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Prenatal Stress and Externalizing Behaviors in Childhood and Adolescence: A Systematic Review and Meta-Analysis

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Accumulating evidence suggests that psychological distress during pregnancy is linked to offspring risk for externalizing outcomes (e.g., reactive/aggressive behaviors, hyperactivity, and impulsivity). Effect sizes across studies have varied widely, however, due to differences in study design and methodology, including control for the confounding continuation of distress in the postnatal period. Clarifying these inconsistencies is necessary to guide the precision of prevention efforts and inform public health policies. A meta-analysis was conducted with 55 longitudinal studies to investigate the association between prenatal psychological distress (anxiety, depression, and perceived stress) and offspring externalizing behaviors. Results revealed a significant but small effect (r = .160) of prenatal distress on externalizing behaviors. The magnitude of the prenatal effect size remained largely unchanged after adjusting for postnatal distress (r = .159), implicating a unique effect of psychological distress during the prenatal period in the etiology of externalizing behaviors. Moderation tests showed that prenatal effects did not vary based on type and timing of psychological distress during pregnancy. Greater instability of distress from prenatal to postnatal periods predicted larger effects. Prenatal effects were comparable across most externalizing outcomes, consistent with the common comorbidity of externalizing spectrum disorders, although effects appeared smaller for nonaggressive rule-breaking (vs. aggressive) behaviors. Significant associations persisted across all developmental periods, appearing slightly larger in early childhood. We discuss these results in the context of developmental and psychobiological theories of externalizing behavior, offer preliminary clinical and public health implications, and highlight directions for future research including the need for longitudinal studies with more racially and socioeconomically diverse families.

Public Significance Statement

This meta-analysis suggests that psychological distress during the pregnancy period uniquely increases children's risk for aggressive, disinhibited, and impulsive behaviors. Effects are relatively small but persist across developmental periods from early childhood through adolescence. Providing widely accessible mental health care and support during pregnancy may be a critical step to early prevention of childhood behavior problems.

Keywords: prenatal stress, prenatal mental health, externalizing behavior, child and adolescent behavior problems, meta-analysis

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Early exposure to stress and adversity is one of the most consistent predictors of child behavior problems, including the onset and development of aggressive, disinhibited, and impulsive behaviors (Busso et al., 2017; Doom et al., 2016; Hunt et al., 2017; Sanchez et al., 2013; Snyder et al., 2019). Early expressions of these externalizing behaviors often begin to emerge during the preschool period and are the most common reason for children's initial referral for mental health services (Hansen et al., 2021; Pikard et al., 2018). Indeed, externalizing spectrum disorders in the *Diagnostic and Statistical Manual of Mental Disorders, 5th Edition* (*DSM-5*), such as attention-deficit/hyperactivity disorder (ADHD), oppositional defiant disorder (ODD), and conduct disorder (CD), along with related dimensional constructs such as aggression and rule-breaking behaviors, are linked to substantial individual-level impairment across social, academic, and mental health domains (Burke et al., 2014; Cadman et al., 2016; Gordon & Fabiano, 2019; Hinshaw & Beauchaine, 2015; Szentiványi & Balázs, 2018; Tung et al., 2016). These behaviors are accompanied by significant downstream social and economic costs for families and the broader community, including substantial costs related to increased lifetime service use (e.g., social welfare, emergency health care, criminal convictions; Rissanen et al., 2022; Rivenbark et al., 2018; Sciberras et al., 2022). Given the serious clinical and public health significance of externalizing behaviors, there is a clear need to identify sources of stress exposure that can be modified during early sensitive periods of development to prevent the onset of these behaviors.

Externalizing Behaviors as Developmental Adaptations to Stress

Multiple theories of developmental adaptation (e.g., developmental origins of health and disease theory, adaptive calibration model, dynamic systems theory) offer a conceptual framework for understanding the association between early stress exposure and externalizing behaviors (D. J. P. Barker, 2007; Del Giudice et al., 2011; Thelen & Smith, 1998). These theories emphasize that development is experience-driven, with stress systems and subsequent behaviors adapting over time to promote survival in the expected environment. Indeed, early exposure to social-environmental stressors (e.g., adverse childhood experiences, parent psychopathology, harsh parenting behaviors) has been shown to critically shape neurobiological systems underlying vulnerability to externalizing behaviors. These changes include alterations in emotional processing and reactivity to threat (e.g., changes in the amygdala, hippocampus) and physiological systems involved in stress reactivity and regulation (e.g., hypothalamic–pituitary-adrenal axis; Barch et al., 2018; Bernard et al., 2015; Hanson et al., 2015; Saxbe et al., 2018). Early alterations in children's neurobiological and physiological responses to the environment, in turn, have been implicated in the development of impulse control, emotion regulation, and subsequent externalizing behavior problems (Barch et al., 2018; Hanson et al., 2015).

Although most studies have investigated these developmental pathways during childhood, a growing body of evidence influenced by evolutionary psychology theories suggests that developmental adaptation to stress may begin *before* birth (Ellis & Del Giudice, 2019; Tremblay et al., 2018), starting from the prenatal period when the pregnant person's experiences of distress can shape or "calibrate" fetal stress systems to the anticipated postnatal environment (Glover, 2011; Glynn et al., 2018; Seckl, 1998). This early calibration of the stress system based on the prenatal environment is theorized to play an important role in predicting early differences in the way young children attend to the environment (e.g., attention to threat) as well as their physiological and behavioral reactions to the environment (e.g., responses to perceived threat or ambiguous situations; Davis et al., 2011; Laurent, 2017; Monk et al., 2019).

Evidence for Prenatal Psychological Distress Effects

In support of these theoretical models, accumulating empirical evidence demonstrates a potential causal association between prenatal stress and the development of emotional and behavioral difficulties in childhood and adolescence (Glover, 2011). The term "prenatal stress" broadly refers to wide range of exposures during pregnancy that may exert stress on the developing fetus. In humans, one of the most frequently investigated subdomains of prenatal stress is the pregnant parent's *psychological distress* during pregnancy, such as prenatal anxiety, depression, and perceived stress. Although both "distress" and "stress" have been used to reference these psychological constructs during pregnancy, we will use the term "psychological distress" in this article moving forward as an inclusive shorthand when referencing the specific exposure of an individual's experiences of anxiety, depression, and perceived stress during pregnancy (Glover et al., 2023). To date, prenatal psychological distress has been linked to a range of offspring externalizing outcomes, including hyperactivity and impulsivity (D'Souza et al., 2019; MacKinnon et al., 2018), reactive and aggressive behaviors (D. F. Hay et al., 2010; Lahti et al., 2017), and symptoms of ADHD, ODD, and CD (Bendiksen et al., 2020; Leis et al., 2014; O'Connor et al., 2002). The biological programming of risk for externalizing behaviors during the prenatal period is supported by emerging work from prenatal brain development research, which has demonstrated prenatally induced structural alterations in several brain regions underlying risk for externalizing outcomes, including the amygdala, hippocampus, and prefrontal cortex (Jones et al., 2019; Van den Bergh et al., 2018). In addition, exposure to prenatal psychological distress is linked with alterations in offspring's regulatory circuitry connectivity (e.g., connectivity between the amygdala and the medial prefrontal cortex and frontal cortex; Hay et al., 2020; Humphreys et al., 2020), as well as alterations in attentional networks that underlie susceptibility to neurodevelopmental outcomes (Van den Bergh et al., 2018).

Together, this growing literature suggests that reducing prenatal psychological distress may be an early prevention pathway to reducing offspring risk for externalizing behaviors. This pathway represents an important shift in focus from prevailing approaches to addressing externalizing problems, which are often reactive (e.g., intervening once families seek help for disruptive child symptoms) rather than preventative in nature. From a prevention science perspective, pregnancy represents a unique window of increased contact with health care providers, and thus is an opportunity for systematic screening and intervention of prenatal risk factors such as parent psychological distress. A major impediment to addressing prenatal depression, anxiety, and stress, however, is the common lack of universal screening for mental health symptoms during pregnancy as well as the lack of accessible mental health treatment

options covered by insurance. Shifting these public health policies to improve child behavioral health outcomes requires clear evidence of the unique effect of psychological distress during pregnancy on child outcomes such as externalizing behaviors.

Despite the important clinical and public health implications of this work, the strength of the effect of psychological distress during pregnancy on offspring externalizing behavior remains unknown. Our review of existing studies reporting this information revealed substantial variation in the reported magnitude of prenatal distress effects. For example, some data suggest that an estimated 10%–15% of the variability in child behavior problems may be attributed to prenatal distress (Glover, 2014), with one previous study of school-aged children reporting that the presence of maternal depression symptoms during pregnancy predicted over three times greater odds of offspring externalizing behavior problems (Luoma et al., 2001). Other studies have reported more modest or even nonsignificant effects, particularly after accounting for parent psychological distress in the postnatal period or other sample characteristics (Betts et al., 2014; Leis et al., 2014). Differences in findings across studies likely reflect heterogeneity in study sample (e.g., sample size, selection criteria, race and ethnicity and other demographic factors), rigor of study design (e.g., prospective vs. retrospective), measures used (e.g., dimensional, diagnostic), and the extent to which the study accounts for potential confounding factors such as the continuation of parent psychological distress in the *postnatal* period. Indeed, many studies of prenatal distress have either not accounted for postnatal distress or relied on different constructs or measures of distress before versus after pregnancy. This constraint has made it difficult to specify timing of effects to the prenatal period. This limitation in study design is important, given that individuals who experience psychological distress during pregnancy often continue to experience psychological distress after pregnancy (Ahmed et al., 2019; Dipietro et al., 2008). Childhood exposure to parental depression and anxiety is linked to the onset and exacerbation of child externalizing outcomes (Hentges et al., 2020). Given the growing number of studies reporting prenatal distress effects on externalizing spectrum outcomes over the past two decades, conducting a meta-analysis of the most rigorously designed studies to clarify these inconsistencies is timely and needed to inform the direction of future research as well as the timing of prevention efforts during the pregnancy versus postnatal periods.

Accounting for Continuity of Psychological Distress Before and After Pregnancy

Postnatal psychological distress represents a significant potential confounding factor when interpreting effects of prenatal psychological distress on offspring outcomes. To this end, there are two potential models of prenatal and postnatal distress that can be examined meta-analytically. First, based on fetal programming theories, prenatal distress may be conceptualized as a causal factor that influences risk for externalizing outcomes, *independent* of the correlated effects of postnatal distress on externalizing outcomes. Evidence supporting these theorized causal pathways has been demonstrated by preclinical animal studies using controlled experimental methods (Thayer et al., 2018). Although causality can only be *inferred* in observational human studies, these theorized effects are partially supported by rigorously controlled longitudinal human studies showing that even after covarying for the effect of postnatal distress on externalizing outcomes, prenatal psychological distress continues to have a unique independent association with offspring stress physiology and later externalizing outcomes (Bush et al., 2017; D'Souza et al., 2019; Faleschini et al., 2019; Korhonen et al., 2014; Leis et al., 2014; Rash et al., 2016; Rice et al., 2010). For example, previous reports from the population-based Avon Longitudinal Study of Parents and Children indicate a strong association ($OR = 1.85$) between anxiety in late pregnancy and boys' ADHD symptoms in preschool, and the magnitude of this effect size remained similar once postnatal anxiety was included in the model (O'Connor et al., 2002). These findings are consistent with more recent studies reporting that the association between maternal lifetime diagnosis of anxiety and depression and offspring ADHD is particularly magnified for children exposed to maternal anxiety and depression during the pregnancy period (Vizzini et al., 2019). Similarly, another large prospective pregnancy cohort study found that both prenatal and postnatal depression symptoms were associated with offspring conduct problems and inattention/hyperactivity in mid-childhood but controlling for prenatal symptoms significantly attenuated the effect of postnatal maternal depression on externalizing outcomes (Faleschini et al., 2019). Thus, exposure to parent psychological distress specifically during pregnancy may uniquely confer risk for externalizing behaviors in childhood, independent of the effects of the parent's postnatal distress.

An alternative model conceptualizes prenatal psychological distress as an "indicator" of risk, but not a causal risk factor. Prenatal distress is hypothesized to be statistically correlated with externalizing behavior, but becoming negligible once the parent's postnatal distress is included as a covariate. That is, this alternative model posits that prenatal distress is not a causal risk factor for child outcomes, but instead, represents an indicator of offspring risk due to its correlation with parent psychological distress (e.g., psychopathology) in the postnatal period (the "true" causal factor). Evidence for this conceptualization is supported by studies reporting that once postnatal distress is covaried, the effect of prenatal distress on externalizing behavior becomes nonsignificant (Hentges et al., 2019; van der Waerden et al., 2015). However, a limitation to studies investigating this question is that the measure of postnatal distress often varies from the measure of prenatal distress (e.g., prenatal perceived stress vs. postnatal depression). As a result, it is unclear if the differences are due to timing or *type* of psychological distress. To address this issue, consistency in measurement of psychological distress across the prenatal and postnatal periods is needed. To capture the studies that used the most rigorous methodology for examining prenatal stress effects, the current meta-analysis focused on prospective longitudinal studies that assessed psychological distress using the same repeated measure before and after pregnancy. Doing so enabled us to meta-analytically test for the unique effect of prenatal psychological distress on externalizing outcomes, *independent* of the same measure postnatally.

Exploring Heterogeneity in Type, Timing, and Stability of Psychological Distress

In addition to differences in study design, heterogeneity in effect sizes across studies may also be explained by differences in the measure of psychological distress or externalizing behavior, or participant characteristics such as offspring age and sex. To date, the potential contributions of these measurement and sample

characteristics have not been included in systematic meta-analyses. There are several reasons to expect that the association of prenatal distress on externalizing outcomes may meaningfully differ based on these factors.

Some studies suggest that the magnitude of prenatal distress effects on offspring externalizing behaviors may differ depending on the type of psychological distress, such as depression versus anxiety or perceived stress. Although many studies focus on a single type of psychological distress (typically prenatal depression), some studies comparing multiple types of psychological distress have found stronger associations for prenatal anxiety and perceived stress than for prenatal depression in prediction of offspring externalizing outcomes (Glasheen et al., 2013; Glover & Hill, 2012). For example, a study from the Growing Up in New Zealand cohort found that maternal perceived stress, but not depression, during pregnancy was associated with increased risk of offspring exhibiting clinically significant hyperactivity-inattention and conduct problems at age 2 years (D'Souza et al., 2019). Similarly, another study that compared prenatal anxiety and depression effects on the trajectory of offspring externalizing behaviors found that prenatal anxiety in late gestation uniquely predicted heightened risk for an early onset and persistent trajectory of conduct problems (E. D. Barker & Maughan, 2009). In contrast, some studies have reported that the effects of prenatal anxiety became nonsignificant after controlling for co-occurring prenatal depression when predicting ODD symptoms (Ayano et al., 2021) and other externalizing behaviors (Gjerde et al., 2020).

Similarly, there may be periods during pregnancy when fetal development may be particularly sensitive to maternal psychological distress (Davis et al., 2018; Glover et al., 2018). For example, rapid organogenesis (formation of organs) including the development of the heart and central nervous system occurs during the first trimester (Coles, 1994). In contrast, the latter half of pregnancy—particularly the third trimester, is characterized by rapid fetal maturation of the autonomic stress system (Schneider et al., 2018) as well as brain regions such as the limbic system and prefrontal cortex (R. E. Hay et al., 2020), which play an important role in early emotional and behavioral reactions to stress. In general, studies exploring timing effects of prenatal psychological distress on externalizing behaviors have been relatively few and inconsistent in their findings (Van den Bergh et al., 2020). Some evidence suggests that prenatal depression specifically in the third trimester is associated with child externalizing behaviors in preschool-aged boys, an association mediated by altered amygdala-prefrontal connectivity (R. E. Hay et al., 2020). Similarly, previous evidence from the Avon Longitudinal Study of Parents and Children study showed that prenatal anxiety in the third trimester uniquely predicted conduct problems and ADHD symptoms in childhood, above and beyond stress during earlier trimesters (O'Connor et al., 2002, 2005). In contrast, a study of preschool-aged children from the Norwegian Mother and Child Cohort Study found that psychological distress during mid-gestation was particularly linked to ADHD, and when accompanied by high maternal distress postnatally, additionally increased risk for ODD and CD (Bendiksen et al., 2020). Other studies have reported no trimester-specific differences in the magnitude of the association between prenatal depression and offspring externalizing behaviors (Lahti et al., 2017). Given the inconsistency in findings regarding timing of prenatal distress, a meta-analysis directly comparing effects in each trimester across all available studies while accounting for sample size can help to inform the extent to which there may be sensitive periods in timing of effects.

The stability of psychological distress across the prenatal to postnatal period may also influence offspring risk for externalizing behaviors (E. D. Barker, 2013; Guyon-Harris et al., 2016). For example, based on cumulative risk hypotheses (e.g., McEwen & Stellar, 1993), prenatal and postnatal distress may have an additive effect that cumulatively increases risk for offspring psychopathology. Indeed, one study found that offspring of mothers with prenatal depression symptoms were about 1.75 times more likely to meet diagnostic criteria for ODD, but this risk for ODD showed a fourfold increase when maternal depression symptoms persisted into the postnatal period (Dachew et al., 2021). Similarly, data from the population-based Norwegian Mother and Child Cohort Study suggest that children with mothers who have persistent anxiety and depression spanning both prenatal and postnatal periods show the highest levels of physical aggression by age 3 (Bekkhus et al., 2011). These findings suggest that the effects of prenatal stress on offspring risk for externalizing outcomes may be particularly heightened when psychological distress demonstrates stability into the postnatal period. In contrast, the "mismatch" hypothesis based on evolutionary biology posits that exposure to the stress in utero may "forecast" a stressful postnatal environment, calibrating offspring physiology adaptively to maximize fitness in the context of an expected stressful postnatal environment (Frankenhuis & Del Giudice, 2012). For example, elevated maternal perceived stress during pregnancy has been associated with greater physiological reactivity to a laboratory stressor and lower behavioral self-regulation in offspring during infancy (Bush et al., 2017). These early individual differences have been theorized to serve as adaptive protective mechanisms in a threatening postnatal environment but may manifest as functionally impairing externalizing behavior problems when mismatched with the postnatal environment. Thus, it is possible that prenatal psychological distress may demonstrate the largest effect sizes on offspring externalizing behavior when there is *low* stability (i.e., a mismatch) in distress between prenatal and postnatal periods. Low stability of distress could reflect pregnant people who experience elevated psychological distress during pregnancy (e.g., pregnancy-specific anxiety) that is reduced after pregnancy, or alternatively, low distress during pregnancy that is followed by high levels of parent psychological distress related to caregiving after childbirth. To date, existing longitudinal studies examining the effect of pre- and postnatal distress continuity generally appear consistent with the cumulative risk model, although there is an overall dearth of empirical studies comparing these theoretical models when investigating the effect of prenatal psychological distress on offspring externalizing outcomes in humans.

Heterogeneity in Type and Timing of Externalizing Behavior

Importantly, externalizing behaviors are inherently developmental and multidimensional in nature, manifesting differently across developmental stages and ranging widely from normative levels of behavior to clinical levels of symptoms (Hinshaw & Beauchaine, 2015). Despite evidence that the etiology of externalizing behaviors may differ by subtype (e.g., aggressive vs. nonaggressive

rule-breaking behaviors; Burt, 2013; Olson et al., 2013), studies of prenatal distress often rely on unspecified "general externalizing" measures or focus on one specific measure only (e.g., ADHD). Few studies have explored potential differences in prenatal distress effects based on type of externalizing outcome, such as differences across *DSM*-keyed diagnoses and dimensional measures of empirically clustered behaviors (e.g., aggressive behavior, rule-breaking behaviors; Krueger & Tackett, 2015). Identifying specific outcomes that may be linked to prenatal psychological distress exposure may help to advance our understanding of the etiology and pathophysiology of different externalizing outcomes, as well as inform the clinical significance of prenatal distress effects, both of which can help to inform targeted intervention.

Although most studies of prenatal distress focus on young children, some studies have found that the effects of prenatal distress extend into late childhood and adolescence (MacKinnon et al., 2018; K. J. O'Donnell et al., 2014). Evidence that prenatal distress effects contribute uniquely to offspring behaviors in later development has important implications for the etiological and developmental pathways underlying externalizing behaviors across the lifespan. Nonetheless, because most studies measure externalizing behavior at a single time point, it is unclear if there may be developmental differences or sensitive periods when externalizing behaviors may be particularly attributed to neurodevelopmental differences shaped by prenatal stress. By using meta-analysis to aggregate studies that have measured externalizing outcomes across a range of child ages, the present study aimed to explore potential sensitive windows in which prenatal psychological distress has the strongest effect on offspring externalizing behavior outcomes.

Sex Differences

Finally, some evidence suggests that sex differences may moderate the effect of prenatal stress on offspring behavior (Braithwaite et al., 2017; Glover & Hill, 2012; Sutherland & Brunwasser, 2018). Reviews of this literature suggest that male fetuses may be less adaptable to changes in the prenatal environment and thus more vulnerable than female fetuses to prenatal stress exposure, which may contribute to boys' heightened vulnerability to neurodevelopmental disorders such as ADHD (McCarthy, 2019; Meakin et al., 2021). These sex-specific patterns may reflect sex differences in prenatal epigenetic programming of stress pathways or alterations in placental functioning that affect fetal exposure to in utero inflammation and hormone levels underlying sex-specific intrauterine growth differences in neurodevelopment (Bale, 2011; Meakin et al., 2021). Given that externalizing disorders are more prevalent among boys than girls, some research suggests that the effects of prenatal psychological distress on fetal neurodevelopment may be more likely to manifest as externalizing behaviors specifically for boys (Hicks et al., 2019). For example, in longitudinal studies of preschool and school-aged children, prenatal depression demonstrated significant associations with externalizing behavior problems for boys, but not for girls (Eichler et al., 2017). These associations varied depending on the type of externalizing behavior (e.g., CD vs. ADHD; Bendiksen et al., 2020). Other studies found diverging patterns of association by sex: persistent anxiety across the prenatal and postnatal period predicted higher risk for CD in adolescent boys, but *lower* risk for CD in girls (Glasheen et al., 2013). Nevertheless, several studies have also reported no sex differences in prenatal stress effects (Ali et al., 2020; Hentges et al., 2019; Pietikäinen et al., 2020), emphasizing the need to systematically meta-analyze these associations.

The Present Study

The goals of this study were threefold. First, we systematically reviewed the literature and used meta-analytic procedures to summarize the overall association between prenatal psychological distress and offspring externalizing behaviors in childhood and adolescence (Aim 1). To address potential confounding effects of the postnatal environment, we focused specifically on longitudinal studies that measured psychological distress during the prenatal *and* postnatal periods. By doing so, we were able to test the *independent effects* of prenatal distress on externalizing outcomes while covarying for the effects of postnatal distress on externalizing outcomes (Aim 2). Finally, to explore heterogeneity in effect sizes, we examined whether the magnitude of association differed based on type (i.e., perceived stress, anxiety, depression) or timing of prenatal distress, stability of stress from prenatal to postnatal periods, type or timing of externalizing behavior, or offspring sex (Aim 3).

We hypothesized that psychological distress during pregnancy would have a significant association with offspring externalizing outcomes. After controlling for the association between postnatal psychological distress and externalizing outcomes, we expected psychological distress during pregnancy to continue to significantly predict offspring externalizing outcomes (i.e., incremental prediction). Regarding moderators of effect sizes, based on the prior literature, we hypothesized that prenatal anxiety and perceived stress would have a stronger effect on externalizing outcomes than prenatal depression, and we additionally explored whether effects differed across trimesters of pregnancy. We expected psychological distress to show moderate stability from the prenatal to postnatal period, and we explored the extent to which the rank-order stability of distress from prenatal–postnatal periods relates to the magnitude of association between prenatal distress and externalizing outcomes. Finally, based on the evidence that male fetuses may be more vulnerable to prenatal distress in the context of neurodevelopmental outcomes (McCarthy, 2019), we hypothesized that the magnitude of prenatal distress effects on externalizing outcomes would be larger for boys than for girls. Given that few studies have examined differences in prenatal distress effects based on the type and timing of child externalizing behavior, we explored whether these factors explained additional heterogeneity in effect size but did not make directional hypotheses.

Method

Search Strategy

Studies were identified by conducting searches in the bibliographic databases Pubmed, Embase, Ovid APA PsycInfo, and Web of Science, with the original search conducted on June 16, 2020 and then updated on September 20, 2022 (Pubmed, APA PsycInfo, Web of Science) and September 27, 2022 (Embase). A health sciences librarian (JEF) developed search strings using controlled vocabulary (Medical Subject Headings, Emtree terms, Thesaurus of Psychological Index Terms) and natural language

words representing the concepts of "prenatal exposure," "stress," "externalizing," and "youth." The Pubmed search strings appear in the Supplemental Materials. The search was limited to English language studies, human studies, and initially included any studies published since 1980 (beginning of *DSM-III*). To maximize generalizability of findings to recent trends, we focused on studies published since 2000 for the final sample. A total of 8,904 citations were retrieved from the four databases. Citations were downloaded from each database into EndNote and duplicates were removed using the Bramer method (Bramer et al., 2016). The remaining citations were then uploaded to DistillerSR for review and screening (see Figure 1, for Preferred Reporting Items for Systematic Review and Meta-Analysis flowchart).

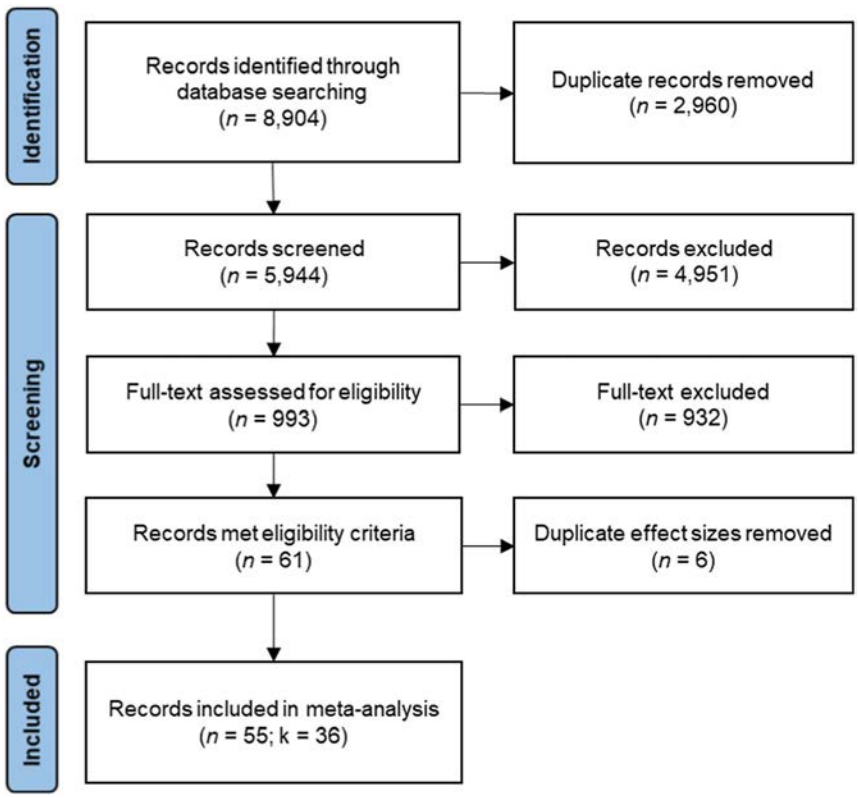
Inclusion and Exclusion Criteria

Studies were included in the meta-analysis if they met the following inclusion criteria: (a) described human subjects, (b) written in English, (c) published since 2000, (d) empirical observational study with longitudinal study design, (e) included at least one measure of psychological distress measured during pregnancy *and* after childbirth, (f) included at least one measure of offspring externalizing behavior assessed during childhood or adolescence (defined as ages 2–18), and (g) reported an effect size (Pearson correlation) between prenatal psychological distress and externalizing outcome or reported data that could be used to calculate an unbiased estimate of effect size. Studies were excluded if they met any of the following criteria: (a) intervention study, case study, review article, or nonempirical study, (b) measured externalizing outcome using a legal proxy (e.g., arrested) without specific measurement of actual behavioral outcome, (c) did not measure psychological distress during pregnancy (e.g., used retrospective measures collected after childbirth or used a proxy for prenatal stress [e.g., birth weight]), (d) did not include an identical measure of postnatal distress, or (e) effect size was based on the same data as another citation in the present meta-analysis (e.g., duplicate effect size from the same larger sample).

It was common for several studies to be drawn from the same longitudinal sample (see Supplemental Table S1) and for studies to include multiple unique combinations of prenatal distress-externalizing behavior correlations (e.g., a study could include multiple types of prenatal psychological distress, multiple types of externalizing behavior, or multiple ages of externalizing behavior assessment). To maximize available information for analysis, we included all possible combinations of unique prenatal distress-externalizing behavior correlations for each longitudinal sample,

Figure 1

PRISMA Flowchart for the Identification, Screening, and Inclusion of Publications in the Meta-Analysis



Note. *n* = number of distinct reports; *k* = number of distinct samples; PRISMA = Preferred Reporting Items for Systematic Review and Meta-Analysis. See the online article for the color version of this figure.

which were analyzed as within-sample and/or within-citation effects using multilevel meta-analytic modeling (see Data Analysis).

Screening and Data Extraction Procedures

Article screening and data extraction were systematically conducted with DistillerSR software (Evidence Partners, Ontario, CA) using standardized forms developed for title/abstract screening, full-text review, and data extraction. Screening and data extraction forms were piloted and revised accordingly prior to use for this review. Prior to screening any articles, the first author (IT) intensively trained a team of coders (LB, EC, GE, ADQ, BL, MT) on screening and coding procedures. All coders trained on 50–100 practice files until they achieved a consistent κ above .80 agreement with the first author. All study titles/abstracts resulting from searches were independently screened by two coders in duplicate to identify studies that likely met the inclusion criteria outlined above. The same process was repeated for full-text screening and data extraction. The interrater reliability for title/abstract screening ($\kappa = .84$) and data extraction coding were both excellent ($\kappa = .96$ for categorical and ICC = .80 for continuous variables). All coding discrepancies were discussed and resolved by the first author by going back to the original article. In addition, all effect sizes extracted from the citations were double-checked by the first author by referencing the original article. Missing data were requested from study authors.

Coded Variables

Study Characteristics

We coded descriptive and demographic information for all studies included in the meta-analysis. Variables included: study authors, journal, publication year, sample size, country of participants, and maternal demographics (i.e., race and ethnicity, average income, education level).

Psychological Distress During and After Pregnancy

Psychological distress included the following constructs: depression (e.g., prenatal and postnatal depression severity scores, *DSM*-based depression symptom counts, *DSM* diagnoses of major depressive disorder or other depressive disorder), anxiety (e.g., prenatal and postnatal anxiety severity scores, trait or state anxiety scores, *DSM* anxiety symptom counts, *DSM* diagnoses of anxiety disorders), and perceived stress (e.g., perceived stress severity scores, self-reported frequency of "feeling stressed" during and after pregnancy).

Externalizing Behavior

Offspring externalizing behavior included the following constructs: aggressive/violent behavior (e.g., hitting, fighting), rule-breaking behavior (e.g., delinquency, property/status violations), and general unspecified externalizing behavior (e.g., measures of "externalizing behavior," "conduct problems," or "antisocial behavior"). The following *DSM*-based child and adolescent externalizing disorders were also included: ADHD and ODD or CD.

Effect Sizes

Pearson's correlation (r) was used as the effect size statistic (Lipsey & Wilson, 2001). For studies where r was not presented, available statistics (e.g., M and SD, t value, χ^2) were converted to r using effect size calculators (Wilson, 2001). To enable testing of independent effects of prenatal distress on externalizing behavior while controlling for effects of postnatal distress, correlations for each citation were extracted for: (a) prenatal distress and externalizing outcomes, (b) postnatal distress and externalizing outcomes, and (c) prenatal distress and postnatal stress.

Moderator Variables

We coded the following variables whenever available to investigate moderators of effect size heterogeneity: *prenatal distress type* (depression, anxiety, or perceived stress), *prenatal distress timing* (first trimester [Week 1–12], second trimester [Week 13–26], or third trimester [Week 27-delivery]), *externalizing behavior type* (aggression, rule-breaking, ODD/CD, or ADHD), *externalizing behavior timing* (early childhood [age 2–5 years], middle childhood [6–12 years], or adolescence [13–18 years]), and *offspring sex* (% participants female). Given that prenatal substance exposure has been linked with externalizing outcomes, we additionally coded for *prenatal alcohol use* (% participants reporting any alcohol use during pregnancy) and *prenatal cigarette use* (% participants reporting any smoking during pregnancy). In addition, because severity of externalizing behavior may differ depending on informant, we coded for the use of *multiple informants* as well as *type of informant* (e.g., parent, teacher) to measure externalizing behavior.

Data Analysis Plan

Data were analyzed in R using the *metafor* package for meta-analysis combined with the *robumeta* package to accommodate robust standard error measurement with clustering factors. The primary effect size statistic used was product-moment correlation coefficient (using Fisher's Z transformed values; Lipsey & Wilson, 2001). To examine the overall effect of prenatal psychological distress on offspring externalizing behavior (Aim 1), we conducted an initial meta-analysis that included all effect sizes across eligible studies. To maximize available data while controlling for effect size dependences, we used multilevel random effect meta-analysis with robust variance estimation, a modern metanalytic approach that adjusts standard errors for effect size clustering. Specifically, we used a multilevel random effects modeling approach that allowed up to three levels to control for clustering effects within a single study (e.g., multiple effect sizes reported in one study) and within a sample (e.g., multiple articles drawn from the same longitudinal study). The number of levels used for each model was determined through model comparisons of 1, 2, and 3 level models. The covariance structure was hierarchical. In addition to the multilevel model with nested effects, we used robust variance estimation to provide more robust estimation of confidence intervals and p values in the presence of potential dependencies that may not be accounted for in the modeling approach.

To test for the independent prediction of prenatal stress on externalizing behavior after accounting for postnatal stress (Aim 2),

we added the correlation between postnatal distress and externalizing behavior as a covariate to the metaregression to examine the unique effects of prenatal distress after controlling for postnatal stress. This model additionally covaried for the correlation between prenatal and postnatal distress as well as the child's age at the postnatal distress timepoint. Each variable was centered at its mean to allow interpretation of the model intercept as an adjusted effect size after controlling for these covariates. To further quantify incremental effects, we estimated the percentage of unexplained variance in the prenatal distress and externalizing behavior model that was explained after including postnatal distress as a covariate. The reduction in explained variance between the unadjusted and adjusted model was calculated as an overall percentage of variance reduced, as well as at between cluster and within cluster portions of the model. The inclusion of the correlation between pre- and postnatal distress as a covariate also enabled us to test the extent to which the rank-order stability of stress across prenatal and postnatal timepoints explained variability in effect size (part of Aim 3, in which the rank-order stability of stress across pre- and postnatal time points is evaluated as a potential "moderator" to predict variability in effect size).

Heterogeneity in effect sizes was estimated using the Cochran Q test and I^2 values. To explore potential variables that may explain heterogeneity in effect sizes (Aim 3), we conducted multilevel random effects models separately for each moderator. For categorical moderators (type of externalizing, age of externalizing [early childhood vs. middle childhood vs. adolescence], type and timing of prenatal psychological distress, multi-informant measurement, parent vs. teacher informant), we conducted metaregressions to investigate moderator variables as potential explanations of heterogeneity. Variance structure was defined to allow unique variance components for each level of the moderator. Linear contrasts were then conducted to compare all pairs of levels for the categorical variable to determine whether they differed significantly in terms of the effect size. Bonferroni correction of p values was used to adjust for multiple testing. For continuous moderators (prenatal alcohol use, prenatal smoking, offspring sex [% female]), univariate two-level random effects metaregression models were carried out to examine whether each continuous moderator significantly predicted the effect size of prenatal distress and externalizing behavior. Finally, publication bias was evaluated through visual inspection of Begg's funnel plot (Begg & Mazumdar, 1994) and Egger's test for funnel plot asymmetry (Egger et al., 1997).

Transparency and Openness

This meta-analysis was conducted following standard guidelines from the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (Moher et al., 2009, 2015; Shamseer et al., 2015) and the MARS guidelines for meta-analytic reporting (Appelbaum et al., 2018). The protocol was preregistered on International Prospective Register of Systematic Reviews (CRD42020171511; https://www.crd.york.ac.uk/prospero). The meta-analysis database and analysis code are included in the Supplemental Materials. Data were analyzed using R, Version 4.1.3 (R Core Team, 2022) and the package *metafor*, Version 3.0-2 (Viechtbauer, 2010). The university institutional review board declared this study exempt as a meta-analysis of published studies.

Results

From the 8,904 identified citations, 5,944 were confirmed as unique records (Figure 1). After title/abstract screening, full-text assessment for eligibility, and removal of duplicate effect sizes within the same sample, $N = 55$ records met eligibility criteria (drawn from $k = 36$ distinct longitudinal samples), which included a total of 200 prenatal distress and externalizing behavior correlations available for analysis. Full-text reports were typically excluded because the study did not have an eligible measure of externalizing behavior, prenatal distress, or postnatal distress, or because the data required to obtain or calculate an unbiased estimate of the effect size (Pearson's correlation) between prenatal psychological distress and externalizing outcome were unavailable (i.e., not reported in the published article and unavailable from the study authors when contacted). The final data set used for the meta-analysis is included in the Supplemental Materials.

Description of Studies

Sample characteristics of the included studies are reported in Supplemental Table S1. The 55 studies were drawn from 36 distinct longitudinal samples (k) across five continents, with the majorities of studies including participants from countries in Europe ($k = 17$) and North America ($k = 14$), and a minority of studies from countries in Australia/Oceania ($k = 3$), Asia ($k = 2$), and South America ($k = 1$). Of the 36 unique longitudinal samples, about 22% ($k = 8$) were population-based samples. Approximately 25% ($k = 9$) recruited pregnant participants from the general community (e.g., public flyers), and over 80% ($k = 20$) recruited pregnant participants from general hospitals or prenatal clinics, whereas only one study specifically recruited a portion of their participants from a reproductive mental health program. (Note that studies included multiple recruitment sources; see Supplemental Table S1). Regarding participant selection criteria, most studies focused on recruiting a "general" pregnancy population from these recruitment sources, whereas a minority of studies (18% of the 55 studies) used specific mental health or demographic characteristics as part of their inclusion criteria for their analysis sample (see Supplemental Table S1 footnotes for details on special sampling criteria). Race and ethnicity distributions across the 55 included studies was predominantly non-Hispanic White (77%), whereas other racial and ethnic groups were underrepresented: 12% Asian, 8% Black, <1% Indigenous/Native, 3% Latinx/Hispanic. An average of 60% of pregnant participants in each study completed at least some college education (range: 2%–98%). Prenatal smoking and drinking status varied across studies (when reported), with a mean of 14% (range: 0%–59%) for smoking and 30% (range: 0%–70%) for any alcohol use during pregnancy. Offspring sex was evenly distributed across studies (mean: 50% female; range: 43%–61%).

Prenatal psychological distress and offspring externalizing measurement characteristics are provided in Supplemental Table S2. The most common type of psychological distress measured both during and after pregnancy was depression (included in 89% of studies), followed by anxiety (36%), whereas only three studies (5%) measured perceived stress at both prenatal/postnatal time

points. Among studies that specified trimester of assessment ($N = 39$), most (79%) included a measure of psychological distress specifically from the third trimester, 49% included a measure from the second trimester, and only three studies (8%) included a measure collected specifically during the first trimester.

Approximately 47% of studies only had an unspecified "general externalizing" measure as their offspring externalizing outcome. For studies that specified type of externalizing outcome ($N = 29$), the most common types were ODD/CD (59%), ADHD (52%), and aggression (28%), whereas nonaggressive rule-breaking behavior (7%) was assessed in only two studies. Studies ranged in their age of externalizing behavior assessment, with most studies (85% or $N = 47$) having measures of externalizing behavior that could be specified to a certain age group. Among these studies, 75% included a measure of externalizing behavior in early childhood (age 2–5), 36% in middle childhood (age 6–12), and 11% in adolescence (age 13–18). Most studies (76%) used a single parent informant to assess externalizing behavior. Teachers were the next most common informants (13%; typically paired with parent report), followed by child informant (10%; always paired with parent report). Only one study included clinician ratings of externalizing behavior, and only one study included behavior ratings of externalizing behavior from observation.

Overall Association Between Prenatal Psychological Stress and Offspring Externalizing Behavior

Initial Effect Size

All 200 unique effect sizes from the 55 studies were included in the initial general meta-analysis, which used multilevel modeling with robust variance estimation to account for clustering by study and sample. Overall, there was a significant but relatively small effect of prenatal psychological distress on offspring externalizing behavior ($r = .160$; Table 1). A significant amount of heterogeneity in the effect sizes was indicated ($I^2 = 85.1\%$; $Q = 745.2$, $p < .0001$). To explore the sources of effect size heterogeneity, we partitioned variance components by level, which revealed that a minority (14.9%) of the total variability in effect sizes was accounted for by sampling error, whereas 43.6% and 41.6% were attributed to between-study and within-study variabilities, respectively. The substantial percentage of between-study variability in effect sizes supports the plausibility that differences between studies may be explained by potential moderators.

Effect Size Adjusted for Postnatal Distress

As expected, prenatal and postnatal distress were moderately correlated, and postnatal distress was significantly correlated with child externalizing behavior (Table 1), highlighting the importance of accounting for parents' postnatal distress when investigating prenatal distress effects. After adjusting for the effect of postnatal distress, the effect of prenatal distress on externalizing behavior was reduced slightly (from $r = .160$ original to $r = .159$ adjusted; Table 1). Controlling for these postnatal factors resulted in a reduction of 24.8% of the unexplained variance compared to the initial effect size model. Specifically, there was a reduction of 63.7% and 12.6% of the unexplained variance for between-study differences and within-study differences, respectively.

Metaregression Models Testing Moderation

Table 2 displays the results from the metaregressions testing each moderator variable as a predictor of effect size. To probe the pattern of moderation for categorical moderators, pooled effect size estimates are reported for the effect of prenatal distress on offspring externalizing behavior for each subgroup of the moderator. Corresponding forest plots are displayed in Figure 2.

Prenatal Distress Type

Metaregression results showed that prenatal anxiety and depression had a significant effect on offspring externalizing behavior (Table 2). Linear contrasts showed that the correlation between prenatal distress and externalizing behavior did not differ between anxiety and depression ($Z = 0.642$, $p > .999$), anxiety and perceived stress ($Z = 1.551$, $p = .363$), and depression and perceived stress ($Z = -1.457$, $p = .436$). Compared to the initial effect size estimate model, accounting for prenatal distress type reduced unexplained variance by 8.9%.

Pregnancy Trimester

Prenatal distress during the second and third trimesters were both significantly associated with externalizing outcomes (Table 2),

Table 1
Correlations Between Prenatal and Postnatal Distress With Externalizing Behavior

Correlation	*k*	*r*	*p*	95% CI *LL*	95% CI *UL*	I^2	τ^2
Prenatal distress and externalizing behavior (unadjusted effect size)	200	.160	<.001	.142	.181	82.4%	.002
Prenatal distress and externalizing behavior (adjusted for postnatal distress)	173	.159	<.001	.140	.177	70.1%	.001
Postnatal distress and externalizing behavior	183	.178	<.001	.158	.197	86.1%	<.001
Prenatal distress and postnatal distress[a]	189	.422	<.001	.378	.464	98.4%	.019

Note. CI = confidence interval; *LL* = lower limit; *UL* = upper limit; *k* = number of effect sizes contributing to the effect size for that subgroup. Effect size represented by Pearson's *r*.
[a] The correlation between prenatal distress and postnatal distress reflects the average correlation coefficient extracted or reported by authors across the 55 studies included in the meta-analysis.

Table 2
Correlations Between Prenatal Distress and Offspring Externalizing Behavior for Each Subgroup of Categorical Moderators

Subgroup	*k*	*r*	*p*	95% CI *LL*	95% CI *UL*	I^2	τ^2
Pregnancy distress type							
Anxiety	66	.146	<.001	.122	.170	85.1%	.002
Depression	122	.154	<.001	.138	.169	81.5%	.002
Perceived stress	12	.248	.087	−.092	.536	78.7%	.016
Pregnancy trimester							
First	6	.164	.111	−.094	.425	65.3%	.007
Second	69	.147	<.001	.116	.178	90.3%	.003
Third	82	.154	<.001	.133	.174	85.8%	.002
Externalizing behavior type							
Aggression	15	.153	<.001	.118	.188	45.3%	.001
Rule-breaking	5	.072	.255	−.306	.430	18.5%	.001
ODD	43	.138	<.001	.111	.164	91.8%	.002
ADHD	40	.135	<.001	.117	.153	69.2%	.001
Externalizing behavior age							
Early childhood	92	.166	<.001	.151	.181	52.3%	.001
Childhood	59	.132	<.001	.109	.156	86.2%	.001
Adolescence	16	.131	.010	.053	.208	95.0%	.003
Externalizing informant number							
Single informant	181	.149	<.001	.134	.165	83.0%	.002
Multiple informants	19	.200	<.001	.128	.270	75.3%	.005
Externalizing informant type							
Parent	164	.159	<.001	.143	.175	85.7%	.002
Teacher	17	.091	<.001	.072	.109	15.0%	<.001

Note. CI = confidence interval; *LL* = lower limit; *UL* = upper limit; ADHD = attention-deficit/hyperactivity disorder; ODD = oppositional defiant disorder; *k* = number of effect sizes contributing to the effect size for that subgroup. Effect size represented by Pearson's *r*.

and linear contrasts probing the metaregression indicated that the effect of prenatal distress compared across trimesters of pregnancy did not significantly differ from each other ($p > .999$ for all pairwise comparisons). Compared to the initial effect size estimate model, accounting for prenatal distress type reduced unexplained variance by 11.5%.

Stability of Prenatal–Postnatal Distress

The correlation between prenatal and postnatal distress ranged across studies from no association ($r = .03$) to highly stable/positively correlated ($r = .78$). Metaregression showed that the rank-order stability of psychological distress (i.e., correlation between prenatal and postnatal distress) significantly predicted the effect of prenatal distress on externalizing behavior after controlling for age of child at the postnatal timepoint and correlation between postnatal distress and externalizing behavior. Specifically, the greater the stability in stress between prenatal and postnatal periods, the smaller the correlation between prenatal distress and externalizing behaviors, $t(32) = -3.486$, $p = .001$.

Externalizing Behavior Type

Metaregression results showed that prenatal distress had a significant effect on aggression, ADHD, and ODD/CD (Table 2). In contrast, the effect of prenatal distress on rule-breaking behavior was not significant (Table 2). Linear contrasts revealed that the effect size was significantly higher in aggression studies compared to rule-breaking studies ($Z = -2.854$, $p = .026$). Notably, four of the five effect sizes for rule-breaking behavior were drawn from the same study; thus, these results should be interpreted with caution. Forest plots for each subtype of externalizing behavior appear in Figures 3–6. Compared to the initial effect size estimate model, accounting for externalizing behavior type reduced unexplained variance by 0.5%.

Child Age

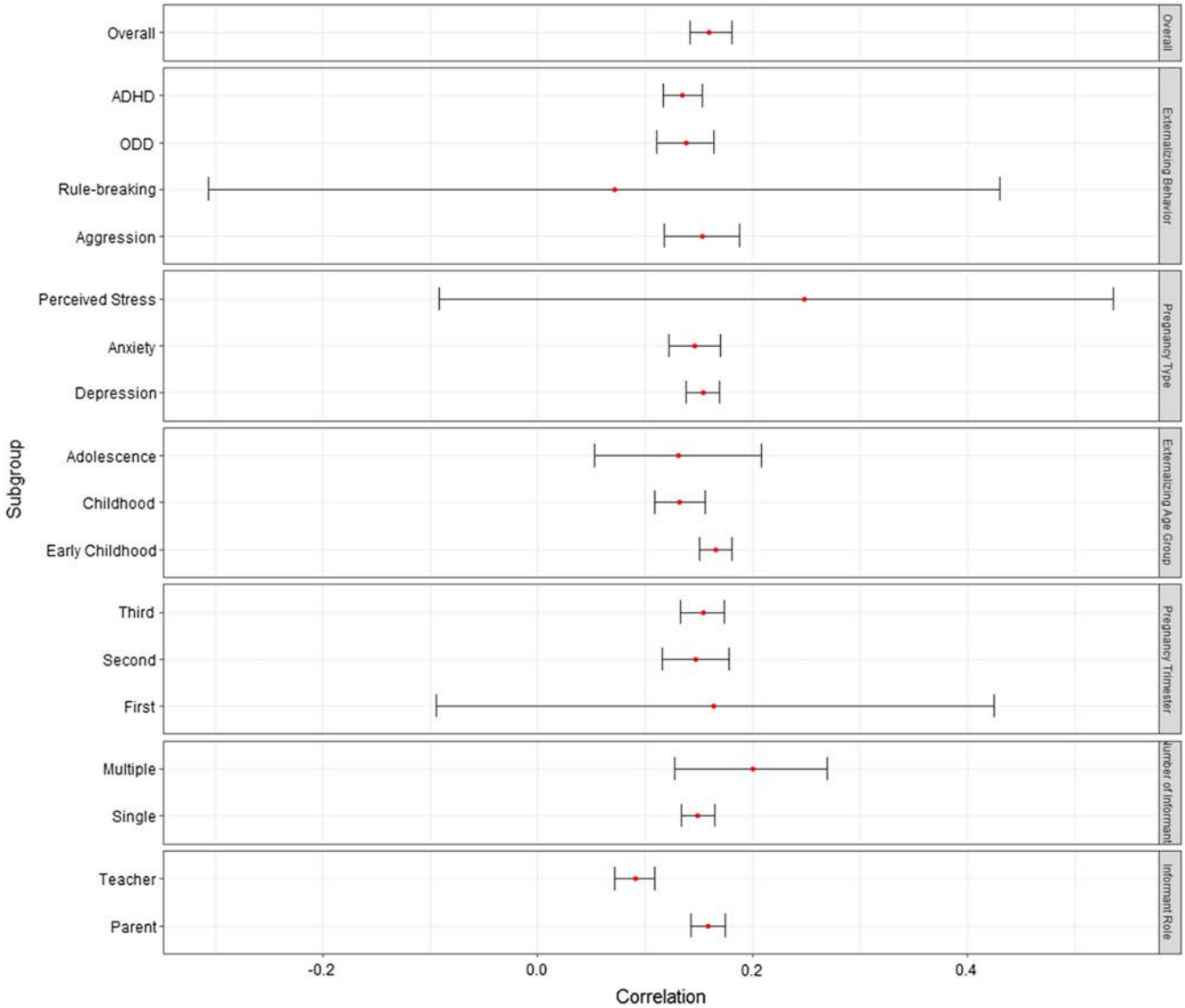
The correlations between prenatal distress and externalizing behavior were significant across all three age subgroups (Table 2). Bonferroni corrected linear contrasts comparing effect sizes between subgroups indicated that effect sizes in early childhood (2–5 years old) were significantly larger than effect sizes in middle childhood (6–12 years old; $Z = -2.489$, $p = .037$). In contrast, effect sizes in adolescence (13–18 years old) did not significantly differ from effect sizes in earlier periods ($Z = -1.289$, $p = .593$ and $Z = 0.047$, $p > .999$, respectively). Compared to the initial effect size estimate model, accounting for child age group reduced unexplained variance by 12.4%.

Sex Differences

Differences across studies in the proportion of female versus male children did not significantly predict the magnitude of correlation between prenatal distress and externalizing outcomes, $t(49) = 1.426$, $p = .160$, suggesting that the effect of prenatal distress on externalizing outcomes was not moderated by sex. Compared to

Figure 2

Correlation Between Prenatal Distress and Offspring Externalizing Behaviors Across Levels of Moderators



Note. ADHD = attention-deficit/hyperactivity disorder; ODD = oppositional defiant disorder. See the online article for the color version of this figure.

the initial effect size estimate model, accounting for percentage of female offspring in the study reduce unexplained variance by 5.4%.

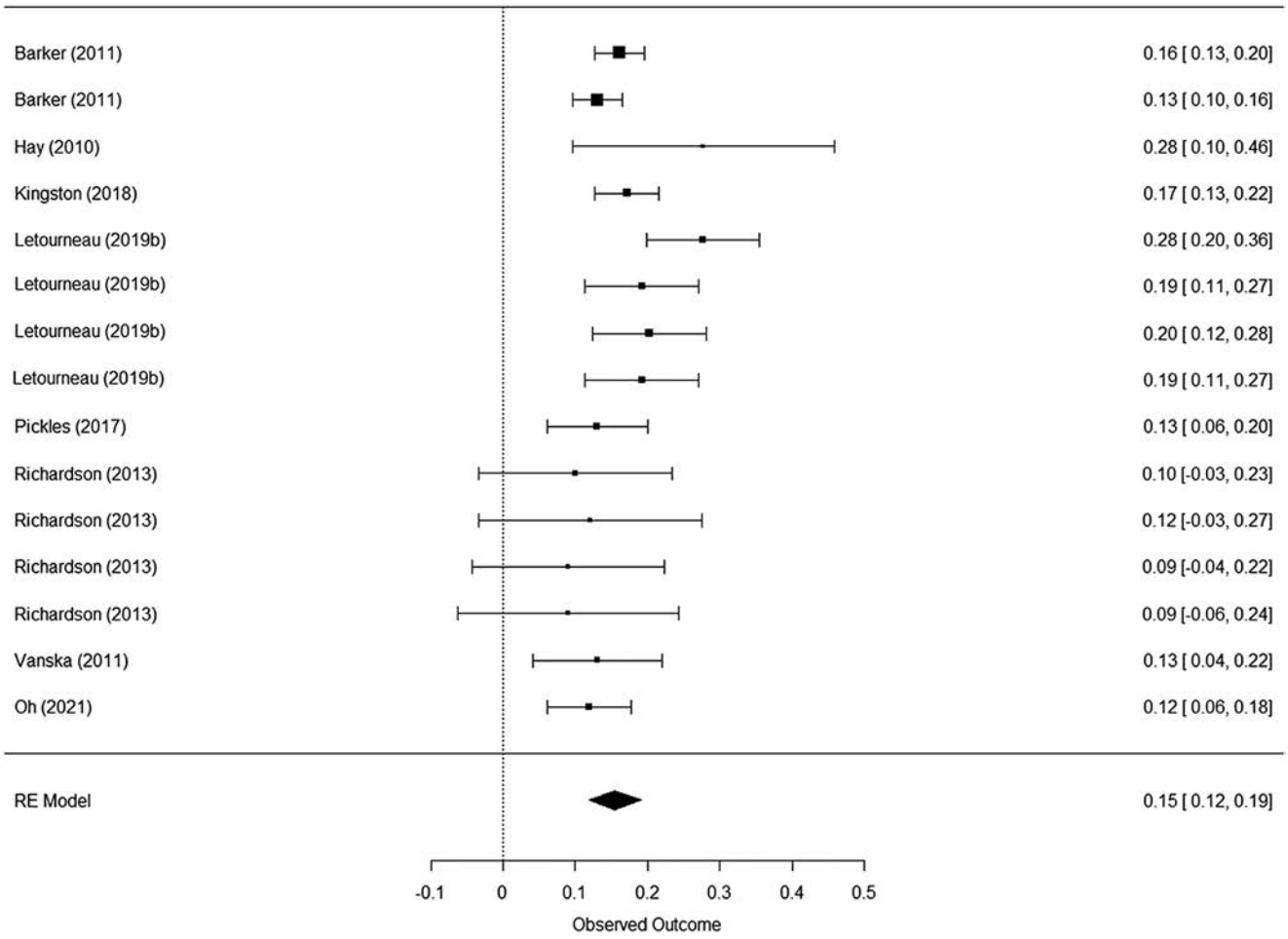
Externalizing Behavior Informant

The effect of prenatal distress on externalizing behavior was significant for studies using either parent or teacher informants, as well as for studies relying on single or multiple informants (Table 2). Linear contrasts indicated that magnitude of effect size was significantly greater when externalizing behavior was measured using parent versus teacher-rated questionnaires ($Z = -7.835$, $p < .001$). Compared to the initial effect size estimate model, accounting for informant type reduced unexplained variance by 17.9%. Linear contrasts indicated that magnitude of effect size did not significantly differ between studies using single versus multiple informants ($Z = 1.687$, $p = .092$). Compared to the initial effect size estimate model, accounting for number of informants reduced unexplained variance by 10.6%.

Alcohol and Smoking During Pregnancy

Metaregression models testing the moderating effect of prenatal alcohol use and smoking during pregnancy showed that the percentage of participants in a study who used alcohol during pregnancy was not associated with effect size, $t(28) = -1.012$, $p = .320$, and reduced the unexplained variance by 12.9% compared to the initial effect size model. The percentage of participants in a study who smoked cigarettes during pregnancy significantly

Figure 3
Forest Plot of Effect Sizes for Prenatal Distress and Offspring Aggression



Note. It was common for studies to include multiple unique effect sizes. To maximize available information for analysis, we included all possible combinations of prenatal distress-aggressive behavior, which were analyzed as within-citation effects using multilevel meta-analytic modeling (resulting in multiple effects that are drawn from the same citation). RE = random effects.

predicted the effect size, $t(31) = -2.37$, $p = .024$, such that smaller correlations between prenatal distress and externalizing behaviors were observed in studies with larger percentages of prenatal smoking endorsed. The percentage of the sample that smoked cigarettes during pregnancy accounted for a reduction of the unexplained variance by 16.5% compared to the initial effect size model.

Publication Bias

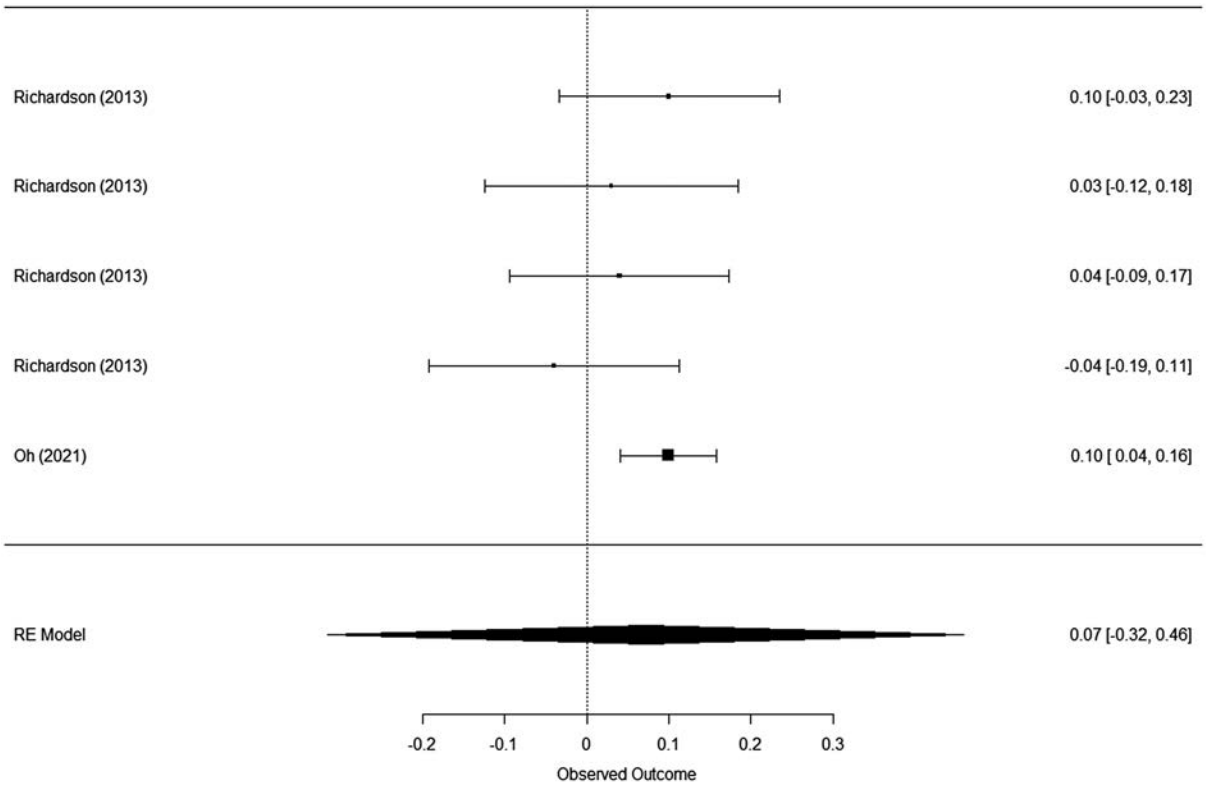
The funnel plot displayed in Figure 7 provides a visual display of the effect sizes by standard error size, with smaller standard error for larger sample studies. Egger's test indicated the presence of funnel plot asymmetry ($t = 2.47$, $p = .014$), which suggests that potential publication bias cannot be ruled out. Inspection of the plot suggested that most studies included in the meta-analysis had large sample sizes (more points clustered toward the top with small standard errors), and studies with smaller effect sizes showed a wider range of effect sizes, which may reflect heterogeneity in sample characteristics.

Discussion

In this meta-analysis of 55 longitudinal studies, prenatal psychological distress showed a significant—but relatively small—effect on offspring externalizing behaviors, *independent* of the effects of postnatal psychological distress. The magnitude of the prenatal distress effect size remained largely unchanged after adjusting for postnatal distress ($r = .159$ adjusted vs. $r = .160$ unadjusted), implicating a potentially unique role of psychological distress exposure during the pregnancy period on child externalizing behavior outcomes. Tests of moderation suggested that prenatal stress effects did not substantially vary based on type and timing of prenatal distress or by offspring sex, whereas the stability of distress from prenatal to postnatal periods significantly moderated

Figure 4

Forest Plot of Effect Sizes for Prenatal Distress and Offspring Rule-Breaking Behavior



Note. All available effect sizes specific to rule-breaking behavior were drawn from the same study. To maximize available information for analysis, we included all possible combinations of prenatal distress-rule-breaking behavior, which were analyzed as within-citation effects using multilevel meta-analytic modeling (resulting in multiple effects that are drawn from the same citation). RE = random effects.

prenatal distress effects. Regarding differences by type and timing of offspring behavior, we observed slightly larger effects of prenatal distress in early childhood (age 2–5) compared to middle childhood (age 6–12), but prenatal distress effects remained significantly related to externalizing behaviors across all developmental periods. Prenatal distress also showed comparable effect sizes in relation to most of the externalizing outcomes (i.e., ADHD, ODD/CD, aggression), with nonsignificant effects specifically for nonaggressive rule-breaking behaviors. Below, we discuss these meta-analytic results in the context of biopsychosocial and developmental theories of prenatal stress and externalizing outcomes and then highlight important directions for future research, including the need for studies with more racially and socioeconomically diverse and representative samples.

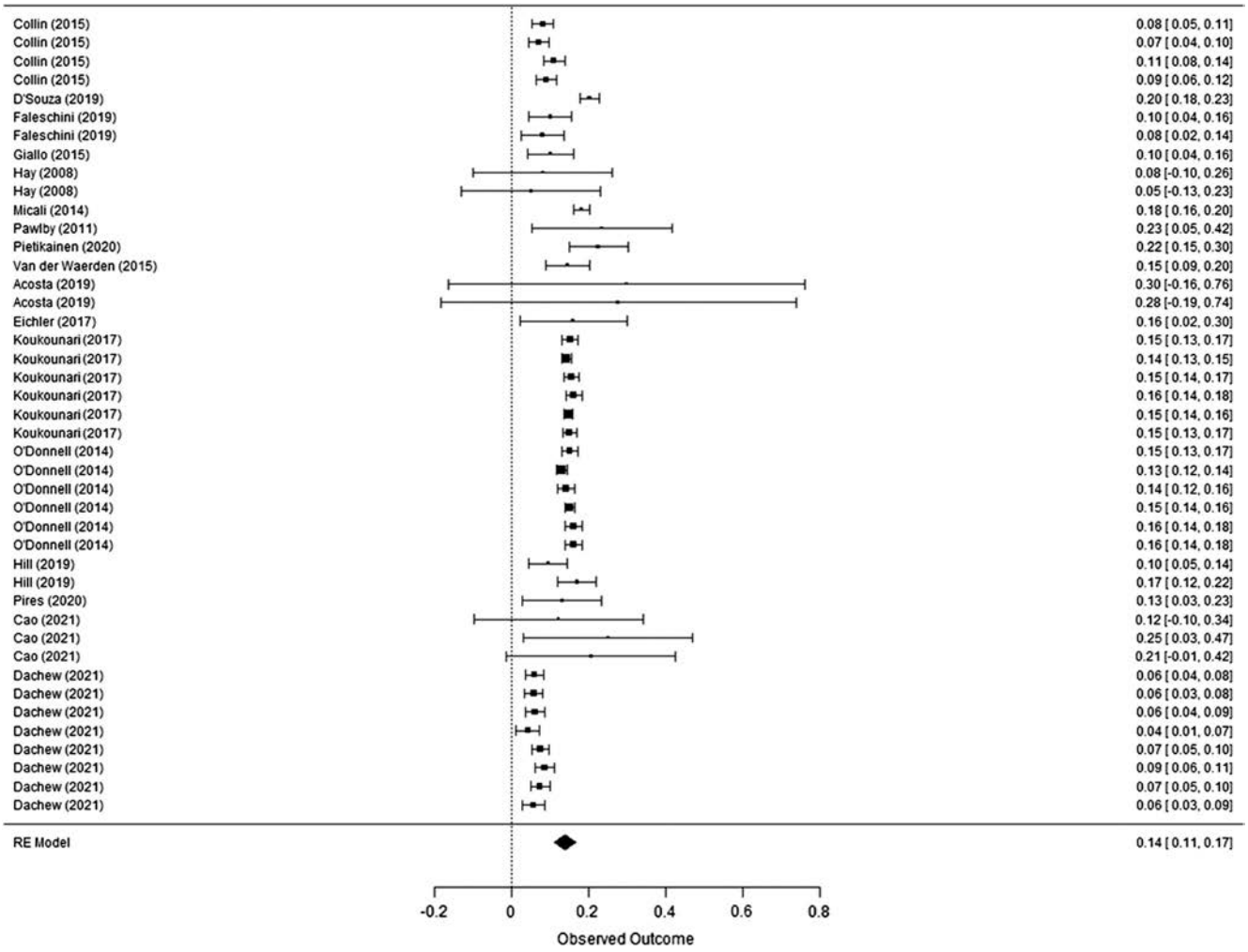
Predictive Effects of Prenatal Psychological Distress Independent From Postnatal Distress

The predictive effects of prenatal psychological distress on externalizing behaviors, independent of postnatal distress, are consistent with longitudinal studies suggesting there are unique causal effects of the prenatal environment on risk for externalizing behaviors (D'Souza et al., 2019; Faleschini et al., 2019; Hentges et al., 2020; O'Connor et al., 2002). Because our meta-analysis focused exclusively on longitudinal studies that controlled for the same measure of psychological distress in both life stages, we were able to investigate the timing of parent psychological distress effects using the most rigorously designed studies currently available to answer this research question. The persistence of a significant and independent effect of psychological distress during pregnancy on externalizing behavior, even after controlling for the same construct in the postnatal period, suggests that prenatal psychological distress is not purely an "indicator" of risk or proxy for later postnatal parent psychological distress effects. Instead, psychological distress during the pregnancy period may represent one important modifiable risk factor before birth that confers risk for offspring externalizing behaviors.

Although the specific mechanisms through which prenatal psychological distress affects offspring behavior are an active area of research, our findings are consistent with developmental theories of prenatal biological programming (D. J. P. Barker, 2007; Glover, 2011; Monk et al., 2019; Seckl, 1998). A large body of work has shown that experiences of psychological distress during pregnancy can disrupt maternal neuroendocrine and autonomic stress systems (Peterson et al., 2020). These experiences of prenatal distress may lead to greater fetal exposure to glucocorticoids and proinflammatory cytokines as stress systems are developing, contributing to alterations in fetal brain development (Jones et al., 2019; Monk et al., 2019; Van den Bergh et al., 2018). Prenatally

Figure 5

Forest Plot of Effect Sizes for Prenatal Distress and Offspring ODD/CD



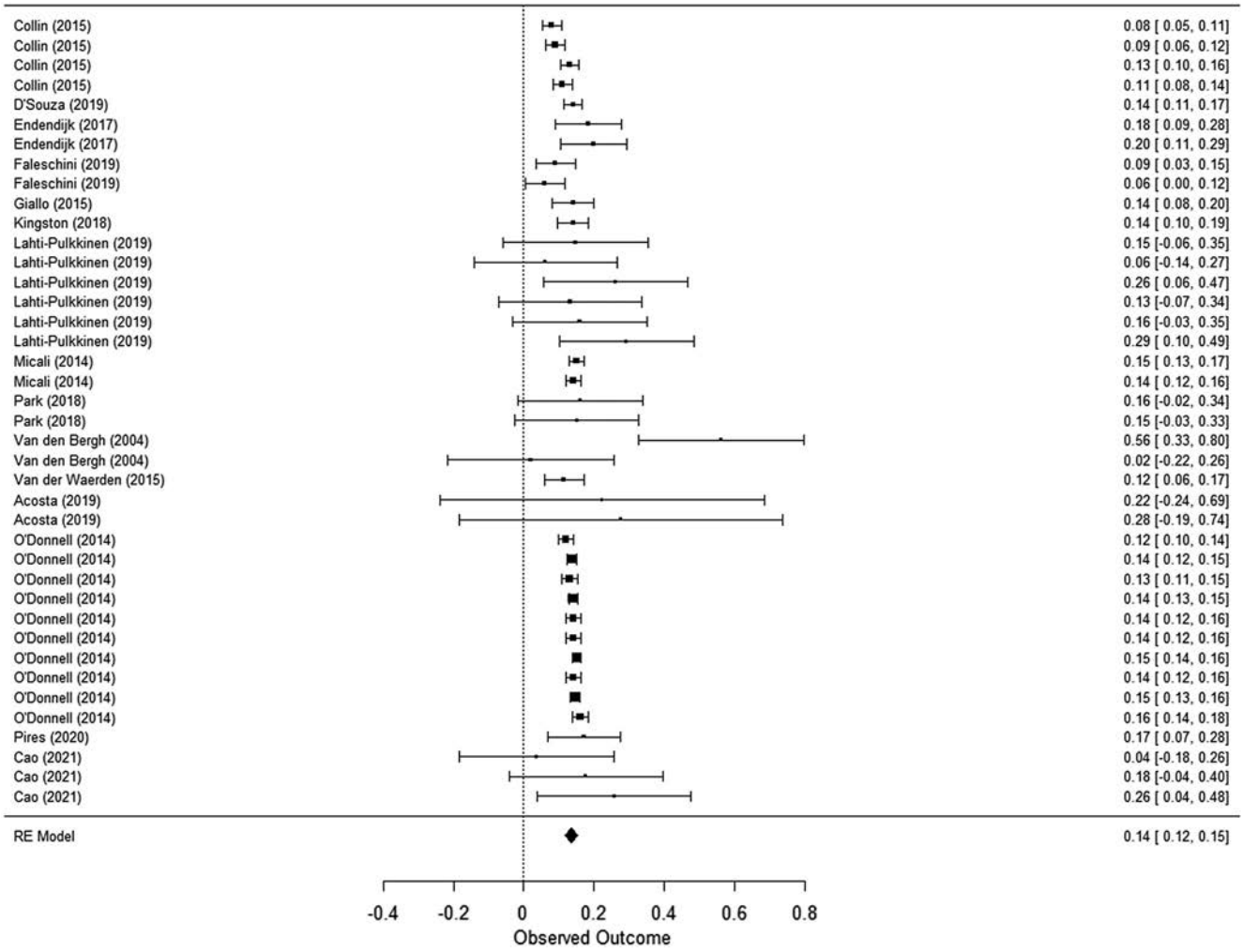
Note. It was common for studies to include multiple unique effect sizes. To maximize available information for analysis, we included all possible combinations of prenatal distress-ODD/CD, which were analyzed as within-citation effects using multilevel meta-analytic modeling (resulting in multiple effects that are drawn from the same citation). ODD = oppositional defiant disorder; CD = conduct disorder; RE = random effects.

induced shifts in fetal and infant brain-behavior development, in turn, have been linked to difficulties with physiological stress reactivity and behavioral regulation in infancy and childhood (Austin et al., 2005; Isaksson et al., 2015; Sandman et al., 2012; Van den Bergh et al., 2020), early differences that are implicated in the developmental origins of externalizing behavior (Barch et al., 2018; Hanson et al., 2015). Thus, consistent with developmental psychobiological models of externalizing behavior, the results of the current meta-analysis suggest that mechanisms of stress transmission during pregnancy may have small but unique downstream effects on offspring risk for externalizing behaviors in childhood and adolescence.

Of note, studies investigating physiological mechanisms mediating prenatal stress transmission rarely control for these constructs before or after pregnancy, which has limited the ability to infer causal effects. In our initial search for studies to include in this meta-analysis, we encountered four studies that examined physiological stress measures during pregnancy (i.e., cortisol) in relation to offspring externalizing behavior (Gutteling et al., 2005; Isaksson et al., 2015; Susman et al., 2001; Thomas-Argyriou et al., 2021). Only one study, however, covaried for measures of maternal stress collected *after* pregnancy to probe specific timing effects (Susman et al., 2001). Thus, to improve interpretation of potential causal pathways of stress transmission, there is a need for longitudinal studies that take a repeated, multimodal measurement approach, modeling offspring behavioral outcomes into later development while including parallel measures across both prenatal and postnatal timepoints.

Figure 6

Forest Plot of Effect Sizes for Prenatal Distress and Offspring ADHD



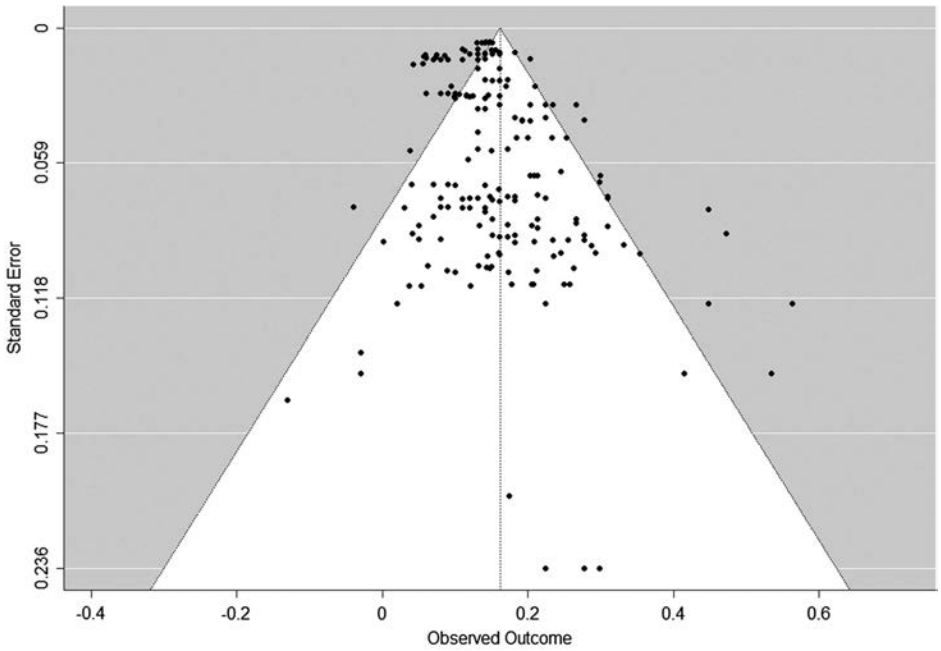
Note. It was common for studies to include multiple unique effect sizes. To maximize available information for analysis, we included all possible combinations of prenatal distress-ADHD, which were analyzed as within-citation effects using multilevel meta-analytic modeling (resulting in multiple effects that are drawn from the same citation). ADHD = attention-deficit/hyperactivity disorder; RE = random effects.

Moderators of Effect Size: Considering Type, Timing, and Stability

Findings from this meta-analysis suggest that the effect of prenatal psychological distress on offspring externalizing behavior does not significantly differ based on type or timing of psychological distress. Both prenatal depression and prenatal anxiety were significantly associated with externalizing behavior, and associations were generally similar in magnitude across trimesters. Of note, because few studies measured psychological distress specifically during the first trimester of pregnancy, we had limited power to evaluate these associations during the earliest part of pregnancy. Some evidence from studies of prenatal exposure to natural disasters (e.g., Project Ice Storm) have found greater effects of stress exposure on offspring neurodevelopment during the first trimester of pregnancy (Walder et al., 2014). Thus, there is a need for more studies that focus specifically on this early pregnancy period to better understand the mechanisms by which psychological distress is linked to offspring outcomes.

Although the type and timing of stress did not moderate effect size, the rank-order *stability* of psychological distress between the prenatal and postnatal periods did. On average, psychological distress showed moderate stability from prenatal to postnatal periods, but the effect of prenatal distress on offspring externalizing behavior was larger for individuals with *lower* rank-order stability of stress from prenatal to postnatal periods. One interpretation of these findings is that "state-like" psychological distress that occurs specifically during pregnancy may play a bigger role in shaping offspring risk for externalizing outcomes than stable "trait-like" symptoms of psychological distress. Consistent with these findings, there is some evidence that after controlling for trait anxiety, which is stable across time, state anxiety during pregnancy uniquely

Figure 7
Funnel Plot of Effect Sizes by Standard Error



Note. Studies with larger sample sizes have smaller standard errors, and asymmetry in the plot may indicate potential publication bias.

predicts externalizing spectrum behaviors in school-aged children (e.g., ADHD, aggression, and rule-breaking behaviors; Van den Bergh & Marcoen, 2004). In the context of theories related to the developmental origins of psychopathology, these preliminary findings appear consistent with the "mismatch" hypothesis derived from evolutionary biology (e.g., Frankenhuis & Del Giudice, 2012). Specifically, high prenatal psychological distress may "forecast" that there is an adaptive benefit to being more reactive or vigilant to threat in the postnatal environment, thus increasing offspring phenotypes implicated in externalizing behaviors (e.g., attention to threat, reactive aggression). Lower stability between the prenatal and postnatal environment may represent a mismatch in the expected environment, resulting in a larger unique effect of prenatal distress (and smaller effect of postnatal distress) on externalizing outcomes. In contrast, when there is high continuity of psychological distress across the prenatal to postnatal period, postnatal distress may partially mediate the association between prenatal distress and externalizing outcomes, thus resulting in a smaller direct effect of prenatal distress on externalizing behavior. Future studies that use mediation or moderated mediation models to probe these direct and indirect pathways across the prenatal to postnatal period may help to further parse out the interpretation of these findings.

In interpreting these preliminary results, it is important to note that our findings merely highlight the need to consider changes in psychological distress across the prenatal and postnatal periods. Because these metaregression findings were based on correlation coefficients between pre- and postnatal distress, the "stability" construct represents rank-order stability only. As a result, "high stability" alone lacks information regarding the *severity* of psychological distress (e.g., stable-low severity vs. stable-high severity). Some evidence from studies employing latent growth modeling suggests that changes in the severity of psychological distress from pregnancy to postnatal periods may uniquely influence risk for externalizing behaviors (Giallo et al., 2015). For example, a trajectory of increasing maternal depression across the prenatal to postnatal periods was associated with higher levels of offspring behavior problems by age 3, whereas a decreasing symptom trajectory did not differ from a "stable-low" group, suggesting that improvements in maternal depression during the transition to postnatal periods may modify risk for offspring externalizing outcomes (Park et al., 2018). Overall, rather than a specific "sensitive period" of vulnerability during pregnancy, it may be critical to consider prenatal distress in the context of its overall stability and patterns of severity and change during the transition to postnatal periods. More longitudinal studies tracking trajectories of psychological distress before, during, and after the pregnancy period are needed to evaluate their consistency with cumulative risk versus developmental adaptation "mismatch" hypotheses of offspring externalizing behavior. Direct measures of stability could be meta-analytically tested if studies standardly reported standardized mean difference indices between psychological distress scores across the prenatal to postnatal periods along with their correlations with offspring externalizing behaviors.

Our meta-analysis also explored potential differences in prenatal distress effect size based on type, timing, and informant for offspring externalizing outcomes. Overall, effect sizes were similar for ADHD, ODD/CD, and aggressive behavior, supporting the shared etiology underlying these externalizing spectrum outcomes (King et al., 2018; Tackett, 2010), which may additionally relate to a general factor of psychopathology (Lahey et al., 2012). We found

preliminary evidence that prenatal psychological distress may have smaller (nonsignificant) effects on nonaggressive rule-breaking behavior relative to other externalizing outcomes. These findings are consistent with meta-analytic evidence that there are different etiological pathways for aggressive versus nonaggressive rule-breaking dimensions of externalizing behavior (Burt, 2012; Klahr et al., 2014). Still, only two studies in the present meta-analysis focused on nonaggressive rule-breaking behavior as the outcome, which is consistent with the overall need for more developmental research on the phenomenology of nonaggressive rule-breaking behaviors (Burt et al., 2016). More longitudinal studies of prenatal distress that include rule-breaking behaviors as an outcome are needed to confirm potential differences in prenatal etiology between aggressive versus nonaggressive dimensions of externalizing behavior. Regarding timing of child behavior, we observed slightly larger effects of prenatal distress on offspring behaviors in early childhood (age 2–5) compared to middle childhood (age 6–12). Nonetheless, the effect of prenatal distress on externalizing outcomes was significant across all age groups from early childhood through adolescence, suggesting there may be persistent effects of prenatal exposures on vulnerability to externalizing behaviors across later life stages.

Most studies included in this meta-analysis used parent-reported rating scales (e.g., Child Behavior Checklist, Strengths and Difficulties Questionnaire) to measure child externalizing behavior, with the next most common method being teacher-reported versions of these rating scales. Our tests of informant effects suggest that effect sizes were smaller (but still significant) when relying on teacher-reported behavior instead of parent report. These differences may reflect a combination of informant biases and differences in observable child behavior in the home versus school setting (De Los Reyes et al., 2015). Given that our search of eligible studies uncovered only one study using trained clinician ratings and only one that included behaviorally coded observational measures of externalizing behavior, there is a clear need for research that incorporates these rigorous methods of assessment alongside multi-informant approaches to investigate the impact of prenatal stress on offspring behavior. In addition, behavioral assessments to measure attention and executive functioning, behavioral control, and other related neurobehavioral constructs implicated in externalizing behavior problems could be integrated in future studies using tools such as the National Institute of Health toolbox or laboratory paradigms (e.g., Faleschini et al., 2019; Park et al., 2018) to supplement symptom checklists of externalizing behavior.

Preliminary Clinical and Public Health Implications

The findings from this meta-analysis support the need to invest in accessible mental health resources for families specifically during the pregnancy period as one of the first steps to reducing offspring risk for externalizing outcomes. Prenatal depression and anxiety are estimated to affect a significant proportion of pregnant individuals, with prevalence estimates across countries ranging widely from 11% to 65% (Dadi et al., 2020; Field, 2018) and disproportionately affecting individuals living in under-resourced communities (Woody et al., 2017). Although effect sizes were relatively small, the results from this meta-analysis suggest that psychological distress during pregnancy may be one modifiable factor before birth that confers unique risk for vulnerability to externalizing behaviors. Given that pregnancy is a window of increased contact with health care providers, it is important to systematically screen for psychological distress during this period as well as closely monitor changes in these symptoms across the pregnancy to postnatal periods. Indeed, despite increasing recognition of experiences of depression and anxiety during pregnancy, many pregnant individuals go undetected. Although continued replication of findings is warranted, the results from this meta-analysis provide strong support for the role of the pregnancy period in the developmental origins of child externalizing outcomes (Tremblay et al., 2018). Thus, attending to the mental health care of expectant parents starting from the preconception and pregnancy periods may have important public health implications for effective prevention of psychopathology (Bauer et al., 2015).

Limitations and Future Directions

The generalizability of the results from this meta-analysis should be interpreted in the context of the demographic and sampling characteristics of the participants included in the studies. Participants in the 55 studies in this meta-analysis were predominantly White, primarily from European or North American countries, and relatively high in education and income, reflecting a longstanding pattern in psychological science of skewed participant representation from Western, educated, industrialized, rich, and democratic societies (Henrich et al., 2010; Roberts et al., 2020). Families from other racial–ethnic and socioeconomic groups remain highly underrepresented in longitudinal studies of prenatal stress. This is an important limitation given that structural racism, systemic factors underlying economic disparities, and other social determinants of health are known contributors to inequities in prenatal stress and birth outcomes (Alhusen et al., 2016; Brase et al., 2021; Mendez et al., 2013). Importantly, some evidence suggests that experiences linked to psychological stress, such as exposure to racial discrimination and negative experiences with medical providers, increases specifically during the pregnancy period for Black and Latina women in the United States (Rosenthal et al., 2015). Adult perceptions of child behavior and (mis)diagnosis of externalizing disorders have also been shown to differ based on child race and ethnicity (Liang et al., 2016; Nguyen et al., 2007). Thus, there is an urgent need for more culturally informed longitudinal studies of prenatal stress and child behavioral outcomes that include more representative samples of the global population. Relatedly, our meta-analysis only included studies published in English, a methodological limitation that may impact the generalizability of our findings to non-English speaking countries (Neimann Rasmussen & Montgomery, 2018). Although we reported findings from studies across the globe, most of the studies included were based on samples from European or North American countries. Future meta-analyses that incorporate professional translators to include studies published in other languages are needed to ensure that results generalize globally. In addition, most studies included in the present analysis recruited pregnant participants from the "general" population (e.g., public hospitals or population-based studies). Among the minority of studies that used specialized selection criteria (Supplemental Table S1), few overlapped in the type of selection criteria used, which precluded further exploration of differential effects for subpopulations (e.g., clinical samples, pregnant adolescents, pregnant people experiencing substance use

problems). More studies focusing on clinical samples and other marginalized pregnant populations are needed to inform clinical intervention implications.

Additional limitations related to study design should also be considered when interpreting the present findings. First, although a novel contribution of this meta-analysis is that we controlled for postnatal psychological distress to strengthen causal inferences, any meta-analysis relying on observational study design of human development is inherently naturalistic (nonexperimental), precluding causal conclusions. Our meta-analysis focused on psychological distress as a modifiable risk factor in early development, but it is also important to acknowledge the role of shared genetics that may interact with or partially confound psychological distress effects on externalizing outcomes (Gjerde et al., 2017). Second, most studies included in this meta-analysis relied on parent report as the primary source of information for measuring both prenatal distress and externalizing behavior. Shared method variance should be considered given that mood can impact assessments and perceptions of child behavior. Third, potential publication bias cannot be ruled out. In our meta-analysis, studies with smaller sample sizes showed greater variability in their effect sizes than larger studies, and most of the studies included had large samples. Of note, our meta-analysis included all published studies with eligible variables and available data for analyses, including studies that did not focus on externalizing outcomes as a primary aim, a strategy that partially helps to reduce risk for publication bias. Nonetheless, it is possible that studies only reported on the types of psychological distress that had associations with child outcomes, reporting biases that may have limited the ability to test for differences across distress types. Fourth, due to varying availability of data for each moderator across studies, we examined each moderator independently to maximize the use of available data as well as to reduce complexity in interpreting a multimoderator model (all moderators inputted jointly). Thus, our findings do not speak to the specific impact of each moderator while controlling for all other moderators.

Finally, the effect sizes that emerged for prenatal psychological distress were relatively small in magnitude, and significant heterogeneity in effects remained even after controlling for many study characteristics. Of note, our meta-analysis focused on *psychological distress* during pregnancy, which is only one subdomain of potential prenatal stress exposures. There are many other biopsychosocial prenatal stress measures that should be further examined in future meta-analyses, such as the pregnant person's stress physiology, exposure to stressful events during pregnancy, as well as pregnancy health conditions and complications that represent stressors on the developing fetus. Furthermore, consistent with a developmental psychopathology framework for conceptualizing externalizing spectrum behaviors (Hinshaw & Beauchaine, 2015), there is a clear need to consider other individual and contextual factors that may interact with or mediate prenatal stress effects. For example, beyond control for postnatal psychological distress, the original studies often varied widely in the covariates included their models as well as in their analytic approach (e.g., linear regression, structural equation modeling, latent class growth analysis). To allow for meta-analysis of effect size across studies that varied in analytical approach, our meta-analysis examined bivariate correlations extracted from each study (Lipsey & Wilson, 2001). A limitation of this approach is that we were unable to compare whether effect sizes of prenatal distress varied across studies depending on additional covariates or moderators included. Adjusting for these additional covariates using the current metaregression approach would have required studies to systematically measure the same covariates and report the correlation between the covariate and other primary study variables (prenatal distress and externalizing behavior). Thus, although many other covariates are important to consider in the association between prenatal psychological distress and offspring externalizing behaviors, the variability in the selection and measurement of covariates across studies limited the factors we were able to covary using meta-analysis.

Although unable to be tested meta-analytically using the present data set, differences in birth weight, structural and functional alterations in brain regions and brain networks, and other potentially altered biological mechanisms resulting from prenatal stress are important to consider as a covariates, moderators, or mediators of prenatal stress effects in future studies. In addition, parents experiencing psychological distress may be more vulnerable to engaging in reactive or inconsistent parenting behaviors, which contributes to the development of externalizing behaviors in childhood and adolescence (Taraban et al., 2019). Indeed, one study reported that the effect of prenatal and postnatal depression with child externalizing behaviors was no longer significant after controlling for hostile parenting behaviors (Velders et al., 2011), suggesting that parenting behaviors may serve as a critical mediator of the association between parent psychological distress and offspring externalizing outcomes.

Parenting behaviors and postnatal psychological distress could also interact with prenatal distress to exacerbate or buffer risk for externalizing outcomes (Hartman et al., 2020; Tung et al., 2017). For example, one study reported that children exposed to both prenatal depression and childhood maltreatment had almost 12 times greater risk for developing psychopathology than children exposed to either risk factor alone (Pawlby et al., 2011). This pattern of results is consistent with diathesis stress and "double-hit" theories explaining differences in vulnerability to stress (Daskalakis et al., 2013; Monroe & Simons, 1991; Nederhof & Schmidt, 2012), as well as differential susceptibility theories of "prenatal programming of postnatal plasticity" (Hartman & Belsky, 2021; Pluess & Belsky, 2011). Based on these theories, prenatal stress is hypothesized to increase offspring's biological vulnerability or sensitivity to postnatal environmental factors (e.g., stressful life events). Although unable to be tested using the available meta-analysis data, a future meta-analysis could test for these interactive effects by coding prenatal stress severity categorically (e.g., clinically elevated vs. not) along with the correlation between postnatal environmental factors (e.g., parenting behavior) and externalizing behaviors in each included study. This approach would allow meta-analytic testing of potential Prenatal × Postnatal interactions using a metaregression by modeling severity of prenatal stress as a predictor of the variability in effect size of postnatal factors on externalizing behavior. To enable such meta-analytic probing of severity thresholds and moderation effects, however, an important future direction for prenatal stress studies is to use measures of prenatal psychological distress that can be harmonized across studies for meta-analysis, report distributions by established severity cut-offs, and regularly report correlations with contextual factors measured after birth that may interact with these prenatal exposures.

Conclusions

This meta-analysis provides the first formal characterization of the incremental contribution of psychological distress during pregnancy on offspring risk for externalizing behaviors, independent of exposure during the postnatal period. Findings across 55 longitudinal studies point to a unique role of psychological distress during the prenatal period in the etiology of externalizing behaviors, associations that persisted from early childhood through adolescence. Our study revealed several areas within prenatal distress and externalizing study that warrant further investigation, including a clear need for studies with more racially and socioeconomically diverse samples, as well as more studies specifically designed to probe the timing and chronicity of psychological distress before, during, and after pregnancy. Together, these meta-analytic findings highlight the importance of a preventative rather than reactive approach to reducing externalizing behaviors and echo the growing public health recognition that effective prevention of psychopathology must begin with accessible support and mental health care for parents prior to childbirth.

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