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Sex differences in the association between maternal depression and child and adolescent cognitive development: a systematic review and meta-analysis

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Abstract

Background. Maternal depression is negatively associated with cognitive development across childhood and adolescence, with mixed evidence on whether this association differs in boys and girls. Herein, we performed a systematic review and meta-analysis of sex-specific estimates of the association between maternal depression and offspring cognitive outcomes.

Method. Seven databases (PubMed, EMBASE, PsycINFO, ERIC, CINAHL, Scopus, ProQuest) were searched for studies examining the longitudinal association between maternal depression and offspring (up to 18 years) cognitive outcomes. Studies were screened and included based on predetermined criteria by two independent reviewers (Cohen's $\kappa = 0.76$). We used random-effects models to conduct a meta-analysis and used meta-regression for subgroup analyses. The PROSPERO record for the study is CRD42020161001.

Results. Twelve studies met inclusion criteria. Maternal depression was associated with poorer cognitive outcomes in boys [Hedges' $g = -0.36$ (95% CI −0.60 to −0.11)], but not in girls [−0.17 (−0.41 to 0.07)]. The association in boys varied as a function of the measure of depression used ($b = -0.70$, $p = 0.005$): when maternal depression was assessed via a diagnostic interview, boys [−0.84 (−1.23 to −0.44)] had poorer cognitive outcomes than when a rating scale was used [−0.16 (−0.36 to 0.04)].

Conclusions. This review and meta-analysis indicates that maternal depression is only significantly associated with cognitive outcomes in boys. Understanding the role of sex differences in the underlying mechanisms of this association can inform the development of targeted interventions to mitigate the negative effects of maternal depression on offspring cognitive outcomes.

Introduction

Maternal depression consists of persistent sad mood or loss of pleasure accompanied by cognitive and somatic symptoms that are severe and persist over time during pregnancy and postnatally (American Psychiatric Association, 2013). Both clinical (assessed via diagnostic interview; 11–13%) and sub-clinical (assessed via rating scale; 15–25%) levels of maternal depression are prevalent in the general population (Gelaye, Rondon, Araya, & Williams, 2016; Howard et al., 2014). Studies report consistent associations of clinical and sub-clinical maternal depression with poor offspring outcomes across childhood and adolescence (Stein et al., 2014). This includes cognitive developmental outcomes, which consist of age-related increases in language, intellectual, academic, and executive functioning capabilities which are affected by genetic, social, and psychological factors that are sensitive to broader contextual determinants (Walker et al., 2011). Over the past two decades, researchers have systematically investigated the role of maternal depression as a psychological factor associated with offspring's cognitive outcomes (Grace, Evindar, & Stewart, 2003; Liu et al., 2017; Rogers et al., 2020; Sanger, Iles, Andrew, & Ramchandani, 2015), with some studies suggesting that these associations are stronger in boys (Grace et al., 2003; Sanger et al., 2015). However, there is still no clear indication of the role of sex differences in this association. Herein we present findings from the first meta-analysis of differences in the association between maternal depression and cognitive outcomes in boys and girls.

Using both theory and empirical evidence to examine whether there are sex differences in the association between maternal depression and offspring outcomes is relevant for the design,

implementation, and evaluation of interventions that aim to mitigate the negative effects of maternal depression. From a theoretical perspective, biological and developmental factors can contribute to variations in how boys and girls react to maternal depression (Kraemer, 2000). For example, it is possible that the maturational advantage held by girls in cognitive skills (e.g. language, reading) in early childhood might protect from the negative impact of (postnatal) maternal depression (Galsworthy, Dionne, Dale, & Plomin, 2000; Grace et al., 2003; Logan & Johnston, 2010; Sohr-Preston & Scaramella, 2006). This suggests that boys may be more vulnerable to the effect of maternal depression and that they may therefore experience poorer cognitive outcomes compared to girls. Another factor possibly contributing to sex differences is male foetuses' increased vulnerability to antenatal maternal stress (i.e. anxiety, depression, elevated stress levels) and its neurodevelopmental consequences (Bale & Epperson, 2015; DiPietro & Voegtline, 2017; O'Donnell & Meaney, 2017; Sandman, Glynn, & Davis, 2013). However, the specific pathways through which exposure to (antenatal) maternal depression may increase boys' risk for poorer cognitive outcomes are not clear. Although children exposed to antenatal depression are more likely to be born prematurely or with low birthweight – both of which are more prevalent in boys (DiPietro & Voegtline, 2017) – and these conditions are subsequently associated with poorer cognitive outcomes, there is no clear evidence that prematurity or low birthweight mediate the association between maternal depression and offspring cognitive outcomes (Dadi, Miller, Bisetegn, & Mwanri, 2020; Gelaye et al., 2016; Linsell, Malouf, Morris, Kurinczuk, & Marlow, 2015; O'Donnell & Meaney, 2017).

From an empirical perspective, there is mixed evidence of sex differences in the association between maternal depression and offspring cognitive outcomes. Grace et al. (2003) provided the first narrative synthesis of sex differences in this association and concluded that overall, sons of depressed mothers had lower scores on standardized measures of cognitive outcomes than daughters of depressed mothers. In a systematic review focusing on cognitive outcomes in adolescents, Sanger et al. (2015) again found evidence of a stronger association between maternal depression and cognitive outcomes in boys, however some studies found no evidence of sex differences in this association (e.g. Galler et al., 2004). Recent publications do not provide a clear indication of whether boys truly are more vulnerable than girls, with some studies reporting a stronger association in girls (e.g. Ahun et al., 2020) and others reporting no sex differences (e.g. Ng-Knight, Shelton, Frederickson, McManus, & Rice, 2018). Although there have been two recent meta-analyses of the association between maternal depression and cognitive outcomes across childhood and adolescence (Liu et al., 2017; Rogers et al., 2020), neither has advanced our understanding of sex differences in this association.

The objectives of the present study were to systematically review the literature on longitudinal associations between maternal depression and offspring (up to age 18 years) cognitive outcomes and to provide the first meta-analysis of sex-specific estimates of this association.

Methods

This study adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement for standard reporting [PRISMA (Table S1); Moher, Liberati, Tetzlaff, Altman, & PRISMA Group, 2009). The protocol for this review was preregistered on the PROSPERO international prospective register of systematic reviews (registration number CRD42020161001). The only deviation we made from this protocol was the addition of a new subgroup in the meta-regression analyses as specified below.

Search strategy

Studies included in this meta-analysis were identified using both electronic and manual searches. We searched for relevant studies on maternal depression and offspring cognitive outcomes across seven electronic databases (PubMed MEDLINE, Embase, ERIC, PsycINFO, CINAHL, Scopus, and ProQuest Dissertations and Theses Online) from inception to January 2020. Search terms included the concepts of maternal depression ([(*postnatal or postpartum or perinatal or peri-natal or antenatal or maternal or mother*) *AND* (*depression or depressive symptoms*)] *OR major depression OR minor depression*) and cognitive development (*child development OR cognition OR* [*cognitive or language or verbal or intelligence or academic or reading or writing or development or learning*]). The search concepts were combined with the Boolean operator 'and'. The specific search equations used in each database can be found in Table S2. Follow-up manual searches were conducted from the reference lists of systematic reviews, meta-analyses, and theses retrieved from the electronic search (Ebeid, 2018; Grace et al., 2003; Liu et al., 2017; Sanger et al., 2015).

Study inclusion criteria

A study was considered eligible for inclusion if it: (i) provided sex-specific estimates of the quantitative association between clinical or sub-clinical maternal depression and offspring cognitive outcomes in a longitudinal study; (ii) was published in a peer-reviewed journal in English or French; (iii) assessed maternal depression during pregnancy or any time after birth; (iv) assessed cognitive outcomes in offspring 18 years old or younger; (v) did not use data from a case study or randomized controlled trial (to avoid bias introduced by the potential impact of the trial on the association of interest); and (vi) had a population-based sample of children and mothers in that context. If the study population was described as a specific subset of children/adolescents (e.g. born prematurely) or mothers (e.g. recruited because they had a medical condition or were taking medication, alcohol, or other drugs), the study was excluded.

Study selection

The article selection process consisted of three steps. First, MNA and CG independently screened the titles and abstracts of the 9145 articles (after removal of duplicates) identified through electronic and manual searches. Studies deemed by both reviewers to not fulfill the inclusion criteria were excluded. Second, the remaining studies were independently read in full by the two reviewers and selected for inclusion in the analysis if identified as relevant by both reviewers. There was substantial agreement between reviewers (Cohen's $\kappa = 0.76$) (Viera & Garrett, 2005). Disagreements were resolved in team discussions with GG and SMC. Third, data from each selected study were abstracted onto a standardized form independently by the two reviewers, including authors, year of publication, country where the study was conducted, study population, sample size, study design, exposure and

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outcome measures, age of the child/adolescent at exposure and outcome assessments, and sex-specific estimates.

Study quality assessment

We extracted the necessary information to assess the risk of bias using the National Institutes of Health Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies, which was designed to examine study quality according to Cochrane collaboration criteria (National Heart Lung and Blood Institute: National Institutes of Health, 2014). The tool includes items assessing the clarity of the research question and the study design (i.e. definition of sample, reporting of attrition), the use of valid exposure and outcome measures, and whether key potential confounding variables were included in analyses (Table S3). Each item is scored as yes, no, or not reported. To assess publication bias, we regressed studies' effect estimates onto their standard errors using Egger's linear regression test and a funnel plot (Borenstein, Hedges, Higgins, & Rothstein, 2011). A significant result of the test suggests that the plot is asymmetric, and bias is present, while a non-significant result suggests minimal bias.

Meta-analysis

Data were analyzed from September to November 2020 using the *metafor* version 2.0 (Viechtbauer, 2010) and *robumeta* version 2.0 (Fisher, Tipton, & Zhipeng, 2017) packages in R version 4.0.3 (R Core Team, 2019). The *robumeta* package uses a robust variance meta-analysis approach which accounts for multiple effects from the same sample (Hedges, Tipton, & Johnson, 2010). All studies reported offspring cognitive outcomes as continuous variables using a variety of measures. We used maternal depression as our exposure to capture studies using either a rating scale or a diagnostic interview to assess depression. If a study assessed depression at several time points, we used the mean of children/adolescents' age at those time points. When a study used more than one measure to assess depression or cognitive outcomes, we gave priority to the measure that was more commonly used (i.e. more frequently cited) in the literature. If a study used both a rating scale and a diagnostic interview to assess depression, the association with the diagnostic interview measure was used.

We converted sex-specific estimates of the association between maternal depression and cognitive outcomes to a common bias-corrected metric of Hedges' *g* (Borenstein et al., 2011; Lüdecke, 2019; Table S4), which represents the difference between two group means (cognitive scores for daughters and sons of mothers with high *v.* low/no depression or higher *v.* lower levels of depression) divided by the pooled standard deviation (Cohen, 1988; Hedges, 1981). This metric uses a weighted pooled standard deviation to provide an effect size estimate which is not biased by small samples. Where studies did not provide all the relevant data to convert sex-specific estimates into Hedges' *g*, we reached out to authors to provide said data. Out of seven authors contacted, three provided data. We examined the crude effect of maternal depression on offspring cognitive outcomes using Hedges' *g* and used guidelines to interpret effect sizes that are meaningful, where 0.10 is small, 0.20 is medium, 0.30 is large, and >0.40 is very large (Funder & Ozer, 2019). We used standard meta-analytical methods to estimate the summary effect sizes using the inverse variance approach and robust variance random-effects models.

Heterogeneity was assessed by calculating the I^2 index (Table S4). We also conducted subgroup analyses by comparing sex-specific estimates across the following categorical variables: time of exposure to maternal depression (exposure during pregnancy *v.* after birth), method of measuring maternal depression (rating scale *v.* diagnostic interview), child age at cognitive outcome assessment [childhood (birth to 10 years) *v.* adolescence (11–18 years)], and length of time between assessments of exposure and outcome [short (≤1 year) *v.* long (>1 year)]. All subgroups except the length of time between exposure and outcome assessments were prespecified in the registered protocol. Meta-regressions were conducted to determine whether the sex-specific associations between maternal depression and offspring cognitive outcomes varied within these subgroups. Two-sided $p < 0.05$ indicated significance based on the regression of sex-specific meta-analytic estimates onto each of these subgroups. We ran sensitivity analyses to determine whether an outlier study (Ng-Knight et al., 2018) affected reported estimates. Results were similar with and without this study, so the former are henceforth reported.

Results

Study characteristics and quality

Of the 9145 articles assessed for eligibility, we screened the full text of 167 (Fig. 1). In total, 12 articles from eight unique datasets met eligibility criteria and were included in the meta-analysis (Table 1). Studies were conducted in six countries: six in the UK (Hay et al., 2001; Hay, Pawlby, Waters, & Sharp, 2008; Murray et al., 2010; Murray, Hipwell, Hooper, Stein, & Cooper, 1996; Ng-Knight et al., 2018; Sharp et al., 1995), two in Canada (Ahun et al., 2020; Paquin et al., 2020), and one each in Australia (Cornish et al., 2005), the USA (Davies & Windle, 1997), South Africa (Donald et al., 2019), and Finland (Nolvi et al., 2018).

According to the quality assessment, most articles used a range of robust study design features (Table S5). All studies clearly stated their research objectives, allowed sufficient time between the assessment of exposure and outcome (defined as 4 months; Liu et al., 2017), and used valid and reliable measures. However, studies varied as to whether maternal depression was assessed continuously or categorically. The most notable risks of bias related to a lack of information on statistical power to determine sample size (only one study provided this information; Murray et al., 2010) and sample selection and attrition. Five studies reported dropout rates >20%, suggesting a risk of selective sampling bias (e.g. greater loss to follow-up of mothers with higher levels of depression). Another key risk of bias was the lack of sex-specific estimates of the adjusted associations between maternal depression and cognitive outcomes. Although most studies included covariates in their analyses, only two (Ahun et al., 2020; Ng-Knight et al., 2018) reported separate adjusted associations for boys and girls. Results should therefore be interpreted within the context of these limitations. With respect to publication bias, the funnel plot was roughly symmetric with non-significant *p* values from the Egger's linear regression test ($p = 0.176$), indicating minimal publication bias (Fig. S1).

Meta-analysis and meta-regression results

The meta-analysis of crude estimates from the 12 studies showed a statistically significant association between maternal depression and cognitive outcomes in boys and a non-significant association in girls (Figs 2 and 3). This indicates that on average, boys

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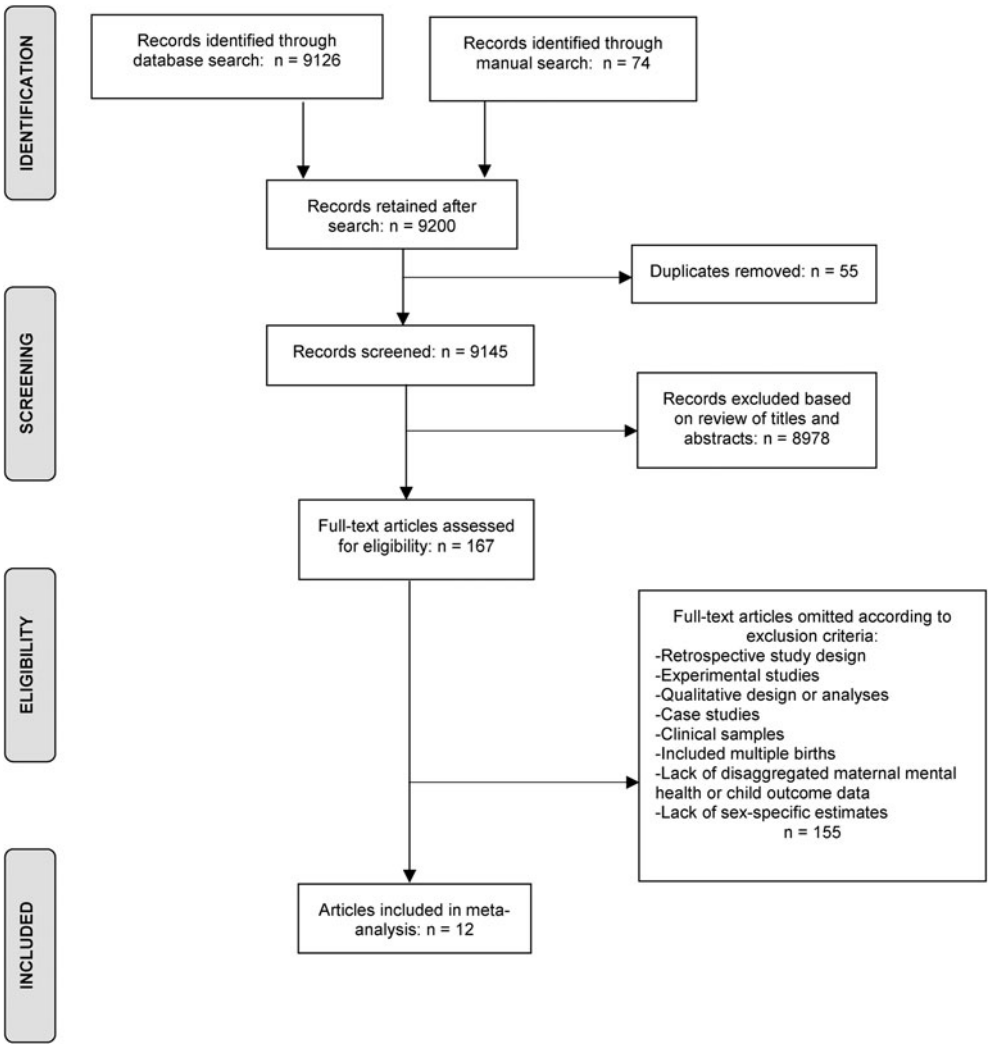


Fig. 1. PRISMA flow diagram of selection procedure. The reasons to exclude initially identified articles to reach $n = 167$ were: (1) the study was non-relevant to our research questions, (2) the study was a systematic review or meta-analysis, (3) study participants were beyond age range or not from a population-based sample, and (4) study outcomes did not focus on cognitive development.

exposed to elevated levels of maternal depression had a −0.36 standardized mean difference on assessments of cognitive outcomes compared to boys who were not exposed. The overall difference between boys' and girls' estimates was not significant ($b = 0.25$, $p = 0.145$). There was significant heterogeneity in the estimates in both boys and girls across studies.

Subgroup analyses (Tables S6–S9) revealed that maternal depression as assessed by a diagnostic interview was more strongly associated with boys' cognitive outcomes [$n = 6$ studies; Hedges' $g = -0.84$ (95% CI −1.23 to −0.44)] than that assessed via rating scales [$n = 6$ studies; −0.16 (–0.36 to 0.04)]. Furthermore, boys exposed postnatally to maternal depression [$n = 10$ studies; −0.40 (–0.73 to −0.08)] had poorer cognitive outcomes than those exposed antenatally [$n = 2$ studies; −0.25 (–1.58 to 1.07)] and boys whose cognitive outcomes were assessed more than 12 months after assessment of maternal depression [$n = 8$ studies; −0.52 (–0.91 to −0.13)] had poorer cognitive outcomes compared to those with a shorter amount of time between maternal depression and cognitive assessments [$n = 4$ studies; −0.16 (–0.65 to 0.33)]. Meta-regression analyses showed that only the difference between boys whose mothers were assessed via diagnostic interview *v.* those whose mothers were assessed via rating scale was significant ($b = -0.70$, $p = 0.005$).

Subgroup analyses in girls revealed that maternal depression remained non-significantly associated with cognitive outcomes across all but one subgroup. Maternal depression was only associated with girls' cognitive outcomes when there was more than 12 months between assessments of maternal depression and cognitive outcomes [$n = 8$ studies; –0.17 (–0.27 to −0.08)]. However, meta-regression analyses revealed that this estimate was not significantly different ($b = 0.07$, $p = 0.890$) from that of girls with a shorter amount of time between assessments [$n = 4$ studies; −0.24 (–1.22 to 0.74)].

Discussion

This is the first meta-analysis of sex-specific estimates of the association between maternal depression and offspring cognitive outcomes. Results from 12 articles showed consistent evidence of moderate-to-large associations in boys. This association varied as a function of the measure of maternal depression used, whereby effect sizes were stronger for boys whose mothers were

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Table 1. Characteristics of studies included in meta-analysis of sex-specific associations between maternal depression and child and adolescent cognitive outcomes

Citation	Cohort/sample	Sample size (B,G)	Country	Race, ethnicity	Overall sample SES	Method of measuring maternal depression	Time of exposure to maternal depression	Child cognitive outcome measure	Age category[c]	Time between exposure and outcome
Ahun et al., 2020	Québec Longitudinal Study of Child Development	1173 (B = 559, G = 614)	Canada	84% White, 3% Native American; 1% African, 12% other	High SES (mean score above centered value of SES index)	RS, CES-D	Postnatal	Academic achievement, maths	Adolescent	9 years 4 months
Cornish et al., 2005	Community sample	112 (B = 58, G = 56)	Australia	93% White, 7% other	High SES (50% have college or university degree)	DI, CIDI	Postnatal	Bayley, MDI	Child	4 months
Davies &Windle, 1997	Community sample	443 (B = 204, G = 239)	USA	97% White, 3% other	High SES (50% >US $40000 per year)	RS, CES-D	Postnatal	Academic achievement, GPA	Adolescent	1 year
Donald et al., 2019	Drakenstein Child Health Study	734 (B = 380, G = 354)	South Africa	Not reported	Low SES (61% >US $100 per month)	RS, EPDS	Antenatal	Bayley, MDI	Child	2 years
Hay et al., 2001	Community sample[a]	132 (B = 62, G = 70)	UK	78% White, 1.5% African, 0.5% Asian, 20% other	Low SES (89% working class)	DI, CIS	Postnatal	WISC, composite	Adolescent	10 years 9 months
Hay et al., 2008	Community sample[a]	121 (B = 55, G = 66)	UK	78% White, 22% other	Low SES (88% working class)	DI, CIS	Postnatal	WASI, composite	Adolescent	16 years
Murray et al., 1996	Community sample[b]	94 (B = 47, G = 47)	UK	Not reported	High SES (65% middle-upper class)	DI, SPI	Postnatal	MSCA, composite	Child	4 years 9 months
Murray et al., 2010	Community sample[b]	89 (B = 43, G = 46)	UK	Not reported	High SES (64% middle-upper class)	DI, SPI	Postnatal	Academic achievement, GCSE	Adolescent	10 years 4 months
Ng-Knight et al., 2018	Community sample	578 (B = 312, G = 266)	UK	60% White, 40% minority (non-White) ethnicity	High SES (16% socioeconomic deprivation)	RS, HADS-D	Postnatal	Academic achievement, maths, english, science	Adolescent	1 year
Nolvi *et al.*, 2018	FinnBrain Birth Cohort Study	214 (B = 114, G = 100)	Finland	Not reported	High SES (74% university or polytechnics degree)	RS, EPDS	Antenatal	Executive function, delayed response task	Child	8 months
Paquin et al., 2020	Québec Longitudinal Study of Child Development	1137 (B = 541, G = 596)	Canada	Not reported	High SES (80.1% sufficient income)	RS, CES-D	Postnatal	Lollipop, composite	Child	3 years 7 months
Sharp et al., 1995	Community sample[a]	135 (B = 60, G = 75)	UK	Not reported	Not reported	DI, CIS	Postnatal	MSCA, composite	Child	3 years 6 months

B,G, number of boys (B) and girls (G) in sample; DI, diagnostic interview; CES-D, Centre for Epidemiological Studies – Depression Scale; CIDI, Composite International Diagnostic Interview; CIS, Clinical Interview Schedule; EPDS, Edinburgh Postnatal Depression Scale; GCSE, General Certificate of Secondary Education; GPA, grade point average; HADS-D, depression subscale of Hospital Anxiety and Depression Scale; MDI, mental development index; MSCA, McCarthy Scales of Children's Abilities; RS, rating scale; SES, socioeconomic status; SPI, Standardized Psychiatric Interview; WASI, Wechsler Abbreviated Scale of Intelligence; WISC, Weschler Intelligence Scale for Children-III.
[a]These studies used data from the same community sample in south London. [b]These studies used data from the same community sample in Cambridge. [c]Child defined as birth to 10 years and adolescent as 11–18 years.

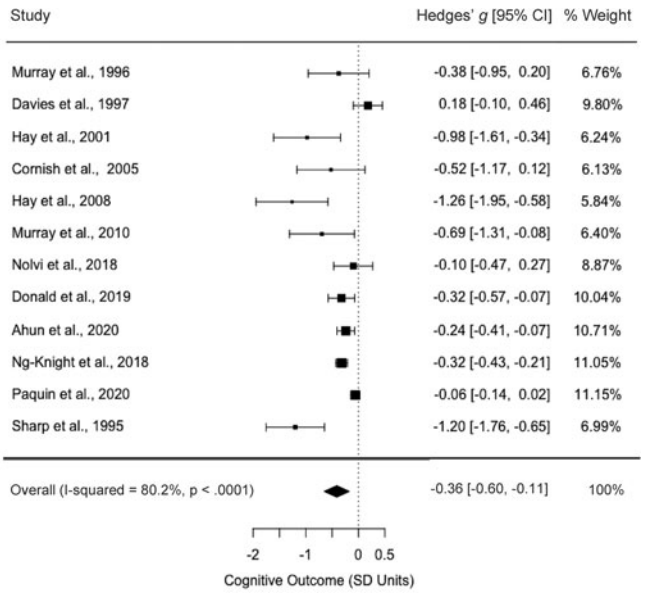


Fig. 2. Association between maternal depression and cognitive outcomes in boys.

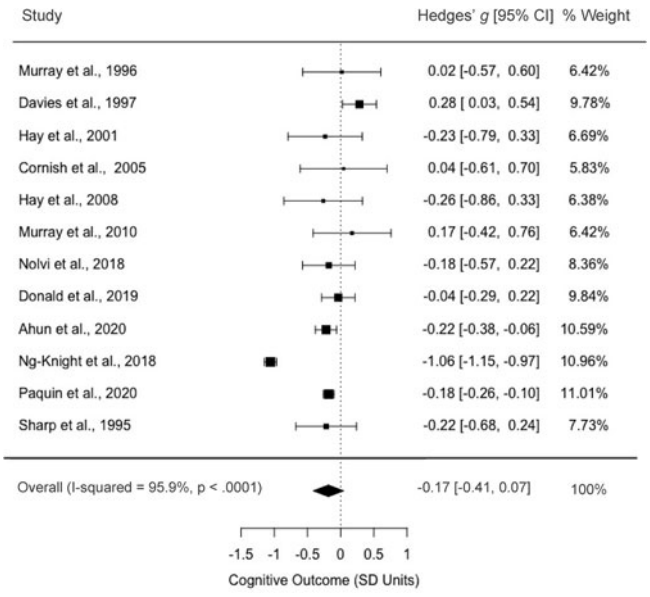


Fig. 3. Association between maternal depression and cognitive outcomes in girls.

assessed via diagnostic interview. The meta-analytic effect of maternal depression on cognitive outcomes in girls was not significant, although subgroup analyses revealed that the effect was significant for girls whose cognitive outcomes were assessed 12 months after assessment of maternal depression. Our findings of sex differences in the association between maternal depression and offspring cognitive outcomes align with consistent findings of sex differences in various child outcomes in response to antenatal maternal stress, although the direction of this difference varies by child outcome (Bale & Epperson, 2015; DiPietro & Voegtline, 2017; Kraemer, 2000; Sandman et al., 2013).

Our results replicate meta-analytic findings of a significant association between maternal depression and cognitive outcomes across childhood and adolescence, and support narrative review findings of stronger associations in boys compared to girls (Grace et al., 2003; Liu et al., 2017; Rogers et al., 2020; Sanger et al., 2015). That we only found this association in boys is in line with the notion that girls' maturational advantage in cognitive skills (e.g. reading) in early childhood may protect from the negative effect of (postnatal) maternal depression (Grace et al., 2003; Sohr-Preston & Scaramella, 2006). However, given the small number of studies that assessed antenatal depression ($n = 2$ in both ours and Liu et al.'s meta-analyses), it is possible that both meta-analyses were under-powered to provide reliable estimates. Rogers et al. (2020) found a slightly stronger association between postnatal (*v.* antenatal) maternal depression and cognitive outcomes but did not test for sex differences. The small number of studies that have examined sex differences in the effects of antenatal and postnatal maternal depression suggest that for some child outcomes (e.g. internalizing symptoms), girls are more vulnerable to variations in the exposure to maternal depression (i.e. low antenatal depression and high postnatal depression or *vice versa*) than boys (Braithwaite, Pickles, Wright, Sharp, & Hill, 2020; Sandman et al., 2013).

Additional subgroup analyses revealed that for both boys and girls, the amount of time between assessments of maternal depression and cognitive outcomes was important. Specifically, maternal depression was associated with cognitive outcomes when there was a longer amount of time between their assessments (i.e. more than 12 months). Liu et al. (2017) also found a significant association between maternal depression and cognitive outcomes when there was a longer amount of time between assessments (defined as 4 months or more). One potential explanation for this may be that a longer amount of time between assessments reflects more chronic exposure to maternal depression. There is evidence that the chronicity, rather than the timing, of exposure to maternal depression is associated with poorer cognitive outcomes (Ahun et al., 2017; Netsi et al., 2018; Sohr-Preston & Scaramella, 2006). For example, Ahun et al. (2017) found that children chronically exposed to maternal depression from birth to age 5 years scored lower on a measure of verbal abilities compared to children exposed earlier (i.e. before age 3) or later (i.e. between 3 and 5 years) in the postnatal period. However, neither Ahun et al. (2017) nor Netsi et al. (2018) tested for sex differences. Only one study in the meta-analysis considered the chronicity of maternal depression and they found that chronically exposed children had worse cognitive outcomes but found no sex differences (Cornish et al., 2005). It is therefore not clear whether boys are also more vulnerable to chronic exposure to maternal depression compared to girls.

The association between maternal depression and cognitive outcomes did not vary as a function of whether cognitive outcomes were assessed in childhood *v.* adolescence in boys or girls. The only other meta-analysis of the association between maternal depression and cognitive outcomes across childhood and adolescence also failed to find a significant variation in this association by child's age at the time of cognitive assessment (Rogers et al., 2020). However, both meta-analyses had relatively low power to detect moderation, so results should be interpreted cautiously. Previous research does suggest that the small-to-moderate yet consistent association between maternal depression and cognitive outcomes persists into adolescence, so it is important to consider the effects of maternal depression across developmental periods (Sanger et al., 2015). Furthermore, as discussed earlier, it is likely that the chronicity of exposure to maternal depression, rather than the child's age at cognitive assessment,

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is important in understanding how the effects of maternal depression on cognitive outcomes persist into adolescence (Ahun et al., 2017; Netsi et al., 2018; Sohr-Preston & Scaramella, 2006).

To translate the findings of this meta-analysis into public health interventions, we need to understand whether sex differences exist in the underlying mechanisms of the association between maternal depression and offspring cognitive outcomes. Studies examining underlying mechanisms are needed to identify modifiable mediators which can be targeted in interventions to mitigate the negative effects of maternal depression. For instance, one study found that although maternal depression was associated with academic performance in both boys and girls, school engagement only mediated the association between exposure and outcome in girls (Ahun et al., 2020). In another study, children's self-control and their perceptions of maternal warmth only mediated the association in girls (Ng-Knight et al., 2018). These findings suggest that the association between maternal depression and girls' cognitive outcomes is explained by an indirect effect. They also suggest that the maturational advantage held by girls in cognitive skills may protect from the direct – but not the indirect – effect of maternal depression. Another key mechanism of this association is maternal parenting, whereby maternal depression negatively influences maternal sensitivity and mother–child interactions which are consequently associated with poorer cognitive outcomes (Ahun & Côté, 2019; Goodman, Simon, Shamblaw, & Kim, 2020). However, there is mixed evidence on the moderating role of sex in these pathways.

Prevention and treatment interventions for mothers at risk of experiencing depression and for those experiencing depression are also important public health interventions for mitigating the negative effect of maternal depression on child outcomes (Cuijpers, Weitz, Karyotaki, Garber, & Andersson, 2015; Goodman, Cullum, Dimidjian, River, & Kim, 2018; Letourneau, Dennis, Cosic, & Linder, 2017; O'Connor, Senger, Henninger, Coppola, & Gaynes, 2019; Rahman et al., 2018; Tsivos, Calam, Sanders, & Wittkowski, 2015). However, there is currently little evidence that such interventions lead to improved child outcomes. Of the handful of prevention and treatment interventions that have assessed impacts on children's cognitive outcomes (Cicchetti, Rogosch, & Toth, 2000; Clark, Tluczek, & Wenzel, 2003; Cooper, De Pascalis, Woolgar, Romaniuk, & Murray, 2015; Hayden et al., 2012; Kersten-Alvarez, Hosman, Riksen-Walraven, Van Doesum, & Hoefnagels, 2010; Letourneau et al., 2011; Makrides et al., 2010; Maselko et al., 2015; Milgrom et al., 2015; Murray, Cooper, Wilson, & Romaniuk, 2003; Verduyn, Barrowclough, Roberts, Tarrier, & Harrington, 2003), few have found a significant impact.

Cicchetti et al. (2000) found no sex differences in the positive impact of the intervention on cognitive outcomes whereas Milgrom et al. (2015) did not test for sex differences. One study found no overall effect of the intervention, however, girls in the intervention group had better post-intervention cognitive outcomes compared to their male counterparts (Cooper et al., 2015). These results indicate that there is no clear evidence of the moderating role of child's sex in the impact of treatment and prevention interventions for maternal depression on offspring cognitive outcomes. Recent evidence suggests that for prevention and treatment interventions to significantly improve child outcomes, they need to be combined with parenting interventions that enhance mothers' overall parenting skills, including specific skills (e.g. cognitive stimulation) which can help improve children's cognitive outcomes (Goodman & Garber, 2017; Goodman et al., 2020).

Recommendations for future research

Our findings highlight important avenues for future research on the role of sex differences in the association between maternal depression and offspring cognitive outcomes. Given the lack of evidence that treating or preventing maternal depression alone leads to subsequent improvements in children's cognitive outcomes, further research is needed on the effectiveness of interventions that jointly treat or prevent maternal depression and focus on improving parenting skills (Goodman & Garber, 2017; Goodman et al., 2020). Additionally, examining the moderating role of sex on intervention impacts can inform researchers and clinicians as to whether such interventions meet the particular needs of boys and girls. For example, moderation analyses of a parenting intervention only found significant improvements in boys' behavioral outcomes, suggesting that the intervention may need to be modified to address behavioral problems in girls (Gardner, Hutchings, Bywater, & Whitaker, 2010). Further research is also needed to clarify the role of sex differences in mediators of the association between maternal depression and offspring cognitive outcomes. Such work could lead to the development of public health interventions that target the sex-specific modifiable factors through which maternal depression influences offspring cognitive outcomes and thus address the particular needs of boys and girls. Furthermore, given the lack of studies reporting sex-specific associations adjusted for covariates, future studies should use a consistent set of covariates to facilitate the interpretation of pooled adjusted associations in meta-analyses (Hutchinson et al., 2015). Finally, an exploration of whether maternal depression influences girls' and boys' cognitive outcomes differently in more ethnically and economically diverse samples is needed. The majority of studies in this meta-analysis included participants who were White and had high levels of socioeconomic status, our results are therefore primarily applicable to families from Western, educated, industrialized, rich, and democratic societies (Henrich, Heine, & Norenzayan, 2010).

Limitations

This meta-analysis was limited by the modest number of studies fulfilling eligibility criteria. We therefore had little power for subgroup analyses and our results should thus be interpreted cautiously. Furthermore, due to a lack of reporting on sex differences in the adjusted association between maternal depression and offspring cognitive outcomes, we were unable to account for the role of covariates in our meta-analysis. Although we restricted the meta-analysis to longitudinal studies and hence were able to establish temporality in reported associations, we cannot comment on the causality of these associations due to the observational nature of included studies. Nevertheless, it is worth noting that maternal depression remained significantly associated with offspring cognitive outcomes after accounting for important covariates such as maternal anxiety and level of education. Furthermore, in the two studies which reported adjusted sex-specific associations (Ahun et al., 2020; Ng-Knight et al., 2018), sex differences remained after adjusting for covariates. It is therefore likely that our findings would hold after accounting for covariates. Our meta-analysis also highlights important limitations in the extant literature on maternal depression and offspring's cognitive outcomes which have already been discussed.

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Conclusion

The results of this meta-analysis underscore the importance of examining the differential impact of maternal depression on boys' and girls' cognitive outcomes. To translate these findings into public health interventions, further research is needed to better understand the modifiable mediators of this association in boys and girls and to examine the differential impact of integrated interventions which aim both to prevent or treat maternal depression and improve parenting skills on boys' and girls' cognitive outcomes.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S0033291721001689

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