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Socioeconomic factors and sex effects of postpartum maternal depression on offspring internalizing symptoms: a systematic review and meta-analysis

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Abstract

Background Postpartum maternal depression and socioeconomic factors are established risk factors for the mental health of offspring. It has been consistently unclear as to whether female or male offspring are more vulnerable to the effects of postpartum maternal depression at different stages of the child's life course. To determine whether the characteristics of postpartum maternal depression with a history of prenatal depression influence sex differences in offspring internalizing symptoms across childhood and adolescence, socioeconomic factors should be considered.

Methods We systematically searched PubMed, Embase, PsycINFO, CNKI, and SinoMed databases from inception to November 28, 2023, and selected longitudinal cohort studies that quantified sex differences in internalizing symptoms of children and adolescents. Pooled standardized mean differences (SMDs) were calculated using random-effects models. ROBINS-E tool was used to rate the quality of evidence.

Results Twenty-eight studies were eligible between 1997 and 2023, including 24,022 mother–child dyads. Sex-difference trajectories of offspring internalizing symptoms were identified after exposure to postpartum maternal depression, ranging from a lack of significant sex differences in childhood to a higher prevalence observed among girls than boys in adolescence (SMD, 0.25, 95% CI, 0.13–0.38). Economic income and maternal education affected the associations between the magnitude and concurrent recurrence of postpartum depression and significant sex differences in adolescent internalizing symptoms, respectively. After adjusting for socioeconomic factors, early nonconcurrent recurrence of postpartum depression was associated with greater odds of internalizing symptoms among adolescent girls than among boys ($\beta = 0.03$, 95% CI, 0.01–0.06); however, there was no statistical significance after adjusting for prenatal depression.

Conclusions Socioeconomic factors differentially impacted the association between postpartum maternal depression and significant sex differences in adolescent internalizing symptoms. Independent of socioeconomic factors and prenatal depression, postpartum maternal depression was not associated with significant sex differences

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in adolescent internalizing symptoms. Therefore, the significant sex effects of postpartum maternal depression are more likely due to complex interactions between maternal depression and the intrauterine and postpartum environments that shape offspring sex-difference trajectories, with consequences occurring for later internalizing symptoms in adolescence.

Trial registration PROSPERO, CRD42022301445.

Keywords Sex difference, Postpartum depression, Child, Adolescent

Background

The prevalence of internalizing symptoms increases significantly from childhood to adolescence, with rates of 2.3% being observed for children and 7.1% being observed for adolescents in high-income countries (HICs) [1]. Compared with HICs, low- and middle-income countries (LMICs) have higher rates of internalizing symptoms, such as 14.7% in Myanmar, 18.3% in China, and 39% in Botswana [2]. With psychological adjustment to motherhood and hormonal changes occurring during the postpartum period, postpartum maternal depression, defined as a depressive episode within 4 weeks of childbirth (Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition) [3], is a significant public health concern for the socioemotional development of children [4–6]. An increasing number of studies have shown that women with postpartum depression have a relapse frequency of 80% and a sixfold increased risk of recurrent symptoms of depression at 4 years after giving birth [7]. Considering the impact of multiple environmental factors, the consequences of recurrent postpartum depression are not restricted to offspring infancy; rather, they can extend into early childhood, school age, or adolescent stages [8]. The specific timing of clinical intervention that targets postpartum maternal depression to reduce offspring internalizing problems is unknown.

Sex-dependent mental susceptibility responses to the progression of postpartum maternal depression can vary with offspring growth [9, 10], thus contributing to the estimation of sex differences as a quantitative method for determining the intergenerational transmission effects of postpartum maternal depression. However, the research on the mental effects of recurrent postpartum maternal depression on offspring has involved the examination of mother–child mental conditions at multiple asynchronous and discrete time points [11], which can lead to possible differences in study design bias. A cross-sectional study of concurrent recurrent maternal depression did not demonstrate any significant sex effects of postpartum depression on internalizing symptoms in early adolescence [12]. Nevertheless, a longitudinal study conducted across 19 counties in a midwestern state of the United States revealed that nonconcurrent recurrent maternal depression exposure among children aged 11 years independently predicted the development of internalizing symptoms among adolescent girls at 18 years of age [13]. The timing of the emergence of adolescent sex differences after exposure to the risk factors for recurrent postpartum maternal depression is unclear. Few mother–child psychological studies have systematically evaluated sex as the main effect [14]. Therefore, uncertainty exists regarding the sex effects of postpartum maternal depression on offspring internalizing symptoms during childhood and adolescence.

Maternal depression during pregnancy has the strongest correlation with early postnatal maternal depression [15, 16]. Increasing evidence suggests that the intrauterine environment, which includes placental responses to prenatal maternal depression and maternal cortisol, negatively impacts fetal neurodevelopment and fetal heart rate reactivity; moreover, these effects are stronger among females than among males, thus leading to sex differences in risk pathways that contribute to future psychopathology [14]. However, studies of offspring mental health have often isolated the relevant effects of postpartum maternal depression from intrauterine environmental influences [15, 16], which may not estimate the true psychological impact of postpartum maternal depression with a history of prenatal depression on offspring.

Socioeconomic factors are associated with an increased prevalence of depression [17]. A systematic review revealed that the prevalence of postpartum maternal depression varies among countries, ranging from 20% in LMICs to 6.9–12.9% in HICs [6]. Adolescent girls are more vulnerable to the effects of maternal depression than adolescent boys in low economic contexts [18]. One review revealed that 9 studies (4864 participants) reported an association between employment status and the duration of depression [17]. High work intensity for women with low educational statuses exacerbates female anxiety and depression, thus leading to preterm birth and stronger stressful experiences in their offspring [19–23]. Few studies have evaluated whether discrepancies in multiple socioeconomic factors impact the differences in the response toward postpartum maternal depression among male and female offspring across childhood and adolescence.

The results of national studies have shown that adolescent girls are more likely to experience internalizing symptoms than boys [1, 18], which aligns with the effect of maternal depression on sex differences in internalizing symptoms. No study has examined the association between postpartum maternal depression and sex differences in offspring internalizing symptoms after adjusting for multiple environmental factors. Therefore, this systematic review and meta-analysis aimed to determine the sex effects of postpartum maternal depression with a history of prenatal depression on offspring internalizing symptoms across childhood and adolescence, with a specific focus on the roles of socioeconomic factors.

Methods

This systematic review was reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA 2020) guidelines in Additional file 1: Table S1 [24]. The study is registered with PROSPERO CRD42022301445.

Data sources and searches

Searches were run from three databases from their inception to October 29, 2021 (PubMed, Embase, PsycINFO), Web of Science (1974–2021) (Science Citation Index Expanded [SCI-EXPANDED] and Social Sciences Citation Index [SSCI]) for references published in English, and two databases in Chinese on May 17, 2022 (China National Knowledge Infrastructure [CNKI] and China Biomedical Literature Service System [SinoMed]) (Additional file 1: Table S2). The reference lists of relevant systematic reviews, conference abstracts, and dissertations published were searched by Web of Science and CNKI. Finally, we updated all studies published before November 28, 2023, using the same search method. Combinations of search terms in the following groups were used: ('Depression' OR 'Depressive symptoms' OR 'Emotional depression'), ('Sex' OR 'Male' OR 'Female'), and ('Postpartum' OR 'Postnatal' OR 'Maternal' OR 'Pregnancy' OR 'Gestation' OR 'Prenatal' OR 'Antenatal'), after which these groups were combined with the term "AND".

Study selection

To be eligible for inclusion in the final analysis, a dataset needed to include the following criteria: (1) the study included longitudinal cohort studies of children and adolescents (aged > 1 year and < 20 years) of postpartum depressed mothers with histories of prenatal depression (aged > 18 years) from various socioeconomic backgrounds; (2) the samples in the included studies consisted of mother–child dyads; (3) maternal depression included postpartum depression with relevant histories, such as comorbid anxiety, depression, and stress during pregnancy; (4) the comparisons included offspring sex differences in response to postnatal maternal depression, as well as sex differences in depression among mothers of boys and girls; and (5) the included studies reported the nonconcurrent temporal relationship of mother–child interactions (a lack of results on concurrent recurrence of maternal depression at the time of performance of offspring psychological measurement, and postpartum maternal depression occurring before the measurement of the child's internalizing symptoms). Studies were excluded from analysis if there was a substantial genetic contribution to the psychological disorders for offspring, such as autism spectrum disorders and schizophrenia; if the participants had depression with delusions or hallucinations; if studies evaluated mothers with severe/traumatic events of cerebrovascular accidents; or if mothers experienced neurological conditions caused by pregnancy, such as eclampsia.

Data extraction and quality assessment

The authors created extraction sheets (Additional file 1: Table S3). Pairs of researchers (YG, WL-L, HZ, and YL) independently reviewed titles and abstracts, screened the full-text articles for eligibility, extracted data from eligible studies (the date of first extraction was on July 11, 2022), and then assessed the risk of bias. We evaluated the risk of bias in the included studies via the 'Risk of Bias in Nonrandomized Studies-of Exposure' tool for follow-up observational studies (ROBINS-E) [25]. Following the recommendations by ROBINS-E, the overall summary "risk of bias" judgement (low; some concerns; high) for each outcome was determined in each of the assessed domains. Discrepancies between investigators were resolved through discussion or contacting the report's authors to provide further details. Sex differences were determined with a standardized mean difference (SMD) that estimated the outcome of interest using multiple measurement scales. Subsequently, we diagrammatically summarized the outcomes from all of the studies, estimated the effect sizes according to the stratification of children's age, and provided a visual overview of the sex-difference trajectory of offspring internalizing symptoms.

Outcomes

The primary outcome measured was the offspring sex differences in internalizing symptoms (depression and anxiety). Study measurements included self-report, mother-report questionnaires, and structural and semi-structural interviews.

Variables

Considering the high variability of offspring exposure to postpartum depression from childhood to adolescence,

it was necessary to identify the exposure periods in which postpartum maternal depression had an equal and consistent impact on the direction of sex differences in offspring internalizing symptoms. Risk factors were implemented to analyze the change in offspring sex differences in internalizing symptoms during the identified postpartum exposure periods. The characteristics that we investigated include the following:

- Income group: income was grouped into WHO global regions and World Bank Country-Level economies (upper-middle-income is a per capita $4,466–$13,845; lower-middle income is $1,136–$4,465; low income is $1,135 or less) as of 2023
- Maternal employment status: employed, not seeking employment, unemployed
- Maternal education: education classification include ≤ 9 years, > 9 and < 13 years, and ≥ 13 years
- Childbirth status: term birth, preterm birth (prenatal depression combined with preterm birth caused severe alteration in the intrauterine environment)

Data synthesis and analysis

Hunter and Schmidt's method was used to better estimate the valid SMD to correct for the underestimation of the true effect size based on the reliability of the questionnaire measurements [26]. Data, including point-biserial correlations and odd ratios, were converted to SMDs. The guidance of high-quality meta-analysis in a systematic review suggested that multiple mathematics measurements or assessments of anxiety should use robust variance estimation in a single analysis [27]. As the effect of offspring outcomes was deemed highly variable according to country, offspring age level, economic status, and ethnicity, a random-effects model was used to pool effect sizes. The restricted maximum likelihood estimator was used to calculate the heterogeneity variance τ^2. Knapp-Hartung adjustments were applied to calculate the confidence interval around the pooled effect. The distribution of heterogeneity was examined using the I^2 statistic.

The magnitude of maternal depression was categorized into the mean maternal depression and sex differences between boys' and girls' maternal depression values. Longitudinal studies of postpartum maternal depression exposure at asynchronous and discrete time points were stratified into concurrent (recurrent postpartum depression at the time of offspring mental measurements) and nonconcurrent temporal relationships with the offspring's psychological outcomes. The impacts of each stratification on sex differences in offspring internalizing symptoms were subsequently analyzed across the studies. Subgroup analyses assessed the effect sizes regarding socioeconomic factors and childbirth status. Meta-regression analysis was used to test for the association of maternal depression and offspring sex differences in internalizing symptoms in the univariable analysis. We tested the associations using a multivariable model adjusted for environmental factors (family income, maternal education, maternal employment status, and histories of prenatal maternal depression).

Sensitivity analysis was restricted in studies removing high-risk bias. Funnel plot and Egger's regression were used to test for small study effects. P-curve analysis was used to check whether existing results drove these findings [28]. All significance testing was 2-sided, and statistical analyses were done using R (version 4.0.2, www.r-project.org).

Results

Search results

A systematic search of the literature identified 14,843 potentially relevant records. Three thousand nine hundred eighteen duplicates were removed, yielding 10,925 studies (Fig. 1). The updated search on November 28, 2023, identified 4659 additional studies. Of these, 15,265 records were excluded after a review of the title and abstract. We then retrieved 319 full-text documents and excluded 291 studies based on the exclusion criteria (no outcomes of interest reported; no sex differences in offspring internalizing symptoms; not focused on postpartum maternal depression and its comorbidity; child age ≥ 20-years-old; insufficient data for meta-analysis; no longitudinal cohort; or different study branches of a large study). Ultimately, 28 eligible longitudinal studies between 1997 and 2023 were included in the current analysis.

Study characteristics

The characteristics of the 28 studies included are summarized in Table 1. Most of the studies (20, 71%) were conducted in North America (Canada and the United States), 4 (14%) were conducted in Asia (China and Singapore), 3 (11%) in Europe (Ireland, Sweden, and the United Kingdom), and 1 (4%) in Australia. In total, 22 studies reported economic income, of which 6 (27%) were rated as an upper-middle income level, 8 (36%) were rated as a lower-middle income level, and 8 (36%) were rated as a low-income level. The study included 24,022 children, 52.35% of whom were female and 57.11% of whom were Caucasian. The mean age of mothers in the individual studies ranged from 20 to 33 years. The mean (SD) ages of children were 2.84 (1.46) in level 1 (> 1 year and < 6 years), 8.91 (1.59) in level 2 (≥ 6 years and < 11 years), and 14.66 (2.24) in level 3 (≥ 11 years and < 20 years).

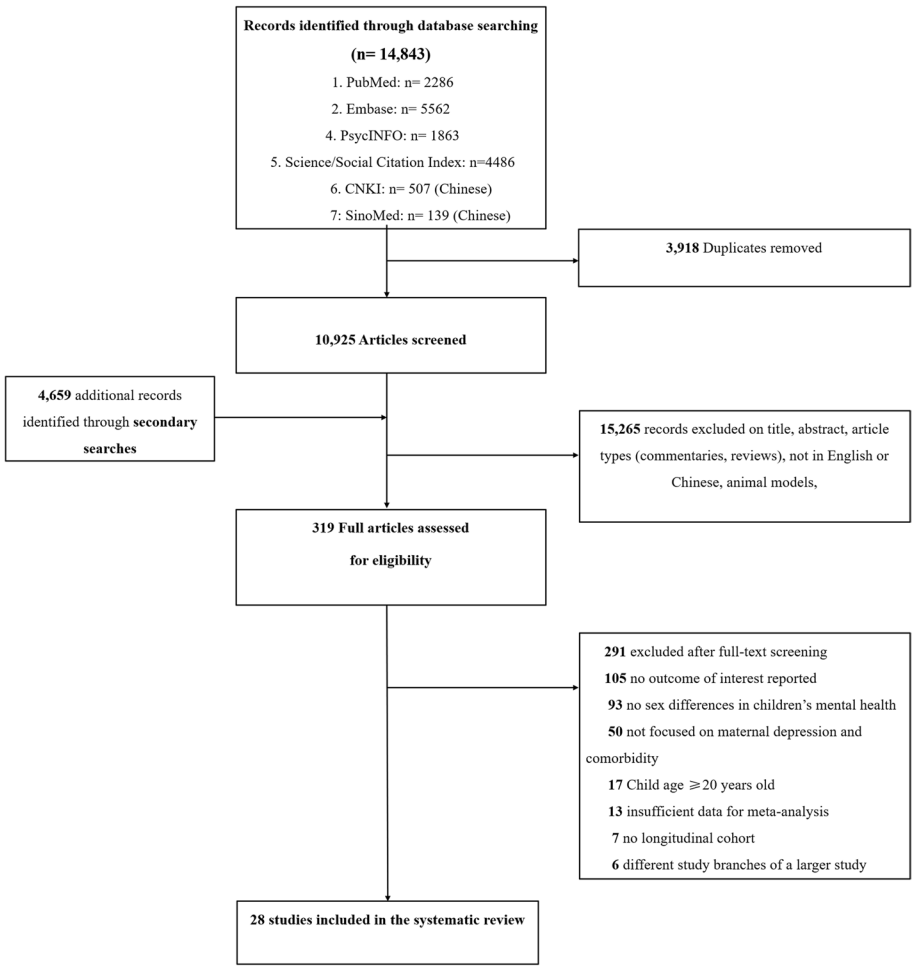


Fig. 1 Literature search flow diagram

Risk of bias of included studies

The results for the risk of bias using the ROBINS-E tool are shown in Additional file 1: Fig. S1. Regarding the overall risk of bias, a large proportion of study quality was considered "some concerns" (15, 53%). Six studies (21%) had a high risk of bias [30, 32, 39, 54–56], of which four studies had bias resulting from confounded time-varying factors (different exposure experiences in offspring development) in longitudinal studies [30, 39, 54, 55].

Synthesis of results

Pooled effect sizes of postpartum maternal depression on offspring internalizing symptoms

Meta-analysis revealed that, after exposure to postpartum depression, there were small but significant sex differences in offspring internalizing symptoms, with increased symptoms being observed among girls compared with boys (SMD, 0.13 [95% CI, 0.05–0.21], $I^2=81\%$) (Fig. 2). Egger's test did not find the presence of funnel plot asymmetry in the offspring psychological studies (Additional file 1: Fig. S2). P curve plots demonstrated a true non-zero effect in offspring internalizing symptoms (Additional file 1: Fig. S3). In sensitivity analyses after removing studies with a high risk of bias, the effect direction did not change (similar to the main analysis), and the pooled effect sizes of offspring internalizing symptoms overlapped (SMD 0.15 [0.05–0.24], $I^2=75\%$) (Additional file 1: Fig. S4).

Evaluation of effect sizes of offspring outcomes and the mean magnitude of postpartum depression by child's age level

When children's age was considered as a continuous variable, the regression results demonstrated that as offspring aged, postpartum depression was associated with higher risks of daughters' internalizing symptoms than sons' symptoms (Additional file 1: Fig. S5). After exposure to postpartum maternal depression, the sex differences in internalizing symptoms among offspring were concentrated in early childhood and adolescence (Additional file 1: Fig. S6).

Table 1 Study and participants characteristics

Author	Geographical region	No. sample size	Race, ethnicity (%)	Income group	Age level of the child	Maternal education (year)	Measure of maternal postpartum depression	Measure of child's internalizing symptoms
Zhang et al. 2021 [29]	Asia	518	Asian (100%)	NR	Level 2	9–13	BDI-II	Mother-Report, CBCL/6–18
Maxwell et al. 2018 [30]	North America	1615	Caucasian (76.28%), African (18.51%), Asian (5.20%)	Upper-middle	Level 3	9–13	CES-D, Self-Report Inventory	Self-Report, Self-Report Inventory
Davies et al. 1997 [31]	North America	443	Caucasian (97.07%)	Upper-middle	Level 3	≥ 13	CES-D	Self-Report, CES-D
River et al. 2018 [32]	North America	137	Caucasian (35.04%), African (18.25%), Asian (2.19%)	Lower-middle	Level 2	NR	BDI-II	Self-Report, CDI
Carter et al. 2001 [33]	North America	29	Caucasian (89.66%)	NR	Level 1	≥ 13	CES-D, SCID-NP	Mother-Report, CBCL/2–3
Chan et al. 2014 [34]	North America	171	Caucasian (67.84%), African (12.87%), Asian (1.75%)	Upper-middle	Level 2	NR	BDI	Self-Report, CDI
Lacey et al. 2023 [35]	Europe	3301	Caucasian (96.09%)	Lower-middle	Level 3	≥ 13	EPDS	Self-Report, Short Mood and Feelings Questionnaire (SMFQ)
Zhang et al. 2023 [36]	Asia	2373	Asian (100%)	Low	Level1	≥ 13	CES-D	Clinician/ Researcher, BSID-III
Fulco et al. 2020 [37]	North America	427	Caucasian (17.10%), African (66.04%)	Low	Level 3	≤ 9	CES-D	Self-Report, CES-D
McGinnis et al. 2015 [10]	North America	198	Caucasian (62.63%), African (23.74%)	Upper-middle	Level 1	≥ 13	Postpartum Depression Screening Scale (PPDS)	Mother-Report, CBCL/1.5–5
Blatt-Eisengart et al. 2009 [38]	North America	1364	NR	NR	Level 2	≥ 13	CES-D	Mother-Report, CBCL
Jenkins et al. 2008 [39]	North America	1659	NR	NR	Level 3	NR	CES-D	Self-Report, Emotional problems scale from the Ontario Child Health Study
Mason et al. 2017 [13]	North America	666	Caucasian (96.92%)	Lower-middle	Level 3	≤ 9	SCL-90R	Self-Report, YSR
Monti et al. 2017 [40]	North America	165	Caucasian (78.18%), African (12.12%), Asian (2.42%)	Lower-middle	Level 3	≤ 9	Nonpatient version of the Structured Clinical Interview for the DSM	Clinician/ Researcher, the Schedule for Affective Disorders and Schizophrenia for School-Age Children Epidemiologic Version 5, DSM
Agnafors et al. 2023 [41]	Europe	547	NR	NR	Level 3	9–13	EPDS	Mother-Report, CBCL
Bureau et al. 2009 [42]	North America	47	Caucasian (80.85%), African (4.26%)	Low	Level 3	≤ 9	CES-D	Self-Report, CES-D

Table 1 (continued)

Author	Geographical region	No. sample size	Race, ethnicity (%)	Income group	Age level of the child	Maternal education (year)	Measure of maternal postpartum depression	Measure of child's internalizing symptoms
Brown et al. 2015 [43]	North America	277	African (35.02%), Asian (14.08%)	Upper-middle	Level 3	9–13	CES-D	Self-Report, Revised child anxiety and depression scale (RCADS)
Wetter et al. 2012 [44]	North America	251	Caucasian (64.14%), African (35.86%)	Lower-middle	Level 2	9–13	SCL-90R	Self-Report, CDI
Leve et al. 2005 [45]	North America	337	Caucasian (88.13%), African (1.00%), Asian (1.00%)	Lower-middle	Level 3	≤ 9	CES-D	Mother-Repot, CBCL
Katz et al. 2013 [46]	Australia	182	Caucasian (96.15%)	Low	Level 3	≤ 9	DSM–IV	Clinician/ Researcher, K-SADS-PL
Zong et al. 2014 [47]	Asia	284	Asian (100%)	Low	Level 1	≤ 9	EPDS-10	Mother-Repot, ITSEA
Guo et al. 2020 [48]	Asia	319	Asian (100%)	Low	Level 3	NR	CES-D	Self-Report, CDI
Roubinov et al. 2022 [49]	North America	162	Caucasian (16.05%), African (32.10%), Asian (3.09%)	Low	Level 1	9–13	Patient Health Questionnaire (PHQ-9)	Mother-Report, CBCL
Feldman et al. 2022 [50]	North America	264	Caucasian (62.12%), African (14.02%)	Low	Level 2	≤ 9	CES-D	Mother-Report, CBCL/6–18
Bechtiger et al. 2022 [51]	North America	389	Caucasian (67.61%), African (25.71%)	Lower-middle	Level 3	9–13	SCL-90R, SCL-91R, SCL-92R	Mother-Report, CBCL
Felton et al. 2021 [52]	North America	232	Caucasian (55.17%), African (37.07%), Asian (1.00%)	NR	Level 3	NR	CES-D	Self-Report, CES-DC
Paige et al. 2022 [53]	North America	338	Caucasian (83.14%), African (8.88%)	Upper-middle	Level 3	NR	CES-D	Self-Report, YSR
Connelly et al. 2021 [54]	Europe	7327	Caucasian (84.50%)	Lower-middle	Level 3	9–13	CES-D8	Self-Report, Short Mood and Feelings Questionnaire (SMFQ)

Measure of maternal depression: EPDS, Edinburgh Postnatal Depression Scale; BDI-II, Beck Depression Inventory-II; CES-D, Center for Epidemiological Studies Depression; SCID-NP, Structured Clinical Interview for the DSM-III-R–Non-Patient Version; SCL-90R, Symptom Checklist-90 Revised

Measure of Child outcomes: CBCL, Child Behavior Checklist; CES-DC, Center for Epidemiological Studies Depression Scale for Children; K-SADS-PL, Kiddie-schedule for affective disorders and Schizophrenia–early, Present and Lifetime Version; CDI, Children's Depression Inventory; YSR, Youth Self-Report; ITSEA, Infant–Toddler Social and Emotional Assessment. BSID-III, Bayley Scales of Infant & Toddler Development-Third Edition

Income group: studies were grouped into WHO global regions and World Bank country-level economies

Age level of child: level 1, > 1 year and < 6 years; level 2, ≥ 6 years and < 11 years; level 3, ≥ 11 years and < 20 years

NR Not report, SMD Standardized mean difference

An evaluation of between-group differences at different offspring age levels revealed that the distribution of offspring sex differences in internalizing symptoms after exposure to postpartum maternal depression was steadily centered at the null point (no significant sex differences) in childhood (> 1 year and < 11 years) (Fig. 3A1 and 3A2). Sex differences in the distribution of internalizing symptoms, as indicated by a density greater than 50%, revealed a gradual increase in girls' internalizing symptoms as they progressed through adolescence, thus leading to a

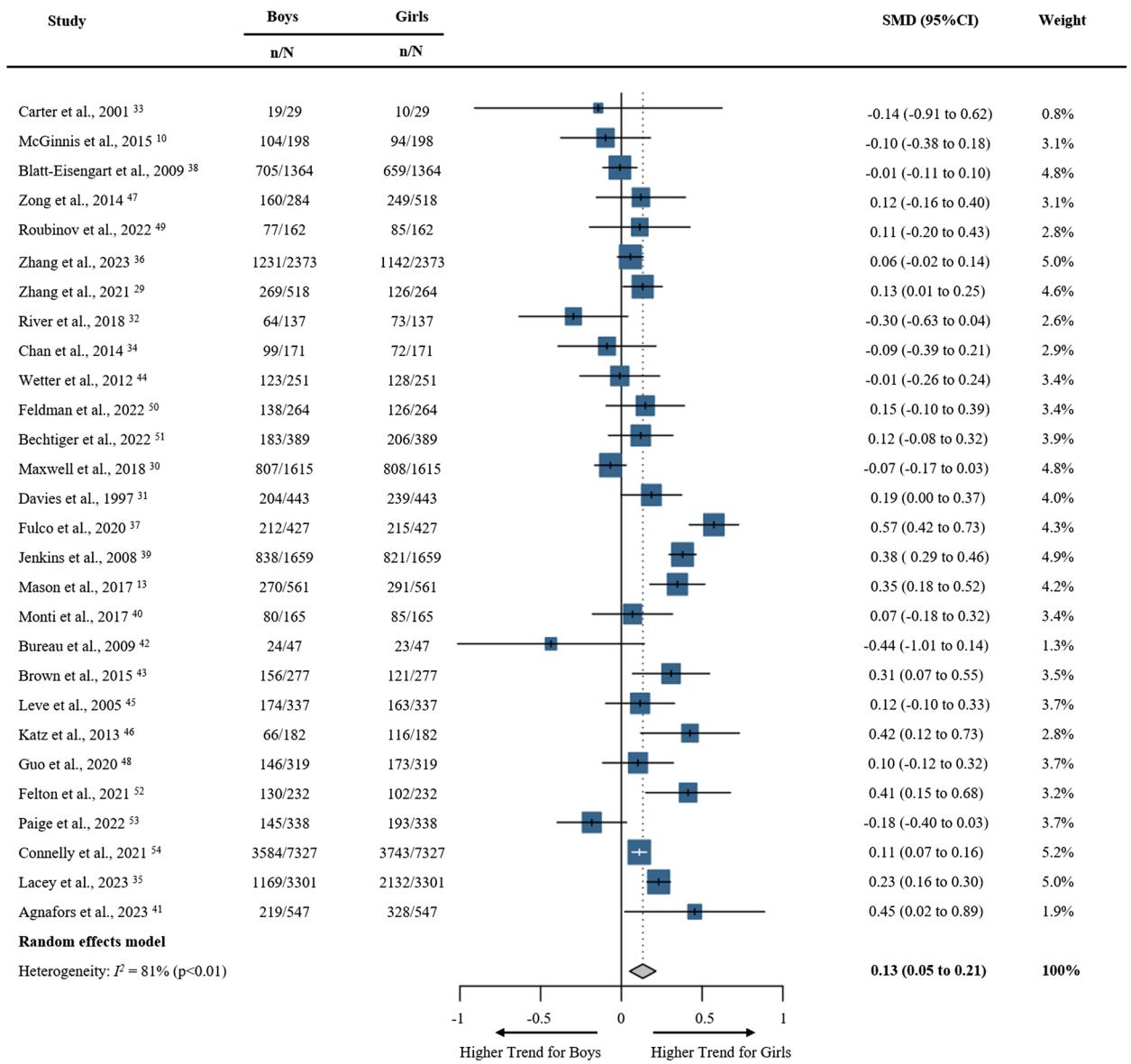


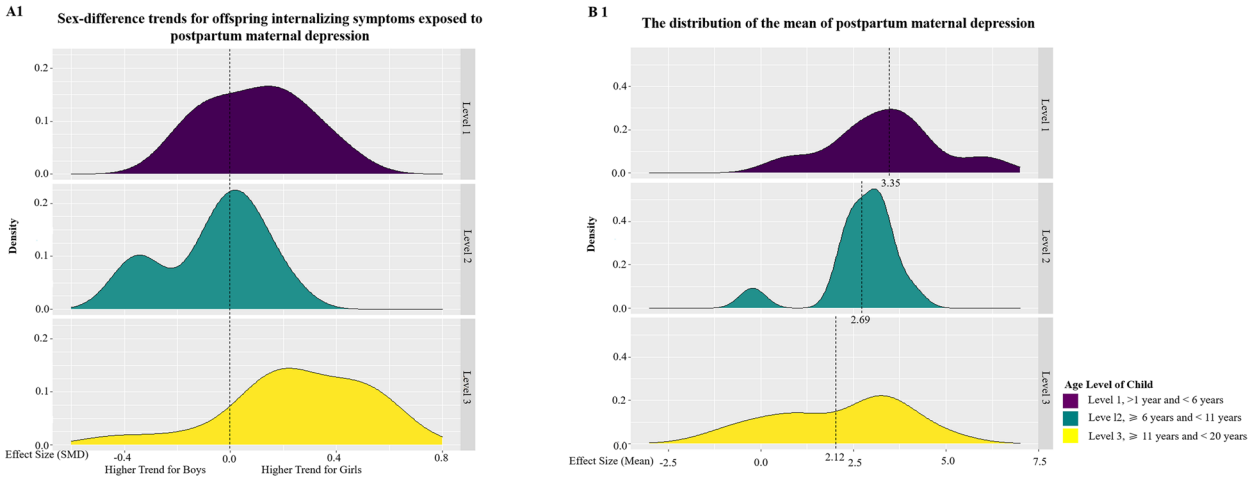
Fig. 2 Forest plots for sex effects of postpartum maternal depression on offspring internalizing symptoms

significant rightward shift in sex-difference trajectories of internalizing symptoms from childhood to adolescence. Robust variance estimation of effect sizes across multiple time measurements in longitudinal cohorts revealed a statistically significant increase in internalizing symptoms among adolescent girls compared with boys when exposed to postnatal maternal depression. (in level3, ≥ 11 and < 20 years, $k = 16$, SMD 0.25 [0.13–0.38]) (Fig. 3A2).

The mean value of postpartum maternal depression in the offspring's childhood was centralized around effect sizes, and the effect sizes and distribution of the mean value of postpartum depression in the offspring's adolescence were lower and more discrete than those in childhood (the mean of postnatal maternal depression, level 1, 3.35 [95% CI, 2.38–4.33]; level 2, 2.69 [2.02–3.37]; level 3, 2.12 [1.37–2.87]) (Fig. 3B1 and 3B2).

Socioeconomic factors and preterm birth for the associations between postpartum maternal depression and sex differences in offspring internalizing symptoms

According to different economic income conditions based on World Bank country-level economies, we did not identify any significant sex differences in childhood internalizing symptoms after exposure to postpartum maternal depression in North America or Asia (Fig. 4). Compared with the lack of sex differences in offspring



A2

Effect size of offspring internalizing symptoms (SMD)

Mother-Child Interaction	k	Boys (N), Girls (N)	SMD	95% CI	I^2
Age Level 1	8	2608, 2403	0.07	-0.01 to 0.15	
Age Level 2	10	3400, 3305	-0.01	-0.09 to 0.08	86%
Age Level 3	16	8275, 9607	0.25	0.13 to 0.38 *	

B 2

Effect size of postpartum maternal depression (Mean, Log_2)

Mother-Child Interaction	k	Mothers (N)	Mean (Log_2)	95% CI	I^2
Age Level 1	6	1645	3.35	2.38 to 4.33 *	
Age Level 2	8	3726	2.69	2.02 to 3.37 *	92%
Age Level 3	12	12372	2.12	1.37 to 2.87 *	

Fig. 3 Evaluation of effect sizes of offspring internalizing symptoms and the mean of postpartum depression by child's age level. **A1**, **A2** A plot of sex-difference trajectories of offspring internalizing symptoms after exposure to postpartum maternal depression. The table showed effect sizes (SMD) for each child's age level, k = number of cohorts. **B1**, **B2** A plot of the distribution of the mean of postpartum maternal depression. The table showed effect sizes (mean of postpartum maternal depression) for each child's age level, k = number of cohorts. *: Statistical significance $p < 0.05$

internalizing symptoms in Asia (via one study focusing on low-income backgrounds), adolescent girls living with depressed mothers in low-income environments in North America and Australia were more likely to have internalizing symptoms than adolescent boys (North America, SMD, 0.41 [0.11–0.71], $k=3$; Australia, 0.42 [0.12–0.73], $k=1$). Unlike unmeaningful sex effects in childhood, postpartum maternal depression with unemployment was associated with sex-difference trends towards increased internalizing symptoms in adolescent girls (SMD, 0.20 [0.03–0.37], $k=6$). Compared with the group of children of depressed mothers with a middle level of education (> 9 and < 13 years), for which the effect size was statistically weak, postpartum maternal depression with low education (≤ 9 years) was significantly associated with increased adolescent internalizing symptoms among girls compared with adolescent boys (SMD, 0.29 [0.11–0.46], $k=6$).

Compared with maternal low education and unemployed statuses, low household income substantially impacted the association between the magnitude of postpartum maternal depression and significant sex differences in offspring internalizing symptoms (Fig. 5). Maternal unemployment status had a stronger influence on the association between concurrent postpartum depression exposure in adolescence and sex-difference trends towards increased internalizing symptoms in adolescent girls than did low maternal education and economic income statuses.

The timing of birth (preterm or full term) of children of depressed mothers was not associated with significant sex differences in internalizing symptoms of children (Fig. 4).

Associations between postpartum maternal depression and sex differences in offspring internalizing symptoms adjusted for socioeconomic factors

After adjustments for socioeconomic factors, the magnitude of postpartum maternal depression and concurrent recurrence of postpartum depression were not associated with significant sex differences in adolescent internalizing symptoms, which was not true (via demonstration of significant sex differences) for the univariable analyses (Table 2). However, nonconcurrent recurrence of postpartum depression remained statistically significantly associated with sex related trends towards increased internalizing symptoms in adolescent girls (β = 0.03 [0.01–0.06]) after controlling for socioeconomic factors. Furthermore, after additional

	Number of Studies	Effect size (SMD)	95% CI
Child Age (> 1 year and < 11 years)			
Income groups			
North America			
Low	2	0.13	-0.03 to 0.30
Lower-middle	4	0.02	-0.11 to 0.15
Upper-middle	3	-0.05	-0.22 to 0.11
Asia			
Low	2	0.06	-0.16 to 0.28
Employment status			
Employed	5	0.03	-0.03 to 0.08
Not seeking employment	2	0.05	-0.01 to 0.12
Unemployed	3	0.11	-0.001 to 0.213
Mother Education (year)			
⩽9	3	0.10	-0.004 to 0.202
9 to 13	5	0.07	0.002 to 0.148 *
⩾13	3	-0.02	-0.101 to 0.068
Childbirth Status			
Preterm	3	0.13	-0.04 to 0.29
Term	5	0.01	-0.08 to 0.10
Child Age (≥ 11 years and < 20 years)			
Income groups			
North America			
Low	3	0.41	0.11 to 0.71 *
Lower-middle	4	0.20	-0.01 to 0.42
Upper-middle	4	0.12	-0.11 to 0.36
Asia			
Low	1	0.10	-0.12 to 0.32
Australia			
Low	1	0.42	0.12 to 0.73 *
Europe			
Lower-middle	2	0.17	-0.59 to 0.93
Employment status			
Employed	2	0.11	-0.37 to 0.60
Not seeking employment	2	0.10	-0.40 to 0.61
Unemployed	6	0.20	0.03 to 0.37 *
Mother Education (year)			
⩽9	6	0.29	0.11 to 0.46 *
9 to 13	3	0.11	-0.12 to 0.34
⩾13	1	0.33	-0.07 to 0.73
Childbirth Status			
Term	1	-0.22	-0.63 to 0.19

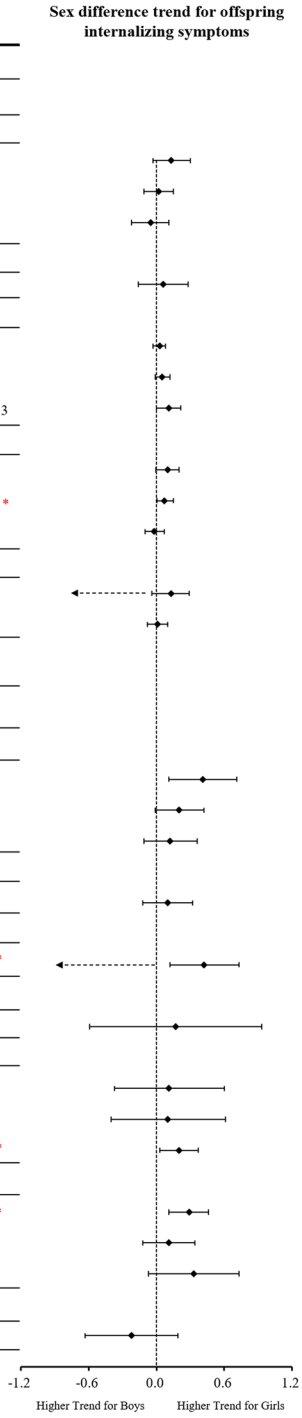


Fig. 4 Socioeconomic factors and preterm for the associations between postpartum maternal depression and sex differences in offspring internalizing symptoms based on unadjusted data. "*" indicates statistically significant $p < 0.05$

adjustments for histories of prenatal depression, nonconcurrent recurrence of postpartum depression was no longer associated with increased odds of internalizing symptoms among adolescent girls compared with boys.

Discussion

This systematic review and meta-analysis identified sex-difference trajectories of offspring internalizing symptoms after exposure to postpartum maternal depression, with trajectories ranging from a lack of significant sex

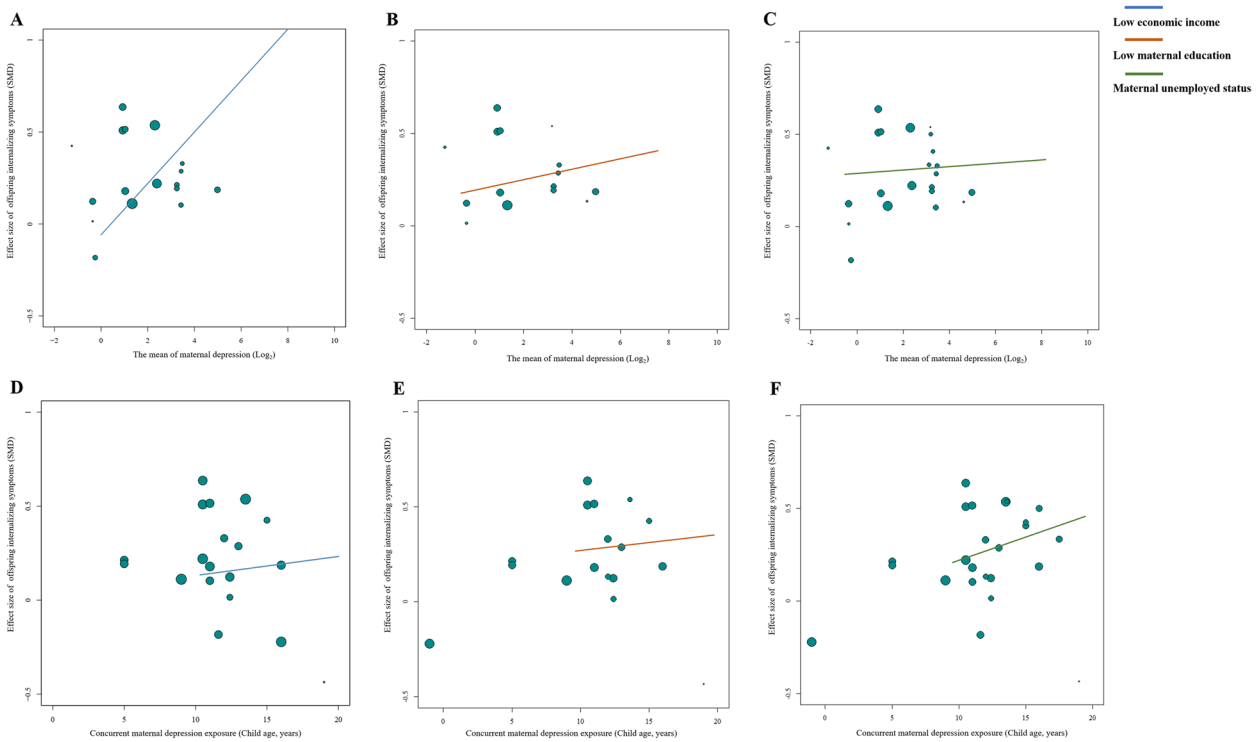


Fig. 5 Socioeconomic factors impacted the sex effects of postpartum maternal depression. **A**, **B**, and **C** illustrated that low family economic income, low maternal education, and maternal unemployed status impacted the association between the mean of postpartum maternal depression and sex differences in adolescent internalizing symptoms. **D**, **E**, and **F** illustrated that low family economic income, low maternal education, and maternal unemployed status impacted the association between concurrent postpartum depression exposure and sex differences in adolescent internalizing symptoms. Positive numbers represent higher rates of internalizing symptoms among girls, and negative numbers represent more significant internalizing symptoms among boys

differences in childhood to a higher prevalence in adolescent girls than in boys. Socioeconomic factors substantially affected the association of postpartum maternal depression with significant sex differences in adolescent internalizing symptoms, thus leading to more internalizing symptoms being observed among girls than boys. Nonconcurrent recurrence of postpartum maternal depression was associated with higher odds of internalizing symptoms among adolescent girls than boys and was independent of socioeconomic factors; however, the association lost statistical significance when adjusted for histories of prenatal maternal depression.

The sex effects of postpartum maternal depression

Our results support previous findings demonstrating that postpartum maternal depression is not associated with significant sex differences in childhood internalizing symptoms [9, 10, 57, 58] and that adolescent girls exposed to maternal depression are more susceptible to internalizing symptoms than adolescent boys [54, 59, 60]. However, during the life histories of offspring, whether females or males are more vulnerable to the effects of postpartum maternal depression has been controversial [10, 45], which is mainly attributed to the sex-specific responses of offspring to progressive alterations in postpartum maternal depression (i.e., antenatal histories of maternal depression and recurrence).

Dean et al. revealed that the impact of maternal prenatal stress on white matter microstructure differed between boys and girls as early as the neonatal period, with effects on maternal cortisol causing alterations in network connectivity in girls but not in boys [61]. We found that postpartum maternal depression with a history of prenatal depression was not associated with significant sex differences in childhood internalizing symptoms in univariable and multivariable analyses. A systematic review and meta-analysis, including 23 studies, demonstrated that untreated depression during pregnancy was associated with significantly increased risks of preterm birth [62]. In this review, alterations in the intrauterine environment caused by maternal depression combined with preterm birth had no significant effect on the association between postpartum maternal depression and sex differences in childhood internalizing symptoms. This result may suggest that postpartum maternal

Table 2 Association of postpartum maternal depression and sex differences in offspring internalizing symptoms

Trend estimate (coefficient *β*; 95% CI)		
Variables	**Univariable analysis (> 1 year and < 11 years)**	**Multivariable analysis (> 1 year and < 11 years)**
Magnitude of maternal depression		
The mean of maternal depression	0.01 (−0.02 to 0.03)	−0.04 (−0.10 to 0.02)
Sex differences in maternal depression	0.41 (−0.23 to 1.04)	0.40 (−0.23 to 1.03)
Timing of depressive exposure		
Concurrent temporal relationship	−0.01 (−0.03 to 0.01)	−0.04 (−0.08 to 0.01)
Non-Concurrent temporal relationship	−0.001 (−0.023 to 0.022)	−0.01 (−0.03 to 0.02)
Variables	**Univariable analysis (≥ 11 years and < 20 years)**	**Multivariable analysis (≥ 11 years and < 20 years)**
Magnitude of maternal depression		
The mean of maternal depression	0.09 (0.04 to 0.13)*	0.01 (−0.07 to 0.09)
Sex differences in maternal depression	0.13 (−1.29 to 1.55)	−0.89 (−1.06 to 0.22)
Timing of depressive exposure		
Concurrent temporal relationship	0.02 (0.01 to 0.03)*	−0.18 (−0.76 to 0.39)
Non-concurrent temporal relationship	0.03 (0.01 to 0.04)*	0.03 (0.01 to 0.06)*
Non-concurrent temporal relationship[a]	0.03 (0.01 to 0.04)*	0.01 (−0.05 to 0.07)

Negative numbers represent more significant internalizing symptoms among boys, and positive numbers represent higher rates of internalizing symptoms among girls

Multivariable analysis adjusted for family income, maternal education, and maternal employment status

[a] Adjusted for histories of maternal prenatal depression

[*] Statistically significant $p < 0.05$

depression has a further impact on the direction of childhood sex differences in internalizing symptoms following offspring exposure to the intrauterine environment altered by prenatal depression. For example, male infants may be more susceptible to maternal risk earlier in development than female infants, based on the greater need for maternal support to help these infants in maintaining affective regulation in infancy [63].

A meta-analysis suggested that increased internalizing symptoms among girls significantly surpassed those among boys after the age of 13 years [57], which was consistent with our findings on the effects of postpartum maternal depression on offspring. Specifically, these findings demonstrated that trajectories of sex differences in offspring internalizing symptoms that were increasingly inclined towards girls were predominant in adolescence (≥ 11-years-old). A cohort study found that women from urban disadvantaged populations had a high prevalence of elevated maternal postnatal depressive symptoms [15]. When we adjusted for socioeconomic factors, the concurrent recurrence of postpartum depression was not associated with sex-difference trends towards increased internalizing symptoms among adolescent girls. Socioeconomic environments could influence the association between postpartum maternal depression and sex differences in adolescent internalizing symptoms by affecting the recurrence of postpartum maternal depression. A large birth-cohort survey from South Africa revealed that, independent of socioeconomic status, postnatal maternal depression at 6 months was significantly associated with the internalizing problems of children at the ages of 2, 10, and 14 years [18, 64, 65]. We found that after controlling for multiple socioeconomic factors, significant sex effects of early nonconcurrent recurrence of postpartum depression on offspring internalizing symptoms did not concurrently emerge in childhood; rather, they were observed in adolescence. However, this association was no longer statistically significant when adjusted for histories of prenatal maternal depression. Evidence from human studies suggests that female adolescents' vulnerability to the effects of early maternal depression is attributed to the influences of fetal programming during pregnancy [38]. Therefore, the significant sex effects of the postpartum maternal depression are more likely to be due to a complex interaction between fetal programming during the intrauterine development period and postpartum environments that shape offspring functionality.

A meta-analysis of 193 studies suggested that children are more sensitive to maternal depressive symptoms than adolescents because they are less social and more

dependent on their mothers to cope with stressful life events [66, 67]. Our review found a more centralized and steady distribution of postpartum maternal depression across childhood compared with the lower magnitude and discrete distribution of postpartum maternal depression in adolescence. Hence, environmental risk factors are more likely to influence the sex effects of postpartum maternal depression on offspring internalizing symptoms in adolescence than in childhood.

Economic income impacted the sex effects of postpartum maternal depression

Consistent with a meta-analysis of 310 studies from North America (Canada and the United States), economic factors were not associated with significant sex differences in childhood mental outcomes [57]. Similar to findings in North American studies, we found that postpartum depression in low-income environments in Asia (China) was not associated with significant sex differences in childhood internalizing symptoms. Other studies on the differences in susceptibility between boys and girls speculated boys might experience a longer period of early sensitivity, which made boys more impacted by risk in postpartum [10]. Therefore, boys from low socioeconomic environments may be more vulnerable to exposure to postpartum maternal depression than girls in earlier developmental stages. The Early Childhood Development Index reported by the United Nations Children's Fund (UNICEF) demonstrated that 37% of 3- and 4-year-old children in 35 LMICs had poor social-emotional skills and developmental delay [68]. The multicountry studies reported that boys in Southeast Asia performed higher rates of developmental delay than girls, and boys from low-income families in China had poorer neurodevelopment than girls [69, 70]. Sex differences in affective desire and early neurodevelopment affect the dependence of boys on their mothers in LMICs, which may be related to the lack of significant sex differences in childhood internalizing symptoms in China.

In contrast, consistent with previous findings, adolescent female participants exposed to maternal depression had more significant increases in the likelihood of internalizing symptoms than boys in low economic contexts in North America and Australia [18]. In this review of adolescent internalizing symptoms, only one study involved low-income families in LMICs (China), and this study revealed no significant sex differences in adolescent internalizing symptoms. However, a survey of low-income families in LMICs (South Africa) showed that postpartum depression was associated with sex differences in internalizing symptoms among adolescent girls [18]. It is essential to understand the reasons underlying the discrepancies between different regions. A number of studies have shown that adolescents from Asia are likely to make strong voluntary choices not to receive a diagnosis and treatment for mental disorders, as mental illness is highly stigmatized in Asian culture [71, 72].

Economic income has a direct effect on the process of social mobility of mothers and adolescents. In the Avon Longitudinal Study of Parents and Children in the UK, children exposed to the same level of perinatal depression were more likely to experience increased rates of internalizing symptoms with greater economic adversity [73]. Our results indicated that compared with low maternal education and maternal unemployment statuses, low household income substantially impacted the association between postpartum depression severity and sex-related trends towards increased internalizing symptoms among girls. After adjusting for socioeconomic factors, the magnitude of postpartum depression was not associated with significant sex differences in adolescent internalizing symptoms. Therefore, the economic factor was a more critical prerequisite than other socioeconomic factors for the postpartum depression transmission pathway, in which the magnitude of maternal depression was associated with significant increases in the likelihood of internalizing symptoms occurring among girls compared with boys in adolescence.

Maternal unemployment impacted the sex effects of maternal postpartum depression

In addition to slightly affecting the relationship between the magnitude of maternal depression and adolescent psychological outcomes, we found that maternal unemployment had more substantial impacts on the association between concurrent recurrence of postpartum maternal depression and significant sex differences in adolescent internalizing symptoms than did low economic income and maternal education. A recent study found unemployment as being clinically meaningful, as the outcomes were more important than previous estimates for patients with recurrent depression [17]. When controlling for recurrent maternal depression in U.S. families, the association between maternal depression and children's concurrent psychological symptoms in adolescence became nonsignificant [42, 74]. As maternal unemployment exhibits clinical indicators of a poorer prognosis for postpartum depression, longer follow-ups are needed to manage the relationship between unemployed mothers with postpartum depression and sex differences in adolescent internalizing symptoms.

Strengths and limitations

This study had some limitations. First, given that most socioeconomic studies were conducted in Asia, Europe, and North America, we cannot rule out the possibility

that some unpublished and published studies in other languages were not included in this analysis, thus reducing the generalizability of our results to other countries. The studies originated from LMICs, where studies of offspring sex differences in internalizing symptoms and specialist child services may be rare. Second, the interpretation of the evidence primarily relied on observational studies, which may have resulted in selection bias and exaggeration of the strength of the association. This review revealed that pre- and postnatal maternal depression and socioeconomic factors interact and collectively affect the higher prevalence of internalizing symptoms in adolescent girls than in adolescent boys. Future studies are necessary to determine whether interventions for prenatal maternal depression alone can effectively reduce the risk of internalizing symptoms among adolescent girls exposed to postpartum maternal depression with prenatal histories of depression. In addition, we mainly focused on the impacts of maternal depression during pregnancy on the association between postpartum maternal depression and sex differences in offspring internalizing symptoms; however, we did not consider the risk of maternal depression before pregnancy. Further research using multiple methods, such as randomized, epidemiological intervention trials, and policy perspectives, is needed. Finally, in addition to socioeconomic factors, other mediating factors, including postpartum parenting quality, child attachment, maladaptation, and school engagement, may impact the association between maternal depression and sex differences in offspring internalizing symptoms. Despite these limitations, our study provides a comprehensive review of the sex effects of maternal postpartum depression on offspring internalizing symptoms across childhood and adolescence.

Conclusions

In conclusion, our findings demonstrated that socioeconomic factors differentially influence the association of postpartum maternal depression with significant sex differences in adolescent internalizing symptoms. Early nonconcurrent recurrence of postpartum maternal depression with histories of prenatal depression was independently associated with a greater incidence of internalizing symptoms among girls than boys during adolescence (≥ 11 years) but not during childhood (< 11 years). For depressed females during pregnancy, postpartum depression is easy to measure; moreover, measurements and interventions conducted at earlier time points can help to inform and manage the risks of sex differences in offspring psychological symptoms after birth. There are more measures for the early prevention of the high prevalence of internalizing symptoms among adolescent girls. Specifically, interventions can be implemented that target the severity and concurrent recurrence of postpartum maternal depression in the contexts of greater socioeconomic adversity, and the continuous monitoring of the psychiatric statuses of daughters of mothers with pre- and postpartum depression from childhood to adolescence.

Abbreviations

HICs	High-income countries
LMICs	Low- and middle-income countries
PRISMA	Preferred reporting items for systematic reviews and meta-analysis
SCI-EXPANDED	Science citation index expanded
SSCI	Social sciences citation index
CNKI	China National Knowledge Infrastructure
SinoMed	China biomedical literature service system
ROBINS-E	"Risk of Bias in Nonrandomized Studies-of Exposure" tool for follow-up observational studies
SMD	Standardized mean difference
UNICEF	United Nations Children's Fund

Supplementary Information

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Additional File 1. Tables S1-S3, Figures S1-S6. Table S1. PRISMA 2020 Checklist. Table S2. Table of full research strategy. Table S3. Template data extraction sheet for inclusion criteria. Fig. S1. Quality assessment of the risk of bias in the systematic review. Fig. S2. Funnel plots and Egger's test. Fig. S3. P curve test for effect size. Fig. S4. Sensitivity analysis of forest plots for sex effects of maternal postpartum depression. Fig. S5. Sex-difference trends in offspring internalizing symptoms after exposure to postpartum maternal depression, by children's age. Fig. S6. The distribution of sex differences in offspring internalizing symptoms from childhood to adolescence.

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Authors' contributions
YG, WL, ZY, and WZ conceptualized the study and developed the protocol. YG, ZY, and WL designed the search strategy and analyzed the data. HZ and YL did the literature search. YG, ZY, and YL screened titles, abstracts, and full texts. YG, HZ, and WZ extracted data and assessed data quality. YG, WZ, and ZY interpreted the data. YG wrote the first draft of the manuscript. All authors reviewed, edited, and approved the final manuscript. YG, ZY, and WZ are the study guarantors and corresponding authors. All authors had full access to all the data in the study, and the corresponding author (YG) attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. All authors read and approved the final manuscript.

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Data availability
The data are available from the corresponding authors on reasonable requests.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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