). As a proxy for a woman's mental health history we used the Depression Anxiety Stress Scales (DASS) short version (Lovibond and Lovibond, 1995a, 1995b), which was employed using trait wording (Lovibond and Lovibond, 1998). The DASS score (possible range 0 – 126) was used as a continuous variable indicating emotional condition throughout adult life course, which we refer to as a participant's *general tendency towards depression, anxiety, and stress* (*DAS*) symptoms.

We also controlled for the current depressive state of participants when assessing PND retrospectively with the BPDS, because depression at the time of completing the survey may negatively bias reflections on past events. *Current depression* was measured by the Beck Depression Inventory – Short Form (BDI-SF) (Beck and Steer, 1993). A cut-off of ≥ 5 was used to indicate depressive symptoms at the time of survey completion (Stukenberg et al. 1990).

Socioeconomic status. Low socioeconomic status (SES) is a risk factor for PND (Beck, 2001), therefore we controlled for a participant's SES during her childbearing years. SES was assessed using the Social Class Based on Occupation method (CeLSIUS, 2007); participants classified the occupation of the household member contributing the majority of finances, thus allowing for the fact that women might not have worked whilst raising children. SES was categorised as either 'high' – professional occupation; 'medium' – managerial and technical occupations, or; 'low' – skilled non-manual, skilled manual, partly-skilled, and unskilled occupations.

Social support. Social isolation is linked to depression throughout the life course (Slavich et al., 2010a) and lack of social support is a risk factor in PND (Beck, 2001; Hahn-Holbrook et al., 2013;

Yim et al., 2015). Participants reported the level of perceived support received during pregnancy and offspring infancy from their own mother on a Likert scale of 0 (*none*) to 5 (very *high*). The levels of perceived support from family, friends, and offspring's father during the first year after each birth were recorded on a scale of 1 (*very low*) to 5 (*very high*). These scores were then aggregated and assigned to the lowest ('low'), middle ('medium'), or highest ('high') third.

Data Analysis

To test hypothesis 1, the relationship between infant sex and PND was assessed (*Model 1*) with a hierarchical multilevel generalised estimating equation (GEE) model, which allowed for multilevel analysis of a binary dependent variable; data were hierarchically nested by individual woman and the birth order of each of her birth events using an independent correlation matrix structure; *PND incidence* (according to the BPDS or clinical diagnosis) acted as our dependent variable in a binary logistic model structure and *infant sex* acted as the predictor variable– *current depression* at the time of the questionnaire was additionally controlled for when predicting PND according to the (retrospective) BPDS. Next, to test hypothesis 2, the relationship between birth complications and PND was assessed following the same procedure, this time using *occurrence of birth complications* (*Model 2a*) or *recovery time from birth complications* (*Model 2b*) as the predictor variable. Then, to further test hypotheses 1 and 2, we ran full models containing the predictor variables *SES, social support*, and *general tendency towards DAS, infant sex*, and either *occurrence of birth complications* (*Model 3a*) or *recovery time from birth complications* (*Model 3b*), again controlling for *current depression* when predicting retrospective PND. Finally, to test hypothesis 3, we ran separate models each with a term for the interaction between *occurrence of birth complications* and one other predictor variable: *Model 4 – *infant sex*; *Model 5 – *SES*; *Model 6 – *social support*; *Model 7 – *general tendency towards DAS*. To understand interactions which were significant at an $\alpha < 0.05$, we then split birth events by the *occurrence of birth complications* variable and assessed the simple slopes for the interacting variables while controlling for the remaining predictor variables (*Model 8a – no complications* and *Model 8b – complications*). We did not test for interactions using the *recovery time from birth complications* variable due to sample size constraints.

Participants were included in the analysis if complete information on all of their births for a given model was available. Four participants were excluded in the BPDS models due to non-response for the control variable *current depression*, and sample sizes vary by model due to the inclusion or exclusion of women who had multiple births (n = 10) and other non-systematic missing data.

The GEE has no standard absolute goodness-of-fit measure; however, we report the corrected quasi likelihood under independence model criterion (QICC) scores (Pan, 2001) for all models, with a smaller score indicating a better fit. We also report the results in the form of odds ratios (*OR*) – the continuous variable *general tendency towards DAS* has been centred and standardised for the purpose of testing interaction effects, also allowing odds ratios to be interpreted as relative effect sizes. Huber-White standard errors account for potential heteroscedasticity, and significance values are the product of Wald Chi-square tests and are two-tailed.

All statistical analysis was conducted using SPSS (IBM, v.24, 2016); the figure was created using ggplot in R (The R Foundation for Statistical Computing Platform, v.3.4.2, 2017). The dataset used in the analyses is open access via Mendeley [dataset] (see Myers and Johns, 2018).

Sample Characteristics

All respondents were born between 1930 and 1966, and their average age at the time of questionnaire completion was 59.2 years (*SD* = 7.5). The majority of respondents were of high SES (professional occupation – 67.2%), followed by medium (managerial and technical occupations – 20.9%), and low (skilled non-manual, skilled manual, partly-skilled, and unskilled – 11.8%). Most women did the majority of their childrearing in the UK (74.7%), followed by the United States (12.6%), and the rest of the World (12.7%). Respondents had an average completed fertility of 2.24 children (range 1 – 6, *SD* 0.83), with a sex ratio of 1.09 (not including infants from multiple births). Women reported receiving a clinical diagnosis of PND in association with 8.0% of all births (no PND n = 599, PND n = 52) – 9.9% were diagnosed after the birth of a singleton male infant, and 6.2% after the birth of a singleton female infant. PND was not diagnosed in any women after a multiple birth. However, when assessed retrospectively using the BPDS, PND was associated with 14.3% of all births (no PND n = 558, PND n = 93) – 17.1% reported PND after the birth of a singleton male infant,

11.1% after the birth of a singleton female infant, and 20% after a multiple birth. Some degree of birth complication occurred with 44.1% of all births, 48.2% of male births, 41.7% of female births, and 80% of multiple births – the distribution by type of complication, infant sex, and PND incidence can be seen in the Supplementary Information.

Results

Supporting hypothesis 1, we find that when mothers gave birth to male infants they had increased odds of developing PND according to the BPDS (*Model 1*, *3a*, *3b*) and clinical diagnosis (*Model 3b*) compared to when they gave birth to female infants (Table 1); the odds of PND increased after the birth of male infants by 71-79% after controlling for other PND risk factors and individual effects of the mother.

Supporting hypothesis 2, we find that the experience of birth complications, as measured by the *occurrence of birth complications* variable (*Model 2a* and *3a*), increased the odds of PND when assessed by clinical diagnosis (Table 1); the odds of PND increased by 174% after controlling for other PND risk factors and individual effects of the mother. Yet, this finding was not replicated when PND was retrospectively assessed, and only when complications were grouped by *recovery time from birth complications* was an effect found (Table 1); compared to the experience of no complications, experiencing complications which required an extended recovery time (*Model 2b* and *3b*) increased the odds of PND by 151-168% after controlling for other PND risk factors and individual effects of the mother. When predicting PND retrospectively QICC comparison indicates models containing the *recovery time from birth complications* variable performed better than those containing the *occurrence of birth complications* variable (ΔQICC 5.821 to 8.43), while the reverse was marginally the case when predicting PND using clinical diagnosis (ΔQICC 1.642 to 1.838).

<INSERT TABLE 1 ABOUT HERE>

We find limited support for hypothesis 3, with only one significant interaction effect in the anticipated direction out of the eight tested (for full results see the Supplementary Information). When predicting PND (clinical diagnosis), the *occurrence of birth complications* interacted with infant sex (*Model 4* interaction $p = 0.016$), lowering the QICC compared to *Model 3a* (ΔQICC 2.387). The odds of PND increased by 166% when male infants were born from complicated births (*Model 8b OR* =

2.656, *CI* = 1.179 to 5.979), but not when they were complication free (*Model 8a OR* = 0.659, *CI* = 0.253 to 1.715) (Figure 1).

The *occurrence of birth complications* also interacted with *general tendency towards DAS* when predicting both PND measures (*Model 7* interactions $p < 0.05$) and QICC comparison indicates the addition of the interaction term improved the model performance compared to *Model 3a* (ΔQICC BPDS 10.781 and clinical diagnosis 12.83); however, the interaction effect was not in the anticipated direction. Specifically, the odds of PND increased as a mother's general tendency towards DAS increased, but the effect was greater when births were not complicated (*Model 8a BPDS OR* = 5.668, *CI* = 3.250 to 9.884, clinical diagnosis *OR* = 11.358, *CI* = 3.469 to 37.184) compared to when births were complicated (*Model 8b* BPDS *OR* = 1.531, *CI* = 1.110 to 2.114, clinical diagnosis *OR* = 1.856, *CI* = 1.275 to 2.702) (Figure 1). For full results see Supplementary Information.

<INSERT FIGURE 1 ABOUT HERE>

Discussion

We find that in a sample of post-reproductive women from contemporary, low-fertility, contexts, PND incidence increased when mothers gave birth to male infants. We also find that the experience of complications during birth increases the odds of PND occurring, with experiencing birth complications which required an extended period of recovery potentially being particularly salient. It is estimated that 50% of (what could be) clinically recognised cases of PND (at least in the UK) go undiagnosed (Paulden et al., 2009) and universal screening is not widespread; the need for women at high risk of PND to be identified by screening has been stressed (Musters et al., 2008) and any findings pointing to novel, easily identifiable PND risk factors are thus important.

Our hypotheses were predicated on a growing body of literature linking inflammation and depression; while we do not have data to support the causal role of inflammation in our sample, these results clearly point to the utility of exploring the predictive potential of factors with known associations with inflammation in order to identify novel risk factors for PND. Male foetuses have been known for some time to increase the risk of pre-eclampsia (Basso and Olsen, 2001; Elsmén et al., 2006), which is associated with elevated levels of the pro-inflammatory cytokines (Germain et al.,

2007). Gestational diabetes mellitus, which is linked with subsequent increases in maternal inflammation (Di Benedetto et al., 2005), is also more likely when the foetus is male (Di Renzo et al., 2007). Our findings replicate and, with a multilevel approach, expand those of de Tychey et al. (2007) and support the addition of PND to the list of perinatal conditions for which male foetuses pose increased risk. Further, it is worth noting that if foetal sex related inflammation does underlie these results, the risk of antenatal depression during pregnancy is likely to be similarly increased by male foetuses–an avenue for future research.

While our results replicate the finding of de Tychey et al. (2007), it must be noted that the opposite relationship between PND and infant sex has been found outside of a Western context. For instance, PND has been found to be more common in association with female infants in India (Patel et al., 2014), Nigeria (Adewuya et al., 2005), Turkey (Ekuklu et al., 2004), and China (Xie et al., 2007), and daughters are reported to be source of stress in Chinese mothers with PND (Leung et al., 2005). The authors of these studies note these are all societies with strong cultural preferences for sons, and where having a daughter may eventually result in significant economic costs, for example payment of bridewealth or dowry. In such circumstances, one could hypothesise that the birth of a daughter may be associated with inflammation as a result of post-birth psychosocial stress that outweighs the effect of inflammation from male gestation.

However, we also cannot rule out the possibility that, as de Tychey et al. (2007) conclude, an undocumented preference for daughters in our sample underpins our results. A brief review of the literature on offspring sex preferences in individuals from WEIRD populations sheds conflicting light on this explanation. For instance, using parity progression likelihood to infer preferences, demographic data from Nordic countries in the latter half of the 20th century indicate no impact of first-born sex on the occurrence of a second birth and a preference for one child of each sex in parents who stop at two children (Andersson et al., 2006). Yet, a preference for having a son is detected in parents of two daughters in Finland, while Norwegian, Danish, and Swedish parents show a preference for daughters if they have two sons. A general preference for a mixed sex ratio has been found across contemporary Europe (Hank and Kohler, 2003; Mills and Begall, 2010). In Germany,

childless women report a preference for their first-borns to be daughters, while parents who have a son first are less likely to continue childbearing and, in those that do, existing sex ratio does not influence the chances of having a third child (Hank and Kohler, 2003). Marriage stability is adversely linked with the birth of daughters in the U.S. (Bedard and Deschenes, 2005; Katzev et al., 1994) and a preference for sons is also indicated in the decision to have a third child in European countries with lower gender equity or higher chance of poverty in later life (Mills and Begall, 2010). While the likelihood of our sample having captured a clear gender preference, given its span of time and geography, seems debatable, we do not have the data to assess this. A neat way for future research to tease apart the potential roles of inflammation caused by a male foetus, versus psychosocial stress related to a preference for daughters, would be to assess whether foetal sex predicts antenatal depression in mothers who do not know the sex of their unborn infant.

When assessing PND risk in association with birth complications we find less congruence between our retrospective depression screen and reported diagnostic history than when assessing infant sex. All birth complications were found to predict increased risk of having been clinically diagnosed with PND, but only complications *requiring an extended recovery* increased the risk of screening positively for PND according to the BPDS. As this effect is in the opposite direction as might be expected if the BPDS were too liberal in its categorising of women as having experienced PND, the reason for this disparity is unclear–the α cut-off of 0.05 is only just exceeded when assessing the relationship with birth complications *per se*, and replication in a larger sample may find the confidence intervals narrow.

Alternatively, the finding, resulting from the use of the BPDS, that only birth complications which required an extended period of recovery, rather than complications *per se*, are associated with increased incidence of PND, potentially indicates that not all complications confer the same risk. An inflammation-based framework of PND may provide an explanation of why the research literature on obstetric complications and PND aetiology is ambiguous, as according to this view it is only when complications lead to a sustained inflammatory response that they would be expected to trigger depressive symptoms. It is plausible that an extended period of recovery is indicative of a prolonged inflammatory response resulting from post-birth infection, or generates more stress, during the early

postnatal period. However, given this is based on our retrospective measure of PND, such a conclusion should be considered speculative for the time being. The results, when PND incidence was assessed according to clinical diagnostic history, offer more convincing evidence to support our second hypothesis. Irrespective of whether post-birth infections are experienced, birth complications are likely to be stressful for women, particularly if they resulted in emergency procedures being undertaken. A mismatch between early maternal expectations and experience has been found to predict PND (Beck, 2002)–unanticipated birth complications seem a likely candidate to create such a mismatch. The consequences of complicated births may also lead to women experiencing seemingly unrelated depressive risk factors; for instance, the experience of severe perineal trauma is associated with women becoming socially isolated (Priddis et al., 2012)–another potential cause of inflammation.

We did not find much evidence for the additive effects of birth complications with other PND risk factors in our sample (low SES, low social support, and a history of depression, anxiety, and stress) as anticipated. Only one predicted interaction effect was found; male infants increased PND risk when associated with complicated births when PND was measured by clinical diagnosis, but not when PND was determined retrospectively, and inclusion of the interaction term only marginally improved the model performance. Interestingly, however, we did find evidence for an interaction effect counter to our expectations. We interpret scores on the DASS as a being a proxy for a woman's mental health history, which in turn is the product of a combination of her exposure to stressful life events (Mazure, 1998) and genetic predispositions (Sullivan et al., 2000; Flint and Kendler, 2014). While a tendency to generally experience symptoms of depression, anxiety, and stress (as measured by the DASS) was associated with increased odds of PND across all births, the odds were *lower* when births were complicated. A potential explanation for this is that women with a history of mental health problems are typically identified as a high-risk group for PND (Musters et al., 2008; NICE, 2014); it may be that these women were provided with more support when they also experienced birth complications than when they had uncomplicated births, thus reducing, but not eliminating, their relative risk of PND. It is important that health professionals ascertain whether this is the case and, if so, elevate the level of support such women receive to equalise levels of help, irrespective of other aspects of their

perinatal experience. Indeed, if our interpretation is correct these results point to the effectiveness of additional screening and support in reducing postnatal depressive risk.

Identifying key risk factors for PND is critical for mothers and their children. Whilst the weight placed on our results must be constrained due to the nature of our data (see *Limitations* below), we find grounds to encourage future replication attempts to ascertain the utility of considering infant sex, and whether mothers experience obstetric complications, particularly if the physical and psychological consequences are prolonged, in relation to PND risk.

Limitations

While the retrospective nature of our data is not ideal, we know of no other data set containing information of PND whereby the complete reproductive histories of women have been collected prospectively, thus allowing for a multilevel approach; future work should seek to rectify this. As with any retrospective study, recall bias cannot be ruled out; however, respondents are more likely to forget, thus not report, depressive symptoms than they are to report them as having occurred when they did not (Wells and Horwood, 2004). We also control for depressive symptoms being experienced at the time of survey completion when using the BPDS and find results using self-reported receipt of clinical diagnosis, although constrained by sample size, to be broadly similar. Both of our PND depression measures are somewhat blunt, only capturing whether or not PND occurred, so we cannot speak to the severity of the depression experienced. Our measure of birth complications unfortunately lacks detailed information on the nature of the complication–this lack of nuance may explain why we did not find the predicted pattern of interaction effects. Our suggestion that prolonged post-birth infection and PND are comorbidities is based on inference, drawing from the literature on inflammation and depression. Studies are now urgently needed to ascertain whether women developing post-birth infections, experiencing extended periods of post-birth recovery more generally, or giving birth to male infants are more likely to become postnatally depressed using prospective data, as our results predict.

Conclusions

Our results indicate that PND may be included amongst what is a growing list of perinatal complications associated with carrying a male foetus. Birth complications also appear to be associated with a greater likelihood of developing PND, and we hope these findings will encourage further investigation of whether women experiencing complications, particularly if their consequences are prolonged, should be monitored for depressive symptoms. Finally, the support offered to women known to be of elevated risk of developing PND due to a history of mental health issues should also be of equally high quality, so as to avoid inadvertently creating situations in which women with a history of emotional instability may actually be *better off*, in terms of receiving support and interventions for PND, if they have complicated births.

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Table 1. Results of generalised estimating equation regression models assessing the odds of postnatal depression (PND) dependent on infant sex, the occurrence of birth complications, and a variety of other PND risk factors.

Variables		**PND Assessed by BPDS**				**PND Assessed by Clinical Diagnosis**			
		p	*OR*/ Effect size	95% Wald *CI* Lower	Upper	*p*	*OR*/ Effect size	95% Wald *CI* Lower	Upper
Model 1									
(Intercept)		<0.001	0.214	0.128	0.358	<0.001	0.066	0.040	0.110
Current depression	No	**0.012**	**0.488**	**0.279**	**0.854**	-	-	-	-
	Yes (ref)	-	1	-	-	-	-	-	-
Infant sex	Male	**0.033**	**1.635**	**1.041**	**2.568**	0.083	1.684	0.935	3.035
	Female (ref)	-	1	-	-	-	1	-	-
QICC					*511.678*				*361.868*
Sample size		*Mothers n = 282, Births n = 626*				*Mothers n = 286, Births n = 635*			
Model 2a									
(Intercept)		<0.001	0.219	0.133	0.361	<0.001	0.049	0.028	0.087
Current depression	No	**0.016**	**0.507**	**0.292**	**0.882**	-	-	-	-
	Yes (ref)	-	1	-	-	-	-	-	-
Occurrence of birth complications	Complications	0.058	1.616	0.985	2.653	**0.002**	**2.841**	**1.477**	**5.464**
	None (ref)	-	1	-	-	-	1	-	-
QICC					*522.917*				*353.490*
Sample size		*Mothers n = 289, Births n = 637*				*Mothers n = 294, Births n = 647*			
Model 2b									
(Intercept)		<0.001	0.219	0.133	0.360	<0.001	0.049	0.028	0.087
Current depression	No	**0.017**	**0.509**	**0.293**	**0.886**	-	-	-	-
	Yes (ref)	-	1	-	-	-	-	-	-
Recovery time from birth complications	Complications with extended recovery	**0.001**	**2.637**	**1.498**	**4.642**	**0.003**	**3.194**	**1.504**	**6.786**
	Complications with no extended recovery	0.864	0.946	0.501	1.787	**0.012**	**2.572**	**1.231**	**5.377**
	No complications (ref)	-	1	-	-	-	1	-	-
QICC					*514.487*				*355.132*
Sample size		*Mothers n = 289, Births n = 637*				*Mothers n = 294, Births n = 647*			
Model 3a									
(Intercept)		<0.001	0.029	0.011	0.080	<0.001	0.014	0.004	0.042
Current depression	No	0.688	1.151	0.579	-	-	-	-	
	Yes (ref)	-	1	-	-	-	-	-	-
Infant sex	Male	**0.027**	**1.786**	**1.069**	**2.984**	0.054	1.729	0.991	3.017
	Female (ref)	-	1	-	-	-	1	-	-
Occurrence of birth complications	Complications	0.053	1.688	0.993	2.872	**0.004**	**2.739**	**1.391**	**5.391**
	None (ref)	-	1	-	-	-	1	-	-
SES	Low	**0.002**	**3.170**	**1.501**	**6.695**	**0.004**	**4.136**	**1.578**	**10.845**
	Medium	0.658	1.176	0.573	2.416	0.388	1.550	0.606	3.636
	High (ref)	-	1	-	-	-	1	-	-
Social support	Low	**0.001**	**4.563**	**1.937**	**10.751**	0.710	1.258	0.375	4.224
	Medium	0.106	1.817	0.880	3.753	0.386	1.550	0.575	4.178
	High (ref)	-	1	-	-	-	1	-	-
General tendency towards DAS		**<0.001**	**2.223**	**1.642**	**3.010**	**<0.001**	**2.660**	**1.748**	**4.048**
QICC					*441.273*				*296.303*
Sample size		*Mothers n = 279, Births n = 620*				*Mothers n = 281, Births n = 623*			
Model 3b									
(Intercept)		<0.001	0.029	0.010	0.080	<0.001	0.014	0.004	0.042
Current depression	No	0.675	1.158	0.582	2.304	-	-	-	-
	Yes (ref)	-	1	-	-	-	-	-	-

Infant sex	Male	**0.042**	**1.712**	**1.019**	**2.874**	**0.049**	**1.752**	**1.002**	**3.065**
	Female (ref)	-	1	-	-	-	1	-	-
Recovery time from birth complications	Complications with extended recovery	**0.002**	**2.679**	**1.457**	**4.924**	**0.026**	**2.511**	**1.116**	**5.652**
	Complications with no extended recovery	0.963	0.982	0.469	2.058	**0.008**	**2.963**	**1.336**	**6.570**
	No complications (ref)	-	1	-	-	-	1	-	-
SES	Low	**0.002**	**3.261**	**1.550**	**6.860**	**0.004**	**4.118**	**1.569**	**10.808**
	Medium	0.747	1.129	0.540	2.360	0.383	1.493	0.606	3.678
	High (ref)	-	1	-	-	-	1	-	-
Social support	Low	**0.001**	**4.771**	**1.964**	**11.595**	0.723	1.245	0.371	4.173
	Medium	0.086	1.937	0.910	4.126	0.399	1.531	0.569	4.118
	High (ref)	-	1	-	-	-	1	-	-
General tendency towards DAS		**<0.001**	**2.192**	**1.619**	**2.967**	**<0.001**	**2.677**	**1.765**	**4.061**
QICC					*435.452*				*298.141*
Sample size		*Mothers n = 279, Births n = 620*				*Mothers n = 281, Births n = 623*			

Note. PND assessed either retrospectively using the Bromley Postnatal Depression Scale (BPDS) or by self-reported clinical diagnosis. The continuous variable *general tendency towards DAS* has been centred and standardised to make the odds ratios interpretable as effect sizes. The scale of all models = 1. Significance values are two-tailed and results in bold where $\alpha < 0.05$. Abbreviations: odds ratio (*OR*); confidence interval (*CI*); reference (ref); socioeconomic status (SES); depression, anxiety, stress (DAS); corrected quasi likelihood under independence model criterion (QICC).

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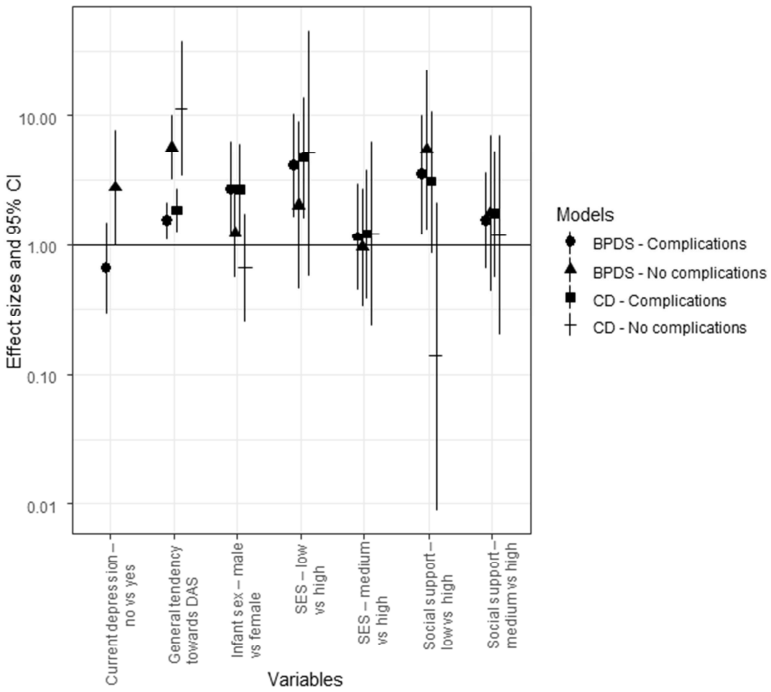
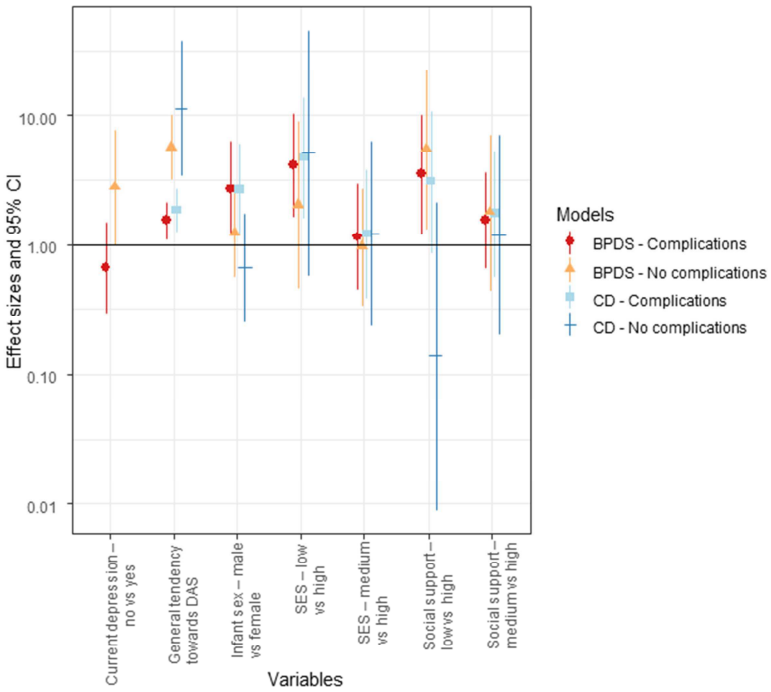


Figure 1. Plot exploring the interaction between the *occurrence of birth complications* and other postnatal depression (PND) risk factors.
Plot shows the effect sizes and 95% confidence intervals (*CI*) of variables effecting PND incidence depending on the occurrence of birth complications: *Model 8a* clinical diagnosis (CD) or Bromley Postnatal Depression Scale (BPDS) – No complications and *Model 8b* CD or BPDS – Complications. The continuous variable *general tendency towards depression, anxiety, stress (DAS)* has been centred and standardised to make the model odds ratios interpretable as effect sizes. The scale of the y-axis has been subjected to log transformation.
Abbreviations: socioeconomic status (SES).



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Abbreviations: socioeconomic status (SES).

Research Highlights

- Recent research indicates depression is linked to prolonged inflammation.
- Factors triggering inflammation may highlight novel depressive risk factors.
- Male foetuses and birth complications are likely to cause inflammation.
- Giving birth to male infants increases the odds of postnatal depression.
- The experience of birth complications increases postnatal depression odds.