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Rachel Robinson, Marius Lahti-Pulkkinen, Kati Heinonen, Rebecca M Reynolds, Katri Räikkönen

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Fetal programming of neuropsychiatric disorders by maternal pregnancy depression: A systematic mini review

Rachel Robinson[1], Marius Lahti-Pulkkinen[1-3], Kati Heinonen[1], Rebecca M Reynolds[2], Katri Räikkönen[1]

[1]Department of Psychology and Logopedics, University of Helsinki, Helsinki, Finland

[2]University/British Heart Foundation Centre for Cardiovascular Science, Queen's Medical Research Institute, University of Edinburgh, Edinburgh, UK

[3]National Institute for Health and Welfare, Helsinki, Finland

Corresponding Author:

Rachel K. Robinson

University of Helsinki, Meilahti

Medicum, Haartman Institute, E219

Haartmaninkatu 3, FI-00290 Helsinki

Rachel.robinson@helsinki.fi

(Phone) +358456421030

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Abstract

BACKGROUND: Maternal depression complicates a large proportion of pregnancies. Current evidence shows numerous harmful effects on the offspring. Reviews, which include depression, concluded that stress has harmful effects on the offspring's outcomes neuro-cognitive development, temperament traits and mental disorders.

OBJECTIVE: This mini review of recent studies, sought to narrow the scope of exposure and identify studies specifically assessing prenatal depression and offspring neuropsychiatric outcomes.

STUDY ELIGIBILITY CRITERIA: The review included longitudinal, cohort, cross-sectional, clinical, quasi-experimental, epidemiological or intervention study designs published in English from 2014-2018.

PARTICIPANTS: Study populations included mother-child dyads, mother-father-child triads, mother-alternative caregiver-child triads and family studies utilizing sibling comparisons.

METHODS: We searched PubMED and Web of Science. Study inclusion and data extraction were based on standardized templates. The quality of evidence was assessed using the Newcastle-Ottawa Scale(NOS).

RESULTS: Thirteen studies examining neuropsychiatric outcomes were included. We judged the evidence to be moderate to high quality.

CONCLUSIONS: Our review supports that maternal prenatal depression is associated with neuropsychiatric adversities in children.

IMPLICATIONS: Future investigations should unravel the biological underpinnings and target timely interventions as early in pregnancy as possible to prevent offspring neuropsychiatric harms.

Introduction

Early life environmental adversities may exert consequences upon developing cells, tissues, and organs, their structure and function. These biological alterations may result in phenotypic differences between individuals that persist throughout the lifespan – a developmental plasticity phenomenon called 'prenatal programming'(1–4).

Maternal depression complicates a large proportion of pregnancies with 7.4%-20% of women experiencing major or minor depression, dysthymia or clinically significant depressive symptomatology during pregnancy(5). Yet, a large proportion of pregnant women with depression remain undetected(6). This does not merely reflect a lack of systematic screening, but also an unwillingness of women to admit experiencing depressive symptoms(7). Nearly half of women reported feeling too embarrassed to confess to a healthcare professional that they are not feeling well and almost one-third were afraid that if they divulged their feelings, their baby would be taken away(7). Many of the rest feared repercussions such as stigma(7).

Due to the high prevalence, maternal depression is a major complication of pregnancy and childbirth. Strongly predicted by prenatal depression(8), maternal postpartum depression also carries adverse consequences for the offspring(9). One systematic review and meta-analysis of studies published between 2010-2015, concluded that offspring of women with untreated depression during pregnancy were 56% more likely to be born preterm(< 37 gestational weeks) and 96% more likely to be born with a low birth weight(< 2.5 kg)(10). Another review of studies published up to2015 focused on the effects of maternal untreated pregnancy depression on a series of offspring outcomes ranging from birth outcomes and physiological effects to cognitive and psychopathological effects(11). While the evidence of the reviewed studies showed a

number of harmful effects on the offspring, yet the evidence was controversial, particularly regarding preterm birth and low birth weight(11). Pregnancy factors such as maternal age, gestation length, current maternal depressive status, pre-pregnancy obesity, gestational diabetes/hypertension, pre-eclampsia, and substance use during pregnancy, if not properly considered, may inflate the to the body of evidence. Yet, another recent review of studies published between 2010-2017 concluded that maternal stress in pregnancy, which included depression, has harmful effects on the offspring's neuro-cognitive development, negative affectivity, difficult temperament and mental health(2). As it is important to consider the althernative possibilities, numerous reviews explore the harmful effects of offspring exposure to pharmacologically treated(e.g. SSRIs) maternal prenatal depression(12–15).

To the best of our knowledge, no reviews have focused specifically on the consequences of prenatal depression on offspring neuropsychiatric outcomes. Hence, the objective of this review was to assess all recent studies assessing prenatal depression and offspring neuropsychiatric outcomes. We evaluate the quality of the evidence of the reviewed studies using the Newcastle-Ottawa Scale assessment(NOS). To deepen the discussion, we examine whether potential harmful effects of maternal depression on offspring neuropsychiatric outcomes are specific to the pregnancy period or explained by postnatal depression and whether a specific window of vulnerability exists when the effects of prenatal depression on offspring neuropsychiatric outcomes are most detrimental. Furthermore, we briefly explore the potential mechanisms through which prenatal depression may exert harmful consequences on offspring neuropsychiatric development. Lastly, we highlight treatment methods for prenatal depression, thereby possibly preventing offspring neurodevelopmental harm**.**

Methods

We searched Pubmed/MEDLINE and Web of Science databases for human longitudinal, cohort, and cross-sectional studies, published between January 2014 and February 2018 in English, with either clinical, quasi-experimental, epidemiological or intervention study designs.

We included studies focusing on mother-child dyads, mother-father/alternate caregiver-child triads. Study criteria included maternal prenatal depression with any depressive disorder diagnosis identified via medical registries, psychiatric interview, or depressive symptoms measured with self-report questionnaires. We excluded studies that used antidepressant use as the sole exposure measure, reported only on lifetime history of depression, used retrospective self-reports or unclearly defined exposure. We excluded studies that used other forms of psychological stress or only a combined exposure measure, such as a depression and anxiety mean score. For offspring neuropsychiatric outcomes, we considered internalizing and externalizing problems, including anxiety, depression, attention, conduct problems, Attention Deficit Hyperactivity Disorder(ADHD), autism spectrum disorders and schizophrenia.

We utilized RevMan5 software to generate the PRISMA flow diagram(16) that describes the study selection process(Figure 1). The studies' characteristics, participant demographics and data were systematically collected from each study using a standardized template.

We assessed risk of bias and the methodological quality in non-randomized, non-intervention, observational studies using NOS, a recommended method from the Cochrane Handbook of Systematic reviews(17,18).

Results

The sensitive search strategy applied produced 5712 articles(1083=Pubmed, 4629=Web of Science) for all studies up until February 2018. Refining the results to publications from 2014-

2018, rendered 766 articles(PubMed, n=135; Web of Science, n=631 for title and abstract review. Further hand searching of reference lists and other sources augmented the search findings(n=9). We included 13 empirical studies that examined prenatal depression and neuropsychiatric outcomes in offspring. See Figure 1 for the PRISMA diagram of inclusion.

Summary of Main Findings

Refer to Table 1 for a complete list of included studies, study characteristics and main findings, as well as each studies covariates.

A Finnish longitudinal cohort study by Korhonen et al.(21), among 192 mother-child dyads, found that prenatal depression was significantly associated with the 16-year-old child's externalizing behavior problems. Notably, in this study population, maternal depression, when the child was 8-9-years-old, was not significantly associated with the child's behavior problems, but when measured at the child's age of 16 years it was associated with the child's externalizing behavior problems(19). The study reported that children of women who had a 'high stable' trajectory of depressive symptoms from pregnancy to the child's adolescence had the highest risk for externalizing problems, suggesting that both pre-and-postnatal depression increase the child's risk(19).

The Finnish Prediction and Prevention of Preeclampsia and Intrauterine Growth Restriction (PREDO) study by Lahti et al.(15) of 2296 mother-child dyads found that higher maternal prenatal depressive symptoms were associated with higher internalizing, externalizing and total psychiatric problems of the child aged 1.9-5.9 years. These effects were independent of maternal depressive symptoms measured at the childhood follow-up, suggesting that the harmful effects on the child outcomes are specific to the prenatal period. The effects were gestation-week non-

specific, meaning that higher maternal depressive symptoms at the 14 biweekly measurements between 12-39 gestational weeks, were associated with more problems across a broad range of child behaviors(20). The study found that maternal depressive symptoms at the child follow-up partially mediated the prenatal depression effects. Additionally, the offspring of women who were consistently more depressed during pregnancy and at the childhood follow-up displayed the most problems(20), supporting the concept that both pre- and postnatal factors play a role.

In another study from the Finnish PREDO cohort by Wolford et al.(18), among 1779 mother-child dyads, higher maternal depressive symptoms during pregnancy were associated with significantly increased ADHD symptoms in children aged 3-6 years. These effects were independent of and partially mediated by maternal depressive symptoms measured in the childhood follow-up and were gestation-week non-specific; children of mothers with consistently high depressive symptoms both during pregnancy and in early childhood had the most ADHD symptoms (18).

The German Franconian Cognition and Emotion Study(FRANCES) study by Eicheler et al., which assessed children of 61 depressed and 143 non-depressed mothers, found that at age 6-9 years, offspring of depressed mothers scored higher on anxiety, depression and antisocial behavior(21). The associations with child depression and anxiety were independent of maternal depressive symptoms measured at the child follow-up, pointing to prenatal specificity of these effects(21). Yet, it remains unknown if the prenatal depression effects on child antisocial behavior would have been explained by maternal depressive symptoms during the child follow-up as the authors did not report these effects in the paper. This study also was unable to address if there would be a vulnerability window when maternal depressive symptoms would have had

the most harmful offspring consequences, as the study measured depressive symptoms only once, during the third pregnancy trimester(21).

In the Dutch Generation R study by El Marroun et al., among 5596 mother-child dyads, 1.5-6-year-old children exposed to maternal depressive symptoms (without SSRIs) at 20 weeks of gestation showed more pervasive developmental problems than the control group(22). These associations remained significant after adjusting for maternal postnatal depression. Supplemental analysis indicated that prenatal depressive symptoms tended to be associated with autistic traits even after adjusted for maternal depression at the child's age of 3 years(23) . This study also measured affective problems and found an increased risk for affective problems in children who were exposed to prenatal maternal depression (without SSRIs)(23). With only one measure of prenatal depression, this study, however, leaves the vulnerability window unclear.

In the UK Avon Longitudinal Study of Parents and Children (ALSPAC) by Capron et al. among 4303 mother-child dyads, higher maternal depressive symptoms at 18th gestational week were associated with and increased risk for anxiety disorder in the 18-year-old offspring(25).

In another ALSPAC study by Leis et al. among 2891 mother-child dyads, higher maternal depressive symptoms at 18th and/or 32nd gestational weeks were associated with higher risk of hyperactivity, emotional symptoms, conduct problems and total difficulties in the 11-year-old offspring (26). When the child problems were rated by the child's teacher, maternal prenatal depressive symptoms remained a significant predictor of the child's hyperactivity(24).

In the third ALSPAC study by O'Donnell et al. among 7944 mother-child dyads, maternal depressive symptoms at 18 weeks gestation predicted consistently elevated levels of the child's behavior problems through ages 4 to 14 years(25).

All the ALSPAC study findings were independent of maternal postnatal depressive symptoms measured at the childhood follow-ups. While the ALSPAC study has maternal depressive symptoms measurements at 18th and 32nd gestational weeks, these are not systematically reported in the studies, hence leaving open the question of a window of vulnerability.

In another UK study by Plant et al., in the South London Child Development(SLCD) study of 103 mother-child dyads maternal depressive symptoms at 20 or 30 weeks of gestation were associated with an increased risk of depression in the 25-year-old offspring (26). In this study maternal prenatal depressive symptoms were correlated with maternal postnatal depressive symptoms measured up to 12 months after delivery. Yet, the postnatal depressive symptoms were not associated with the adult offspring depression. In contrast, children exposed to maternal depression in early childhood(1-6years) were at an increased risk for adult depression(26). This study also revealed an additive effect where each additional exposure to maternal depression measured at different developmental stages increased the risk of depressive symptoms in the offspring in adulthood(26). This study concluded that childhood maltreatment mediated the effect of maternal prenatal depressive symptoms on the child's adulthood depression(28).

In another US longitudinal study of 196 young, low income, African American mothers and their children, a path analysis indicated two indirect paths mediating the effects of maternal prenatal depression on toddler total behavior problems(27). One indirect path indicated a significant path of maternal prenatal depression on toddler total problems at 24 months via maternal sensitivity at 24 months(27). The other indirect path showed that maternal depressive symptoms at 24 months mediated the effect of maternal prenatal depression on toddler total behavior problems at 24 months(27). It is unclear from this study whether prenatal depressive symptoms had effects on toddler behavior problems that were independent of maternal sensitivity and concurrent

depression. As this study measured maternal depressive symptoms only once during pregnancy, the study was not able to address the question of specific vulnerability window(27).

In another US study by Johnson, in a clinical subsample of 178 depressed mothers from the Emory Women's Mental Health Program for perinatal mental illness, 2.5-5-year-old children exposed to maternal pregnancy depression (without SSRI) were less likely to score in the 'at-risk range' for pervasive developmental disorder than those exposed to SSRI(28). The post hoc nested sibling analysis found that the decreased likelihood for pervasive developmental disorder in children with depressed mothers without SSRIs to compared to those with SSRIs remained significant(28).

The US Californian registry study by Wieckowski et al., comprising nearly 9 million mother-child dyads, found that maternal major depressive disorder(MDD; recurrent and single episode), dysthymia, depressive disorder not otherwise specified, and bipolar disorder increased the 4-21-year-old offspring's risk of autism spectrum disorder by 1.6-2.75-fold(21). While the timing of the maternal hospitalizations during pregnancy and at delivery were available, the study did not report the associations separately by trimesters or delivery; nor reported data on maternal hospitalizations during the child follow-up period. Hence, it remains unclear if the effects were specific to the prenatal period and if effects varied according to pregnancy trimester.

Quality of the evidence

We found the overall quality of the evidence as high to moderate based on the NOS Assessment, which judged cohort and case-control studies on three domains; 1)selection, 2)comparability, and 3)outcome(Table 2 & Table 1).

The 13 prospective studies included in this review represent participants from 6 high income countries, 5 of which are European. The ALSPAC(n=3)(1,24,29) and SLCD studies(n=1)(26) both drew their cohorts from the southern UK population at around the same time-period. The PREDO(n=2)(20,30), MoBA(n=1)(31) and Korhonen et al.(n=1)(19)studies examined Nordic populations. The German FRANCES(21) and the Dutch Generation R study(22) both examined southern European populations with Generation R comprising a multi-ethnic European population. In the US studies(n=3)(27,28,32), however, the populations' distinct geographic, socioeconomic and clinical characteristics and ethnic variation, separate these three studies from each other.

All of the studies used mother-child dyads(n=14), however, some studies used an additional caregiver measure(i.e. teacher or father)(n=3)(22,24,29), or a sibling comparison model (n=2)(28,31). Non-exposed participants were all drawn from the same populations as the exposed participants(1,19–22,24,26–32). Notably. there was one clinical subsample study(28). Only two studies used an objective maternal depression exposure measure, i.e medical records diagnosis(32)and the Clinical Interview Schedule (CIS) structured interview(26). Nine of the other studies used validated maternal report measures such as the Center for Epidemiological Studies Depression Scale(CES-D)(20,27,30), Edinburgh Postnatal Depression Scale(EPDS) (19,21) for measuring prenatal depressive symptoms. The bi-weekly CES-D measurements in the PREDO on maternal prenatal depression sets a gold standard for understanding the stability and trajectory of symptoms throughout gestation and allows for time point vulnerability exploration(20,30), a key tenant missing from the other studies in this review. The ALSPAC study also measured maternal depression at multiple prenatal and postnatal timepoints with the EPDS, however, only selective timepoints were used in each of the studies' analyses(24–26,29).

The clinical subsample from the Emory Women's Mental Health Program measured exposure using self-reports of SRI use and the Beck Depression Inventory, 2nd Edition (BDI-II)(28). Although the BDI-II is a commonly used measure for depression in the general population, findings suggest questionable validity in prenatal and postnatal samples, especially when compared to the EPDS(33,34). The Norwegian MoBa study(31) used 3 selected items from the Symptoms Checklist(SCL) version 5 comprising an externally non-validated measure of maternal depressive symptoms(31). Internally, a Norwegian study reporting on the reliability and validity of the short form the psychometric measures used in the MoBA study, indicates a strong correlation between the 5 items in the SCL-8 short form and in 3 items in the SCL-5 with the original SCL-25 for depression(35). Authors, cited their previous work reporting a moderate level of agreement between the self-report and diagnostic interview measures, however using the 5-item version of the SCL-5(36).

For comparability, ten studies controlled for the sex of the offspring as the most important confounder(20–22,24–28,30,31), while three studies(19,29,32) did not control for sex, reducing comparability. All 13 studies controlled for at least one other important factor such as age, gestation length, current maternal depressive status, maternal pre-pregnancy obesity, gestational diabetes/hypertension, pre-eclampsia, smoking and alcohol use during pregnancy all of which may significantly impact the findings(See Table 1 for all covariates used in each analysis). Although one study, did not report any of the adjusted analysis in the paper, as the author's indicated that it had no effect on the results(21). Select studies accounted for novel confounders such as childhood maltreatment in path analysis which significantly attenuated the results(26), paternal pre and postnatal depression or sibling analysis(28,31), both of which account for genetic and environmental effects supporting the prenatal programming hypothesis. Yet,

regarding the sibling analyses, maternal depressive symptoms show high continuity from pregnancy to postpartum(16,27), and the Gjerde MoBA study(19) did not describe the level of differential exposure among siblings or the inter-correlations between antenatal and postpartum symptoms that would have been needed to assess whether multi-collinearity posed a concern for any analyses. Overall differences in adjustment for confounders decreased the comparability of the results across studies(19–22,24–32).

Regarding outcomes, 3 studies used an objective neuropsychiatric outcome measure removing the subjectivity of parental report questionnaires via medical records diagnosis (32), the Clinical Interview Schedule-Revised (CIS-R)(29) validated in young adult populations for identifying anxiety and depression (37), and the Structured Clinical Interview (26). All other studies (n=10) used mother/father/caregiver-rated questionnaires. Six studies used the Child Behavior Checklist(CBCL), which measures internalizing, externalizing and total problems, emotionally reactive, anxious/depressed, somatic, withdrawn, sleep, attention and aggressive behavior problems, and affective, anxiety, pervasive developmental, attention deficit/hyperactivity, and oppositional defiant problems alone(19,20,22,23,28,31) or in combination with the Youth Self Report(YSR)(19), or the Social Responsiveness Scale(22). Other studies measured parental reported symptoms using the Conners' Hyperactivity Index for ADHD(30), the Brief Infant-Toddler Social and Emotional Assessment (BITSEA), which assesses internalizing, externalizing, dysregulation and competence(27,38) and the SDQ for assessing prosocial behavior, hyperactivity, emotional symptoms, conduct problems, peer problems, and total difficulties(1,39). The FRANCES study measured internalizing and externalizing behaviors using a psychologist administered set of mother-rated questionnaires from the ICD-10 and DSM-

IV which are not well-known and are available only in the German language; hence it remains challenging to evaluate their reliability and validity(21) .

All 13 studies followed participants for a suitable length of time for the designated outcome of interest. Notably, however, the CBCL has only been validated for ages 1-5, and inclusion of some participants at age 6 could have impacted the results in the Generation R study (40% age 6)(22). Nine studies retained adequate numbers for follow-up and clarified how the authors dealt with missing data(19–22,26–28,30,31). Originally a very large cohort, the long term follow up of the ALSPAC studies(n=3)(1,24,29) experienced a high attrition rate, especially by follow up at 18 years(24,25,29). However, the long-term adulthood follow-up in the ALSPAC studies(24,25,29) and the US register study(32)is a valuable addition to the literature. Notably, although the majority of studies have sample sizes in the thousands(20,22,24,25,29–31), one even over 8,000,000(32) five studies in this review have relatively small sample sizes(19,21,26–28).

Limitations for this review as a whole, include the small number of studies which met the inclusion criteria and a high risk of publication bias across the included studies. Furthermore, our data extraction was performed by only one author. One question pinpointed at the beginning of this review, e.g. a specific gestational vulnerability timepoint, could not be fully elucidated based on the current body of evidence and the lack of replication multi-point measures across studies.

Discussion

This review of 13 studies supports the previous findings reviewed by Van den Bergh et al.(2017), suggesting that prenatal depression is associated with adverse neuropsychiatric consequences on the offspring. Ten studies(19,20,22,24–30) favored the conclusion that the

effects of maternal depression on offspring neuropsychiatric outcomes are specific to the maternal pregnancy period and are not accounted for by depression after pregnancy. Two studies(21,32), however, did not address the pre vs postnatal specificity question, and another(31) concluded that the offspring neuropsychiatric effects are not specific to the prenatal period, but are rather a consequence of maternal depression during the offspring postnatal development. As discussed previously, the one dissenting study used non-validated measures of maternal depression, which hampers it's reliability(31). Importantly, maternal depression shows high continuity from pregnancy onwards, with study populations(20,30) indicating that in over 50% of the women, clinically relevant depressive symptomatology during pregnancy persists after delivery. Therefore, the question of exposure timing during pregnancy or after delivery of the maternal effects may be difficult to disentangle because of statistical multi-collinearity problems. Only the PREDO cohort from this review, with 14 by-weekly gestational measurements of maternal depressive symptoms was able to address the question of a specific vulnerability window, which showed that the effects on child problem behaviors were gestation week non-specific(20,30).

Pathways

Prenatal depressive symptoms may influence child neuropsychiatric outcomes via multiple psychological, health behavior, and biological pathways. An important component of understanding theses pathways, involves disentangling the effects of other pregnancy and perinatal complications, which may contribute to the severity, duration, and complexity of maternal prenatal depression. For instance, recent meta-analyses and systematic reviews show that maternal obesity in early pregnancy is associated with an increased risk of depression during pregnancy(40,41). Also in the PREDO cohort, from a study not in this review, women with early

pregnancy overweight and obesity had consistently elevated depressive symptoms throughout pregnancy and after delivery(8). Evidence suggests that gestational diabetes and hypertension spectrum disorders may also be associated with prenatal depression(42), but these findings remain controversial(8).

Maternal cardio-metabolic conditions might contribute as one of the pathways, as a meta-analysis found that maternal obesity predicted an increased risk of autism and ADHD, developmental delay and emotional/behavioral problems in children(43). Also, we recently showed that maternal severe obesity in early pregnancy is associated with hyperactivity, sleep problems, conduct, externalizing and total problems, depressive symptoms, anxiety and ADHD problems in children(44). Gestational diabetes has repeatedly been associated with an increased risk of neuropsychiatric disorders, particularly of autism and schizophrenia in the offspring(45–48). Yet, in the PREDO maternal obesity or gestational diabetes were not associated with mother-rated internalizing, externalizing or total psychiatric problems in 1.9-5.9-year-old children (20), but were associated with child neurodevelopmental delay(49).

Prenatal depression also increases risks of preterm birth and low birth weight(42,50). Also in the PREDO cohort, maternal depressive symptoms during pregnancy predicted shorter gestation length(51). Preterm birth and low birth weight have been consistently shown to be risk factors for neuropsychiatric disorders(52–56), and in sibling comparisons(53,54).

Evidence from a meta-analysis and from large population-based studies suggests that depressed mothers are more likely to smoke throughout pregnancy(42,57), and prenatal smoking has been repeatedly associated with the risk of neuropsychiatric disorders in the offspring(20,58,59). Also in the PREDO, prenatal smoking was associated with increased internalizing, externalizing total psychiatric and ADHD problems in children(20,30).

Biological Mechanisms

The biological mechanisms possibly linking maternal depression and psychological distress more generally with offspring neuropsychiatric outcomes were reviewed in Van den Bergh et al.(2017)(2). According to this review, and studies published since, prenatal depression may be associated with child neurodevelopment via 1)alterations in hypothalamus-pituitary-adrenal(HPA)-axis functioning, 2) functional and structural changes of related brain areas including amygdala and prefrontal cortex, 3)changes in autonomic nervous system and 4) immune system functioning and in gut microbiota(2,60,61).

At population level, one of the most consistent biological changes in depression is altered cortisol levels, indicating altered HPA-axis functioning(2,62,63). However, studies linking maternal depression specifically during pregnancy with maternal or infant cortisol levels have yielded inconsistent findings(2,62,63). Yet, maternal HPA axis functioning during pregnancy has been linked with offspring neuropsychiatric problems(2). For instance, we recently showed that maternal licorice consumption during pregnancy predicted an over 3-fold risk of ADHD problems in the offspring(64) due to Glycyrrhizin, which inhibits the placental 11β-hydroxysteroid dehydrogenase type 2(*11βHSD2*) enzyme. This enzyme protects the fetus from maternal glucocorticoids, hence leaving the fetus vulnerable to maternal glucocorticoid excess. Furthermore, structural and functional changes in the infant amygdala, which regulates HPA axis functioning, have been repeatedly reported as a consequence of prenatal depression(2,65–67) and are also associated with child psychopathology risk(68,69). Also, alterations in the functioning of the autonomic nervous system that also plays a key role in the stress response have been found in children exposed to prenatal depression(2).

Changes in inflammatory pathways and gut microbiota, as a consequence of prenatal depression, offer another route through which prenatal depression may affect child neuropsychiatric problems. Maternal prenatal cytokine levels present questions for epigenetic programming as cytokines may pass through the placenta(70). Higher prenatal depression has also been directly associated with maternal inflammatory cytokine levels during pregnancy(71,72), but the findings are inconsistent. Correspondingly both anti-inflammatory drugs(73) and probiotics(74) have antidepressant effects. Prenatal levels of C-reactive protein(CRP), a key inflammatory marker, have been associated with offspring risk of different neuropsychiatric disorders (75–78), and prenatal depression is associated with offspring CRP levels(79). Evidence for the gut microbiota pathway predominately stems from animal studies but two recent studies have shown microbiota changes in offspring exposed to prenatal depression(80,81). Nonetheless, the biological mechanisms involved warrant further research.

Cellularly, depression-related changes in fetal biology studies have specifically focused on epigenetic modifications. There are several recent systematic reviews on the effects of maternal psychological distress during pregnancy and more specifically antenatal depression on placental and infant DNA methylation(2,82,83). Overall, these reviews state that the findings are inconsistent but many candidate gene studies have linked methylation of the *NR3C1*, the glucocorticoid-receptor gene, with maternal prenatal depression. Other potential, often examined, candidate genes include 11BHSD2, FKBP5, IGF2, SLC6A4, OXTR, CRH and BDNF, genes that also play roles in HPA axis regulation. Most studies have focused on either assessing placental DNA methylation or infant cord-blood methylation levels. The studies have identified some significant effects, which still need validation. Future larger epigenome-wide-

association studies harmonizing and pooling data into meta-analyses will overcome the current single study limitations.

Recent findings from the PREDO suggest that changes in placental gene expression and infant DNA cord blood methylation as well as morphological changes in placental structure may be among the mediating biological pathways between antenatal depressive symptoms and child psychiatric problems. Among approximately 60 PREDO participants, prenatal depressive symptoms were associated with higher placental mRNA levels of glucocorticoid and mineralocorticoid receptor genes. Findings which suggest higher placental glucocorticoid sensitivity (84,85). In a UK longitudinal study among 93 participants, we found that higher prenatal depressive symptoms were associated with reduced placental IGF2-2 mRNA levels and, particularly in the placentas of female fetuses, with altered mRNA levels of several genes regulating fetal glucocorticoid exposure(86). Furthermore, among PREDO participants, maternal prenatal depressive symptoms were associated with lower infant epigenetic gestational age at birth, a biomarker of the developmental maturation level of the fetus. This biomarker predicted increased total and internalizing psychiatric problems in boys, and partially mediated the effects of maternal prenatal depression on boys' internalizing problems(87). Another PREDO study assessing placental morphology among 86 participants found less variation in placental villous barrier thickness of gamma-smooth muscle actin-negative villi in the placentas of antenatally depressed mothers, indicating reduced placental maturation, due to prenatal depression. This placental structural change predicted internalizing and total psychiatric problems in 60 toddlers(88).

Treatments of prenatal depression

Predictors for full recovery from prenatal depression include the absence of maternal health concerns, low total parental stress status, and limited child behavior issues(89), while maternal sensitivity has been found to attenuate the effects of maternal prenatal depression on toddler total problems (27), all which underscore the need for a comprehensive treatment approach for prenatal depression. Antidepressant medication may offer an option as several reviews indicate the likelihood of serious harms is low (12–15). Although, investigations into specific medications and classes of anti-depressants (90–92) complicate the literature, suggesting serious harmful effects, leading many doctors not to prescribe and/or many women refuse/discontinue medication in pregnancy(5). Until the data on the safety and efficacy of antidepressant therapies is clearly defined, efforts should be concentrated to assess alternative therapies. Although, they stray from antidepressants, pregnant women have reported an interest in cognitive behavioral therapy(5), which recent review evidence suggests has robust effects for the treatment of women with MDD(93). However, due to a lack of resources and limited access to standard therapies: nearly half of diagnosed women fail to receive timely evidence-based treatment(94). In lieu of standard delivery, online cognitive behavioral therapy interventions may serve as an effective measure for improving maternal perinatal mental health(95,96). Recent studies have considered the effectiveness of relaxation practices through musical therapy(97), fish oil supplementation (98), dietary supplementation(99) and future studies could consider probiotics supplements.

Conclusions

Our review found a limited amount of high to moderate quality evidence supporting the association of prenatal depression and neuropsychiatric outcomes in children, published 2014-2018. More, carefully conducted cohort studies with multi-time point, validated exposure and

outcome measures investigating epigenetic and protective factors are needed to further corroborate the findings relating to a specific developmental vulnerability period. Further investigations into the implications of the timing and consistency of exposure, confounding by other perinatal conditions, and possible biological mechanisms would bolster the evidence. Future research needs continuous and prospective measures of maternal depressive symptoms throughout pregnancy and beyond, in order to better scope the prenatal and postnatal trajectories of depression, risk factors, and include follow-up of offspring into adulthood to assess long-term neuropsychiatric effects.

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Disclosure

The authors declare no conflict of interest.

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Figure 1. PRISMA Flow Diagram: Study inclusion and exclusion process

Table Summary of Included Study Characteristics & Main

Stud	Sourc	Populati	Sampl Siz	Study	Maternal Measureme	Offspring Measureme	Result Statistical
FINLAND							
Korhonen et al. 2014	Finnish longitudinal cohort study	Finnish mother-child dyads	192	cohort	Prenatal: EPDS[4] in the last trimester Postnatal: EPDS[4] 2 weeks, 2 months, 6 months, 4-5 years, 8-9 years & 16-17 years	CBCL[1] & YSR[11] at multiple times up to age 16	Time of the initial exposure for materna adolescent CBCL/YSR outcomes were sig Initial Prenatal (Last trimester) exposure Initial Postnatal (2 months) exposure & i standard effect size 0.90 (YSR) Initial Pos externalizing problems: P=0.003, standa Adjusted Covariates: Int.Epis.Time
Lahti et al 2017	PREDO[1]	Finnish, mother-child dyads	2296	cohort	Prenatal: CES-D Bi-weekly between weeks+days 12+0/13+6 and 38+0/39+6 or delivery. Postnatal: Becks Depression Inventory 1½−5 years	CBCL[6] at ages 1.9-5.9years	Maternal depressive symptoms during pregnancy predicted significantly highe internalizing (0.28 SD unit per SD unit in [95% CI = 0.24, 0.32]), externalizing (0.2 0.30]), and total problems (0.31 [0.27, children. Adjusted Covariates: Hist.Dep, Antidep., P M.Diab., Sex, GL, BWT, Fam.Stat., ADP, M.E CA
Wolford et al 2017	PREDO	Finnish, mother-child dyads	1779	cohort	Prenatal: CES-D Bi-weekly between weeks+days 12+0/13+6 and 38+0/39+6 or delivery. Postnatal: Becks Depression Inventory 1½−5 years	CHI questions (ADHD) at 3-6 years old	Children of mothers with consistently hi showed higher average levels (MD = 0.46 SD units, 95% CI 0.36, 0.56, p group), and proportion (32.1% vs. 14.7%) and o p < 0.001) of clinically significant ADHD s Adjusted Covariates: M.ADHD, Hist.Dep, An PPH, M.Diab., Sex, GL, BWT, Fam.Stat., ADP,, M.Edu, CA
NORWAY							
Gjerde 2017	MoBA	11,599 Norwegian families	17830 siblings	cohort	Prenatal: SCL-90 Short form SCL-5 and SCL-8 selfrating questionnaires 17th week & 30th week gestation Postnatal: 6 months, 18 months, 3 years & 5 years after birth	CBCL[6 at] 1.5, 3 and 5-years	In sibling comparison, concurrent mater depression was significantly associated internalizing [estimate = 2.82(1.91, 3.73, CI)] and externalizing problems [estimat 2.40(1.56, 3.23, 95% CI)] Adjusted Covaria CA, Sex, Par., M.Edu
GERMANY							
Eichler et al 2017	FRANCES	German, mother-child dyads randomly selected from the FRAMES study population	204	case-control	Prenatal: EPDS 3rd trimester Postnatal: EPDS 6-9 years	Parental Questionnaire from ICD-10 and DSM-IV aged 6-9	Total Sample: 6.74(4.95) , Mother not de Mother depressed: 13.07(3.01) Not-depressed vs. depressed: −21.7** P Adjusted Covariates: Sex, Fam.Stat., CMD
THE NETHERLANDS							

El Marroun et al. 2014	Generation R	Dutch mothers-child dyads & father-child dyads	5976	Cohort	Prenatal SSRI Exposure: 1) SSRI use self-report, 2) pharmacy prescription records Prenatal Depression Exposure: BSI[12] at 20 weeks gestation	CBCL & SRS[13] at ages 1.5, 3 and 6 years	Maternal depressive symptoms (withou rated child affective problems (OR=1.44 Maternal depressive symptoms (withou child affective problems were also signif 2.45, P=0.03) Prenatal depressive symptoms as a cont associated with affective problems (OR= P=0.001). Maternal prenatal depressive symptoms had more pervasive developmental prob 95% CI 1.53, 2.66). Maternal prenatal depressive symptoms after adjusting for depression at age 3 had more pervasive developmental pr 1.93, p=0.02) Maternal prenatal depressive symptoms traits (β=0.05, 95% CI 0.01, 0.08, P=0.001)
							Maternal prenatal depressive symptoms autistic traits (β=0.05, 95% CI 0.03, 0.07) Direct comparison of the effect estimate symptoms without SSRI use (β=0.09, 95% Adjusted Covariates: MA, Sex, M.Edu, ethni
UNITED KINGDOM							
Capron 2014	ALSPAC[14]	Avon region, UK Mother-Father-Child triads	4303	Cohort	Prenatal: EPDS[4] at 18 weeks gestation Postnatal: EPDS[4] 8 weeks & 21 months	CIS-R[16] at age 18 years	Children exposed to maternal prenatal d increased risk of anxiety at age 18: (Adjusted for postnatal depression at 8w (Adjusted for postnatal depression at 21 OR=1.62 (95% CI 1.06, 2.47)* The risk fro prenatal depression at 18 weeks was not Adjusted Covariates: MA, BWT, Par., ACDP, PNDA
Leis et al 2014	ALSPAC[14]	Avon region, UK Mother-Teacher-Child triads	2891	Cohort	Prenatal: EPDS[4] at 18 & 32 weeks gestation Postnatal: EPDS[4] at 8 weeks, 8, 21, 33, 61 & 73 months	SDQ[17] at age 10-11 years	Children exposed to elevated levels of m depression (>13 EPDS) at one time-point scores (adjusted β (SE)) for: (hyperactivity) 0.35(0.13) p <0.01 (also si teacher rated SDQ) (emotional symptoms) 0.24 (0.09) p <0.0 (conduct problems) 0.20 (0.08) p <0.01 (for teacher rated SDQ) (peer problems) (<0.05 (total problems) 1.00 (0.27) p <0.001 (als teacher rated SDQ) Adjusted Covariates: P BWT, Sex, SDP, ADP, M.Edu, Fam.Stat.
O´Donnell et al. 2014	ALSPAC	Avon region, UK Mother-Child dyads	7944	Cohort	Prenatal: EPDS[4] 18 weeks gestation [4] Postnatal: EPDS at 8 weeks & 33 months postpartum	SDQ[17] at age 4, 7, 9, 11.5 & 13 years	Intercept Estimate Maternal prenatal depression (32 weeks) 0.077 Maternal postnatal depression (8 weeks) 0.127 S 0 Maternal depression at 33 months post. 0.183 0 Adjusted Covariates: MA, M.Edu, SES BWT, GA, Sex, SDP, ADP, P

Plant et al. 2015	SLCDS[17]	UK mother-child dyads	103	Cohort	Prenatal: CIS-R[16] at 20 & 36 weeks gestation Postnatal: CIS-R[16] at 3 months & 12 months SADS-L[18] at 4 years, 11, and 16 years	Structured Clinical Interview for DSM-IV Axis I Disorders at age 25	Offspring exposed to maternal prenatal depressed in adulthood. OR=3.4(95% CI 1.15, 8.1) $X^2(1)=8.4$, p=0. Mean number of depressive symptoms exposed to prenatal depression (M=3.4, Than those unexposed (M=1.7, SD 2.(, z= Maternal depression in the postnatal pe associated with adult depression: OR=1.8, (95% CI 0.8, 4.2) $X^2(1)=2.1$, p=0. Maternal depression in offspring childho with depression in adulthood OR=4.2 (95% CI 1.8, 10.2)) $X^2(1)=11.1$, p= Maternal prenatal depression effects on mediated by childhood maltreatment B= Adjusted Covariates: MA, ethnicity, SES, M. SDP, ADP, GA, BWT, Sex, Ethnicity, C.Edu, C.IQ
UNITED STATES OF AMERICA							
Edwards et al. 2016	US longitudinal study	Young, low SES, African American mother-child dyads	196	Cohort	Prenatal: CES-D during pregnancy Postnatal: CES-D at 24 months	BITSEA at age 24 months	Path analysis Prenatal Depression→ maternal Sensitiv (Full Sample) B(SE) 0.031 (0.02 (Boys) B (SE) 0.052 (0.035) 95% (Girls) B (SE) 0.002 (0.015) 95% Prenatal Depression→ 24 month depres (Full Sample) B(SE) 0.086 (0.03 (Boys) B (SE) 0.073 (0.016) 95% (Girls) B (SE) 0.097 (0.061) 95% 0.016, 0.225) Adjusted Covariates: Sex, mo
Johnson 2016	Emory Women's	Clinical sample of USA Mother-child-child triads	178	Clinical, observational	Prenatal: BDI[7] during pregnancy Postnatal: BDI at follow-up	CBCL[6] PDD[15] in sibling pairs at ages 2.5-5 years	Children exposed to prenatal depression to score in the high risk range on the PDI

1. Prediction and Prevention of Preeclampsia and Intrauterine Growth Restriction
2. Center for Epidemiologic Studies Depression Scale
3. Franconian Cognition and Emotion Studies(Follow-up study to the FRAMES cohort)
4. Edinburgh Postnatal Depression Scale
5. Norwegian Mother and Child Cohort study
6. Child Behavior Checklist
7. Beck Depression Inventory/ Beck Depression Inventory II
8. Selective Serotonin Reuptake Inhibitors
9. Medically untreated depression group
10. Control group
11. Youth Self Reports

Adjusted Covariates: Antidep. (Antidepressant Use), ACDP (Alcohol Consumption During Pregnancy), Apgar(Apgar Score),BWT (Birthweight), CA(Child Age), C.EarlyLearn.(Child Early Learning Center attendance), C.Ethnicity (Child ethnicity), C.IQ (Child IQ score) C. Mal.(childhood maltreatment), CMD(Concurrent Maternal Depression), Deliv.Meth.(Delivery Method), Deliv.Comp(Delivery Complications), Fam.Stat (Family Status), GA(Gestational Age), GL(gestational length), GDH(Gestational Diabetes/Hypertension), Glob.Funct.(Global assessment of Functioning), HC(Head Circumference), Hist.Dep(History of Diagnosed Depression) , Int.Epis.Time (Initial episode timing), M.ADHD (Maternal ADHD), MA (Maternal Age), MDep(Maternal Prenatal Depressive Symptoms), M.Edu(Maternal Education Status), M.

						(mother rated): β= -0.163 Unstandard 0.001, 0.002, P=0.048)* Adjusted Covariates: CA, Sex, MA, Fam.S SDP, ADP, Antidep., Psycho.Meds, BWT, DelivComp, NumbComp, MDep, MoodEp
Wieckowski et al 2017	Hospital discharge records	California singleton births occurring 1/1/91-12/31/08 8951763	retrospective cohort	Medical records ICD-9-CM code for Depressive disorder NOS 311.x Anytime in the prenatal or perinatal period	California Dept. Of Developmental services diagnosis (Autism) age 4-21years	Mothers diagnosed with one individu psychiatric condition were 1.2-2.8 tim more likely to have a child who develo autism. Mothers diagnosed with any o more psychiatric condition were twice likely to have a child with autism comp with unaffected or unreported wome 1.97; 95% CI 1.83, 2.12). Adjusted Cova M.Origin, MA, M.Edu, Ethnicity

12. Brief Symptom Inventory
13. Social Response Scale
14. Avon Longitudinal Study of Parents and Children
15. Pervasive Developmental Disorders (CBCL Subscale)
16. Clinical Interview Schedule- Revised
17. South London Child Development Study
18. Schedule for Affective Disorders and Schizophrenia

Ethnicity (Maternal Ethnicity), M.Occup (Maternal Occupation/Status), M.Epilep.Stat.(Maternal Epileptic Status), MoodEpi.(Mood Episodes), Numb.Comp(Number of Pregnancy Complications), Par. (Parity), Pater.Anxi.(Paternal pre/postnatal Anxiety), Parent.Index(Parenting Index Score), PE(Pre-Eclampsia, Mom dad(mother-father relationship), PD(paternal depression), PND(Postnatal depression), PNDA(Maternal Postnatal Depression & Anxiety), PPObes.(Pre-Pregnancy Obesity), Psycho.Meds.(Psychotropic Medication use), Psycho.Vari.(Psychological Variables), SDP(Smoking During Pregnancy)

Table 2. NOS Quality of Evidence (Table listed in order of source country and then alphabetically.)

The Newcastle-Ottawa Scale assesses studies on 3 domains: Selection of study participants, Comparability of the studies, and the selection of the Outcomes. A study can receive a maximum of 4 stars in the Selection domain, 2 stars in the comparability domain, and 3 stars in the Outcomes domain.

Quality Assessment Criteria	**Selection (⋆⋆⋆⋆)**				**Comparability (⋆⋆)**		**Outcome**	
	Representativeness of exposed cohort?	Selection of the non-exposed cohort?	Ascertainment of exposure?	Demonstration that outcome of interest was not present at start of study?	Study controls for sex?	Study controls for at least one additional factor?	Assessment of outcome?	Was follow-u enough outcome to oc
Acceptable (⋆)	Representative of average in community	Drawn from same community as exposed cohort	Secured records, Structured interview	Children not yet born, therefore outcome not yet possible.	Yes	Age, pre-pregnancy obesity, gestational length, current maternal depression status, gestational diabetes/hypertension, pre-eclampsia, smoking & alcohol use during pregnancy, mother-father relationship, paternal depression, childhood maltreatment	Independent blind assessment, record linkage	Follow-up period suffici measure outc
Korhonen et al. 2014	⋆	⋆		⋆		⋆		⋆
Lahti et al. 2017	⋆	⋆		⋆	⋆	⋆		⋆
Wolford et al. 2017	⋆	⋆		⋆	⋆	⋆		⋆
Gjerde et al. 2017	⋆	⋆		⋆	⋆	⋆		⋆

Eichler et al. 2017	⋆	⋆		⋆	⋆	⋆		⋆
El Marroun et al. 2014	⋆	⋆		⋆	⋆	⋆	⋆	
Capron et al. 2014	⋆	⋆		⋆			⋆	⋆
Leis et al. 2014	⋆	⋆		⋆	⋆	⋆		⋆
O'Donnell et al. 2014	⋆	⋆		⋆	⋆	⋆		⋆
Plant et al. 2015	⋆	⋆	⋆	⋆	⋆	⋆	⋆	⋆
Edwards et al. 2016	⋆	⋆		⋆	⋆			⋆
Johnson et al. 2016	⋆			⋆	⋆	⋆	⋆	⋆
Wieckowski et al 2017	⋆	⋆	⋆	⋆		⋆	⋆	⋆

[1] High quality : ≥ 7⋆ (Additional requirements: Selection domain 3-4 stars AND Comparability domain 1-2 stars AND Outcome domain 2-3 stars)

[2] Moderate quality: ≥ 5⋆ (Additional requirements: selection domain 2 stars AND comparability domain 1-2 stars AND outcome domain 1-3 stars)

[3] Poor quality: ≤ 4⋆ (Additional requirements: selection domain 0-1 stars OR comparability domain 0 stars OR outcome domain 0 stars)