Women's health and wellbeing: the roles of early life adversity, stress and lifestyle

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Chapter 3

Hypothalamic-pituitary-adrenal axis and autonomic nervous system reactivity in children prenatally exposed to maternal depression: a systematic review of prospective studies

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Abstract

Depression is a common condition affecting up to 20% of all pregnant women, and is associated with subsequent developmental and behavioural problems in children, such as conduct disorder and ADHD. One proposed mechanism underlying these associations is modification of the fetal hypothalamic pituitary adrenal (HPA) axis and the autonomic nervous system (ANS), resulting in altered responses to stress. This review examined the evidence regarding altered HPA axis and ANS reactivity in children prenatally exposed to high maternal depressive symptoms. A systematic search was conducted in the electronic databases MEDLINE, EMBASE and PsycINFO, for studies published until 25 July 2017. A total of 13 studies comprising 2 271 mother-infant dyads were included. None of the studies were suitable for *meta-analysis*. Risk of bias assessment showed low risk for four studies. Only three studies described an independent association between exposure to high maternal prenatal depressive symptoms and altered stress reactivity in children. There is limited evidence of an independent association between prenatal exposure to maternal depression and altered HPA or ANS reactivity in children.

Introduction

Depression has been estimated to affect up to 20% of all pregnant women (1). Besides being a major burden for the pregnant woman herself, the unborn child might also be affected. Women who are depressed during pregnancy more often deliver prematurely and have babies with lower birth weights (2). Also, their children more often develop depression in childhood, adolescence and adulthood themselves, and exhibit more behavioural problems (3-6). A large cohort study found that higher antenatal depression and anxiety was associated with more attention problems in children at age 3 - 4, and more emotional and behavioural problems at age 10 - 11, independent of postnatal maternal mood (7). A similar cohort study replicated these findings in 3 to 4-year-olds, however, their results were no longer significant after adjusting for maternal mood symptoms after giving birth (8). Another prospective cohort study, which comprised 2 296 mother-child dyads, found associations between internalizing, externalizing and total behavioural problems in children with prenatal exposure to maternal depression throughout the entire pregnancy, which was also independent of, but partly mediated by, maternal depressive symptoms after pregnancy, in early childhood at the time of child ratings (9). Waters et al. systematically reviewed studies that investigated associations between prenatal exposure to depression and children's neuropsychological developmental outcomes, and reported that prenatal exposure to depression increased the occurrence of conduct problems and antisocial behaviour, however, effects on cognition were less consistent (10). Studies that have emerged in the past decade, show increased methodological validity in comparison with prior studies, using larger sample sizes and more often controlling for relevant confounders. They add to the growing body of evidence showing increased adverse behavioural, emotional and psychopathological outcomes in children prenatally exposed to several indices of stress or depression (11).

The underlying biological mechanisms that mediate the associations between prenatal exposure to depression and behavioural, developmental and psychopathological outcomes in children remain to be fully elucidated. One hypothesis states that depression in pregnancy leads to dysregulated reactivity to stress in the pregnant woman, which in turn affects development of the stress system of the foetus. The hypothalamic pituitary adrenal (HPA) axis responds to psychological or physiological stress with the production of corticotrophin-releasing hormone (CRH) from the hypothalamus, stimulating the pituitary to produce adrenocorticotropic hormone (ACTH), resulting in higher production of cortisol from the adrenal glands, enabling body functions to meet physical demands in

response to the stressor. It has been shown that depression in adults is associated with dysregulated reactivity to stress, as reflected by increased HPA axis activity (12, 13). Chronic increased HPA axis activity in depressed pregnant women may lead to desensitization of the fetal glucocorticoid receptor (GR), potentially through increased methylation of *NR3C1*, the gene encoding for the GR. The association between prenatal depressive symptoms and increased *NR3C1* methylation has been the most consistent finding in the growing body of literature on epigenetic changes through environmental exposures, and has also been linked to exaggerated cortisol stress responses in the children (14-16). The set-point of the developing fetal HPA axis has been shown to be influenced by external stimuli and may be altered in response to dysregulated cortisol exposure as a result of maternal depression (17), as reflected in studies in which maternal depressive symptomatology predicted baseline and diurnal levels of cortisol in children (18, 19). However, the association between prenatal exposure to high maternal depressive symptoms and children's cortisol reactivity has been less often studied, with mixed results (20-22). Cortisol reactivity has been shown to be a relevant predictor of later life health, contributing to pathology associated with advancing age such as neurodegeneration, immune and metabolic disorders (23).

Besides the HPA axis, the autonomic nervous system (ANS) also responds to stress by exerting more rapid effects through its innervating nerves in many organ systems. The ANS consists of a sympathetic (SNS) and a parasympathetic (PNS) division, acting in opposite directions, the former stimulating the body's "fight-or-flight-response" and the latter activating the body to "rest-and-digest". Heart rate variability (HRV) is one of the most used methods to measure ANS functioning, based on interactions between the parasympathetic and the sympathetic nervous system (24). Other proximal measures of ANS activity are changes in blood pressure (BP) and heart rate (HR), respiratory sinus arrhythmia (RSA), reflecting the neural regulation of HR as a result of PNS activation (25), and salivary alpha-amylase (sAA) as a proxy for neural adrenergic stimulation and release of plasma catecholamines as a result of SNS activation (26). The HPA axis and ANS are regarded as complementary systems (27). The ANS responds within seconds after a stressor, whereas the HPA axis is involved in a more prolonged response. Adults with higher levels of depressive symptoms showed greater decrease in the magnitude of parasympathetic cardiac control during stressors and greater changes in peak HR during mental stress (28, 29). The few studies that have addressed the association between prenatal exposure to maternal depressive symptoms and ANS function in children report an absence of associations, but these studies focused on basal ANS function rather than its

reactivity to an induced stressor (30, 31). ANS reactivity reflects adaptive responding above resting ANS function, and studies suggest that altered ANS reactivity is associated with vulnerability to psychopathology rather than ANS dysregulation during baseline conditions (28, 29).

The aim of this paper was to systematically review the existing literature on the association between prenatal exposure to high levels of maternal depressive symptoms and hypothalamic pituitary adrenal (HPA) axis and autonomic nervous system (ANS) stress reactivity profiles.

Methods

Eligibility criteria

This systematic review followed the PRISMA guidelines for conducting and reporting systematic reviews and the protocol was registered at the international Prospective Register of Systematic Reviews (PROSPERO) (registration number CRD42016039064, last version 20 June 2016). We used the following inclusion criteria: (1) human studies, (2) studies addressing the association between a depressive disorder or symptoms of depression prospectively assessed during pregnancy and response of the stress system in children, in terms of the HPA axis or the ANS, to an induced stressor. Exclusion criteria were: (1) studies in which symptoms of depression were retrospectively assessed after childbirth, (2) studies in which no induced stressor was used to assess stress reactivity, and (3) studies that included solely cumulative measures of stress including depression among other psychosocial stressors or mood symptoms such as anxiety or parenting hassles in the statistical analysis.

Search strategy

An information specialist (JL) developed a comprehensive search in the electronic databases MEDLINE, Embase and PsycINFO from inception to 24 July 2017, using the OVID interface. The search included both free text and controlled terms (i.e. MeSH in MEDLINE). A search for pregnancy / prenatal AND child / offspring was combined with either 1. depression and stress response or 2. maternal stress and infant stress response. Part 2 was added to retrieve publications not explicitly mentioning depression in the abstract. The search was limited to English, German, French or Dutch language papers. The entire MEDLINE search strategy is shown in Appendix 1. On completion, citations identified in each database were imported into EndNote X7 and de-duplicated. The cited and citing references of the included studies were also screened for additional relevant publications.

Study selection

Two authors (LB and LvD) independently screened titles, abstracts and full texts of the articles, using Covidence, a web-based systematic review tool (www.covidence.org). Disagreements were resolved by consensus or a third reviewer (SdR).

Data extraction

One author extracted data (LB), of which 20% was checked by the second author (LvD). Data was extracted twice and collected separately from selected papers using Covidence. Extracted data included information on study author, year, country, study aim and design, number of participating pregnant women, gestational age when maternal depressive symptoms were assessed, maternal age, the scales used for assessing depressive symptoms, the number of participating children, children's age at baseline, the stressor used, main outcome(s) as reported in the study and covariates included in the analysis. Relevant outcomes were pre- and post-stressor indices of the HPA axis (cortisol) and the ANS (HR, SBP, DBP, RSA, and sAA).

Risk of bias

Risk of bias was assessed using the Newcastle Ottawa Scale (NOS) (32), which assesses the quality of nonrandomized cohort studies to be included in systematic reviews. Papers were scored on the domains 'selection', 'comparability' and 'outcome'. The risk of bias was rated as 'high risk', 'intermediate risk' or 'low risk'. The following criteria were deleted: 'demonstration that outcome of interest was not present at the start of the study' and 'was follow-up long enough for outcomes to occur', because both criteria were already taken into account in the study selection procedure and therefore did not apply to the study articles that were included in this review.

Data synthesis

Studies were assessed for homogeneity in terms of design and comparator to be included in a *meta-analysis*, and if not, qualitatively reviewed. In the qualitative synthesis, the relationships and findings both within and between the included studies were provided, in line with the guidance from the Centre for Reviews and Dissemination.

Results

Of the identified 1 014 unique articles, 914 studies were excluded after screening of title and abstract and the full-text of 100 articles were assessed on relevance and eligibility criteria (see Figure 1). The major reasons for exclusion were the absence of an induced stressor to measure stress reactivity and the absence of assessing antenatal depressive symptoms as an independent factor in relation to stress reactivity. After full-text assessment, 13 articles were included in the review, with a total of 2 271 mother-child pairs that completed both the pre- and postnatal assessments, ranging from 58 to 272 dyads per study. Besides a broad age range in both women and children (16.9 - 32.8 years old in women, 1 month - 15 years old in children), seven different scales were used to assess depression or depressive symptoms during pregnancy and eight different stress tests were used to induce a reaction to stress in children. Although many studies had similar outcomes, there was hardly any overlap in time-points when reactivity was measured. Because of the large heterogeneity between studies, a *meta-analysis* was not feasible.

Characteristics of studies

A total of 13 articles were qualitatively reviewed. Characteristics of the included studies for which data were extracted, are presented in table 1. The studies were performed between 2007 and 2017, and all were prospective cohort studies. Studies either divided women into a group with high depressive symptoms versus a group with low depressive symptoms during pregnancy and compared means of stress reactivity measures in children between both groups (33-39), or used depression symptom score as a continuous measure to calculate bivariate correlations with stress reactivity measures in children (40-45). The assessments for depressive symptomatology were performed in various pregnancy trimesters.

Stressors and outcomes

An overview of the outcomes is shown in table 2. The stressors used to provoke a stress response differed greatly among the studies. Arm restraint was used in four studies, in which a research assistant gently restrained both of the child's arms for two minutes to prevent the child from moving (33, 41, 42, 44). In three of these studies, the toy retraction task and the plastic barrier task were performed additionally, which respectively involved the child playing with a toy after which the toy was repeatedly moved outside the child's reach and returned to the child and consecutively put behind a Plexiglas barrier, to elicit frustration (41, 42, 44). Inoculation or immunization

was used as a stressor in three studies (34, 35, 40). The remaining six studies all used a different stress test, including a video stress test, which involved playing stressful video games (36), the still face procedure, in which the woman denied her baby attention for a short period of time (43), the Neonatal Intensive Care Unit (NICU) Network Behavioural Scale, a neuro-behavioural examination (38), a CO_2 test, involving a single breath of 35% CO_2 (45), the strange situation procedure, in which the child was observed playing for 20 minutes while caregivers and strangers entered and left the room (37), or a picnic scenario, an 8-minute setup during which two costumed characters entered the room and encouraged the child to share plastic picnic food and dance with them (39). Although all studies included one time-point pre-stressor ("baseline measure"), this varied from 2 to 5 minutes prior to the stressor. Some studies also added, or performed exclusively, continuous measurements of the stress parameters throughout the task and calculated means.

Confounding factors

Confounding factors per study are listed in table 3. Confounding factors that were included in the analyses differed between studies. In most of the studies, various potential confounders were explored and included in the analysis as a covariate if they were associated with the predictor and the outcome measure. One study included no covariates in the final analysis, because preliminary analyses of potential confounders indicated that none of them influenced cortisol levels in the child (33), and two studies did not include confounders because only bivariate correlations were calculated (35, 44). Covariates included in the analyses were postnatal depressive symptoms (34, 41, 43, 45), gestational age (34, 41, 45), age of the child (34), gender (40, 41, 45), birth-weight (36, 41, 42, 45), behavioural state of the child (41), maternal age (41, 45), parity (41), socio-economic status (SES) (38, 42), alcohol and smoking behaviour of the women during pregnancy and early postnatally (45), arrival time at the lab on the day of the stress procedure (37), breast-feeding status (38, 43), the women's' "overall degree of social risk", a 5-item social risk index that was constructed to reflect women's' social circumstances, and women's' lifetime caseness of anxiety disorders (10).

Prenatal depression and stress reactivity

A summary of the results of the studies is listed in table 3. 10 studies measured cortisol levels in saliva before and after the stressor (33-35, 37-40, 42, 44, 45). Of these studies, eight did not show an independent association or correlation between prenatal exposure to maternal depressive symptoms and cortisol reactivity in children (33-35, 37-39, 42, 44), whereas two studies did (40, 45). Fernandes et al.

found that prenatal exposure to high maternal depressive symptomatology was associated with high cortisol reactivity to immunization in 2-month-old children from rural South India. The association was U-shaped, showing the lowest levels of reactivity in the children prenatally exposed to modest maternal depressive symptoms, and the highest levels of reactivity in the children prenatally exposed to very low and very high levels of maternal depressive symptoms (40). Vedhara et al. reported that prenatal exposure to high maternal depressive symptoms at 32 weeks gestational age was associated with a blunted cortisol response in children. Five studies measured the ANS, in terms of Cardiac Vagal Control (CVC) (41), RSA (42, 43), HR (36, 45), SBP (36, 45), DBP (36), and sAA (37, 42). Three studies reported the absence of an association between prenatal exposure to maternal depressive symptoms and ANS reactivity in children (41-43), whereas two studies did show an association. Fan et al. reported that children born to women who responded positively to a depression questionnaire during pregnancy showed higher SBP reactivity and slower DBP recovery as opposed to children born to women who responded negatively to the questionnaire (36). Vedhara et al. reported that prenatal exposure to high maternal depressive symptoms at 18 weeks gestational age was associated with greater SBP reactivity and slower SBP recovery in children (45).

Mediation and moderation

The majority of studies examined various potential mediators and moderators on the association between prenatal exposure to maternal depressive symptoms and cortisol reactivity in children (Table 3). One study reported that women with higher social support from partners during pregnancy experienced fewer depressive symptoms. Lower self-reported depression during pregnancy was associated with higher mother-child interaction quality, which on its turn was associated with lower child cortisol reactivity (44). Another study showed that children from women with both prenatal anxiety and depression had delayed recovery in DBP and SBP compared to children from women reporting solely anxiety or depression (36). Laurent et al. reported that children from women who shifted from low depression during pregnancy to high depression post-partum, and vice versa, showed the largest effects on HPA axis reactivity, as well as an inverse coordination of cortisol with sAA, compared to children of women with consistently high or low depressive symptoms in the perinatal period (37). Another study showed that prenatal depression was associated with decreased vagal withdrawal only in the children that were often stroked by their mothers, whereas in children from non-stroking mothers, the association was reversed (43). Azar et al. showed that children of average to highly over-controlling

women had a significant larger increase in cortisol levels after stress compared to children from low controlling women, however, there was no significant interaction between lifetime major depression and over control (33).

Gender differences

Vedhara et al. reported that prenatal exposure to high maternal depressive symptoms was associated with higher SBP reactivity and slower recovery, only in boys (45). Stroud et al. could not detect an independent association between prenatal exposure to maternal depressive symptoms and children's cortisol reactivity, but after sample stratification for gender, an association appeared, in females only. In contrast, placental serotonin transporter gene (*SLC6A4)* expression moderated the association between prenatal depressive symptoms and cortisol reactivity, in boys only (38). Two other studies tested for, but could not detect an interaction between offspring gender and cortisol reactivity (34, 39).

Risk of bias

The risk of bias for each individual study is listed in table 4. Four studies were judged to have low risk (33, 36, 38, 43), seven studies to have intermediate risk (34, 37, 40-42, 44, 45), and two studies to have high risk of bias (35, 39). Risk of bias was induced mostly because the authors did not clearly state whether the assessor of the outcome measures in the children was blinded to the women's state of depressive symptom scores during pregnancy, and because many studies used self-reported measures for prenatal depressive symptoms. Some cohorts were not representative of the general pregnant population because investigators recruited their sample from a selected population of pregnant teens (33), women with a high risk for psychopathology (37), women with a low SES with a high percentage of unplanned pregnancies (38) or women with eating disorders (35). Also, bias may have been induced by a lack of, or indistinctness about, adjusting for postnatal depressive symptoms or birth weight (36, 39, 42, 43), and because follow-up rates were less than 70% (36, 41, 45). Of the studies that did show an association between prenatal exposure to maternal depressive symptoms and stress reactivity in children, two of them were assessed to have intermediate risk (40, 45) and one to have low risk (36) of bias.

Discussion

In this systematic review, little evidence for an association between prenatal exposure to high levels of maternal depressive symptoms and altered HPA axis and ANS reactivity to stress in children was shown. Three out of 13 studies reported significant differences, showing higher cortisol reactivity to immunization in 2-month-old children prenatally exposed to either very high or very low levels of maternal depressive symptoms (40), blunted HPA axis response and higher SBP reactivity with slower recovery (45), higher SBP reactivity, delayed SBP and DBP recovery, and a blunted HPA axis response in children prenatally exposed to high maternal depressive symptoms (36). In 10 studies, no clear evidence was found to support the hypothesis, showing no independent association between prenatal exposure to high maternal depressive symptoms and stress reactivity in children in any of these studies. Based on these results, prenatal exposure to maternal depressive symptoms appears to be un-, or weakly related to the physiological stress response in children. However, the studies included in our review were very heterogeneous and a*meta-analysis* could not be performed.

Although the majority of studies could not detect a clear independent association between prenatal exposure to maternal depressive symptoms and stress responses in children, a considerable amount of studies reported that, when taking into account certain moderating or mediating factors such as postnatal depressive symptoms (37), maternal stroking of the baby postnatally (43), or partner support in pregnancy (44), prenatal exposure to high levels of maternal depressive symptoms did seem to be indirectly associated with stress reactivity in children. Rash et al. examined, but could not detect, an early or late pregnancy depressed mood by cortisol interaction on child stress reactivity. They showed that not maternal depressive symptomatology but maternal cortisol was associated with children's stress responses. They stressed the point that other, or a combination of multiple, psychological stressors might be responsible for the increase of cortisol levels rather than depressive symptoms alone (41).

Accordingly, Easter et al. showed correlations between prenatal depression, stress, eating disorder and maternal cortisol decline, suggesting that a combination of these exposures may contribute to maternal cortisol patterns, which in turn may affect child cortisol patterns (35). This suggestion was again demonstrated by Fan et al., who reported a significant delay for all cardiovascular recovery measures in children from women with both prenatal anxiety and depression compared to those experiencing solely depression or anxiety symptoms during pregnancy (36). Stroud

et al. examined the moderating role of placental DNA expression or methylation in *SLC6A4* and *HSD11B2* genes respectively. For cortisol reactivity, their results showed that male foetuses expressing low *SLC6A4* gene expression in the placenta are most susceptible for effects of maternal depression on cortisol stress reactivity at one month of age (38).

The observations from these studies all imply that the stress systems of the developing foetus might not be affected by exposure to maternal depressive symptoms *in utero* per se, but through a complex combination of exposure to maternal depressive symptoms, physiological changes in the pregnant women caused by objective stress not (fully) captured by depressive questionnaires (alone), in both the pre- and postnatal environment, with potential mediating or moderating effects by prenatal social support, epigenetic variations, gender, and reversal effects by positive postnatal behaviour such as stroking of the baby and maternal-child interaction quality. A recent longitudinal study on the association of maternal depressive symptoms with child behaviour up to 5 years of age that included over 17 000 children reported that concurrent maternal depression mainly affected internalizing and externalizing disorders in the child, as the contribution of prenatal depression was attenuated after correcting for familial confounding through sibling comparisons (46). This is also supported by animal and human studies in which effects of maternal prenatal stress on brain development in the foetus can be compensated for by postnatal care-giving factors (47, 48).

Nevertheless, studies that examined stress reactivity in foetuses of depressed pregnant women directly have provided evidence for an independent prenatal causal component of maternal mood on development and function of the fetal autonomic system. Pregnant women with anxiety that completed the Stroop colour-word test exhibited greater fetal heart rate (fHR) increase during stress as well as greater fHR decrease in the recovery period compared to less anxious women (49-52). Studies with direct fetal stress exposure through a vibroacoustic stimulus reported an increase in fHR from baseline to stimulation in depressed compared to non-depressed women (53), and a 3.5 fold delay in return to baseline fHR after the stressor (54). Long-term follow-up of these children would be highly insightful to further quantify the contribution of prenatal depression and anxiety in the presence or absence of protective factors in the postpartum period.

The studies included in this review had several limitations, such as a wide range in severity of maternal depressive symptoms between studies. Most studies used a screening tool to assess depressive symptoms, using a cut-off value to identify women *at risk* for a depressive disorder. In other words, of all women that were

categorized as experiencing high levels of depressive symptoms during pregnancy, not all will or would have developed a clinical depression, potentially overestimating the amount of prenatal exposure to depressive symptoms, and concurrently, exposure to high cortisol levels of the developing foetus in these groups.

Although most studies used valid cut-off values to allocate the pregnant women to the low versus the high depressive symptom group, one study used a cut-off value of 10 points on the EPDS, whilst a score of 13 is more commonly used to indicate likelihood of being clinically depressed, resulting in a sample of women with relatively 'mild' depressive symptoms. Studies that divided pregnant women in groups of low versus high levels of depressive symptoms based on screening tool cut-off values, reported percentages ranging from 0.9% (36) to 29% (35) of the sample experiencing high depressive symptoms. Five studies used the EP(D)S as a screening tool, with mean scores varying from 5.08 (41) to 8.33 points (43). One study that did detect a significant association between prenatal exposure to high maternal EP(D)S scores and high cortisol reactivity in children reported a relatively high EP(D)S mean score of 8.07 points (40). However, a study with similar means for depression, did not detect such an association (43). Only Fan et al. identified and reported women in the severely depressed range, and the trend in this study suggested a dose-dependent effect of prenatal exposure to maternal depressive symptoms.

Mild depressive symptoms may induce only mild physiological effects in the woman, for example small increases in cortisol, which are not strong enough to exert altering effects on brain and stress system development of the foetus. This is nicely reflected by Braithwaite et al., who did not detect an association between prenatal exposure to high levels of maternal depressive symptoms and cortisol reactivity in children, but also failed to confirm an association between high maternal depressive symptoms and hypercortisolism in a sample of relatively mildly depressed women, a finding that has been confirmed in many studies examining associations between depressive symptoms in pregnant women and concurrent cortisol values (55-57). However, the three studies included in this review that used a clinically administered interview by a health professional, and were thus able to identify women with an actual diagnosis of depressive disorder, were also unable to detect an association between prenatal exposure to a maternal depressive disorder and increased or decreased stress reactivity in children. However, these studies did not investigate associations between maternal depression and concurrent cortisol values (33, 38, 39). Another explanation for the lack of associations between prenatal exposure to high maternal depressive symptoms and stress reactivity in children is that differences in HPA- or ANS function due to prenatal programming may become apparent only in

later life. The only study in a Western population in which an association was found included participants with a mean age of 15 years (45). Possibly, prenatal exposure to an adverse intrauterine environment affects compensation mechanisms, resulting in earlier 'exhaustion' of buffers and altered stress-reactivity only later in life. An alternative explanation for the absence of an association between prenatal exposure to high maternal depressive symptoms and stress reactivity in children might be that most studies measured depressive symptoms in mid-to late pregnancy, whereas some studies suggests that early pregnancy, or even the preconception period, might be the most vulnerable time-window for programming effects of maternal stress on the developing fetal brain (58, 59). None of the studies included in this review measured depressive symptoms exclusively in early pregnancy. The studies that did report an association between prenatal exposure to high maternal depressive symptoms and stress reactivity in the children measured depressive symptomatology across all pregnancy trimesters, without specifically examining separate effect sizes according to the trimester in which the depression occurred (36, 40, 45).

Also, there was inconsistency across studies in terms of whether the stressor evoked a relevant response at all. Three studies that reported no independent association between prenatal exposure to maternal depressive symptoms and stress reactivity in children were also unsuccessful in detecting a significant stress response in general (33, 37, 43). However, prenatal exposure to maternal depression may affect the *shape* of the response trajectory rather than its magnitude, which in case of opposite directions of effects according to very low or very high levels of depression, might cancel each other out in the whole sample (37, 43). Nonetheless, of all studies that did substantiate a significant stress response, not one reported an association between prenatal depression and stress reactivity in children (34, 39, 41, 42, 44). The three studies that did observe an association between prenatal depressive symptoms and child stress reactivity, did not clearly describe whether the stressor had exerted an overall significant response to the stressor.

Key psychological elements that are related to the size of the HPA axis response have been analyzed in a *meta-analysis*, and a combination of social-evaluative threat and uncontrollability appeared to have the greatest impact (60). The Trier Social Stress Test, which includes all of these features, is widely known and validated, but used in none of the studies included in this review, because of the young age of the children. Noise exposure, emotion or pain induction has shown to induce variable HPA axis responses or no response at all (60). Two out of three studies that reported an association between prenatal exposure to high maternal depressive symptoms and stress reactivity in children either used a physiological stressor, namely inhaling

a single breath of 35% O2 (45), or immunization, which is both a psychological and a physiological stressor (40), whereas of the studies that reported negative findings, eight out of 10 studies used solely (a) psychological stressor(s). Timing of assessing stress reactivity indices is also of importance, considering that the ANS responds more rapidly to stress than the HPA axis. All of the studies measured indices of either the ANS or the HPA axis at appropriate times, so this is not likely to contribute to the fact that some of the studies yielded significant results, but most did not.

It is not yet clear which mood variable has the greatest impact on cortisol regulation, and it might be that the effect of depressive symptoms (alone) on maternal cortisol dysregulation is too small to affect fetal stress regulatory systems. Depression is often comorbid with anxiety, and evidence from the literature has shown that women suffering from both depression and anxiety exhibit higher cortisol levels than women experiencing anxiety or depression alone (61). One of the included studies in our review found that prenatal anxiety in combination with depression strengthened the sole effects of depression or anxiety during pregnancy on children's stress reactivity (36). An earlier study demonstrated that antenatal anxiety above depression was strongly associated with children's cognitive development (62). Because the current review focused on depressive symptomatology, studies in which depression or depressive symptomatology was not included as an independent factor were excluded. In fact, a substantial number of articles that were excluded in the screening phase used a different definition for the term 'stress'. The need for studies that clearly define separate mood variables is evident to be able to distinguish the influence of prenatal exposure to maternal depressive and anxiety symptoms and other measures of stress on the development of stress regulatory systems in children.

Another point of interest is gender differences. Vedhara et al. observed that the association between prenatal exposure to high depressive symptoms and SBP reactivity and recovery was restricted to males only, whereas Stroud et al. observed that females drove the association between prenatal exposure to high depressive symptoms and altered offspring cortisol reactivity. Possibly, the susceptibility for programming effects on stress-regulatory mechanisms differs according to gender. Rodent studies have shown that prenatal stress exposure selectively affected the HPA axis in the female rat (63, 64). A study in humans showed that prenatal maternal anxiety predicted lower vagal reactivity only in boys (65). Differences in stress reactivity profiles have been proposed to be an important risk factor for health problems that are related to a specific gender (66). These findings might have important implications for our understanding of gender-specific physiological development and function, and why certain disorders such as

anxiety occur more often in women and why men are more sensitive to trauma (67).

Strengths, limitations and implications

A strength of this review was the fact that studies were systematically reviewed and assessed. However, none of the studies were feasible for *meta-analysis.* This is, above all, a limiting factor, as the true effect of high maternal depressive symptomatology during pregnancy on developing fetal stress systems remains unclear, but it also emphasizes the lack of systematic approaches in study methodology in this specific area of research. In line with recent studies that show promising improvements in this field (11), future studies should measure maternal depression, anxiety and stress as separate factors throughout all the stages of pregnancy, prior to conception and postnatally. Stress reactivity in children should be assessed in childhood, adolescence and adulthood, by examiners blinded to prenatal maternal mood. Preferably, the TSST should be used, and indices of both the HPA axis and the ANS in response to the stressors should be included.

Conclusion

Prenatal exposure to high depressive symptoms as an independent factor does not seem to be consistently associated with hypothalamic pituitary adrenal (HPA) axis or autonomic nervous system (ANS) stress reactivity in children, but high heterogeneity among studies preclude robust conclusions. Study results imply that certain factors are likely to mediate and moderate associations between prenatal exposure to high maternal depressive symptoms and HPA axis and ANS reactivity in children, such as partner support, postnatal depression and caregiving behaviour postnatally.

Conflict of interest

None reported.

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Figure 1. PRISMA Flowchart of study selection

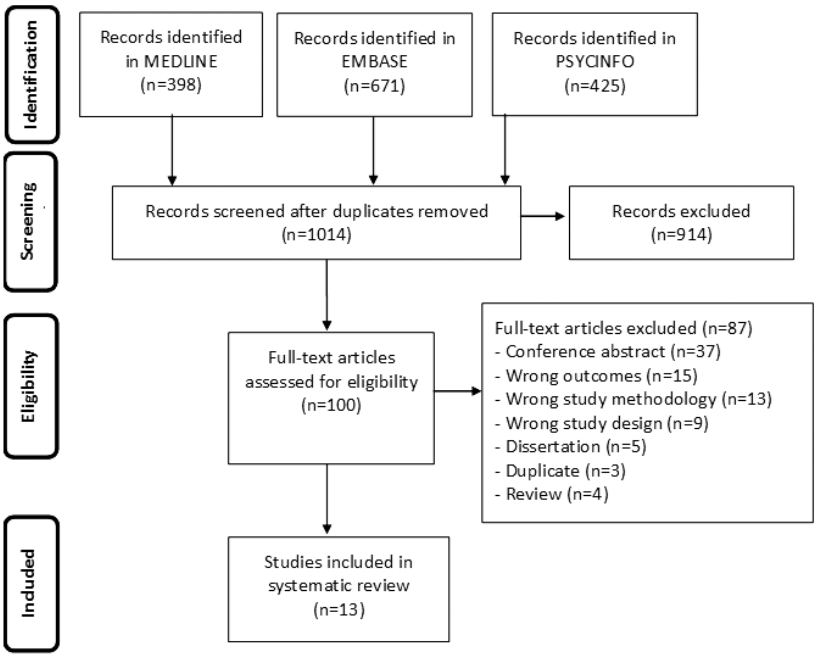

Table 1. Study characteristics

Author	Year	Country	Number of pregnant women	Maternal age	Method for identifying depression[a]	Assessments (Trimester)	Number of children	Age at stress procedure
Azar	2007	USA	212	16.9	NIMH-DIS	3	212	4m
Braithwaite	2016	UK	88	31.0	EPDS	2 & 3	71	2m
Easter	2017	UK	117	32.1	BDI	2 & 3	91	2m
Fan	2015	China	231	NA	HRSD	1 or 2 or 3	216	7-9y
Fernandes	2015	India	133	21.5	EPDS (>12) & K10 (>3)	3	58	2m
Laurent	2011	USA	86	24.0	CES-D (>16)	3	86	18m
Rash	2015	Canada	301	31.8	EPDS	2 & 3	194	6m

Table 1. Continued

Author	Year	Country	Number of pregnant women	Maternal age	Method for identifying depression[a]	Assessments (Trimester)	Number of children	Age at stress procedure
Rash	2016	Canada	254	31.7	EDS	2 & 3	254	6m
Sharp	2012	UK	316	26.8	EPDS	3	271	7m
Stroud	2016	USA	153	26	DSM-IV & the Inventory of Depressive Symptomatology	2 & 3	153	1m
Thomas	2017	Canada	272	32.8	EDS	1, 2 & 3	272	6m
Vedhara	2012	UK	139	29.0	EPDS	2 & 3	139	15y
Waters	2013	UK	332	NA	SCAN	3	257	12.8m

[a]Abbreviations: NIMH-DIS = National Institute of Mental Health Diagnostic Interview Schedule, E(P)DS = Edinburgh (Postnatal) Depression Scale, BDI = Beck Depression Inventory, HRSD = *Hamilton Rating Scale for Depression*, K10 = Kessler Psychological Distress Scale, CES-D = Centre for Epidemiologic Studies Depression Scale, DSM-IV = Diagnostic and Statistical Manual of Mental Disorders version IV, SCAN = Schedules for Clinical Assessment in Neuropsychiatry

Table 2. Stress assessments

Author	Stressor	T1	T2	T3	T4
Azar	Arm restraint	5 min pre-stressor	20-25 min post stressor		
Braithwaite	Inoculation	Baseline	Immediately post stressor	Braithwaite	Inoculation
Easter	Immunization	Immediately pre-stressor	20 min post-stressor		
Fan	Video stress test	Baseline	2 minutes after onset stressor	5 minutes after onset stressor	5 min post stressor
		Baseline	2 minutes after onset stressor	5 minutes after onset stressor	5 min post stressor
		Baseline	2 minutes after onset stressor	5 minutes after onset stressor	5 min post stressor
Fernandes	Immunization	10 min pre-stressor	20 min post-stressor		
Laurent	Strange situation	15 min pre-stressor	15 min post-stressor	30 min post-stressor	
		15 min pre-stressor	5 min post-stressor	15 min post-stressor	

Table 2. Continued

Author	Stressor	T1	T2	T3	T4
Rash 2015	Toy retraction task, toy barrier & arm restraint	3 min pre-stressor	Continuously during stressor		
Rash 2016	Toy retraction task, toy barrier & arm restraint	5 min pre-stressor	15 min post-stressor		
		5 min pre-stressor	15 min post-stressor		
		3 min pre-stressor	Continuously during stressor		
Sharp	Still face procedure	During non-frustrating tasks (average of continuous measure)	Continuously during stressor		
Stroud	NICU network behavioural scale	Baseline	Immediately post-stressor	20 min post-stressor	40 min post-stressor
Thomas	Toy retraction task, toy barrier & arm restraint	Baseline	20 min post-stressor		
Vedhara	CO2 stress test	10 measurements every minute from 5 min pre-stressor to 5 min post-stressor			
		10 measurements every minute from 5 min pre-stressor to 5 min post-stressor			
		2 min pre-stressor	10 min post-stressor	20 min post-stressor	30 min post-stressor
Waters	Teddy bear's picnic scenario	Baseline	Immediately post-stressor	25 min post-stressor	

Table 3. Summary of the results

Author	Outcome[a]	Confounders	Moderating and mediating factors[b]	Stressor evoked significant stress response	Association[c]
Azar	Salivary cortisol	-	-	No	-
Braithwaite	Salivary cortisol	Postpartum depression, gestational age, infant age	No interaction effect of trimester (2nd versus 3rd) or gender on infant cortisol reactivity	Yes	-
Easter	Salivary cortisol	-	-	Unclear	-
Fan	HR and BP	Birth weight	An interaction effect of prenatal anxiety on infant recovery HR, SBP and DBP	Unclear	+
Fernandes	Salivary cortisol	Birth weight, postpartum depression, infant age, infant sex, infant weight standardized for age, infant health and maternal postnatal cortisol	-	Unclear	+
Laurent	Salivary cortisol sAA	Medication, eating / drinking / tooth brushing before measures, illness, sleep time, BMI, age and arrival time	An interaction effect of postnatal depression on infant cortisol reactivity	Partly	-

Table 3. Continued

Author	Outcome[a]	Confounders	Moderating and mediating factors[b]	Stressor evoked significant stress response	Association[c]
Rash 2015	RSA	Gestational age, gender, birth weight, behavioural state of the infant, maternal age, maternal parity, SES, maternal postpartum depression	No interaction effect of early or late maternal cortisol during pregnancy on infant RSA reactivity	Yes	-
Rash 2016	Salivary cortisol RSA, sAA	Infant birth weight	-	Yes	-
Sharp	RSA	Maternal depressing postpartum and breastfeeding	An interaction effect of maternal stroking of the baby postnatally on infant vagal withdrawal No interaction effect of breastfeeding on infant vagal withdrawal	No	-
Stroud	Salivary cortisol	Maternal education, time since feeding	An interaction effect of gender and placental *SLC6A4* gene expression on infant cortisol reactivity No interaction effect of placental *HSD11B2* methylation on infant cortisol reactivity	Unclear	-
Thomas	Salivary cortisol	Gestational age at measuring depression, income, marital status, maternal education, ethnicity and postpartum depression	A mediation effect of social support on prenatal depression, of prenatal depression on maternal-infant interaction quality, and of maternal-infant interaction quality on infant cortisol reactivity	Yes	-

Table 3. Continued

Author	Outcome[a]	Confounders	Moderating and mediating factors[b]	Stressor evoked significant stress response	Association[c]
Vedhara	Salivary cortisol HR, SBP	Maternal age, alcohol, smoking, birth weight, gestational age, gender, postpartum mood	An interaction effect of gender on infant SBP reactivity	Unclear	+
Waters	Salivary cortisol	The family's overall degree of social risk and for the women's lifetime caseness for anxiety disorder	No interaction effect of gender on infant cortisol reactivity. Higher order interactions were not interpreted due to small sample sizes	Yes	-

[a]Abbreviations: HR = Heart Rate, SBP = Systolic Blood Pressure, DBP = Diastolic Blood Pressure, SAa = Salivary Alpha amylase, RSA = Respiratory Sinus Arrhythmia, SES = Socioeconomic Status. [b]described as interacting (moderator) of mediating (mediator) effects on the association between prenatal depression and stress reactivity in children. [c]indicates whether a significant independent association between prenatal exposure to maternal depressive symptoms and stress reaction in the children was found, + = significant, - = non-significant

Table 4. Newcastle-Ottawa Scale (NOS) quality assessment scale

	Criterion scores			
	Cohort selection (max=*)**	**Cohort comparability (max=**)**	**Validity of outcome measure (max=**)**	**Overall risk of bias**
Azar	**	**	**	Low
Braithwaite	*	**	*	Intermediate
Easter	*	-	-	High
Fan	**	*	**	Low
Fernandes	**	**	-	Intermediate
Laurent	*	**	*	Intermediate
Rash	**	**	-	Intermediate
Rash	**	*	*	Intermediate
Sharp	***	*	*	Low
Stroud	**	**	**	Low
Thomas	**	*	*	Intermediate
Vedhara	**	**	-	Intermediate
Waters	**	-	*	High

Appendix. Search Strategy

Database(s): Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present
Search Strategy: 2017-07-25

#	Searches	Results
1	prenatal exposure delayed effects/	24899
2	((perinat* or peri-nat* or prenat* or pre-nat* or antenat* or ante-nat* or intrauterine or intra-uterine or "in utero") adj3 (expos* or programming)).tw,kf.	21639
3	**or/1-2 [PRENATAL & CHILD A]**	**36960**
4	pregnancy/ or pregnancy complications/ or gravidity/ or pregnant women/ or maternal exposure/	826579
5	(pregnan* or prepregn* or gestat* or pregestat* or gravidit* or prenat* or pre-nat* or antenat* or ante-nat*).tw,kf.	613404
6	((maternal* or mother*) and (perinat* or peri-nat*)).mp.	26815
7	((intra-uterine or intrauterine or "in utero" or f?etal or f?etus*) not ((intra-uterine or intrauterine or "in utero" or f?etal or f?etus*) adj growth adj (restrict* or retard*))).tw,kf.	321870
8	**or/4-7 [PRENATAL/PREGNANCY]**	**1109533**
9	exp child/ or exp infant/	2303277
10	adolescent development/ or child development/ or exp child behavior/ or child behavior disorders/	78228
11	(offspring or newborn* or new* born* or neonat* or baby or babies or progeny* or progenies or intergenerat* or inter-generat* or multigenerat* or multi-generat* or girls or boys or infant* or infancy or toddler* or kid or kids or graders or child*1 or children* or childhood or schoolchild* or school age* or schoolage* or teens or teenager* or puber* or juvenil* or youth or adolescence or adulthood or adult life or young adult* or "later in life" or "later life" or "later age*").tw,kf. or p?ediatric.tw,kf,jw.	2277672
12	(programming or ((developmen* or neuroendocr* or endocrin* or hormon*) adj2 program*)).tw,kf.	43635
13	**or/9-12 [CHILD/OFFSPRING]**	**3225701**
14	**8 and 13 [PRENATAL & CHILD B]**	**404686**
15	**3 or 14 [PRENATAL & CHILD A B]**	**413072**
16	**limit 15 to (dutch or english or french or german)**	**374343**
17	(animals/ not humans/) or behavior, animal/ or exp murinae/ or (rodent* or mice or mouse or murine or rat or rats or rabbit* or sheep or lamb or lambs or ewe or ewes or ovine or pig or pigs or piglet* or porcine or sus or swine* or dog or dogs or bitch or bitches or canine or cat or cats or feline or primate* or monkey* or macac* or macaq* or rhesus).ti. or (dam or dams or pup or pups or C57BL* or C3H* or Balb-c or Balbc or Wistar or Dawley).tw,kf.	5266681
18	**16 not 17 [HUMAN studies on PRENATAL & CHILD]**	**319118**
19	depression/ or mood disorders/ or depressive disorder/ or depressive disorder, major/ or depressive disorder, treatment-resistant/ or dysthymic disorder/	194985
20	anhedonia/ or *affect/ or affective symptoms/	27061

21	depress*.jw.	2352
22	((depression or depressiv*) not (((neonat* or neo-nat* or new* born* or newborn* or birth* or childbirth*) adj depress*) or ((respirator* or cardiorespirator* or pulmon* or ST or baroceptor* or myocard*) adj4 depres*))).tw,kf.	310038
23	(depressed adj6 (mother* or women or behav* or stress* or anx* or symptom* or individual* or parent* or feel* or state*1)).tw,kf.	12382
24	(sadness* or melanch* or moros* or mood or moods or d#st*mic* or d#sphor* or anhedon*).tw,kf.	78001
25	(feel* adj3 (low or sad* or negative)).tw,kf.	2727
26	((maternal or mother* or women or feel*) adj2 (blue or blues)).tw.	141
27	(negativ* adj3 (emotions or recall*)).tw,kf.	4633
28	(affective adj3 (disorder* or symptom*)).tw,kf.	19073
29	((maternal or perinat* or peri-nat* or prenat* or pre-nat* or antenat* or ante-nat* or pregnan* or gestat* or gravidit*) adj3 (psycholog* adj2 symptom*)).tw,kf.	61
30	(MDD or EPDS or BDI or HDRS* or GDS*1 or HADS* or MADRS or K10 or Kessler-10 or Kessler10 or SMFQ* or POMS or ((EDS or PRAQ or PSS or PPP) adj3 (scor* or scal* or subscal* or subscor*))).tw,kf. or (MDA.tw,kf. not m#londiald*.mp.)	56828
31	antidepressive agents/ or antidepressive agents, second-generation/ or exp serotonin uptake inhibitors/ or Paroxetine/ or Fluoxetine/	70383
32	(serotonin reuptake inhibitor* or anti-depres* or antidepres* or SSRI* or SRI or fluoxetin* or paroxetin*).ti,kf.	36831
33	**or/19-32 [DEPRESSION]**	**499347**
34	psychiatric status rating scales/	71512
35	((maternal or perinat* or peri-nat* or prenat* or pre-nat* or antenat* or ante-nat* or pregnan* or gestat* or gravidit*) adj3 stress*).ti,kf.	2544
36	(((((experienced or perceived) adj3 stress*) or ((psychological or emotional) adj3 (symptom* or distress* or wellbeing or well-being or complaint*))) adj12 (maternal or perinat* or peri-nat* or pregnan* or gestat* or gravidit* or prenat* or pre-nat* or antenat* or ante-nat* or intra-uterine or intrauterine or "in utero")).tw,kf.	1495
37	**or/34-36 [PRENATAL STRESS]**	**75265**
38	hypothalamo-hypophyseal system/ or pituitary-adrenal system/	23952
39	((cortisol or sCORT or stress or stressor* or amylas* or AA) adj6 (reactivit* or response or responses or responsiv*)).tw,kf.	108749
40	((biobehavi* or behavio?ral or neurobehav* or neuro-behav* or neuroendo* or neuro-endo*) adj2 (reactivit* or response or responses or responsiv*)).tw,kf.	19958
41	((infant* or child* or neonat* or neo-nat* or newborn*) adj3 cortisol).tw,kf. and stress*.mp.	543
42	(hormone adj2 (reactivit* or response or responses or responsiv*)).tw,kw. and cortisol.mp.	822
43	(((pituit* or neuropitui* or hypofys* or neurohypophys*) adj2 (adrenal or adrenocort* or hypothal*)) or HPA or HPAA or hypothalamohypophys* or hypothalamoneurohypophys* or hypothalamopituit* or adrenohypophys* or hypophysoadren*).tw,kf.	41576

44	autonomic nervous system/ or autonomic pathways/ or vagus nerve/ or parasympathetic nervous system/ or sympathetic nervous system/ or exp vasomotor system/	99791
45	heart rate/ph or *heart rate/ or respiratory sinus arrhythmia/ or *blood pressure/	131364
46	salivary alpha-amylases/	293
47	(autonomic or parasympath* or sympathetic or sympathic* or orthosympath* or CAB or ANS or SNS or (vasomotor adj3 reflex*)).tw,kf.	148980
48	(((vagal or vagus) adj6 (cardiac or heart or tone or nerv* or control or activ* or reactiv* or response or responses or responsiv* or stress* or withdraw* or modulat* or d#sfunct*)) or CVC).tw,kf.	25492
49	((adrenerg* or cholinerg*) adj2 (system* or innerv* or nerv* or mechanism*)).tw,kf.	19176
50	(((HV or RR or R-R) adj2 interval*) or HRV or HRR or RRV or pre-ejection period*).tw,kf.	18879
51	((heart rate* or heartrate* or HR or blood pressur* or arterial pressur* or systol* or diastol* or BP or SBP or DBP or pulse) adj5 (variabil* or dynamic* or response or responses or responsiv* or reactivit* or reacted or stress-induced or stressor* or (stress* adj (challeng* or expos* or test* or scale* or score* or induc*)))).tw,kf.	54427
52	(respiratory sinus arrhythm* or RSA).tw,kf.	5154
53	(((facial adj3 express*) or heel or postheel or HL) and (pain* or nocicept*)).mp.	3622
54	((pain or facial or HL or postheel or heel) adj3 (reactivit* or respons* or recovery or action or coding or videotap*)).tw,kf.	14373
55	**or/38-54 [STRESS RESPONSE BROAD]**	**534920**
56	((cortisol or sCORT or stress or stressor* or amylas* or AA or HPA or HPAA or ((pituit* or neuropitui* or hypofys* or neurohypophys*) adj2 (adrenal or adrenocort* or hypothal*)) or biobehavi* or behavio?ral or neurobehav* or neuro-behav* or neuroendo* or neuro-endo*) adj3 (reactivit* or response or responses or responsiv*) adj20 (offspring or newborn* or new* born* or neonat* or progeny* or progenies or infant* or infancy or toddler* or kid or kids or graders or child or children* or childhood or schoolchild* or school age* or schoolage* or teens or teenager* or puber* or juvenil* or youth or adolescence or adulthood or adult life or young adult* or "later in life" or "later life" or "later age*" or p?ediatric)).tw. **[INFANT STRESS RESPONSE NARROW]**	5491
57	**18 and 33 and 55 [PRENATAL DEPRESSION + STRESS RESPONSE]**	**368**
58	**18 and 37 and 56 [PRENATAL STRESS + INFANT STRESS RESPONSE]**	**76**
59	**57 or 58 [PRENATAL DEPRESSION/STRESS + STRESS RESPONSE]**	**415**
60	**remove duplicates from 59**	**398**