Maternal and paternal depression and anxiety and offspring infant negative affectivity: A systematic review and meta-analysis

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Abstract

Maternal internalizing symptoms during pregnancy, specifically depression and/or anxiety, are commonly linked to negative affectivity (NA) in infant offspring. These links are commonly attributed to biological effects of the in utero environment on fetal development. However, research suggests that internalizing symptoms before and after pregnancy, as well as in fathers, may also be associated with NA in infant offspring. Such findings suggest greater complexity in transmission than can be explained by biological in utero programming alone. Further, infant NA is often treated as an homogenous construct, yet it covers a range of facets including fear, frustration, sadness, and slow recovery from distress that may each be differentially associated with parent internalizing distress. Here we aimed to (1) meta-analytically quantify associations between maternal and paternal internalizing symptoms and infant offspring NA, (2) examine how associations varied as a function of distinct phenotypic facets of NA, and (3) examine how associations varied by timing of parental symptoms (preconception, antenatal, postnatal) and infant age. Using random-effects meta-analysis, we found that maternal internalizing symptoms were positively associated with infant NA ($r = 0.17$ [95% CI 0.14, 0.21], 42 studies, 149 estimates). Preliminary evidence from studies of fathers likewise suggested a positive association with infant NA ($r = 0.13$ [95% CI 0.04, 0.22], 6 studies, 40 estimates). We observed associations with the global infant NA construct, as well as effect modification by infant NA facet (maternal r range .12 to .22; paternal r range .03 to .21). In mothers, there was no evidence of effect modification by timing of internalizing symptoms or infant age; in fathers, preliminary associations were larger for postnatal than antenatal symptoms. Further studies of preconception and paternal symptoms are now needed, and we suggest avenues for research to advance understanding of the relations between parent internalizing symptoms and infant NA.

Key words: Perinatal depression; preconception; father; mother; negative affect; infant development; intergenerational; emotional reactivity

Highlights

- In mothers, both antenatal and postnatal internalizing symptoms predict infant negative affectivity.
- In fathers, postnatal internalizing symptoms predict infant negative affectivity.
- Findings are consistent with both in utero biological programming and postpartum interpersonal stress transmission models.
- The strength of associations between parent symptoms and infant negative affectivity varies by type of infant negative affectivity assessed.
- Further research on potential preconception, paternal and confounding influences is needed.

Introduction

Children differ in the way they react to the environment. These differences, evident from infancy, interact with experience to shape lifelong patterns of mental health and disorder. One of the earliest emerging dispositional traits is negative affectivity (NA), a bias to negative mood that is characterized by individual differences in tendency to emotional distress (Rothbart & Bates, 2006). NA is conceptually related to the personality trait of neuroticism, as well as the more recently proposed *p*-factor, a transdiagnostic risk factor for psychopathology (Hankin et al., 2016). Across the life-course, dispositional NA is a key risk factor for depression and anxiety disorders, as well as greater comorbidity and poorer prognosis (Cuijpers et al., 2010; Kotov et al., 2010; Lahey, 2009; Letcher et al., 2009). Understanding the development of NA has therefore been an important transdisciplinary research goal.

Rothbart's psychobiological model of temperament has emerged as a dominant theoretical foundation for research investigating the development of NA, integrating neuroscientific, developmental and comparative lines of inquiry (Gartstein, 2019). According to this model, individual differences in NA develop as a function of biological, maturational and contextual influences (Goldsmith et al., 1987; Rothbart & Derryberry, 1981). There is increasing evidence that NA is evident as early as the first days of life, and underpinned by differences in brain regions implicated in the stress response system (Gunnar & Davis, 2013; Shackman et al., 2016). Stability estimates of NA are typically low to moderate in early infancy, increasing across the first year postpartum (Bornstein et al., 2015; Carranza Carnicero et al., 2000). This consolidation of trait-like NA over time is thought to be influenced by maturation and contextual input; in infancy, contextual inputs are mostly parent-mediated (Putnam et al., 2002; Rothbart, 2004).

The most studied predictors of infant NA are maternal internalizing symptoms (depression and/or anxiety). Depression and anxiety affect up to 24% of women during pregnancy and the first year postpartum (Woody et al., 2017), and reliably predict increased risk for mental health difficulties in offspring that extend into adulthood (Madigan et al., 2018; O'Connor et al., 2014; Sanger et al., 2015; Stein et al., 2014). Understanding the early emergence of these intergenerational links may elucidate transmission pathways and aid in early identification of children at risk. Because NA is one of the earliest observable dimensions of socio-emotional development in infants, associations between maternal internalizing symptoms and infant NA have thus received considerable attention (Davis et al., 2004; Gustafsson et al., 2018; Henrichs et al., 2009; Nolvi et al., 2016).

Although the literature has focused primarily on maternal associations, there is increasing interest in the role of fathers (Connell & Goodman, 2002). Perinatal depression affects up to 13% of fathers (Cameron et al., 2016; Paulson & Bazemore, 2010), and has been linked to increased risk of emotional and behavior difficulties in offspring (Gutierrez-Galve et al., 2015; Sweeney & MacBeth, 2016). These associations may occur both via and independently of maternal symptoms (Goodman, 2020), with increasing involvement of fathers in caregiving potentially leading to greater influences on children's emotional development (Natsuaki et al., 2014; Ramchandani & Psychogiou, 2009). Paternal internalizing symptoms during pregnancy and postpartum are also implicated in the early emergence of offspring NA and related behaviors during infancy (Ting, 2012; van den Berg et al., 2009).

Is there early specificity in intergenerational patterning of infant NA?

Though often described as a unitary construct that reflects general distress-proneness, NA also comprises several narrower, interrelated, dimensions. The number and definition of these facets varies somewhat across developmental stage of the life-course, but most models include sadness, anxiety/fear, and anger/frustration (Hankin et al., 2016). In infancy, NA is thought to encompass distinct facets of sadness, fear, frustration/irritability, and falling reactivity or rate of recovery from distress (Table 1). Typically, these emotional states are inferred by caregivers or other observers on the basis of infant behavioral patterns in response to specific contextual cues, commonly associated with each emotional state (Planalp & Goldsmith, 2019). While the extent to which observers can accurately infer infant emotional experience is unclear (Barrett et al., 2019), there is some evidence that these behavioral patterns differ in expected ways in their situational triggers, neurobiological correlates and mental health outcomes, and therefore may act as discrete behavioral markers of risk (Clauss & Blackford, 2012; Kagan et al., 1999, 2007; Planalp & Goldsmith, 2019; E. Thomas et al., 2019). It is unclear whether associations between parent internalizing symptoms and infant NA reflect an intergenerational patterning of broad distress-proneness, as reflected by the general NA construct, or whether associations vary by facet of infant NA.

Insert Table 1 here

Studies examining the potential role of infant NA in intergenerational transmission of internalizing symptoms focus on two overarching symptom categories: depression and anxiety. Though

comorbid, depression and anxiety are partially discrete disorders with distinct predictors, onset and course trajectories, and functional outcomes (Kessler et al., 2015; Korja et al., 2018; Penninx et al., 2011). Perinatal depression and anxiety differ in their biological correlates and links to broad offspring socio-emotional development (Field, 2011; Madigan et al., 2018), and may similarly differ in their associations with infant NA. One mechanism may be the way in which depressive and anxious symptomatology differentially impact parent-infant interactions, with evidence of dyadic gaze and touch synchrony differing between depressed and anxious mothers and their infants (Granat et al., 2017).

Parental depression and anxiety may also relate differently to the various facets of infant NA. Latent structural models of psychopathology suggest that fear and sadness are dimensions of internalizing distress, associated with anxiety and depression respectively (Hankin et al., 2016), while frustration/irritability are more closely aligned with externalizing difficulties (Muris & Ollendick, 2005; Stanton & Watson, 2014). More broadly, prior work on intergenerational transmission suggests homotypic continuity from parent to child is stronger than heterotypic continuity (Warner & Weissman, 2013). It is not known whether this pattern of intergenerational homotypic continuity is evident from early infancy of offspring but if so, we may expect to see stronger associations of parental anxiety with infant behavioral patterns commonly attributed to fear, and parental depression with infant behavioral patterns commonly attributed to sadness, and weaker associations of both parent depression and anxiety with infant behavioral patterns commonly attributed to frustration/irritability (Hankin et al., 2016; Stanton & Watson, 2014).

Does timing of parent internalizing symptoms or infant NA matter?

The timing of children's exposure to parent internalizing symptoms may implicate different mechanisms of risk transmission (Goodman, 2020). Theoretical explanations tend to emphasize potential influences of parental symptoms during a critical or sensitive developmental window of offspring development, and vary in the extent to which they emphasize processes before or after birth. It is worth noting that these perspectives are not mutually exclusive or incompatible. Overwhelmingly, the current narrative in the literature on predictors of infant NA is dominated by the *fetal programming hypothesis*, which posits that maternal antenatal symptoms affect infant neurodevelopment, affect and behavior via in-utero exposure to stress hormones, immune-inflammatory processes, or microbiota (Chan et al., 2017; Glover, 2011; Van den Bergh et al., 2017). Accordingly, most prospective studies of parental internalizing symptoms and infant NA focus on

maternal exposure *during pregnancy* (Davis et al., 2004; Gustafsson et al., 2018; Henrichs et al., 2009; Nolvi et al., 2016; Rouse & Goodman, 2014).

However, biopsychosocial models of infant NA also suggest a role of *postnatal* processes (Rothbart & Bates, 2006). According to *interpersonal stress transmission* models, postnatal internalizing symptoms may impact infants' emotional development via parent-infant interactions and the broader relational environment (Hammen et al., 2004; Meaney & Szyf, 2005). Much postnatal evidence is cross-sectional (Beck, 1996; Pickens & Field, 1993), reflecting potential bidirectional effects or common causes (Yim et al., 2015). Nonetheless, there is also prospective evidence for both mothers and fathers (Jonas et al., 2015; Potapova et al., 2014). Further, emerging findings also link maternal stress-related exposures *before pregnancy* to infant behavior and affect (Hipwell et al., 2019; Petzoldt et al., 2015; Spry et al., 2019). Evidence from animal studies suggests *preconception programming* of the germline or reproductive biology by both maternal and paternal preconception stress, impacting the future gestational environment and fetal development (Keenan et al., 2018; Klengel et al., 2015). Alternative explanations include confounding by common causes, or mediation by perinatal processes.

Comparing the size of maternal and paternal associations within and across phases has become one widely used strategy for drawing inferences from observational data (Thapar & Rice, 2020; Thapar & Rutter, 2019). While this strategy cannot directly test mechanisms, it can provide some evidence in support of, or against, theoretical perspectives and inform future mechanistic research. In particular, antenatal paternal exposures are often employed as a 'negative control' when evaluating evidence for the fetal programming hypothesis (Gage et al., 2016). Under this model, antenatal associations should be much smaller for paternal than maternal symptoms, given the absence of a direct in-utero programming pathway. Thus, similar sized maternal and paternal antenatal associations may suggest confounding. In contrast, maternal and paternal associations are both plausible postnatally and before conception, under the interpersonal stress transmission and preconception programming models. Differences in magnitude of associations over time may provide a further line of evidence. For example, evidence of postnatal, but not antenatal associations may support an interpersonal stress transmission model. Conversely, similar sized associations at each phase may suggest either multiple processes operating over time, or confounding either by earlier/later symptoms or common causes. While not definitive, these lines of evidence have the potential to advance thinking in the area.

Infant age at the time of NA assessment may similarly moderate associations. As already described, individual differences in NA are evident from early infancy with stability increasing across the first year postpartum. This suggests a potential role of parental factors both before and after birth. According to fetal/preconception programming hypotheses, associations between parent internalizing symptoms and infant NA may be apparent from the early postpartum. An interpersonal stress transmission model may suggest that associations increase across infancy, with exposure to postpartum symptoms (Newland et al., 2016). Additionally, while individual differences in undifferentiated distress-proneness are discernible from early infancy, more nuanced dimensions may begin to cohere across infancy. Distinct behavioral patterns commonly attributed to sadness, fear, and frustration to limitations are discernible by 3 months postpartum, with frustration and fear reactions increasing across the first year of life (Gartstein & Hancock, 2019; Gartstein & Rothbart, 2003; Stenberg & Campos, 1990). Associations of parental internalizing symptoms with each facet may thus differ across this maturational timeline.

Methodological considerations

The magnitude of associations between parental internalizing symptoms and infant NA may also be influenced by measurement approaches. While some studies have employed diagnostic assessments of parent symptoms to identify probable disorder, others have used screening checklists. Similarly, there is debate surrounding the assessment of infant NA via maternal report, as compared to observational assessment (Luoma et al., 2004; Najman et al., 2001). In most studies of parent-reported infant NA, the same parent reports on both on their own internalizing symptoms and on their infant's NA. This introduces potential biases, including inflated effect sizes due to shared method variance (Richters, 1992). However, observational assessments are typically conducted under artificial conditions that limit their ecological validity (Bates et al., 2014; Shiner & Caspi, 2003). Because each measurement mode assesses slightly different constructs and may be susceptible to different forms of bias, it is important to compare studies using parent report with those using observational ratings.

The current systematic review and meta-analyses

Because infant NA is associated with parent depression and anxiety and is, in turn, one of the earliest infant predictors of emotional or behavioral difficulties, this early life disposition has been implicated in the intergenerational transmission of risk for depression and anxiety (Bruder-Costello

et al., 2007; Rothbart et al., 2000). In this context, understanding links between parental internalizing symptoms and infant NA may inform early interventions for children at greater risk, and ultimately reduce enduring negative impacts on the mental health of the next generation. However, gaps in our understanding remain. First, although many studies have examined prospective associations between parent internalizing symptoms and infant NA, these have not been quantitatively synthesized. Past reviews confound multiple infant dispositional traits with distinct etiological pathways and links to parental symptoms, or identify associations broadly across childhood / adolescence rather than specifically in infancy (Beck, 1996; Erickson et al., 2017; Goodman et al., 2011). Further, prior empirical studies vary considerably in the nature and timing of measurement of infant NA and parental symptoms. Examining this variability would allow us to address key conceptual questions relating to the complex nature of infant NA, and the implications of assessment timing for dominant theoretical models of transmission.

The purpose of this systematic review and meta-analyses was thus threefold. First, we sought to meta-analytically quantify the prospective associations between parent internalizing symptoms and offspring NA in infancy, for mothers and fathers. Second, we sought to examine whether there is early specificity in the intergenerational patterning of infant NA, as reflected by effect modification by parent internalizing construct and/or infant NA facet assessed. Third, we sought to examine whether associations vary by timing of parental symptoms (postnatal, antenatal or preconception) and infant age. Addressing these questions can inform our understanding of the associations between maternal and paternal internalizing symptoms and the early emergence of NA in offspring, with lifelong implications for mental health and ill health.

Methods

Research design and methods

This systematic review and meta-analysis was carried out according to the preferred reporting items for systematic review and meta-analysis guidelines (Moher et al., 2009), and in adherence to a predefined study protocol registered on PROSPERO (CRD42019118033).

Search strategy

We searched Medline, PsycINFO, CINAHL, PubMed, OpenGrey and OpenDissertations to identify published and unpublished literature (initial search conducted 4/12/2018; search update conducted 11/4/2020). Our search was based on five broad criteria, each of which was translated into a set of key words for searching in title and abstract. These categories are: (S1) *reactivity* (key words AB “negative affect” OR AB “negative affectivity” OR AB “negative react*” OR temperament OR “emotion* react*” OR “react* N0 behavi*” OR colic OR fussy OR crying OR “behavi* N0 difficult*” OR “emotion* difficult*” OR “stress sensitiv*” OR “stress react*” OR “temperamental negativity” OR “stress respons*” OR “emotional problems” OR “behavi*ral problems” AB sadness OR fear OR “frustration tolerance” OR irritability OR mood OR “falling reactivity” OR “distress to limitations” OR “recovery from distress”); (S2) *infancy* (key words infan* OR toddler* OR newborn OR baby* OR neonat* OR offspring OR preschool OR child); (S3) *parent* (key words maternal OR mother OR parent* OR paternal OR father); (S4) *preconception, pregnancy or postpartum* (key words prepregnancy OR “pre-pregnancy” OR lifetime OR preconception OR “pre-conception” OR perinatal OR postnatal OR postpartum OR antenatal OR antepartum OR pregnancy OR pregnant OR gestation OR periconception* OR “in-utero” OR trimester OR peripartum); and (S5) *mental health* (key words internalizing OR internalizing OR externalizing OR externalizing OR “mental disorder” OR “mental health” OR “depress*” OR “anxi*” OR “mood disorder OR “affective disorder” OR “anxiety disorder” OR “PTSD” OR MDD OR “posttraumatic stress” OR psychopathology).

These criteria were combined as follows: (a) studies with at least one key word within both (S1) and (S2) to obtain studies that included NA during infancy (S6); (b) studies with at least one key word within (S3), (S4) and (S5) to obtain studies that included parent internalizing symptoms prior to, during, and/or after pregnancy (S7); and (c) studies with at least one key word within each of (S6) and (S7) to obtain studies that included both infant NA and parent internalizing symptoms.

Reference lists of relevant papers were also searched.

Eligibility

Inclusion criteria. Studies were included if: (a) the study included NA as an outcome, assessed via parent rating or observer report; (b) mean age of children at the time of the outcome assessment was 18 months or younger; (c) the study included a measure of maternal and/or paternal internalizing symptoms before pregnancy, during pregnancy, or in the first year postpartum, assessed using a diagnostic interview or validated rating scale; (d) the study used a prospective longitudinal design to assess antenatal or postnatal internalizing symptoms, with parental symptoms assessed prior to offspring outcome; for preconception symptoms only, we also included retrospective assessment because we expected few studies with prospectively assessed preconception symptoms in the literature; (e) sufficient information to calculate an effect size was presented; and (f) the study was written in English.

Exclusion criteria. Physiological, biochemical, immuno-inflammatory or other biological measures of NA were excluded, as well as the conceptually distinct constructs of difficult temperament, which encompasses a range of temperamental traits, and behavioral inhibition/avoidance and its components .

Data extraction and study quality

Data from each included study were coded using a pre-piloted data extraction form, including: study characteristics (country, number of participants); study design; gender of parent; exposure measure, assessment method, and timing; sex of infant; outcome measure, assessment method, and timing; and estimates of association. All studies and key variables were coded by primary coder (SA), and verified by a second coder (ES). Results were compared and disagreements resolved by consensus coding. Inter-rater reliability was Cohen's $k = 0.88-1.00$ for the categorical coding of studies and variables, and Pearson's $r = .99$ for effect sizes. Study quality was assessed using a 13-point quality assessment tool adapted from the National Institutes of Health Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies (Madigan et al., 2018; National Heart Lung and Blood Institute: National Institutes of Health, 2014). This tool is designed to evaluate study design elements according to Cochrane collaboration criteria (Downes et al., 2016) and adapted for relevance to intergenerational cohorts (Supplementary Table 1).

Statistical analysis

For mothers and fathers separately, we first used meta-analytic methods to provide a general quantitative synthesis of the literature. Associations between maternal and paternal internalizing

symptoms and infant NA were examined using univariate random effects models, based on the assumption of between-study heterogeneity. Most studies reported multiple effect sizes (e.g., associations of antenatal v. postnatal symptoms, or associations of parental anxiety v. depression). Estimates were therefore nested within studies. We used robust variance estimation with small sample adjustment to account for dependent effect sizes (Hedges et al., 2010; Tipton, 2015). This allowed us to include all estimates of association from each study and avoids the limitations of within-study effect averaging or elimination, such as loss of information or the assumption of homogeneous effect sizes within studies (Assink, 2016).

Heterogeneity was evaluated using prediction intervals, which estimate the range of true effect sizes within which 95% of all populations would fall. In the absence of between study heterogeneity of true effect sizes, the prediction interval mirrors the confidence intervals around the weighted average effect size. If heterogeneity is present, the prediction interval covers a wider range than the confidence interval (Borenstein et al., 2017; IntHout et al., 2016). The I^2 statistic was also evaluated, indicating the proportion of observed variance not attributable to sampling error (Borenstein et al., 2017). To examine the extent to which heterogeneity could be explained by the proposed moderators, analyses were repeated first adjusted for each moderator, and then stratified by each moderator. Where the number of studies was too low for meta-analyses ($k < 2$), data were qualitatively evaluated (Valentine et al., 2010). Where the number of studies was low but sufficient for meta-analysis ($k \geq 2$), data were nonetheless meta-analyzed and results presented to indicate current levels of evidence. Meta-analytic estimates with low k and high variance / low precision as indicated by wide confidence intervals, reflecting wide variation in effect sizes across studies, were not considered substantively meaningful.

The most common metric for reporting effect sizes within included studies was the Pearson correlation coefficient (r). Other effect sizes were therefore converted to r s, using effect size transformation formulae (Borenstein et al., 2011). Because few studies adjusted for potential confounding variables at or before baseline, we meta-analyzed unadjusted estimates. All estimates of association were transformed to Fisher's z -scores for analysis and then back-transformed to aid interpretability. All random effect analyses were conducted in R (R Core Team, 2018). Meta-analyses were conducted using 'robumeta' (Fisher et al., 2017). P-values for moderation analyses were derived using Wald tests with (unless otherwise specified) the default Hotelling's T^2_{df} small sample correction, implemented in 'clubSandwich' (Pustejovsky, 2020; Tipton & Pustejovsky, 2015).

Publication bias

Potential publication bias was examined using five methods, separately for mothers and fathers: the Fail-Safe N, the Egger test, visual inspection of funnel plots, rank correlation test for funnel plot asymmetry, and a stratified analysis by publication status (published versus unpublished studies).

Data and analysis scripts are available at

https://osf.io/nmqdb/?view_only=0a36df8ddd4644d1b4f9d25a0daa8e49

Moderators

Dimension of infant NA was defined according to Rothbart's model (negative affectivity and its four facets: sadness, fear, frustration/irritability, and slow recovery from distress; Gartstein & Rothbart, 2003). We present coding decisions for questionnaire and observational measures in Table 1. For observational measures where both the observational and rating protocol were designed to elicit a range of negative emotions (e.g., the Harvard Infant Behavioral Reactivity Protocol), we coded as general NA; where either the observational or rating protocol was designed to elicit a specific facet of NA (e.g., arm restraint protocol to elicit frustration/irritability) we coded as that facet.

Parent internalizing construct was coded as a binary variable: *anxiety* or *depression*, indicating the presence of anxiety or depressive disorder/symptoms as indicated by diagnostic interview or screening measure.

Infant age at NA assessment was coded as a binary variable: $< \text{ or } \geq 6 \text{ months postpartum}$.

Timing of parent internalizing symptoms was coded as a three-level categorical variable: *preconception*, *antenatal*, or *postnatal*. Within the antenatal category we derived an additional variable denoting: *first*, *second*, or *third trimester*. Within the postnatal category we derived an additional variable denoting: $< \text{ or } \geq 6 \text{ months postpartum}$.

Infant NA assessment mode was coded as a binary variable: *observer-rated* or *parent-reported*.

Parent internalizing symptoms assessment mode was coded as a binary variable: *diagnostic interview* or *self-report via symptom checklist*.

Results

Figure 1 provides a PRISMA flow diagram (Moher et al., 2009) of the article selection process. We identified 601 articles via the database search, and a further 26 articles by manually searching reference lists of key articles. Of these, 547 articles remained after duplicates were removed. Review of the titles and abstracts yielded 156 articles identified as potentially meeting full inclusion criteria. After reviewing the full text of these articles, 45 were identified as meeting full inclusion criteria.

Insert Figure 1 here

Study characteristics and quality

Study characteristics are shown in Table 2. In total, 45 articles with 233 effect sizes were identified through the systematic search. Sample sizes within studies ranged from 22 to 5568 parent-infant dyads. A total of 20 studies were from North America, 18 studies from Europe, five from Asia, and three from Australia/New Zealand. Of the 45 included studies, 41 were peer reviewed journal articles and six were unpublished doctoral theses. Forty-two studies included estimates for maternal internalizing symptoms, and six studies included estimates for paternal internalizing symptoms (three of these studies included estimates for both maternal and paternal symptoms. Mean study quality score was 6.0 (SD = 1.5, range 2-9) (Supplementary Table 2). Although inclusion criteria permitted retrospectively assessed preconception symptoms, the search only yielded studies of prospectively assessed symptoms.

Insert Table 2 here

Maternal internalizing symptoms

Table 3 shows the meta-analytic estimates of associations between mothers' internalizing symptoms and infant NA, as well as the meta-regression and moderator results. A total of 149 effect sizes from 42 studies, including 19,248 mother-infant dyads, were available to estimate the associations between maternal internalizing symptoms and the global construct of infant NA, with correlation coefficients ranging from $r = -.21$ to $r = .56$. The weighted average effect size from the random effects model was $r = 0.17$ (95% CI .14, .21). The variance in effect sizes attributable to true differences between studies was estimated as $I^2 = 81\%$ of total observed variance, suggesting that effect sizes were more heterogeneous than expected by sampling error alone. The prediction

interval ($I = -.02$ to $.37$) was wider than the confidence interval around the weighted average effect size, also indicating some heterogeneity of true effect sizes between populations.

Insert Table 3 here.

Moderator analyses

Infant NA dimension assessed. Maternal internalizing symptoms were associated with all facets of infant NA as well as the general construct, but there was nonetheless meta-analytic evidence of difference in effect size by outcome construct assessed ($p = .044$). Effect sizes were highest for the general construct of NA ($r = .21$ [$.17, .26$], $k = 26$) and sadness ($r = .22$ [$.06, .37$], $k = 8$), and smaller for fear ($r = .12$ [$.07, .16$], $k = 15$), frustration/irritability ($r = .14$ [$.08, .20$], $k = 18$), and slow recovery from distress ($r = .14$ [$.03, .24$], $k = 8$). In supplementary analyses (Supplementary Table 3), we further examined whether associations between maternal symptoms and each dimension of infant NA varied by type of maternal mental health problem. For infant fear, effect sizes were larger for maternal anxiety ($r = .18$ [$.07, .29$], $k = 6$) than maternal depression ($r = .08$ [$.03, .13$], $k = 11$). There was no other evidence that associations between maternal symptoms and each NA dimension varied by type of mental health problem.

Maternal internalizing construct assessed. There was no other meta-analytic evidence of difference in effect size according to the exposure construct measured (anxiety $r = .19$ [$.15, .23$], $k = 19$; depression $r = .17$ [$.12, .21$], $k = 29$; p for test of moderation = $.571$; Table 3).

Infant age at NA assessment. There was no meta-analytic evidence of difference between assessments conducted during or after the first six months postpartum (< 6 months $r = .16$ [$.11, .21$], $k = 22$); ≥ 6 months $r = 0.17$ [$.12, .22$], $k = 24$; p for test of moderation = 0.865). In supplementary analyses (Supplementary Table 3), we further examined whether associations between maternal internalizing symptoms and each dimension of infant NA varied by timing of infant NA assessment. For infant slow recovery from distress, effect sizes were larger for studies where maternal symptoms were assessed after six months postpartum ($r = .17$ [$.03, .30$], $k = 5$) than before six months postpartum ($r = .07$ [$-.029, .42$], $k = 3$), though the test of moderation was not significant ($p = .314$). There was no other evidence that associations between maternal symptoms and each NA dimension varied by timing of infant NA assessment.

Timing of maternal internalizing symptom assessment. There was no meta-analytic evidence of difference between antenatal and postnatal effect sizes (antenatal $r = .18$ [$.13, .22$], $k = 33$; postnatal $r = .17$ [$.10, .23$], $k = 12$; p for test of moderation = 0.081). Similarly, there was no evidence of

difference between pregnancy trimesters or between assessments conducted during or after the first six months post-partum. Only one study examined maternal preconception symptoms, although this study replicated findings across two independent samples (adolescent-only $r = .11$; young adult-only $r = .15$; adolescent and young adult $r = .38$) (Spry et al., 2019).

Assessment mode. For all studies of maternal internalizing symptoms and parent-reported infant NA, mothers reported on both their own symptoms and their infant's NA. There was no evidence that effect sizes varied by mode of maternal symptom assessment (clinical interview $r = .19$ [.09, .30], $k = 6$; self-report via symptom checklist $r = .18$ [.14, .22], $k = 38$; p for test of moderation = .628; Table 3), or mode of infant negativity assessment (parent report $r = .18$ [.15, .22], $k = 38$; observational assessment $r = .16$ [-.08, .38], $k = 6$, test of moderation $p = .674$).

Paternal internalizing symptoms

Table 4 shows the meta-analytic estimates of associations between fathers' internalizing symptoms and infant NA, as well as the meta-regression and moderator results. A total of 40 effect sizes from 6 studies, including 1,235 father-infant dyads, were available to estimate the associations between paternal symptoms and the global construct of infant NA. The weighted average effect size from the random effects model was $r = 0.13$ (95% CI .04, .22). The variance in effect sizes attributable to true differences between studies was estimated as $I^2 = 70\%$ of total observed variance, suggesting more heterogeneity than would be expected by sampling error alone. The prediction interval ($r = -.17$ to .40) was wider than the confidence interval around the weighted average effect size, indicating some heterogeneity of true effect sizes between populations.

Insert Table 4 here.

Moderator analyses

Infant NA dimension assessed. Effect sizes were larger for general NA ($r = .20$ [-.19, .53], $k = 2$), sadness ($r = .20$ [.18, .22], $k = 2$), and slow recovery from distress ($r = .21$ [.08, .35]), $k = 2$, smaller for frustration/irritability ($r = .13$ [-.11, .35], $k = 3$), and negligible for fear ($r = .03$ [-.05, .11], $k = 3$), p for test of moderation = .003.

Paternal internalizing construct assessed. There was no meta-analytic evidence of difference in effect size according to the exposure construct measured (anxiety $r = .10$ [-.05, .10], $k = 4$; depression $r = .12$ [.01, .23], $k = 4$; p for test of moderation = .329).

Timing of infant NA assessment. The weighted average effect size was slightly higher in studies with infant NA assessments at ≥ 6 months ($r = .15$ [.01, .29], $k = 4$) than < 6 months ($r = .09$ [-.04, .21], $k = 3$), though the test of moderation was not significant ($p = .138$).

Timing of paternal internalizing symptom assessment. There was meta-analytic evidence that associations between paternal symptoms and infant NA were larger in studies where paternal symptoms were assessed postnatally ($r = .19$ [.09, .28], $k = 3$) than antenatally ($r = .07$ [.04, .19], $k = 3$), p for test of moderation = .022. No studies examined paternal preconception symptoms.

Assessment mode. For all studies of paternal internalizing symptoms and parent-reported infant NA, fathers reported on their own symptoms and their infant's NA. We were unable to examine effect modification by exposure or outcome assessment mode, because only one study used diagnostic assessment of fathers, and no studies used observational rating of infant NA.

Small sample and publication bias

The Fail-Safe N indicated that 6386 studies for mothers, and 52 studies for fathers, with null results would be needed to negate the significance of our sample of studies. The Rosenthal approach was used for all Fail-Safe N tests with the target significance level $p = .05$ (CRAN; Rosenthal, 1979). The Egger test was significant for mothers ($z = 2.21$, $p = .027$), and non-significant for fathers ($z = .84$, $p = .400$). Funnel plots were examined for indication of bias. When no bias is present, the plot resembles an inverted funnel with effect sizes dispersed symmetrically around the mean effect size. Studies with large samples and small standard error are located closer to the top of the funnel, while studies with smaller effect sizes and larger standard error are closer to the bottom (Borenstein et al., 2011). The funnel plots suggested some asymmetry, though the rank correlation test for funnel plot asymmetry indicated a non-significant relationship between sample size and effect size for mothers (Kendall's Tau B = .05, $p = .636$) and fathers (Kendall's Tau B = .20, $p = .719$). The stratified analysis yielded similar effect sizes for published and unpublished literature for mothers (unpublished $r = .22$, $k = 4$; published $r = .17$; $k = 38$) and fathers (unpublished $r = .12$, $k = 3$; published $r = .15$, $k = 3$).

Discussion

We conducted a comprehensive systematic review and meta-analysis of the associations between maternal and paternal internalizing symptoms and infant NA, and examined the impact of potential moderators. Overall, the evidence suggests a modest association between parental symptoms and infant NA, for both mothers and fathers. These associations were similar in size to those of a prior meta-analysis of maternal depression and offspring NA across childhood and adolescence (Goodman et al., 2011). Our findings suggest that these associations are already evident, to a similar degree, in infancy. In addition to increased general distress-proneness in infants of parents with internalizing symptoms, we also found some specificity in associations with the distinct facets of infant NA. In mothers, there was no evidence that associations varied by exposure or outcome timing. In fathers, preliminary findings suggest that associations were larger when paternal symptoms were measured postnatally.

Is there specificity in associations between parent internalizing symptoms and infant NA?

We investigated potential intergenerational homotypic continuity of parent internalizing distress and related dimensions of infant NA (Hankin et al., 2016). Overall, in mothers, associations were largest for the overall dimension of infant NA, and the sadness facet. Associations were smaller (around two thirds of the size) for fear, frustration/irritability and slow recovery from distress. While few studies have examined paternal associations with each facet, the overall pattern of paternal findings was mostly similar to that observed for mothers. Taken together, these findings provide support for parental patterning of general distress-proneness in infants.

As expected, infant fear was associated with higher maternal anxiety, but not maternal depressive symptoms. Prior research has found homotypic continuity of parent/observer-rated fear from infancy to childhood (Putnam et al., 2008), and associations between early life fear and anxiety symptoms in childhood and adolescence (Kagan et al., 1999, 2007). Our findings build on this research by further suggesting that infant behavioral patterns commonly attributed to fear may be an early marker of intergenerational homotypic continuity of fear-based anxious distress. In contrast, we found no evidence of specificity in relation to infant sadness. Behavioral patterns typically attributed to sadness may reflect a non-specific distress proneness akin to the broad NA construct. This is consistent with prior reports that infant behavioral patterns attributed to sadness non-differentially predict all NA facets in later childhood (Putnam et al., 2008), and highlights the challenges inherent in attributing qualitatively distinct emotional states based on infant behavior (Barrett et al., 2019).

A further consideration relates to the conceptualization of parent internalizing symptoms. Anxiety and depression are broad and comorbid constructs (Kessler et al., 2005). Only one study explored their interaction, finding stronger associations with infant NA for maternal depressive symptoms than anxiety, and no evidence of interaction (Rouse & Goodman, 2014). Further research is needed to elucidate unique and joint contributions of each. Moreover, the heterogeneity of parental anxiety has not been explored in relation to infant NA. Dimensional approaches may clarify whether more nuanced internalizing constructs differentially predict conceptually aligned dimensions of infant NA.

Does timing of parent internalizing symptoms or infant NA matter?

In mothers, associations between internalizing symptoms and infant NA did not vary by timing of exposure across pregnancy and the postpartum, or by age of infant at time of NA assessment. Only one study examined preconception symptoms, replicating findings of preconception associations across two independent samples (Spry et al., 2019). Similar sized associations of maternal antenatal and postnatal symptoms are consistent with both the fetal programming and interpersonal stress transmission models. These explanations are not mutually exclusive; indeed, biopsychosocial models of temperament incorporate biological and social influences occurring both before and after birth (Goldsmith et al., 1987; Rothbart & Derryberry, 1981).

Alternatively, given continuities of maternal depression and anxiety from preconception to perinatal (Patton et al., 2015) and from pregnancy to postpartum (Howard et al., 2014), associations at each phase may reflect confounding or mediation by earlier or later maternal symptoms. Studies that jointly modelled antenatal and postnatal symptoms mostly found independent associations with infant NA (Davis et al., 2004, 2007; Henrichs et al., 2009; Spry et al., 2019; Zhang et al., 2017). Given the small evidence base, further repeated-measures studies are needed. A further possible explanation is confounding. In the few studies with adjusted analyses, associations remained after adjustment for demographic and substance use factors (Erickson, 2018; Nomura et al., 2014, 2019; Spry et al., 2019; Zhang et al., 2017). Nonetheless, potential for confounding remains. For example, genetic factors may act as confounders by direct inheritance of predispositions to both internalizing symptoms and NA (Adams et al., 2019), and also influence infant NA via non-genetic mediational pathways including parental symptoms (Kong et al., 2018). Research using natural experiment designs may shed light on these potential influences (Thapar & Rutter, 2019).

Findings in relation to paternal symptoms are preliminary given the small number of studies. However, it is notable that, like the maternal findings, these are consistent with both the fetal programming and interpersonal stress transmission models. The smaller association of antenatal

symptoms with infant NA in fathers compared to mothers supports the fetal programming hypothesis, due to the lack of direct biological in utero programming in fathers (Gage et al., 2016; Thapar & Rutter, 2019). Further, the association of paternal *postnatal* symptoms was much stronger than paternal *antenatal* symptoms, and similar in size to that observed for mothers, consistent with interpersonal stress transmission models. These models suggest that such postnatal paternal associations operate via multiple relational pathways including impacts on parenting, maternal mental health, and the broader family climate (Glasser & Lerner-Geva, 2018; Narayanan & Nærde, 2016). Potential confounding of paternal associations also remains plausible, though the different paternal ante- and postnatal associations are less consistent with this explanation (Gage et al., 2016).

Assessment mode

Our finding of no difference in strength of association by approach to assessing maternal symptoms was consistent with a prior review of older children (Goodman et al., 2011). We also found no evidence of effect modification by method of outcome assessment in mothers. This is in contrast to the common expectation of larger associations with parent-reported infant NA, due to shared method variance and the tendency for women with internalizing symptoms to describe their infants as more reactive (Luoma et al., 2004; Najman et al., 2001). Maternal report may provide a more valid index of NA, across settings and time, than laboratory assessments often conducted under artificial conditions (Bates et al., 2014; Rothbart & Bates, 2006; Shiner & Caspi, 2003). Notably, there was some variability of observer-rated effect sizes. Associations were larger in studies utilizing validated observational protocols and rating scales (Davis et al., 2007; Werner et al., 2007) than in those employing unvalidated or adapted protocols (de Weerth et al., 2013; Gustafsson et al., 2018; Leerkes & Crockenberg, 2003). We were unable to address these questions for fathers.

Strengths and limitations

Our study has notable strengths. We used a rigorous methodology to search and evaluate literature. The protocol was preregistered, and data and code made publicly available in accordance with open science principles. By including the broad dimension of negative affectivity as well as its component facets, we provided a more nuanced understanding of how these may differentially relate to parental symptoms. Further, by examining both maternal and paternal internalizing symptoms across developmental windows, we indirectly addressed questions of mechanisms in order to advance theoretical understanding.

Our review also has limitations. First, adjustments for confounders were few and inconsistently implemented. We therefore meta-analysed unadjusted results. While associations remained after adjustment for baseline confounders in the few studies with adjustments (Erickson, 2018; Nomura et al., 2014, 2019; Spry et al., 2019; Zhang et al., 2017), potential for confounding remains. Thus, we describe meaningful patterns of associations rather than draw causal conclusions (Hernán et al., 2015). The quality assessment also suggests possible bias due to non-representative sampling or missing data in some studies. Two of the five methods we used further suggested possible publication bias and, as with any review, residual publication bias remains likely. We only included studies published in English, which may limit generalizability, though around one third of included studies used data from non-English speaking countries.

Future research directions

Some aspects of our research questions could not be fully addressed due to limitations of the existing evidence base, representing key directions for future research.

Fathers. Associations between fathers' internalizing symptoms and infant NA are important for two reasons. First, comparison of maternal and paternal associations over time can inform our understanding of potential mechanisms and theoretical models. Secondly, links between fathers' internalizing symptoms and the early emotional development of their infants are important in their own right, given the prevalence of paternal perinatal depression and anxiety, evidence of associations with later child socio-emotional development, and the increasing role of fathers in the care of their infants. Yet only 40 estimates from 6 studies were available. Future research should prioritize assessment of both paternal and maternal symptoms, to facilitate comparison as well as investigating their potential interaction.

Preconception. A growing body of research links preconception parental characteristics with children's socio-emotional development. Various mechanisms have been proposed for these associations, including long-term impacts of chronic stress on reproductive biology, and ongoing difficulties with emotional and interpersonal regulation that persist into pregnancy and are associated with caregiving behavior even without postpartum symptoms. These possibilities carry important implications for our understanding of the intergenerational transmission of mental health risk. Yet only one study has examined prospective associations of maternal preconception internalizing symptoms with infant NA. This represents a key evidence gap.

Conclusions

Overall, we found evidence that both maternal and paternal internalizing symptoms are associated with increased NA in infant offspring. While modest, associations in this review are meaningful at a population level, given high prevalence rates of perinatal depression and anxiety (Funder & Ozer, 2019). Nonetheless, the size of observed associations also serve as a reminder that parental internalizing symptoms are only one of many developmental mechanisms that may contribute to infant NA (Cicchetti & Rogosch, 1996). We found increased general distress-proneness in infants of parents with internalizing symptoms, as well as some specificity in patterning of NA facets. These findings underscore the value of considering both the overarching NA dimension and its facets when investigating pathways from parental symptoms to child socio-emotional development. Findings were consistent with both fetal programming and interpersonal stress transmission models, aligning with biopsychosocial models that propose multiple transmission pathways (Goldsmith et al., 1987; Rothbart & Derryberry, 1981). Careful research design is needed to address questions of exposure continuity, confounding, and associated neurodevelopmental and relational processes, as well as evidence gaps regarding preconception processes and paternal symptoms. Greater understanding of underlying mechanisms will inform the nature and timing of interventions to promote good mental health in parents and enhance targeted early interventions for families at risk, ultimately reducing negative impacts on the mental health of the next generation.

Contributors

ES conceptualized the article, developed the methodology, wrote the protocol, identified potential studies, cross-checked extracted data, assessed study quality, and drafted the manuscript. SA extracted the data and conducted the analysis. GY and ES supervised the analysis planning and implementation. CO reviewed the protocol and contributed to development of the methodology. All authors were involved in reviewing analyses, interpreting results, and critically revising the report.

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Conflict of interest

No conflict of interest declared.

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Table 1. Construct definitions for infant negative affectivity and its dimensions

Construct	Definition ^a	Coded constructs ^b
Negative affectivity	General tendency to experience negative affect, including sadness, fear, frustration and lower rate of recovery.	Negative affectivity (CCTI, IBQ, IBQ-R, IBQ-R VSF) Negative reactivity (DTS, ITSC, HIBRP, still-face/infant negative expression and vocalizations, maternal separation/negative vocalizations) Negative reactivity (ECBQ) Reactivity (STST) Mood (EITQ)
<i>Facet dimensions</i>		
Sadness	Lowered mood and activity in relation to experience of suffering, physical state, object loss, or inability to perform a desired action; general low mood. <i>“Did the baby seem sad when the caregiver was gone for an unusually long period of time?”</i>	Sadness (IBQ-R)
Fear	Showing distress or startled by sudden changes in stimulation or novel stimuli; inhibited response to novelty. <i>“How often during the last week did the baby startle to a sudden or loud noise?”</i>	Fear (IBQ, IBQ-R, TTS)
Frustration / irritability	Showing distress (e.g., crying or fussing) while (a) confined or restricted to a place; (b) involved in normal caregiving activities (e.g., face washing); or (c) unable to perform a desired action. <i>“When placed on his/her back, how often did the baby fuss or protest?”</i>	Frustration tolerance (TTS, RITQ) Distress to limitations (IBQ, IBQ-R, arm restraint/negative affective expression and vocalizations) Irritability (MABS)
Slow recovery from distress	Rate of recovery from peak distress, excitement, or general arousal- <i>“When frustrated with something, how often did the baby calm down within 5 minutes?”</i>	Falling reactivity (IBQ, IBQ-R)

^a Descriptions adapted from Gartstein, M. A., & Rothbart, M. K. (2003). Studying infant temperament via the revised infant behavior questionnaire. *Infant Behavior & Development*, 26(1), 64-86.

^b Scale abbreviations are defined as: CCTI = Colorado Child Temperament Inventory; DTS = Difficult Temperament Scale; ECBQ = Early Childhood Behaviour Questionnaire; EITQ = Early Infant Temperament Questionnaire; HIBRP = Harvard Infant Behavioural Reactivity Protocol; IBQ = Infant Behaviour Questionnaire; IBQ-R = Infant Behaviour Questionnaire-Revised; IBQ-R VSF = Infant Behaviour Questionnaire-Revised Very Short Form; INAS = Infant Negative Affectivity Scale; ITSC = Infant Toddler Symptom Checklist; MABS = Mother and Baby Scale; Lab-TAB = Laboratory Temperament Assessment Battery; RITQ = Revised Infant Temperament Questionnaire; STST = Short Temperament Scale for Toddler; TTS = Toddler Temperament Questionnaire.

Table 2. Characteristics of studies included

Study	Country	N	Exposure	Exposure measure ^a	Preconception exposure	Antenatal exposure ^b	Postnatal exposure	Parent assessed	Outcome	Outcome measure ^{cd}	Infant age at follow-up (months)
Alvik (2011)	Norway	1303	Anx; Dep	H-SCL ^s		T3		Mother	Negative affectivity	DTS ^p ; ITSC ^p ; SD ^p	6
Baibazarova (2013)	Netherlands	158	Anx	STAI ^s		T2		Mother	Frustration/irritability; Fear	IBQ-R ^p	3
Bhat (2015)	India	100	Mixed	GHQ-28 ^s		T3		Mother	Negative affectivity	EITQ ^p	1
Braithwaite (2015)	UK	40; 48	Dep	EPDS ^s		T2; T3		Mother	Frustration/irritability	IBQ ^p	2
Chazan (1998)	USA	93	Dep	CES-D ^s		ns		Mother	Negative affectivity	CCTI ^p	4
Coplan (2005)	Canada	46	Anx	STAI ^s		T3		Mother	Frustration/irritability	IBQ ^p	3
Davis (2004)	USA	22	Anx; Dep	STAI ^s ; CES-D ^s		T3	2 months	Mother	Negative affectivity	HIBRP protocol and scoring ^o	4
Davis (2007)	USA	247	Anx; Dep	STAI ^s ; CES-D ^s		T2; T3		Mother	Fear	IBQ ^p	2
de Weerth (2013)	Netherlands	105; 97; 95	Anx	STAI ^s ; PRAQ-R ^s		T3		Mother	Negative affectivity	Study-derived maternal separation protocol with study-derived scoring ^o	9

Study	Country	N	Exposure	Exposure measure ^a	Preconception exposure	Antenatal exposure ^b	Postnatal exposure	Parent assessed	Outcome	Outcome measure ^{cd}	Infant age at follow-up (months)
Della Vedova (2014)	Italy	107	Anx; Dep	STAI ^s ; CES-D ^s		T3		Mother	Negative affectivity	EITQ ^p	3
Edwards (2017)	USA	99	Anx; Dep	BDI-II ^s ; BAI ^s			6 months	Mother	Negative affectivity	IBQ-R ^p	8
Erickson (2018)	USA	142	Anx; Dep	STAI ^s ; PRAQ-R ^s ; EPDS ^s		T3		Mother	Negative affectivity	IBQ-R ^p	2
Erickson (2019)	Canada	185; 163	Anx; Dep	EPDS ^s ; HAM-D ^s ; HAMA ^s		T3	3 months	Mother	Frustration/irritability; Fear	IBQ ^p	3; 6; 10
Fernandes (2018)	India	58	Dep	EPDS ^s		T3		Mother	Negative affectivity; Frustration/irritability	IBQ ^p	2
Forman (2007)	USA	136	Dep	SCID ^d ; HAM-D ^s			6 months	Mother	Negative affectivity	IBQ ^p	9
Frost (1996)	USA	476	Anx; Dep	STAI ^s ; CES-D ^s		T2		Father	Frustration/irritability	IBQ ^p	1
Gustafsson (2018)	USA	68	Dep	CES-D ^s		T2		Mother	Negative affectivity; Slow recovery from distress; Frustration/irritability; Fear; Sadness	IBQ-R ^p ; Still-face and arm-restraint protocols with study-derived scoring ^o	6
Henrichs (2009)	Netherlands	2997	Anx	BSI ^s ; POQ ^s		T1; T2		Mother	Frustration/irritability; Fear; Slow recovery from distress; Sadness	IBQ-R ^p	6

Study	Country	N	Exposure	Exposure measure ^a	Preconception exposure	Antenatal exposure ^b	Postnatal exposure	Parent assessed	Outcome	Outcome measure ^{cd}	Infant age at follow-up (months)
Isosavi (2017) ^d	Israel	477	Dep	EPDS ^s		T2		Mother	Fear; Frustration/irritability; Sadness; Slow recovery from distress	IBQ-R ^p	4
Jonas (2015)	Canada	170	Anx	STAI ^s			3 months	Mother	Negative affectivity	ECBQ ^p	18
Jover (2014)	Spain	317	Anx; Dep	STAI ^s ; EPDS ^s			2 days	Mother	Frustration/irritability	MABS ^p	2
Kim (2020)	New Zealand	5568	Dep	EPDS ^s		T3		Mother	Negative affectivity; Fear	IBQ-R VSF ^p	9
Kukkonen (2019)	Finland	347	Dep	EPDS ^s			3 months; 6 months	Mother; Father	Negative affectivity	IBQ-R ^p	6; 12
Leerkes (2003)	USA	90	Dep	CES-D ^s		T3	5 months	Mother	Frustration/irritability	IBQ ^p ; Lab-TAB and arm restraint protocols with INAS scoring ^o	5; 6
Lemola (2009)	Switzerland	374; 323	Dep	EPDS ^s			1.5 months; 5 months	Mother	Frustration/irritability	IBQ ^p	5; 17
Luecken (2015)	USA	312	Dep	EPDS ^s		T1		Mother	Negative affectivity	IBQ-R ^p	1
McLean (2019)	Australia	104	Dep	EPDS ^s			6 months	Mother	Negative affectivity	STST	16

Study	Country	N	Exposure	Exposure measure ^a	Preconception exposure	Antenatal exposure ^b	Postnatal exposure	Parent assessed	Outcome	Outcome measure ^{cd}	Infant age at follow-up (months)
Metz (2018)	Netherlands	135; 131; 130	Anx	ADIS ^d		ns		Mother; Father	Fear	IBQ-R ^p	4; 12
Moscardino (2006)	Italy	28	Dep	EPDS ^e ; POMS ^e			2 months	Mother	Negative affectivity	Routine vaccination with study derived scoring ^o	4.5
Nolvi (2016)	Finland	282	Anx; Dep	SCL-90 ^e ; PRAQ-R2 ^e ; EPDS ^e		T1; T2; T3		Mother	Negative affectivity; Fear; Sadness; Slow recovery from distress; Frustration/irritability	IBQ-R ^p	6
Nomura (2014)	USA	141	Dep	SCID ^d		ns		Mother	Fear; Sadness; Slow recovery from distress; Frustration/irritability	IBQ-R ^p	6
Nomura (2019)	USA	310	Dep	EPDS ^e		T2		Mother	Frustration/irritability; Fear; Slow recovery from distress; Sadness	IBQ-R ^p	6
Peltola (2017)	Finland	173	Anx	STAI ^e		T3		Mother	Negative affectivity	IBQ-R ^p	8
Pluess (2011)	Netherlands	1513	Anx	BSI ^e		T2		Mother	Negative affectivity	IBQ-R ^p	6
Potapova (2014)	USA	98	Anx; Dep	BDI-II ^e ; BAI ^e			4 months	Father	Negative affectivity	IBQ-R ^p	6

Study	Country	N	Exposure	Exposure measure ^a	Preconception exposure	Antenatal exposure ^b	Postnatal exposure	Parent assessed	Outcome	Outcome measure ^{cd}	Infant age at follow-up (months)
Prino (2016)	Italy	58	Anx; Dep	STAI ^s ; EPDS ^s		T2		Mother; Father	Frustration/irritability; Fear; Slow recovery from distress; Sadness	IBQ-R ^p	3
Rouse (2014)	USA	77	Anx; Dep	STAI ^s ; SCID ^d ; BDI-II ^s		T1; T2; T3		Mother	Negative affectivity; Fear; Slow recovery from distress; Sadness; Frustration/irritability	IBQ-R ^p	3
Sharp (2012)	UK	271	Dep	EPDS ^s		T3		Mother	Frustration/irritability; Fear	IBQ-R ^p	6
Spry (2019)	Australia	1231	Anx; Dep	EPDS ^s ; CIS-R ^d ; GHQ-12 ^s ; SMFQ ^s ; RBPC-SF ^s ; RCMAS ^s ; DASS-21 ^s	Adolescent; young adult	T3		Mother	Negative affectivity	STST ^p	12
Sugawara (1999)	Japan	817	Dep	SDS ^s			5 days; 12 months	Mother	Fear; Frustration/irritability	RITQ ^p ; TTS ^p	6; 18
Thomas (2017)	Canada	254	Anx; Dep	PAS ^s ; EPDS ^s		T2; T3		Mother	Negative affectivity	IBQ-R ^p	3
Ting (2012)	China	121	Anx; Dep	HADS ^s ; EPDS ^s			1.5 months	Father	Frustration/irritability; Fear; Sadness; Slow recovery from distress	IBQ-R ^p	6
van den Heuvel (2015)	Netherlands	90	Anx	SCL-90 ^s		T2		Mother	Negative affectivity	IBQ-R ^p	10

Study	Country	N	Exposure	Exposure measure ^a	Preconception exposure	Antenatal exposure ^b	Postnatal exposure	Parent assessed	Outcome	Outcome measure ^{cd}	Infant age at follow-up (months)
Werner (2007)	USA	50	Anx; Dep	SCID ^d		T2		Mother	Negative affectivity	IBQ ^p ; HIBRP ^o	4
Zhang (2017)	USA	153	Dep	EPDS ^s		T2		Mother	Negative affectivity	IBQ-R ^p	6

^a s = symptom checklist; d = diagnostic interview

^b T1 = first trimester of pregnancy; T2 = second trimester of pregnancy; T3 = third trimester of pregnancy; ns = pregnancy trimester not specified. If a study reported both trimester-specific estimates and mean pregnancy estimates, we only included trimester-specific estimates.

^c p = parent-report; o = observation

^d Scale abbreviations are defined as: ADIS = Anxiety Disorder Interview Schedule; BAI = Beck Anxiety Inventory; BDI-II = Beck Depression Inventory-II; BSI = Brief Symptom Inventory; CCTI = Colorado Child Temperament Inventory; CES-D = Centre for Epidemiological Studies – Depression; CIS-R = Revised Clinical Interview Schedule; DASS-21 = Depression Anxiety and Stress Scale-21 item version; Dep = depression; DTS = Difficult Temperament Scale; ECBQ = Early Childhood Behaviour Questionnaire; EITQ = Early Infant Temperament Questionnaire; EPDS = Edinburgh Postnatal Depression Scale; GHQ-12 = General Health Questionnaire-12 item version; GHQ-28 = General Health Questionnaire-28 item version; HADS = Hospital Anxiety and Depression Scale; HAMD = Hamilton Rating Scale for Depression; HAMA = Hamilton Rating Scale for Anxiety; HIBRP = Harvard Infant Behavioural Reactivity Protocol; H-SCL = Hopkins Symptom Checklist; IBQ = Infant Behaviour Questionnaire; IBQ-R = Infant Behaviour Questionnaire-Revised; IBQ-R VSF = Infant Behaviour Questionnaire-Revised Very Short Form; INAS = Infant negative affectivity scale; ITSC = Infant Toddler Symptom Checklist; MABS = Mother and Baby Scale; Lab-TAB = Laboratory Temperament Assessment Battery; PAS = Pregnancy Anxiety Scale; POMS = Profile of Mood States; POQ = Pregnancy Outcome Questionnaire; PRAQ-R = Pregnancy-Related Anxiety Questionnaire-Revised; PRAQ-R2 = Pregnancy-Related Anxiety Questionnaire 2-Revised; RBPC-SF = Revised Behaviour Problem Checklist Short Form; RCMAS = Revised Children's Manifest Anxiety Scale; RITQ = Revised Infant Temperament Questionnaire; SCID = Structured Clinical Interview for DSM-IV; SCL-90 = Symptom Checklist 90; SD = study derived items; SMFQ = Short Mood and Feelings Questionnaire; STAI = State-Trait Anxiety Inventory; STST = Short Temperament Scale for Toddlers; TTS = Toddler Temperament Questionnaire.

Table 3. Results of moderator analyses for the association between maternal internalizing symptoms and infant negative affectivity

	k	n	r	95% CI	I ²	p	model p
Overall association	42	149	0.17	(0.14 0.21)	80.76	<0.001	-
Results of moderator analyses							
Exposure and outcome constructs assessed							
Infant negative affectivity ^a	42	193					0.044
General negative affectivity	26	62	0.21	(0.17 0.26)	85.13	<0.001	
Sadness	8	21	0.22	(0.06 0.37)	87.05	0.015	
Fear	15	39	0.12	(0.07 0.16)	81.21	<0.001	
Frustration/irritability	18	50	0.14	(0.08 0.20)	72.22	<0.001	
Slow recovery from distress	8	21	0.14	(0.03 0.24)	74.54	0.021	
Maternal internalizing symptoms ^b	38	135					0.571
Depression	29	76	0.17	(0.12 0.21)	84.53	<0.001	
Anxiety	19	59	0.19	(0.15 0.23)	52.06	<0.001	
Timing of assessment							
Infant negative affectivity	42	149					0.865
<6 months	22	75	0.16	(0.11 0.21)	52.25	<0.001	
≥6 months	24	74	0.17	(0.12 0.22)	87.03	<0.001	
Maternal internalizing symptoms	42	149					0.081
Preconception ^c	1	3	-	- -	-	-	
Antenatal ^d	33	116	0.18	(0.13 0.22)	84.46	<0.001	0.797
Trimester 1	2	5	0.15	(-0.06 0.35)	48.42	0.069	
Trimester 2	15	59	0.18	(0.11 0.25)	74.15	<0.001	
Trimester 3	20	44	0.18	(0.12 0.23)	87.23	<0.001	
Postnatal	12	30	0.17	(0.10 0.23)	53.75	<0.001	0.307
<6 months	9	24	0.14	(0.06 0.22)	55.55	0.005	
≥6 months	5	6	0.19	(0.08 0.31)	44.13	0.012	
Assessment mode							
Infant negative affectivity	42	149					0.674
Observer-rated	6	19	0.16	(-0.08 0.38)	67.94	0.145	
Parent-report	38	130	0.18	(0.15 0.22)	81.83	<0.001	
Maternal internalizing symptoms	42	149					0.628
Self-report	38	135	0.18	(0.14 0.22)	83.28	<0.001	
Clinical interview	6	14	0.19	(0.09 0.30)	81.69	0.006	
Publication status							
Published study	38	140	0.17	(0.13 0.21)	82.11	<0.001	0.076
Unpublished study	4	9	0.22	(0.15 0.29)	0.00	0.006	

Note: k = number of studies; n = number of estimates; r = Pearson correlation coefficient; I² = proportion of observed variance not attributable to sampling error; p = p value for the Pearson correlation coefficient of exposure-outcome associations within the specified subgroup; model p = p value for the test of effect size differences between levels of the moderator variable.

^a The meta-regression and moderation analyses for outcome construct assessed was examined using all estimates from all studies. The remainder of the analyses excluded estimates for the facet dimensions if estimates for the global negative affectivity construct were also provided, to avoid double-counting data points.

^b Studies were excluded from the meta-regression and moderation analysis by exposure construct if depression and/or anxiety were presented as a single combined estimate.

^c Empty rows indicate too few studies in the specified category ($k < 2$) for inclusion in meta-regression or moderator analyses.

^d Studies were excluded from the meta-regression and moderation analysis for exposure timing by pregnancy trimester if pregnancy trimester was unknown.

Table 4. Results of moderator analyses for the association between paternal internalizing symptoms and infant negative affectivity

	k	n	r	95% CI	I ²	p	model p
Overall association	6	40	0.13	(0.04 0.22)	60.69	0.014	-
Results of moderator analyses							
Exposure and outcome constructs assessed							
Infant negative affectivity	6	40					0.003 ^a
General negative affectivity	2	4	0.20	(-0.19 0.53)	0.00	0.099	
Sadness	2	8	0.20	(0.18 0.22)	89.00	0.005	
Fear	3	10	0.03	(-0.05 0.11)	3.10	0.210	
Frustration/irritability	3	10	0.13	(-0.11 0.35)	72.40	0.139	
Slow recovery from distress	2	8	0.21	(0.08 0.35)	59.78	0.033	
Paternal internalizing symptoms ^b	5	39					0.329
Anxiety	4	23	0.10	(-0.05 0.24)	71.12	0.128	
Depression	4	16	0.12	(0.01 0.23)	50.27	0.039	
Timing of assessment							
Infant negative affectivity	6	40					0.138
<6 months	3	27	0.09	(-0.04 0.21)	65.23	0.096	
≥6 months	4	13	0.15	(0.01 0.29)	35.62	0.041	
Paternal internalizing symptoms	6	40					0.022
Antenatal	3	28	0.07	(-0.04 0.19)	65.30	0.109	-
Postnatal	3	12	0.19	(0.09 0.28)	0.00	0.018	
Publication status							
Published study	3	27	0.15	(-0.12 0.40)	71.85	0.140	0.781
Unpublished study	3	13	0.12	(-0.10 0.33)	60.76	0.133	

Note: k = number of studies; n = number of estimates; r = Pearson correlation coefficient; I² = proportion of observed variance not attributable to sampling error; p = p value for the Pearson correlation coefficient of exposure-outcome associations within the specified subgroup; model p = p value for the test of effect size differences between levels of the moderator variable.

^a Using Eigen-decomposition F (EDF) test for small sample correction.

^b Studies were excluded from the meta-regression and moderation analysis for exposure construct if depression and/or anxiety were presented as a single combined estimate.

Figure 1. Prisma flow diagram reporting study selection process.