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Prenatal stress and offspring depression in adulthood: The mediating role of childhood trauma

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\textbf{Abstract}

\textbf{Background:} There is repeated evidence for a prenatal programming effect for the development of offspring depression. However, examination of environmental influences along this pathway is sparse. This study aimed to investigate the direct and indirect effects of pre- and postnatal stress on offspring depression in adulthood, via increased exposure to childhood trauma.

\textbf{Methods:} A large longitudinal population-based cohort (N = 3506) was followed up from birth and assessed at 24 years. Diagnosis of depression was derived using the International Classification of Diseases–10th revision (ICD-10). Two separate sources of pre- and postnatal stress were examined – maternal depression and family adversity, and childhood trauma was assessed prospectively across childhood until 17 years.

\textbf{Results:} Both pre- and postnatal maternal depression and family adversity were associated with offspring depression at 24 years in simple logistic regression models. When all pathways were modelled simultaneously, only childhood trauma was directly associated with offspring depression, and mediated all pathways from both sources of pre- and postnatal stress to offspring depression (7-16% of the total effect mediated). Sensitivity analysis on specific trauma found stronger evidence for a mediated pathway via physical, emotional abuse and peer bullying, compared to emotional neglect, sexual abuse and domestic violence.

\textbf{Conclusions:} These findings indicate that reducing childhood trauma could be a target to decrease depression in the general population, and the focus should also be on families at high risk of experiencing pre- or postnatal stress, to provide them with better support.

1. Introduction

There is substantial evidence in the literature that adverse prenatal environment is associated with diseases and mortality in adulthood (Lewis et al., 2015). This has been formulated into the foetal programming hypothesis, which postulates that intrauterine adversity, for example growth restriction, can alter the biological systems of the developing child and increase their susceptibility to future diseases (Barker, 2007; O’Donnell and Meaney, 2016; Räikkönen and Pesonen, 2009; Van den Bergh et al., 2017). More recently the theory has been applied to the study of mental health disorders such as depression, and other sources of intrauterine adversity have also been investigated, in particular maternal stress in the prenatal period (O’Donnell and Meaney, 2016; Räikkönen and Pesonen, 2009).

Prenatal stress is often indicated by maternal mental health (e.g. depression) and family adversity (e.g. social and economic difficulties) in the literature (Leroya and Wolke, 2013). Although closely associated with each other, both have been independently associated with offspring outcomes and can be considered as two separate sources of stress (Leroya and Wolke, 2013), one from psychological and one from social/economic stress. There is strong evidence that prenatal maternal depression is associated with offspring depression in adulthood (Rogers et al., 2020; Tirumalaraju et al., 2020). Prenatal family adversity such as financial or relationship difficulties have also been associated with offspring depression even after accounting for maternal mental health (Kingsbury et al., 2016; Najman et al., 2017). Both sources of prenatal stress have also been associated with alterations to the hypothalamic-pituitary-adrenal (HPA) axis (Osborne et al., 2018; Van...
There is also evidence for the continuity of prenatal maternal depression into the postnatal period (Barker et al., 2011; Lerery and Wolke, 2013). Both pre- and postnatal maternal depression are also independently associated with emotional problems in childhood and psychopathology in adulthood, with postnatal depression proposed to act via environmental influences such as altered parenting behaviours or family environments (Munhoz et al., 2017; Pearson et al., 2013; Rees et al., 2019). Indicators of family adversity such as social and economic difficulties have also been shown to have a moderate persistence from the prenatal to postnatal period (Lerery and Wolke, 2013). Considering that both sources of stress continue into the postnatal period, it is important to account for these in order to examine the effect of prenatal stress independently from postnatal influences.

These early sources of stress may continue to exert influences throughout the developmental periods. However, periods beyond the early postnatal years are rarely examined when investigating the longitudinal association between prenatal stress and offspring depression. One of the most consistent childhood risk factors for depression is exposure to trauma (Copeland et al., 2018), which can lead to similar alterations to biological systems implicated in depression (Cattaneo et al., 2015). The evidence on childhood trauma is especially strong for caregiver-inflicted trauma, such as emotional, physical and sexual abuse, with lasting effect into adulthood (Lindert et al., 2014; Mandelli et al., 2015). Peer bullying has also been associated with increased risk of depression, even after controlling for childhood psychiatric disorders (Copeland et al., 2013) and genetic liability (Singham et al., 2017), consistent with a causal effect (Moore et al., 2017). As well as being one of the most consistent predictors of depression and other psychopathologies (Sahle et al., 2021; Moore et al., 2017), there is also evidence that childhood trauma may mediate the association between indicators of biological risk and emotional and psychiatric problems such as psychosis (Liu et al., 2020, 2019; Wolke et al., 2015), suggesting that childhood trauma may not just be a risk factor for psychopathologies, but can also be a consequence of earlier experiences.

Indeed, prenatal maternal depression has been associated with increased exposure to childhood trauma, possibly due to poorer attachment, maladaptive parenting and a programming effect of prenatal stress on offspring temperament (Azeredo et al., 2017; Lerery and Wolke, 2013; Pavlby et al., 2011). An indirect pathway has been found from maternal prenatal depression to offspring depression in adulthood via increased exposure to childhood trauma (Plant et al., 2015). However, sample size was small ($N = 103$) and specific trauma types were not examined. Furthermore, given the moderate heritability of depression (Flint and Kendler, 2014), part of the association between prenatal maternal depression and offspring depression may be explained by genetic liability, which should be controlled for. Lastly, family adversity was not examined independently from maternal depression when testing the mediating effect of childhood trauma, thus it would be important to investigate whether the same pathways are found from social/economic stress as well as psychological stress.

The aim of this prospective longitudinal study was to examine the direct effects of pre- and postnatal stress, as indicated by maternal depression and family adversity, and their indirect effects via childhood trauma on offspring depression in adulthood. In a large population-based sample followed up from pregnancy to 24 years, we first investigated the individual effects of pre- and postnatal stress and childhood trauma on offspring depression at 24 years. Secondly, we examined childhood trauma as a mediator in the pathway from pre- and postnatal stress to offspring depression.

2. Methods

2.1. Sample

The sample was drawn from the ALSPAC cohort, a prospective population study of 14,541 pregnant women who resided in the region of Avon, Southwest of England, with expected delivery dates between April 1, 1991 to December 31, 1992, and has been described previously (Boyd et al., 2013; Fraser et al., 2013; Northstone et al., 2019). In total, 3,506 participants who attended clinical assessment at 24 years were included. A fully searchable data dictionary and variable search tool can be found on the study website (http://www.bristol.ac.uk/alspac/researchers/our-data). Study data were collected and managed using REDCap (Research Electronic Data Capture) electronic data capture tools hosted at the University of Bristol, a secure, web-based software platform designed to support data capture for research studies (Harris et al., 2009). Ethical approval was obtained from the ALSPAC Ethics and Law Committee and the Local Research Ethics Committees. Informed consent for the use of data collected via questionnaires and clinics was obtained from participants and parents following the recommendations of the ALSPAC Ethics and Law Committee at the time.

2.2. Measures

2.2.1. Depression at 24 years

Participants attended a study clinic at 24 years and the Computerized Interview Schedule-Revised (CIS-R) was used to derive diagnosis for depression based on the ICD-10 criteria (Bell et al., 2005; Patton et al., 1999). It is a self-administered computerized interview and is the standardized tool for assessing common mental health disorders (Bell et al., 2005; Patton et al., 1999). Severity of depression was categorized into mild, moderate and severe according to symptoms experienced in the past two weeks, using the ICD-10 criteria. The outcome of interest in the current study was a binary variable indicating no depression diagnosis or any depression diagnosis (mild, moderate or severe) (Danchev et al., 2019).

2.2.2. Maternal depression

Maternal depression was assessed using the Edinburgh Postnatal Depression Scale (EPDS), a 10-item self-reported depression questionnaire that is well validated for use during pregnancy and in the post-partum period (Cox et al., 1987). Each item was scored from 0 to 3 and referred to feelings over the past week. Traditionally a cut-off score of 13 or more has been used to indicate clinically significant symptoms (Hewitt et al., 2009; Matthey et al., 2006), however in the current study continuous scores are used to take into account subtle variations in symptoms. EPDS scores are averaged across two periods during pregnancy (at 18 and 32 weeks) and three periods postnatally (2, 8 and 21 months) to indicate prenatal and postnatal maternal depression.

2.2.3. Family adversity

Family adversity was measured during pregnancy and in the postnatal period using the long version of the Family Adversity Index (FAI), a cumulative index developed from the ALSPAC data based on Rutter’s indicators of adversity (Steer et al., 2004). The original long index is comprised of 18 items including age of mother, housing situation, educational qualifications, financial situation, relationship with partner, family characteristics, social network, substance abuse, criminal behaviours and maternal psychopathology (Bowen et al., 2005). As maternal depression was investigated as a separate source of stress in the current study, the scale of maternal psychopathology was removed from the FAI to prevent over-controlling for the effect of maternal mental health. Thus, the FAI index comprised of 17 items and ranged from 0 to 17. Prenatal FAI indicates adversities experienced between 8- and 32-weeks’ gestation, and postnatal FAI indicates adversities between 0 and 2 years of age. The distribution of the FAI within the ALSPAC
cohort showed a non-normal, positively skewed distribution, and so was categorised into no adversity (score of 0), few adversities (score of 1,2), and many adversities (score of 3 or more).

2.2.4. Trauma

Childhood trauma experienced up to 17 years was derived in a previous study from 121 questions completed by either parents or participants on the frequency and severity of caregiver-inflicted trauma (types: physical abuse, emotional abuse, sexual abuse, emotional neglect, domestic violence) and peer bullying (Croft et al., 2018). All trauma assessments up to 5 years were reported by parents, a mixture of parent and child reports were used between 5 and 11 years, and child report was predominantly used between 11 and 17 years. A detailed description of the trauma measure has been described previously (Croft et al., 2018). A composite measure of exposure to any trauma (caregiver or peer inflicted) was derived from these individual trauma exposures, and categorized into no exposure, exposure to one trauma, and exposure to two or more traumas. Specific trauma types were assessed in a sensitivity analysis.

2.2.5. Other control variables

Sex of the participant was coded as male or female at birth. Polygenic risk scores indexing the participants’ cumulative genetic vulnerability for major depressive disorder (MDD) and neuroticism were derived from genome-wide association study (GWAS), using summary statistics from discovery studies (23andMe and UK Biobank), which has been reported previously (Jones et al., 2018). Scores were standardized using a list of single nucleotide polymorphisms (SNPs) associated with these outcomes in the discovery samples at a p-threshold of 0.05 (Jones et al., 2018).

2.3. Statistical analysis

All analyses were conducted in R version 3.6.3. Simple logistic regression models were first used to examine the individual effect of each risk factor (prenatal and postnatal maternal depression, prenatal and postnatal FAI, childhood trauma) on offspring depression. Ordinal logistic regression models also examined the association between each pre- and postnatal risk and childhood trauma. Childhood trauma was coded as an ordered variable with linear terms, and proportional odds assumption was not violated.

Path analysis was used to estimate direct and indirect effects (product of coefficients method) from pre- and postnatal stress via childhood trauma to depression at 24 years, using the “semTools” package. Simple path models were first examined from each of the four indicators of pre- and postnatal stress to offspring depression via childhood trauma. These four pathways were then modeled simultaneously in one path model, controlling for the effects of covariates. Missing data on predictor variables were handled using multivariate imputation by chained equations (“mice” package) with 40 imputed datasets. Data were imputed up to the total sample with complete data on depression at 24 years (N = 3506) using all predictors included in the analysis. Standardised path coefficients and 95% confidence intervals are reported.

2.4. Sensitivity analysis

We further examined the indirect effect of each specific trauma in separate path models. The same model was specified as above, with exposure to childhood trauma replaced by exposure to each specific trauma, and all paths from pre- and postnatal stress were modeled simultaneously.

3. Results

3.1. Sample characteristics

Characteristics of people lost to attrition have been reported previously in this cohort, with those dropping out more likely to be from households with financial difficulties, lower educational qualifications, poor housing and of mothers who were more likely to have experienced psychopathology during pregnancy (Wolke et al., 2009). The proportion of missing data in the current sample ranged from 0.2% to 25% (see supplementary materials, Table S1 for number of missing cases for each predictor).

The majority of participants were female (62.4%). More family adversities were reported during the postnatal period compared to prenatal period (19.5% vs 8.1% who experienced 3 or more adversities), and 29% reported multiple trauma exposure (exposed to two or more trauma) up to 17 years. The prevalence of depression was 10.8% at 24 years (Table 1), consistent with previous reports (Dantchev et al., 2019; Fernandes et al., 2020).

3.2. Risk factors for offspring depression

Simple logistic regression models showed that all risk factors (prenatal and postnatal maternal depression, prenatal and postnatal FAI, childhood trauma) were associated with offspring depression at 24 years. Childhood trauma was associated with the highest odds of offspring depression (Table 2).

3.3. Risk factors for childhood trauma

Both maternal depression and family adversity during the pre- and postnatal periods were associated with increased odds of childhood trauma (Table 3). Each increased point in mothers’ depression score during the pre- and postnatal period was associated with 6 and 7% odds of increased exposure to childhood trauma, respectively. Increased exposure to family adversity during the pre- and postnatal period was also associated with increased exposure to childhood trauma (Table 3).

3.4. Path analysis

Simple path analyses found direct and indirect effects of prenatal maternal depression and prenatal FAI on offspring depression via childhood trauma (supplementary materials, Tables S2–S5). Indirect effects were also found from postnatal maternal depression and postnatal FAI via childhood trauma, but there was weaker evidence for their direct effects. When all pathways were modeled simultaneously and adjusted for control variables, no direct effects were found from pre- and postnatal maternal depression and prenatal FAI on offspring depression.
postnatal maternal depression and FAI. However, indirect pathways were found from all four indicators of pre- and postnatal stress to offspring depression via childhood trauma (Table 4, Fig. 1). The strongest indirect pathway was from postnatal FAI via childhood trauma, which mediated 16% of the total effect of pre- and postnatal stress on offspring depression. This was calculated by dividing the indirect effect by the total effect. Other indirect pathways (from pre- and postnatal maternal depression, prenatal FAI) via childhood trauma mediated between 7 and 10% of the total effect on offspring depression at 24 years. Being female (SE = 0.18, 95%CI: 0.12–0.24) and polygenic risk score for MDD (SE = 0.10, 95%CI: 0.04–0.16) were also associated with increased risk of depression.

3.5. Sensitivity analysis

Indirect pathways were found via physical abuse, emotional abuse and peer bullying when specific trauma types were examined (supplementary materials, Tables S6–S11). Physical abuse mediated the association between postnatal FAI and offspring depression and accounted for 14% of the total effect. Emotional abuse mediated the association between pre- and postnatal maternal depression as well as postnatal FAI on offspring depression, accounting for 9 to 17% of the total effect. Peer bullying further mediated the association between prenatal maternal depression and offspring depression and accounted for 6% of the total effect.

4. Discussion

The current study investigated the longitudinal association between pre- and postnatal stress (maternal depression and family adversity), childhood trauma and offspring depression in adulthood. Although both sources of pre- and postnatal stress were associated with offspring depression, when all pathways were simultaneously modeled, their direct effects were attenuated, and only indirect pathways were found from each of them to offspring depression via increased exposure to childhood trauma.

Maternal prenatal depression was initially associated with increased risk of depression in the offspring, consistent with previous research and the programming model (Kim et al., 2015; Plant et al., 2015; Rogers et al., 2020). Every increased score in mother’s depressive symptoms was associated with a 5% increased odds of offspring depression at 24 years, and both direct and indirect effects were found from prenatal maternal depression to offspring depression via childhood trauma. However, this direct effect was reduced once other pathways from postnatal maternal depression and FAI were controlled for, and only childhood trauma was directly associated with offspring depression. This is consistent with previous findings (Plant et al., 2015), and suggest that part of the effect of prenatal maternal depression may be attributed to a continuity of depression in the postnatal period as well as its association with family adversity, which has been shown previously (Najman et al., 2017).

Childhood trauma has also been consistently associated with risk of depression and offspring depression and accounted for 6% of the total effect. Other indirect pathways (from pre- and postnatal maternal depression, prenatal FAI) via childhood trauma mediated between 7 and 10% of the total effect on offspring depression at 24 years. Being female (SE = 0.18, 95%CI: 0.12–0.24) and polygenic risk score for MDD (SE = 0.10, 95%CI: 0.04–0.16) were also associated with increased risk of depression.
and increased biological and environmental mechanisms. Furthermore, although the proportion of mediated effect varied, these findings consistently support the role of childhood trauma as an important environmental factor that should be routinely examined in longitudinal studies on the effects of prenatal stress on offspring depression.

Analysis of specific trauma revealed stronger evidence for indirect effects from postnatal FAI via physical abuse, and from postnatal maternal depression and FAI via emotional abuse. This suggests that environmental factors, such as increased harsh parenting and reduced emotional availability in mothers with depression and families with increased social and economic stress contributes to childhood trauma and offspring depression (Conrad-Hiebner and Byram, 2020; Conron et al., 2009; Kluczniok et al., 2016). Emotional abuse and peer bullying further mediated the association between prenatal maternal depression and offspring depression, even after accounting for postnatal influences. Biological mechanisms have been previously proposed, such as a programming effect of prenatal maternal depression on infant temperament and emotional reactivity, which may lead to maladaptive parenting and increase vulnerability to peer victimisation (Lereya and Wolke, 2013; O’Connor et al., 2003). Further investigation is needed to better understand biological and environmental mechanisms associated with different types of trauma.

The long-term consequences of early risk and childhood trauma may also be considered from a life history perspective (LHP), where experiences of neglect, abuse, and peer trauma may herald a world where others cannot be trusted or are disappointing (Brüne, 2016; Del Giudice, 2014; Otto et al., 2021). Thus, LHP predicts a faster pace of life with physical and psychological resources expanded to allow to escape a family or context at an earlier age than those in non-abusive contexts. For example, it has been shown that puberty timing is earlier in those who experienced sexual abuse with the possibility of subsequent psychosocial difficulties (Noll et al., 2017). Depression is also associated with an increased risk of cardiovascular disease (Joynt et al., 2003), i.e. a potential trade off for faster living. Thus, depression may be understood as an adaptive response, or the adoption of certain life history strategies to compensate for the accumulation of adversity across the early stages of life. However, LHP or faster pacing of life after trauma including altered health behavior (earlier drinking, smoking) or alternative explanations requires comparative testing in further longitudinal study.

4.1. Strengths and limitations

The longitudinal nature of the study and prospectively measured data allowed the testing of pathways from pre- and postnatal stress to offspring depression in adulthood. The large sample size allowed investigation on the specificity of trauma in a sensitivity analysis, which extends previous research (Plant et al., 2015). The finding of a mediated pathway from prenatal maternal depression to offspring depression via childhood trauma further suggest the involvement of biological mechanisms, such as a programming effect, as some of the indirect effect remained even after postnatal influences were modeled simultaneously in one model. Lastly, the inclusion of family adversity allowed examination of social/economic sources of stress separately to maternal depression and suggest that both may contribute independently to offspring depression via childhood trauma.

Some limitations include the high attrition rate over a period of 24 years which is unavoidable in longitudinal studies, with those dropping out more likely to be from households with lower SES and increased maternal psychopathology, which in turn may also underestimate the prevalence of depression at 24 years (Wolke et al., 2009). However, it has been previously shown in simulations that selective dropout does not affect the validity of predictive associations (Wolke et al., 2009), although statistical power may be affected due to an underestimation in the prevalence rates. Secondly, the measure of trauma used in the current study included abuse or neglect from both the mother and partner (Croft et al., 2018). The differential effect of mother vs partner-inflicted abuse was not examined; thus it is possible that the association between maternal and offspring depression, and apparent mediation via childhood trauma, may be confounded by partner-inflicted abuse leading to depression in both the mother and offspring. The derived trauma variable also included both parent- and child-reported measures, which may introduce measurement error and underestimate the effect of trauma, especially as the proportion of child-reported trauma was roughly twice as high as parent-reported trauma (Croft et al., 2018). Thirdly, polygenic risk scores for MDD and neuroticism were only included in the current study as control variables. Polygenic risk scores account for more
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Supplementary materials


References


