A Meta-Analysis of Maternal Prenatal Depression and Anxiety on Child Socio-Emotional Development

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Abstract

Objective: Observed associations between maternal prenatal stress and children's socio-emotional development have varied widely in the literature. The objective of the current study was to provide a synthesis of studies examining maternal prenatal anxiety and depression and the socio-emotional development of their children.

Method: Eligible studies through to February 2018 were identified utilizing a comprehensive search strategy. Included studies examined the association between maternal prenatal depression or anxiety and the future development of their children's socio-emotional development (e.g., difficult temperament, behavioral dysregulation) up to 18 years later. Two independent coders extracted all relevant data. Random-effects meta-analyses were used to derive mean effect sizes and test for potential moderators.

Results: 91 effect sizes from 71 studies met full inclusion criteria for data analysis. The weighted average effect size for the association between prenatal stress and child socio-emotional problems was OR = 1.66 (95% CI = 1.54-1.79). Effect sizes were stronger for depression (OR = 1.79; 95% CI = 1.61-1.99) compared to anxiety (OR = 1.50; 95% CI = 1.36-1.64). Moderator analyses indicated that effect sizes were stronger when depression was more severe and when socio-demographic risk was heightened.

Conclusions: Findings suggest that maternal prenatal stress is associated with offspring socio-emotional development, with the effect size for prenatal depression being more robust than anxiety. Mitigating stress and mental health difficulties in mothers during pregnancy may be an effective strategy for reducing offspring behavioral difficulties, especially in groups with social disadvantage and greater severity of mental health difficulties.

Keywords: Meta-analysis; Prenatal stress; child socio-emotional behavior

Brain development occurs most rapidly during the fetal period[1]. Consequently, insults to the intrauterine environment and changes to biochemical signalling pathways can have profound impacts on fetal neurodevelopment. Maternal prenatal stress, in both human and animal models, has been recognized as a prenatal programming factor that adversely affects fetal development[2-4]. Maternal prenatal stress has also been associated with preterm birth and low birth weight, two common causes of neurocognitive, as well as socio-emotional and behavioral delays and deficits in childhood [2].

Maternal prenatal stress has been conceptualized and measured in various ways, but the most common has been to measure maternal anxiety or depression during pregnancy[5]. To date, a vast body of literature has examined the impact of maternal prenatal stress on perinatal and postnatal health outcomes. Given the variability in results, several meta-analyses have been performed in an attempt to clarify patterns within this area of research. These meta-analyses have examined associations between maternal prenatal stress and infant gestational age, birth weight, and child cognitive outcomes, revealing weak but consistently significant associations [2-4]. However, a meta-analysis examining the sizeable body of research on maternal prenatal anxiety and depression on children's socio-emotional development has yet to be conducted.

Socio-emotional development is a general construct that encompasses emotional and behavioral problems, and difficulties with self-regulation, social information processing and emotional understanding [6]. Socio-emotional competence in early childhood provides a critical foundation for future academic skills and well-being [7]. However, if dysregulation predominates or maladaptation occurs, delays and deficits in socio-emotional development can lead to mental health difficulties in adolescence and adulthood [8]. By understanding the early determinants of

socio-emotional (mal)adaptation, we can better devise and implement intervention strategies to support children's healthy development [9,10].

Several potential moderators of the maternal prenatal stress to child outcome links have been indicated by past research. One such moderator is the operationalization of constructs that are indicators of stress, such as anxiety and depression. Indeed, analyzing the differential influence of maternal prenatal anxiety and depression on child developmental outcomes has been highlighted as an important area of inquiry for the field[11]. While there is relative uniformity in the definition, operationalization, and measurement of maternal depression during pregnancy, which is most often measured through questionnaires, or less commonly through diagnostic interviews, there is considerable variability in the operationalization and measurement of prenatal anxiety. Some studies assess for trait- or state-based anxiety, perceived stress, or stressful life events, most often via questionnaire measures, and other studies examine physiological indicators of the stress response, such as cortisol assays. This measurement variability may be an important contributor to between-study heterogeneity. Another potential moderator is the timing of exposure to stress. Some studies have suggested that child development is most impacted by exposure to stress during the second trimester of pregnancy [12], whereas others argue that stress during the third trimester is most influential[13]. Finally, greater clinical severity of depression and/or anxiety, as well as the presence of contextual stressors such as socio-economic deprivation, may also exacerbate the biological processes involved in the stress response, and/or increase fetal exposure to prenatal toxins (e.g., drug, alcohol, and tobacco use), which have implications for child neurodevelopment and behavior [4,14].

The overarching objective of the current study is to provide a quantitative synthesis of the literature to provide a more precise determination of the magnitude of association between

maternal prenatal stress and children's socio-emotional development in observational studies. A meta-analysis with all studies on prenatal stress will be provided, followed by two distinct analyses on prenatal depression and anxiety. In order to attain a clear understanding of the methodological factors that may serve to amplify or attenuate observed associations, several sample and methodological moderators will be examined to determine if they predict between-study variation.

Methods

Definitional Criteria

The definition of *socio-emotional development* in the current meta-analysis is guided by the Center on the Social Emotional Foundations for Early Learning (CSEFEL), who define the concept as the developing capacity of the child to "experience, regulate, and express emotions in socially and culturally appropriate ways; and explore the environment and learn—all in the context of family, community, and culture[15] (pg. 2)". This definition includes social and emotional competence (e.g., understanding and selecting appropriate social or emotional responses), temperament (e.g., fussiness; negative affectivity), behavioral problems (e.g., internalizing and externalizing problems), and crying or colic [16].

Search Strategy

This meta-analysis was based on recommendations by PRISMA for reporting systematic reviews [17]. Searches were conducted up to February 2018 in MEDLINE, EMBASE, PsycINFO, and Cochrane databases for published and unpublished studies. Relevant database specific subject headings and text word fields were searched (see Table S1, available online). Synonymous terms were combined with the Boolean "OR", and then these concepts were combined using a Boolean "AND". Truncation symbols were used in searches when appropriate

to capture variant endings and spellings of search terms. No date restrictions were applied, but the search was limited to English language articles.

Study Inclusion and Exclusion Criteria

To identify studies meeting inclusion criteria, titles and abstracts identified in the search strategy were reviewed. Inclusion criteria for the meta-analysis were: (1) maternal depression and/or anxiety was measured in pregnancy; (2) offspring outcomes were collected prior to the age of 18y; (3) the study statistic could be transformed into an effect size; and (4) the full-text article was available and written in English.

A protocol was developed so that each sample of participants was only represented once in the meta-analysis. First, if a study presented more than one predictor (e.g., trait anxiety and pregnancy fears) or outcome (e.g., temperament and behavior problems), a mean effect size across measures was calculated and entered into the meta-analysis. One exception to this rule was if a study presented separate effect sizes for the association between prenatal depression and child socioemotional outcomes and prenatal anxiety and child outcomes, where both were included in the analyses. Second, if more than one time point of maternal prenatal stress or child outcomes were provided, effect sizes were pooled across time points. The average prenatal time point or child age of those pooled effect sizes was used in moderator analyses. Third, if multiple publications emerged from a dataset, we selected the publication with the largest sample size and most comprehensive data extraction information.

Data Extraction

Studies meeting inclusion criteria were coded using a standard data extraction form. Potential moderators included: type of child outcome (colic/crying, temperament, behavior problems), method of assessing child outcome (questionnaire, structured interview, or observation), socio-demographic risk (e.g., low income, low education, single parent), maternal age at pregnancy, gestational age at the time of the prenatal stress measurement, child age at the outcome assessment, percent of children who are male, the type of prenatal anxiety measure (state, trait/pregnancy-stress, cortisol, life events, or mixed measurements), postnatal control for depression/anxiety (yes/no), clinical risk (i.e., syndromal-level of depressive symptoms versus not), and study quality score. Approximately 15% of included studies were double coded for the purpose of establishing reliability of data extraction. For categorical moderators, the percent agreement for all moderators was 100%, for continuous moderators the inter-coder agreement ranged from .79 to .99, and for effect size extraction it was .99. Discrepancies were resolved by consensus coding.

Additionally, an assessment of study quality was conducted based on a 15-point quality assessment tool adapted from the National Institutes of Health Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies (2014)[18] (see Table S2, available online). This assessment rating tool evaluates elements of study quality endorsed by the Cochrane collaboration[19]. Data extraction was conducted by a primary coder, and a proportion of the studies (15%) were verified by a second coder. The inter-coder agreement was .77, and discrepancies were resolved by consensus coding.

Data Analysis

We used a two-step approach to examining mean effect sizes. First, as several studies had assessments of both anxiety and depression, we initially conducted a multivariate test of dependent effect sizes using the robust variance approach methods developed by Fisher and Tipton[20] and the R package robumeta. Second, for the univariate sub-analyses examining the depression to child outcome, as well as the anxiety to child outcome link, we conducted univariate tests of non-overlapping studies using Comprehensive Meta-Analysis (CMA, version 3.0)[21] software, to test for overall effect sizes, publication bias, and potential moderators.

Effect sizes in individual studies were transformed into Odds Ratios (OR), and 95% confidence intervals (95% CI) around the mean point estimate are provided. Effect size calculations were based on random effects modelling based on the assumption that each study has its own population parameters. To assess for heterogeneity of effect sizes, the Q and I^2 statistics were computed. A significant Q statistic suggests that study variability in effect size estimates is greater than sampling error and that moderators should be explored. The I^2 statistic examines the rate of variability across studies due to heterogeneity rather than chance, with values of 50% and 75% or above suggesting moderate to high heterogeneity, respectively[22]. To examine whether moderators could explain variability across studies, categorical and continuous moderators were conducted using Q statistics and meta-regressions[21], respectively. Publication bias was examined using Duval and Tweedie's trim and fill method[23], as well as Egger's Test. If publication bias was indicated, the trim and fill procedure was used to correct for publication bias [23,24].

Results

Studies Selected

The PRISMA flow diagram[17] detailing the search strategy and resulting outcomes can be found in Figure 1. Our electronic search of four databases yielded 8,814 articles after duplicates were removed. Upon review of the titles and abstracts, 518 articles were identified as potentially meeting study inclusion criteria. After further review of full text articles, 73 studies met full inclusion criteria.

Study Characteristics and Quality

Study characteristics are reported in Table 1. The sample sizes of studies ranged from 24 to 8,328 parent–child dyads. The average prenatal stress time point was 27.74 weeks gestation (range = 7.5-37 weeks). At the outcome assessment, child age averaged 30.59 months (range = range .2 months to 17 years). Thirty-one studies were from North America (42.47%), 29 from Europe (39.73%), eight from Australia (10.96%), 4 from Asia (5.48%), and one from Africa (1.41%). For study quality, the mean score across all studies was 8.36 (*SD*=2.1; range 4-14; see Table S2, available online).

Multivariate Testing of Dependent Effect Sizes: Maternal Prenatal Stress and Children's Socio-Emotional Development

Studies with an effect size value larger or smaller than ± 3 standard deviations from the mean were considered outliers. Two studies were identified and removed from subsequent analyses.

Multivariate Testing of Dependent Effect Sizes. Over all the anxiety and depression outcomes (91 effect sizes from 71 studies), the weighted average effect size was OR = 1.66 (natural log Odds Ratio = .51, SE = .038, p <.001, OR 95% CI = [1.54,1.79]. I^2 was estimated to

be 51%. A test of the difference in effect sizes between anxiety and depression outcomes showed that depression was associated with a significantly larger effect than anxiety (difference in natural log odds ratio = .18, SE = .065, p = .009; 95% CI = [.046, .311]). The average effect size for the depression studies was OR = 1.79 (95% CI = [1.61, 1.99]), whereas for anxiety it was OR = 1.50, 95% CI = [1.36, 1.64]). Sensitivity analyses showed that different assumed values for the within-study covariance had a trivial impact on the model estimates (test values ranged from 0 to 1 in .20 intervals). Given the statistically significant difference in effect sizes for the depression-child outcome link and anxiety-child outcome link, subsequent analyses were conducted separately for each construct.

Univariate Analyses: Maternal Prenatal Depression and Children's Socio-Emotional Development

A total of 50 non-overlapping studies (33,211 mother-child dyads) were available to estimate the mean effect size for the association between prenatal depression and socio-emotional development. A random-effects meta-analysis produced a significant combined effect size of OR = 1.76 (CI: 1.60-1.94). Figure 2 depicts the forest plot. Egger's test suggested publication bias (p<.05); and the funnel plot was asymmetric (see Figure S1, available online). Using the trim-and-fill procedure with 8 studies imputed, the adjusted effect size was OR = 1.63 (CI: 1.47-1.81).

Statistically significant heterogeneity between the studies was found *(*Q = 86.4, p < .001; I^2 = 43.28). Effect sizes were stronger in studies examining depression diagnostically (k=13, OR = 2.26; CI: 1.86-2.78) versus depressive symptoms (k=37, OR = 1.60; CI: 1.46-1.75). The proportion of between-study variance explained by this moderator was R^2 = .47. The association

between prenatal depression and socio-emotional development was stronger in studies characterised as being socio-demographically at risk (*k*=10, OR = 2.24; CI: 1.73-2.91) compared to studies without such risk (*k*=40, OR = 1.66; CI: 1.51-1.84). The proportion of variance explained by this moderator was R^2 = .15. The remaining moderators tested did not reliably explain between-study heterogeneity, including type and method of assessing child behavior, pregnancy time point, maternal age, and child age and gender (see Table S4, available online).

Univariate Analyses: Maternal Prenatal Anxiety and Children's Socio-Emotional Development

With the two outliers removed, a total of 41 non-overlapping studies (17,799 mother-child dyads) were included in the meta-analysis on prenatal anxiety and socio-emotional development. In CMA, the point estimate for this association was OR = 1.47 (CI: 1.36-1.57). Figure 3 depicts the forest plot. Egger's test for publication bias was significant (p<.01), and the funnel plot revealed asymmetry (see Figure S2, available online). Using the trim-and-fill procedure, with 12 studies imputed, the adjusted effect size was OR = 1.33 (CI: 1.23-1.44). Statistically significant heterogeneity between the studies was found (Q = 56.63, p < .05, I^2 = 29.36). Moderator analyses were explored, including type of prenatal stress measure, type of child outcome, postnatal controls, method of assessing child behavior, pregnancy time point, maternal age, and child age and gender (Table S5, available online), however none of these moderators explained between-study heterogeneity.

Discussion

Results from this meta-analysis are consistent with the view that prenatal depression and prenatal anxiety have an adverse effect on children's socio-emotional and behavioral

functioning. Specifically, for mothers experiencing prenatal depression and anxiety, the odds of having children with behavioral difficulties were almost 1.5-2 times greater than those not experiencing prenatal depression or anxiety. Although this is the first meta-analysis to rigorously evaluate the literature on maternal prenatal stress and socio-emotional development, our findings build on several studies examining associations between maternal prenatal stress and other child outcomes, including birth weight, gestational age at delivery, and cognitive development [2-4]. Amassing evidence from current and past meta-analyses, maternal prenatal stress, broadly defined, clearly has robust associations with, and may have deleterious effects on, children's developmental health.

The specific mechanisms through which maternal prenatal stress impact brain development and later child outcomes are not well understood. The most widely investigated hypothesis involves programming via the maternal hypothalamic-pituitary-adrenal (HPA) axis, which produces elevated levels of cortisol under stress, which in turn may subsequently disrupt fetal brain development. However, research has shown that the maternal HPA axis is less responsive to stress during pregnancy and that the placenta acts as a shield offering protection against maternal hormones, calling into question the extent to which maternal stress hormones reach the fetus [25]. Thus, a more recent theory has hypothesized that the placenta may play a key regulatory role in the mechanisms underlying fetal programming [26]. During pregnancy the placenta produces the 11B-HSD2 enzyme, which works to transform active cortisol into inactive cortisone [27]. Both human and animal models of maternal prenatal stress have shown a reduction in the expression and activity of the 11B-HSD2 placental enzyme under conditions of maternal prenatal stress [28,29], resulting in increased fetal exposure to maternal hormones. Furthermore, maternal stress, including prenatal depression and anxiety, has been associated with an increased

risk of preeclampsia in later pregnancy [30]. Mothers with preeclampsia show higher levels of placental CRH (corticotropin-releasing hormone) [31] and reduced blood serum levels of Placental Growth Factor (PlGF) [32]. Exposure to both these maternal hormones prenatally may negatively impact the infant's brain and HPA axis development, which have strong associations with socio-emotional and behavioral functioning across the lifespan [33].

There are other mechanisms whereby maternal prenatal stress impacts neural development. As previously discussed, mothers who experience stress are more likely to have preterm and low birth weight babies. Maternal prenatal stress may also affect uterine blood supply and nutrient transport, thus contributing to fetal growth restriction. Maternal prenatal stress has been shown to be associated with reduced blood flow in uterine or umbilical arteries [27], as well as changes in fetal cerebral circulation [34]. A more direct effect of gestational stress on placental nutrient transport has been documented in rodents [35]. These restrictions in turn may contribute to compromised neural development and poorer behavioral outcomes. Finally, it is important to note that most studies cannot rule out genetic confounding as an explanation, although one study using an in-vitro-fertilization design found some evidence for environmental transmission of maternal stress to child conduct problems[36].

We found that effect sizes were stronger in studies that examined depression at the syndromal-level. Not only may clinical depression harm fetal development through the stress mechanisms described above, but women with clinical depression are also less likely to seek out prenatal care compared to those without [37], and have been reported to have poorer overall physical health (e.g., eating, sleeping, and exercise behaviors), as well as psychological health, in the prenatal period [26]. These factors in turn may lead to alterations in biophysiological functioning and fetal development[38]. The prenatal health risk behaviours associated with greater

clinical depression severity, may also explain the stronger effect sizes for the association between prenatal depression and child socio-emotional outcomes compared to that for maternal prenatal anxiety. Prenatal depression may also be more strongly associated with other prenatal risk factors such as smoking, alcohol use, socio-economic deprivation, and adverse life circumstances[14,39].

There are several other possible explanations for the differential association between prenatal depression versus anxiety and child socio-emotional outcomes. Prenatal depression has been associated with dysregulation of the HPA axis as well as other biological and physiological changes, which in turn could affect fetal biological and physiological development. In addition, postnatal depression has been linked to maternal emotional unavailability and unresponsiveness[40], which are linked to delays in development. This draws attention to the critical role of the postnatal environment for the developing child; when depression is maintained or exacerbated in the postnatal period, it may jeopardize child socio-emotional development further. Finally, maternal reports are often used to assess problematic child outcomes and maternal depression can distort perceptions, leading to an overestimation of child behavioral problems [41]. This methodological limitation could influence the magnitude of associations and should be an important consideration in future research.

Moderator analyses revealed that the association between prenatal depression and socio-emotional development was also heightened in families characterized as experiencing socio-economic deprivation. This finding is consistent with a meta-analysis on prenatal stress and perinatal risks [4]. It is well documented that there are large socio-economic disparities in prenatal and perinatal health. In comparison to mothers from middle to high income groups, mothers from lower socio-economic strata are more likely to have inadequate prenatal care, higher rates of

prenatal (e.g., intrauterine growth restriction) and perinatal risks and complications (e.g., low birthweight; preterm birth), leading to increased risk of infant morbidity and mortality [14,39]. Poverty is also associated with a clustering of child-related risks such as food insecurity, chaotic living arrangements, community violence, and stressful events, which have downstream consequences for child development [14]. The developmental resources that are known to enhance child development may also not be attainable for families struggling financially, creating further disparities in children's socio-emotional development.

We did not find that the type of anxiety measure examined (e.g., state, trait, cortisol) in pregnancy differentially predicted child socio-emotional development. Moreover, the timing of the assessment of prenatal anxiety in pregnancy was not found to moderate the association between prenatal stress and socio-emotional development. The majority of past studies are limited by the fact that prenatal stress is typically only examined at one time point [4]. This may create a problem in distinguishing between timing of stress and chronicity of stress. Timing of stress is not analogous with chronicity of stress, and those who report on stress later in their pregnancy may have experienced more chronic and sustained levels of stress, which could be more detrimental to the fetus. A ripe avenue of future longitudinal research is the examination of maternal stress at multiple, discrete time points to provide clarity in this regard.

There are two additional hypotheses worthy of mention that could not be addressed in the current meta-analyses. First, this meta-analysis was unable to examine the potential impact of genetic predisposition to behavioral difficulties for children of mothers who demonstrate higher levels of depression and anxiety. Second, the interaction between maternal prenatal stress and the quality of the postnatal environment could not be examined herein. Child development is critically influenced by the postnatal environment. It has been demonstrated that infants born to

mothers experiencing maternal prenatal stress can be buffered from negative child outcomes if they experience postnatal environments enriched with sensitive and response caregiving behavior [42], as well as secure attachment[42]. Thus, the quality of parenting, attachment, and the provision of social supports may attenuate associations between prenatal stress and child socio-emotional development.

Clinical Implications

An important caveat prior to a discussion of the clinical implications of our findings is that meta-analyses are correlational in nature. Causality between maternal prenatal stress and adverse child socio-emotional outcomes cannot be established. Nevertheless, based on the collective body of research on prenatal stress and deleterious pregnancy, perinatal, and child outcomes, there is a growing awareness of the importance of early intervention services and educational campaigns to mitigate stress and foster healthy fetal neurodevelopment and child outcomes. It is likely that investing in maternal prenatal stress interventions will have broad reaching beneficial effects on the health of mothers, children and their relationship.

Our findings suggest further that the application of preventive interventions in pregnancy may be particularly appropriate for mothers presenting with depression and/or those burdened by demographic risk. However, the current knowledge base for the efficacy of mental health interventions aimed directly at reducing stress and mental health in pregnancy is limited and underdeveloped [43-45]. Research must be conducted on maternal stress interventions during pregnancy and longitudinal follow-up over childhood. Future research should also examine the comparative benefits that different stress reduction strategies, including cognitive-behavioral therapy, interpersonal therapy, and mindfulness approaches, have on child development [46,47].

Moreover, the impact of interventions on women who experience co-morbid depression and anxiety is important, as higher cortisol levels have been found in pregnant women with comorbid anxiety and depression, putting these women's offspring at particular risk of poor developmental outcomes [48].

Limitations and Future Directions

Meta-analytic results from the current study must be interpreted in the context of several limitations. First, publication bias was detected, suggesting that non-significant results were less likely to be published (file-drawer problem) [49]; however adjusted effect sizes were derived to account for publication bias. Although some studies controlled for ongoing maternal stress and psychopathology in the post-partum period, the majority did not. Research on the role of postnatal paternal psychopathology and children's socio-emotional development, in interaction with, or over and above the influence of, prenatal or postnatal maternal stress is sparse. Furthermore, data from fathers can also afford an important test of confounders, as prenatal effects should only be observed in mothers if they are due to intra-uterine mechanisms. Further, many of the studies that have examined the impact of maternal prenatal stress have been conducted in low-risk population samples. This is especially true for prenatal anxiety. It is possible that biological and social mechanisms influencing the association between maternal prenatal stress and child development outcomes could vary based on biological and social vulnerability. Finally, underlying depression and anxiety is a common psychopathologic dimension[50], with shared biological and psychological etiologies[51]; however, the co-morbidity of depression and anxiety on child socio-emotional outcomes was not examined in the current meta-analysis.

All of these limitations warrant future investigation in individual studies with superior methodological quality to enhance understanding of pathways of transmission, and to elucidate moderating factors that can foster resilience in children exposed to prenatal stress. There is strong evidence from animal models [52] that child development outcomes for fetuses exposed to stress in utero improve after a combination of social and physical enrichment, but human studies are needed to support this body of work. Previous research has demonstrated that attachment status moderates the association between maternal prenatal stress exposure and child cognitive development, whereby the association is diminished for children with a secure parent-child attachment [42]; however, this research should be extended to child socio-emotional outcomes, to further inform intervention research.

Conclusions

This research adds support to the increasing body of literature suggesting that prenatal depression and anxiety are potential fetal programming factors, affecting biological, cognitive, and behavioral development in offspring. While overall effect sizes are not large, they suggest, as other research has, a consistent association between maternal prenatal stress, and child socio-emotional development. Extant results from the literature point to the potential importance of the intrauterine environment in setting certain conditions for child development. Such conditions may interact with genetic, epigenetic and postnatal factors to influence a range of social, emotional and behavioral outcomes. Our results suggest an increased risk to children exposed to prenatal depression, as well as to families who are socially disadvantaged. Investing in disadvantaged families with young children has a high return on investment[53], improving outcomes for parents, children and their families and avoiding later, higher-cost interventions.

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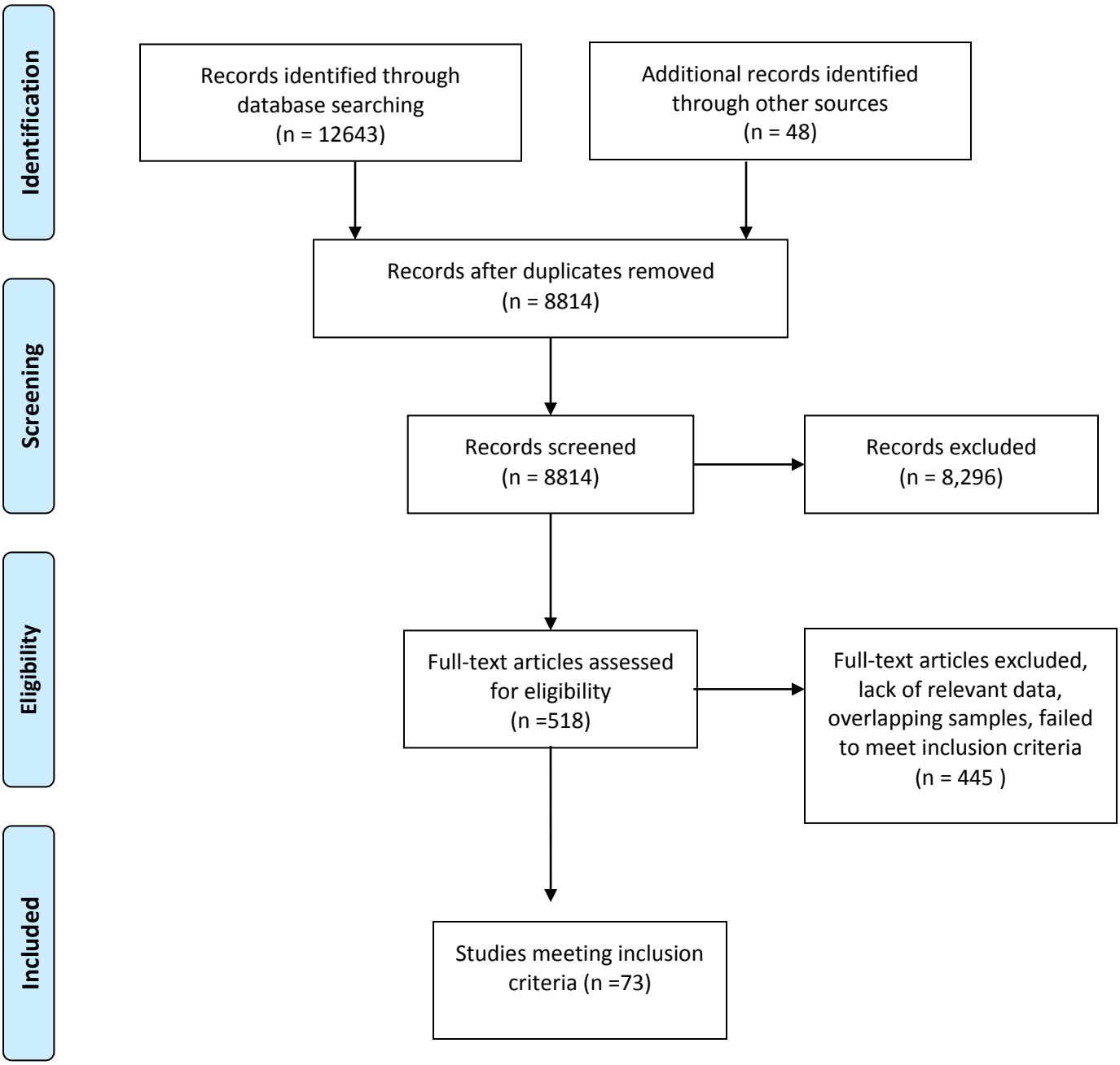

Figure 1
PRISMA flow diagram detailing the search strategy.

Figure 2. Forest plot of the overall mean effect size, as well as the effect size for each study included in the meta-analysis on prenatal depression and child socio-emotional development.
Legend: Observed effect sizes (OR) and 95% confidence intervals are indicated for each study included in the meta-analysis.

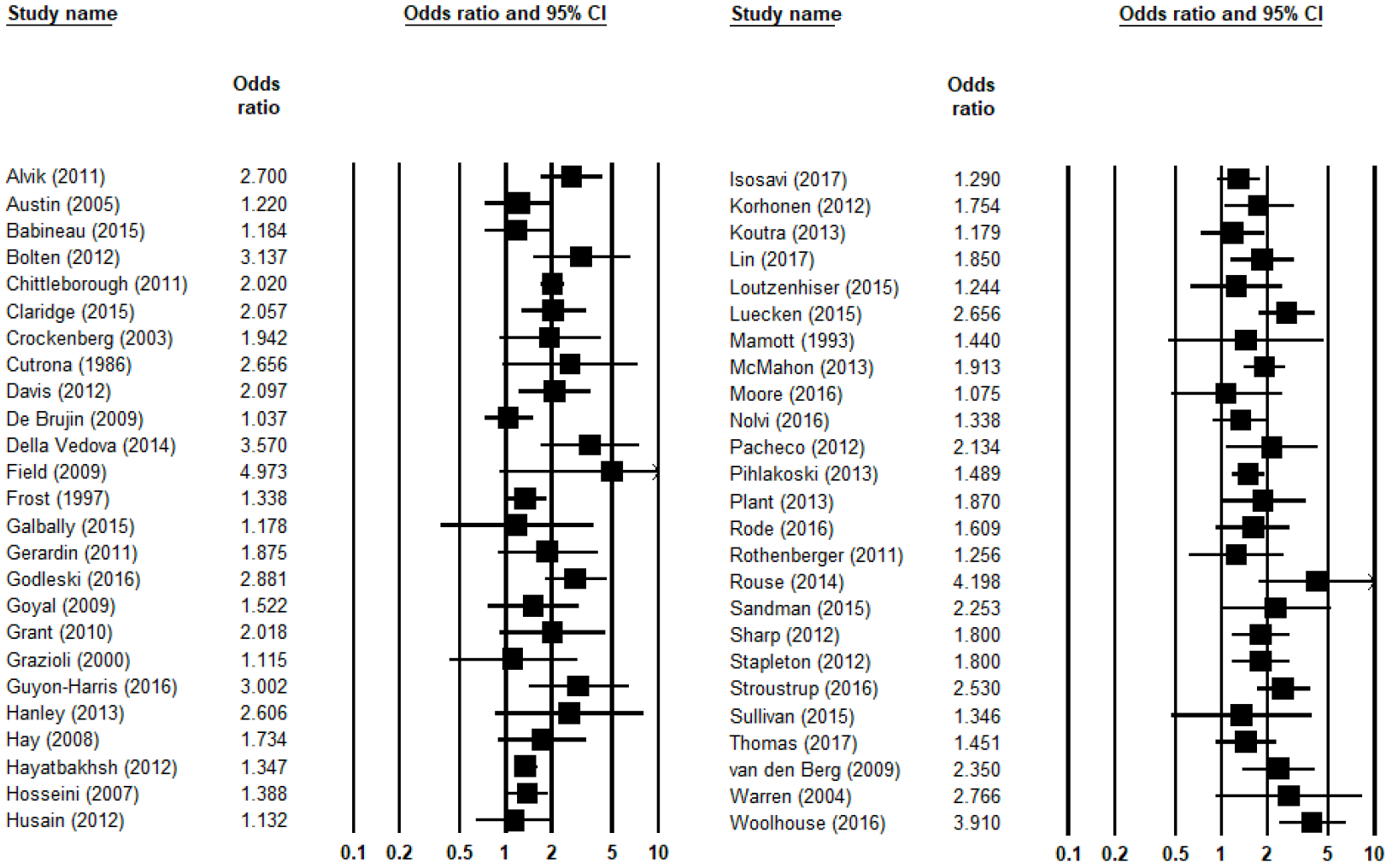

Figure 3. Forest plot of the overall mean effect size, as well as the effect size for each study included in the meta-analysis on prenatal anxiety and child socio-emotional development.

Legend: Observed effect sizes (OR) and 95% confidence intervals are indicated for each study included in the meta-analysis.

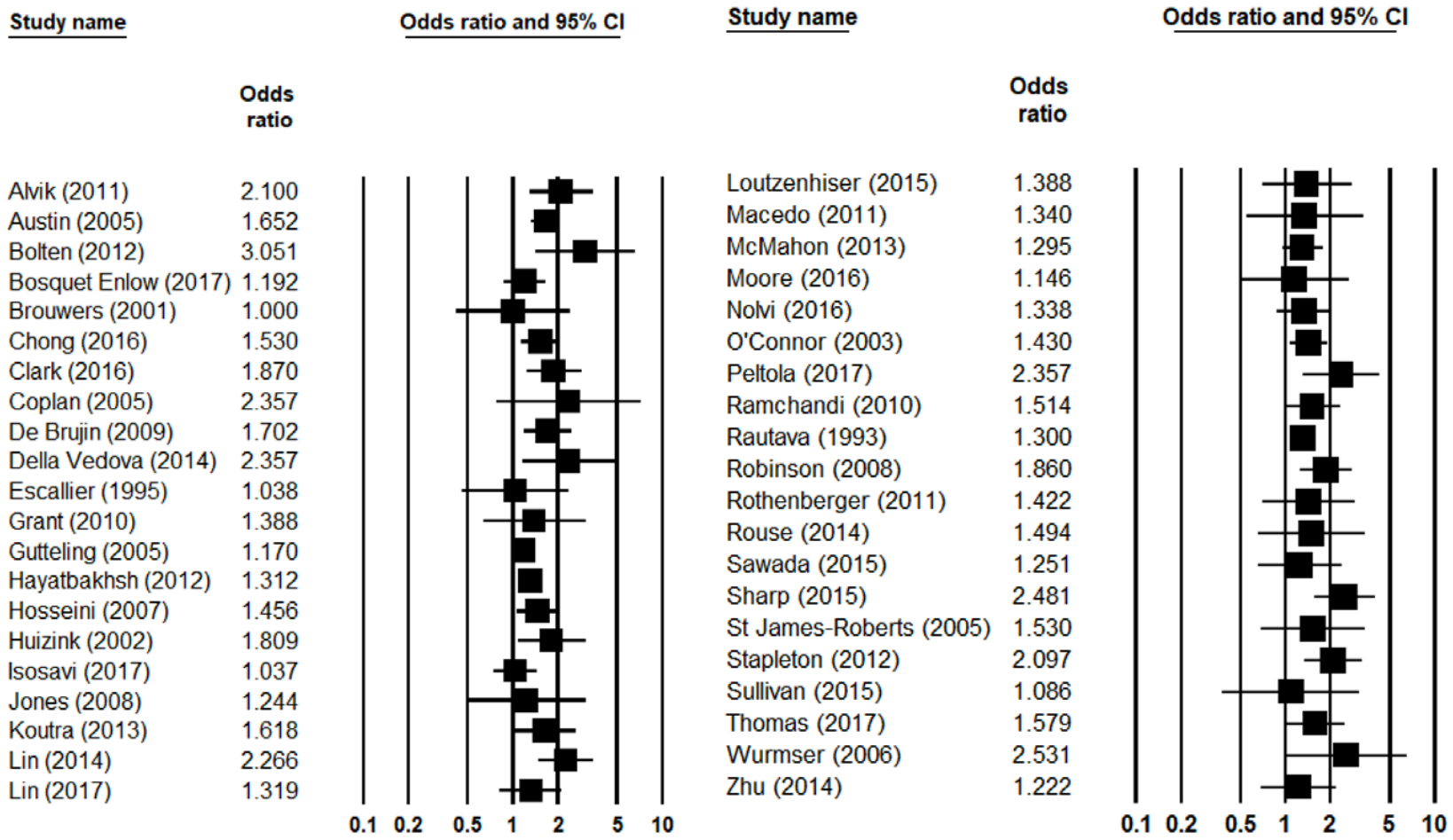

Table S1: Summary of Search Strategy

Database: PsycINFO <1806 to February week 1 2018>

Search Strategy:

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1. pregnan*/ or trimester/
2. anxiet*/ or anxious*/
3. depression*/ or depressive/
4. stress/
5. or/2-4
6. infant/ or infancy/ or newborn*/ or baby/ or babies/ or child*/teen*/or adolesc*/or youth*/
7. behavio*/develop*/temperament/
8. internali*/externali*/
9. emotion*/aggressi*/
10. or/7-9
11. 1 and 5
12. 6 and 10
13. limit 12 to (childhood <birth to age 12 yrs> or adolescence <age 13 to 17 yrs>)
14. 11 and 13

Table S2 Study Quality Criteria Evaluation[1]

1. Defined Sample	Study has a defined eligibility and exclusion criteria for their sample; and time period (dates) and location (s) of recruitment and assessment.	0 = No 1 = Yes
2. Representative Sample	Is the sample representative of a defined population? (i.e. was everyone included who should be and is this sample generalizable) E.g. only selecting mothers of children with disabilities = 0. 1 = Cohorts recruited from the general population or from multi-site studies and/or large databases. 0 = Single site clinical studies.	0 = No 1 = Yes
3. Adequate Sample Size	Power calculation provided	0 = No 1 = Yes
4. Participation/Attrition	Does the study meet satisfactory participation/attrition rates? 0= <60% participation; >40% attrition or not specified 1= 60-79% participation; 21-39% attrition 2= >80% participation, <20% attrition	0 = Not-acceptable 1= Marginally acceptable 2 = Acceptable
5. Missing data	Does the study mention missing data and account for how they were treated in the analysis? Studies that remove incomplete data from the outset and do not include it in the total N are considered meeting the criteria for addressing missing data	0= No 1= Yes
6. Valid Instrument (Stress)	Does the study use a validated instrument for the assessment of maternal prenatal stress? 0 = Non-validated (made up by researcher) 1= validated measure (e.g. Perceived stress scale, parenting stress index, STAI, BDI, EPDS)	0 = Non-validated 1 = Validated
7. Valid Instrument (Child Outcome)	Does the study use a validated instrument for the assessment of child outcome?	0 = Non-validated 1 = Validated

	0 = Non-validated (made up by researcher) 1= validated measure (BSID, IBR, CBCL , BASC, IBQ-R, ASQ)	
8. Subjective vs. objective measures (Stress)	Does the study use different reporters or multiple-methods to measure maternal stress? Objective measure = cortisol, substantiated life stress, diagnosis or physician evaluation. Multiple methods = self-report *and* biological data/substantiated life stress, diagnosis.	0 = Self-report 1 = Objective measure 2 = Multiple methods
9. Subjective vs. objective measures (Child Outcome)	Does the study use different reporters or methods to measure child outcome?	0 = Maternal report 1 = Objective measure 2 = Multiple methods (e.g. two reporters, maternal report and observational data)
10. Confounding Variables	Were confounding variables taken into account in the analysis? E.g. in modeling or regression did they control or adjust for confounding factors.	0 = No 1 = Yes
11. Demographic Information	Does the study report complete demographic data for parents and children included in the study? 0 = No demographic information specified 1 = data for only child or parent 2= demographic data for child and parent.	0 = Not specified 1 = specified for parent or child 2 = specified for parent and child

[1] **Adapted from: The National Institute of Health Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies.**
https://www.nhlbi.nih.gov/health-pro/guidelines/in-develop/cardiovascular-risk-reduction/tools/cohort

Table S3. Quality assessment of included studies

Article	Defined Sample	Represent-ative Sample	Sample Size	Attrition	Missing Data	Valid Instrument (Stress)	Valid Instrument (Child Outcome)	Stress Measure	Child Outcome	Confou-nding Variables	Demo. Info	Score (/15)
Alvik (2011)	Y	N	N	M	Y	Y	N	SR	MR	N	P	5
Austin (2005)	Y	N	N	N	Y	Y	Y	SR	MR	Y	P	6
Babineau (2015)	Y	Y	N	M	Y	Y	Y	SR	MR	Y	C	9
Bolten (2012)	N	N	N	Y	N	Y	Y	SR	MR	Y	C	7
Bolton (2013)[1]	Y	N	N	Y	N	Y	Y	MM	O	N	C	10
Bosquet Enlow (2017)	Y	Y	N	M	N	Y	Y	MM	MR	Y	C	10
Brouwers (2001)	N	Y	N	M	Y	Y	Y	SR	O	Y	C	10
Chittleborough (2011)	Y	Y	N	Y	Y	Y	Y	SR	MM	Y	NS	10
Chong (2016)	Y	N	N	N	Y	Y	Y	SR	MR	Y	P	6
Claridge (2015)	Y	N	Y	N	Y	Y	Y	SR	MR	Y	C	8
Clark (2016)	N	N	N	Y	Y	Y	Y	SR	MM	Y	NS	8
Coplan (2005)	N	N	N	M	N	Y	Y	SR	MR	N	P	4
Crockenberg (2003)	N	N	N	M	Y	Y	Y	SR	MR	Y	C	7
Cutrona (1986)	N	N	N	Y	N	Y	Y	SR	MM	N	P	7
Davis (2012)	Y	N	N	Y	N	Y	Y	MM	MR	Y	C	10
De Bruijn (2009)	Y	N	N	N	N	Y	Y	SR	MM	Y	C	8
Della Vedova (2014)	N	Y	N	M	Y	Y	Y	SR	MR	Y	P	7
Escallier (1995)	N	N	N	Y	N	Y	N	SR	O	Y	C	7
Field (2009)	N	Y	N	Y	N	Y	N	SR	O	N	C	7

Frost (1997)	Y	Y	N	Y	Y	Y	Y	SR	MR	Y	P	11
Galbally (2015)	Y	N	N	M	N	Y	Y	SR	MM	Y	C	9
Gerardin (2011)	Y	N	N	M	N	Y	Y	MM	MM	Y	C	11
Godleski (2016)	N	N	N	Y	N	Y	Y	SR	MM	N	C	8
Goyal (2009)	N	N	N	M	Y	Y	N	SR	MM	Y	C	8
Grant (2010)	Y	N	N	N	Y	Y	Y	MM	O	Y	C	10
Grazioli (2000)	N	N	N	Y	N	Y	Y	MM	MR	Y	P	8
Gutteling (2005)	Y	N	N	N	Y	Y	Y	MM	MM	Y	C	11
Guyon-Harris (2016)	N	N	N	Y	Y	Y	Y	SR	MM	Y	P	9
Hanley (2013)	Y	Y	N	Y	N	Y	Y	MM	O	Y	C	12
Hay (2008)	N	Y	N	M	Y	Y	Y	MM	MM	Y	C	12
Hayatbakhsh (2012)	Y	N	N	M	N	Y	Y	SR	MR	Y	C	7
Hosseini (2007)	N	N	N	M	Y	Y	Y	SR	MR	Y	C	7
Huizink (2002)	N	N	N	M	Y	Y	Y	SR	MM	Y	C	9
Husain (2012)	Y	N	Y	Y	N	Y	Y	MM	O	Y	P	11
Isosavi (2017)	Y	N	N	Y	Y	Y	Y	MM	MR	Y	C	11
Jones (2008)	N	N	N	M	Y	Y	Y	MM	MR	Y	C	9
Korhonen (2012)	Y	N	N	N	N	Y	Y	SR	MM	Y	C	8
Koutra (2013)	Y	Y	N	N	Y	Y	Y	SR	MM	Y	C	10
Lin (2014)	N	N	N	N	Y	Y	Y	SR	MM	Y	C	8
Lin (2017)	Y	Y	N	N	Y	Y	Y	MM	MM	Y	C	12
Loutzenhiser (2015)	N	N	Y	Y	Y	Y	Y	SR	MR	N	P	7
Luecken (2015)	N	N	N	M	Y	Y	Y	SR	MM	Y	P	8
Macedo (2011)	N	N	N	N	Y	Y	N	MM	MR	N	P	5
Mamott (1993)	N	N	N	Y	N	Y	Y	SR	MR	N	P	5

McMahon (2013)	N	N	N	Y	Y	Y	Y	SR	MR	Y	C	8
Moore (2016)	N	N	N	Y	Y	Y	N	MM	O	N	C	9
Nolvi (2016)	N	N	N	Y	N	Y	Y	SR	MR	Y	C	7
O'Connor (2003)	Y	Y	N	M	Y	Y	Y	SR	MR	Y	P	8
Pacheco (2012)	N	N	Y	Y	N	Y	Y	SR	O	Y	P	8
Peltola (2017)	Y	Y	N	Y	Y	Y	Y	SR	MM	Y	P	11
Pihlakoski (2013)	Y	Y	N	M	Y	N	Y	SR	MM	Y	P	9
Plant (2013)	Y	N	N	Y	N	Y	Y	O	O	Y	C	10
Ramchandani (2010)	Y	N	N	N	N	N	Y	O	MR	Y	C	6
Rautava (1993)	Y	Y	N	Y	N	N	N	SR	MR	Y	P	6
Robinson (2008)	Y	Y	N	M	Y	N	Y	O	MR	Y	C	9
Rode (2016)	Y	N	N	Y	Y	Y	N	SR	MR	Y	P	7
Rothenberger (2011)	Y	N	N	Y	N	Y	Y	MM	O	N	C	10
Rouse (2014)	N	N	N	M	Y	Y	Y	MM	MR	N	C	8
Sandman (2015)	N	N	N	N	N	Y	Y	SR	MR	Y	C	5
Sawada (2015)	N	Y	N	M	Y	Y	N	MM	MR	Y	P	8
Sharp (2012)	Y	Y	Y	Y	Y	Y	Y	SR	MM	Y	C	13
Sharp (2015)	Y	N	N	M	N	Y	Y	SR	MR	Y	C	7
Stapleton (2012)	N	Y	N	N	Y	Y	Y	SR	MR	Y	C	7
St James-Roberts (2005)	N	N	N	M	Y	Y	Y	SR	MR	N	NS	4
Stroustrup (2016)	Y	Y	N	N	N	Y	Y	SR	MM	N	P	7
Sullivan (2015)	N	N	N	Y	Y	Y	Y	SR	MM	Y	C	10
Thomas (2017)	Y	Y	N	Y	Y	Y	Y	MM	MM	Y	C	14
van den Berg (2009)	Y	Y	N	M	Y	Y	N	SR	MR	Y	C	8

van den Heuvel[1] (2015)	N	Y	N	N	Y	Y	Y	SR	MR	Y	C	7
Warren (2004)	N	N	N	Y	N	Y	Y	SR	MR	Y	C	7
Woolhouse (2016)	Y	Y	N	M	Y	Y	Y	SR	MR	Y	P	8
Wurmser (2006)	Y	N	N	Y	Y	Y	Y	SR	MR	N	C	8
Zhu (2014)	Y	N	N	Y	N	N	Y	SR	MM	Y	C	9

Total (N = 73)

Criteria		*N* (%)	Criteria		*N* (%)	Criteria		*N* (%)
Defined Sample			Missing Data			Subjective vs. Object Measure (Child)		
	Yes	39 (53.42)		Yes	44 (60.27)		Multiple Methods	24 (32.88)
	No	34 (46.58)		No	29 (39.73)		Objective Measure	11 (15.07)
							Maternal Report	38 (52.05)
Representativeness			Valid Instrument (Stress)			Confounding Variables		
	Yes	24 (32.88)		Validated	68 (93.15)		Yes	58 (79.45)
	No	49 (67.12)		Non-Validated	5 (6.85)		No	15 (20.55)
Adequate Sample Size			Valid Instrument (Child Outcome)			Demographic Information		
	Yes	5 (6.85)		Validated	63 (86.30)		Specified for Parent and Child	47 (64.38)
	No	68 (93.15)		Non-Validated	10 (13.70)		Specified for Parent or Child	23 (31.51)
							Not Specified	3 (4.11)
Participation/Attrition			Subjective vs. Objective Measure (Stress)					
	Acceptable	32 (43.84)		Multiple Methods	19 (26.03)			
	Marginally Acceptable	25 (34.25)		Objective Measure	3 (4.11)			
	Not Acceptable	16 (21.92)		Self-report	51 (69.86)			

[1] This study was not included in analyses as the effect size was an outlier
N = No; Y = Yes
Demo.Info. = Demographic Information
Attrition: Y = acceptable; M = marginally acceptable; N = unacceptable
Stress Measure: SR = self-report; MM = mixed methods
Child Outcome: MM = mixed methods; O = observation; MR = maternal report only
Demographics: C = complete; P = partial; NS = Not-specific

Table S4

Results of Moderator Analyses for the Association between Maternal Prenatal Depression and Child Socio-Emotional Development

Categorical Moderators	***k***	***OR***	***95% CI***	***Homogeneity Q***	***P-value***
Syndromal-Level Symptoms				9.34	.01
No	37	1.60**	1.46-1.75		
Yes	14	2.26**	1.86-2.78		
Socio-Demographic Risk				4.37	.05
No	40	1.66**	1.51-1.84		
Yes	10	2.24**	1.73-2.91		
Type of Child Measure				.19	.91
Temperament	27	1.78**	1.56-2.02		
Behavior Problems	20	1.74**	1.49-2.04		
Crying/Colic	3	1.98**	1.14-3.42		
Method of Assessing Child Behavior				0.16	.92
Questionnaire	40	1.77**	1.59-1.96		
Structured Measure	5	1.68**	1.29-2.19		
Observation	5	1.86*	1.16-2.99		
Postnatal Depression Control				0.25	.62
No	39	1.79**	1.62-1.99		
Yes	11	1.68**	1.32-2.13		

Continuous Moderators	***k***	***b***	***95% CI***	***Z-value***	***P-value***
Pregnancy Time Point	48	.006	-.007-.019	0.90	.37
Maternal Age	48	-.019	-.043-.005	-1.56	.12
Child age	50	-.001	-.002-.001	-0.94	.35
Percent of Males in Sample	50	-.013	-.041-.016	-0.88	.38
Study Quality	50	-.034	-.082-.015	-1.37	.17

k = sample size; *b* = estimate; 95% CI = 95% confidence intervals; *p < .01; **p<.001; *p<.01

Table S5

Results of Moderator Analyses for the Association between Maternal Prenatal Anxiety and Child Socio-Emotional Development

Categorical Moderators	***k***	***OR***	***95% CI***	***Homogeneity Q***	***P-value***
Socio-Demographic Risk				1.24	.27
No	4	1.444**	1.34-1.56		
Yes	37	1.64**	1.34-2.03		
Maternal Stress Measure [a]				4.34	.23
State	14	1.64***	1.41-1.90		
Trait	12	1.48***	1.28-1.70		
Life Events	3	1.29	0.96-1.74		
Mix of measures	12	1.36***	1.22-1.52		
Type of Child Measure				0.68	.72
Temperament	23	1.51***	1.37-1.68		
Behavior Problems	9	1.55***	1.37-1.77		
Colic/Crying	7	1.41***	1.41-1.72		
Method of Assessing Child Behavior				1.83	.40
Questionnaire	30	1.49***	1.37-1.62		
Structured Measure	5	1.27**	1.02-1.58		
Observation	4	1.39	0.92-2.11		
Postnatal Depression Control				0.01	.91
No	33	1.47**	1.35-1.61		
Yes	8	1.49**	1.29-1.71		

Continuous Moderators	***k***	***b***	***95% CI***	***Z-value***	***P-value***
Pregnancy Time Point	40	.007	-.004-.017	1.30	.20
Maternal Age	37	-.001	-.018-.018	0.00	.99
Child age	40	-.000	-.002-.011	-0.57	.57
Percent of Males in Sample	40	-.012	-.002-.025	1.67	.10
Study Quality	41	-.008	-.017-.002	-1.52	.13

k = sample size; *b* estimate; 95% CI = 95% confidence intervals; *$p < .05$; **$p < .01$; ***$p<.001$

[a] There were too few studies exclusively examining prenatal anxeity via prenatal cortisol to include these measures in this moderator analysis.

Figure S1. Funnel plot of the meta-analysis of included studies on prenatal depression and child socio-emotional development.
Legend: The y-axis on the funnel plot represents the standard error, and the x-axis is the effect size. The white circles indicate studies that were included in the meta-analysis, and black circles indicate values to adjust for asymmetry in the funnel plot. The white diamond at the bottom of the funnel plot represents the observed mean effect size, and the black diamond represents the adjusted mean effect size.

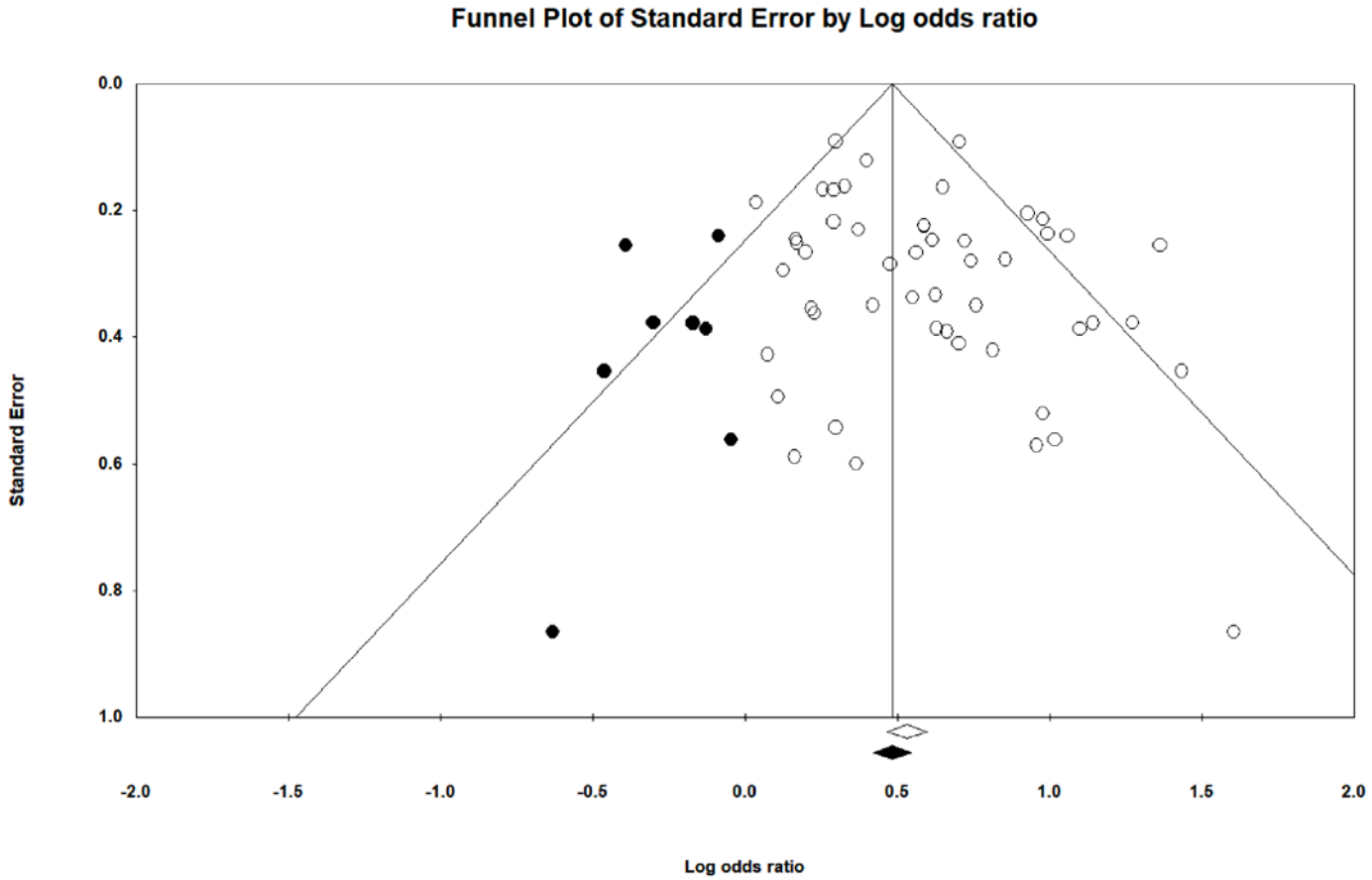
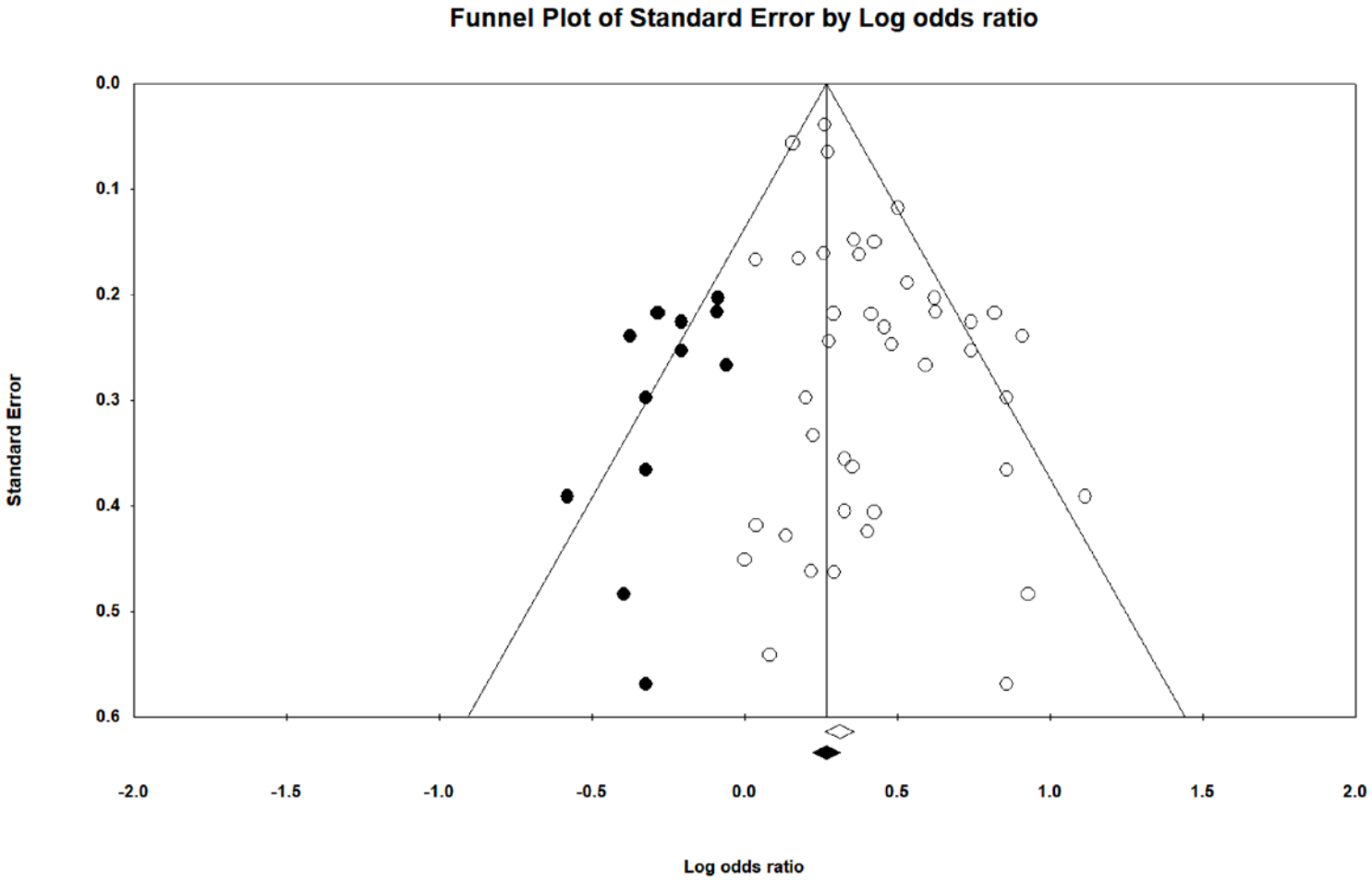


Figure S2. Funnel plot of the meta-analysis of included studies on prenatal anxiety and child socio-emotional development.
Legend: The y-axis on the funnel plot represents the standard error, and the x-axis is the effect size. The white circles indicate studies that were included in the meta-analysis, and black circles indicate values to adjust for asymmetry in the funnel plot. The white diamond at the bottom of the funnel plot represents the observed mean effect size, and the black diamond represents the adjusted mean effect size.



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