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Does maternal anxiety and depression increase the risk of asthma in the offspring? A systematic review and meta-analysis

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Abstract. – OBJECTIVE: Adverse exposures during pregnancy have been linked with respiratory disorders in the offspring. Research also shows that maternal mental disorders can influence the risk of respiratory illnesses. We hereby systematically examined if specific mental disorders during pregnancy, namely, anxiety and depression, can increase the risk of asthma in the offspring.

MATERIALS AND METHODS: A literature search of PubMed, CENTRAL, Scopus, Embase, and Web of Science databases from inception to 15th October 2023 was undertaken for cohort studies assessing the association between maternal anxiety/depression and the risk of asthma in the offspring. Adjusted data was quantitatively synthesized in a random-effect meta-analysis model.

RESULTS: Nine studies with 1,027,469 mother-child pairs were included. Studies reported data on anxiety, depression, or both anxiety and depression. Maternal anxiety (OR: 1.61 95% CI: 1.29, 2.01 I^2=0%), maternal depression (OR: 1.25 95% CI: 1.07, 1.45 I^2=12%), and both combined (OR: 1.28 95% CI: 1.16, 1.41 I^2=93%) were associated with significantly increase the risk of asthma in childhood. Overall, the pooled analysis showed that maternal anxiety or depression significantly increased the risk of asthma in childhood by 30% (OR: 1.30 95% CI: 1.20, 1.40 I^2=75%). Results remained significant on multiple subgroup analyses.

CONCLUSIONS: Maternal anxiety and depression can increase the risk of asthma in childhood. The observational nature of studies, differences in adjusted founders, methodological variations, and predominance of European data are important limitations. Further prospective research taking into account present limitations is needed for improved evidence.

Key Words:
Wheeze, Mental disorder, Pregnancy, Mother, Child, Anxiety, Depression.

Introduction

Maternal health is a key contributor to the health and development of the fetus, which can carry forward into early childhood (lassi). One aspect of maternal health often ignored is maternal mental illnesses, which can affect about 23% of mothers during pregnancy[1]. Evidence[2] suggests that maternal mental illness results in children with poor physical health. Children born to mothers with severe mental illnesses also have a high risk of various psychiatric disorders, of which about 1/3rd develop by early adulthood[3]. Mental health disorders in the mother are also a major contributor to neurodevelopmental problems in the offspring causing a higher risk of autism, intellectual disability, and poor school performance[4,5]. Additionally, it also increases the risk of birth defects and could be a contributor to stillbirths and premature death[6,7].

The high incidence of allergic diseases like eczema, atopic dermatitis, asthma, food allergy, and atopic rhinitis in children has led to research focusing on modifiable prenatal factors[8]. Amongst various exposures, evidence shows that maternal mental health could lead to an increased risk of allergic diseases in the offspring[9]. One of the most common allergic diseases in children is asthma, which is considered a global epidemic[10]. The worldwide age-standardized incidence rate was around 1,884.6 per 100,000 children aged 1 to 4 years in 2019. It is also a major contributor to childhood mortality and ranks among the top conditions for disability-adjusted life years in children[11].

Accumulating evidence[12,13] suggests that maternal stress in the prenatal and early postnatal period can heighten the risk of wheezing and asthma in the offspring. Maternal psychological state can influence the biology and progression of respiratory diseases by affecting lung and immune function[14,15]. Specifically, maternal anxiety and depression have been linked as risk factors for asthma in childhood. Previously, Chen et al[16], in a systematic review and meta-analysis, have demonstrated a positive association between

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maternal anxiety and depression and the risk of asthma. However, their review had multiple limitations. Only limited studies were available for analysis, and not all studies were specific to anxiety and depression. Secondly, newer studies published in the past few years have produced conflicting outcomes. Shi et al[9] in a 2023 did not find a link between maternal anxiety/depression and risk of asthma, while Osam et al[17] have shown a significant relationship between the two. Given such contradictory results and limitations of the previous review, we hereby present the results of a comprehensive systematic review and meta-analysis examining the association between maternal anxiety and depression and the risk of asthma in the offspring.

Materials and Methods

Search Protocol

The systematic review was performed and reported by the guidelines of PRISMA[18]. Registration on PROSPERO was completed before the literature search (CRD42023468549). The search encompassed PubMed, CENTRAL, Scopus, Embase, and Web of Science databases from inception to 15th October 2023. Only English-language studies were searched. It was conducted by an experienced medical librarian in collaboration with one of the reviewers (QH). The search strategy can be found in **Supplementary Table I**. It included the keywords: "anxiety", "depression", "stress", "mental disorder", "maternal", "prenatal", "asthma", AND "wheeze". All search results were downloaded into EndNote X8 (Thompson ISI Research soft, Philadelphia, PA, USA), a reference manager software. Duplicate articles were identified and excluded. All remaining unique citations underwent screening by two reviewers (QH and YS). Full texts of articles of relevance for the current literature review were downloaded and further screened based on inclusion criteria.

Inclusion Criteria

Both reviewers independently checked the eligibility of studies based on the following criteria:

1. Cohort study design.
2. Assessing the risk of asthma in the offspring based on the presence or absence of maternal anxiety, depression, or both.
3. Reporting the association as adjusted effect size.
4. The risk of asthma was to be assessed in the pediatric population (up to the age of 18 years).

Case-control, cross-sectional studies, studies not on maternal anxiety/depression, not reporting separate data for asthma, review articles, editorials, and abstracts were excluded.

The reviewers resolved any disagreements (if any) involving the study selection by discussion. In the end, one reviewer (YS) undertook a hand search of a reference list of included studies for any possible inclusions.

Data Extraction

The reviewer YS used a pre-defined data collection form to record data. It included all the data presented in Table I. The second reviewer (QH) then cross-checked the data for correctness. Outcome data presented as adjusted effect size was also extracted and recorded in Word. We extracted data on the association between maternal anxiety only, depression only, or anxiety and depression both with subsequent risk of asthma in the offspring.

Study Quality

We used the Newcastle-Ottawa Quality Assessment Scale (NOS) to judge individual study bias[19]. The scale intends to rate selection bias, comparability of the exposed and unexposed groups, outcome assessment, and completeness of follow-up. Points are awarded based on pre-determined questions, and the final score of each study can be 0, meaning the highest risk of bias, up to 9, meaning the lowest risk of bias.

Statistical Analysis

Adjusted effect sizes reported by studies were pooled to generate a combined Odds ratio (OR) and 95% confidence intervals (CI). Separate analysis was done for anxiety, depression, and studies reporting on both anxiety & depression. The studies were weighted based on their log-transformed inverse variance. A random-effects model was chosen because of anticipated heterogeneity.

The Chi-square test judged the heterogeneity between studies; the I^2 statistic was also calculated. The I^2 statistic gives the percentage of the variability in effect size based on heterogeneity rather than sampling error. Any value >50% was considered substantial heterogeneity. "Review Manager" (RevMan, version 5.3; Nordic Cochrane Centre, Cochrane Collaboration, Copenhagen, Denmark) was the software used.

Table I. Details of included studies.

Study	Database	Type	Measurement of exposure	Measurement of outcome	Age of diagnosis of asthma	Sample size	Maternal age (years)	% with anxiety (A) depression (D)	% with asthma	Covariates adjusted	NOS score
Osam et al[27] 2023	Clinical Practice Research Datalink, UK	RC	Medical records	Medical records	Up to 18 years	590778	NR	A & D: 38.6	8.6	Maternal history of atopic disease, antibiotic use during pregnancy, maternal age,child sex, child ethnicity,birth season, birth year practice, Index of Multiple Deprivation, maternal smoking and practice region	8
Shi et al[9] 2023	Shanghai Maternal-Child Pairs Cohort, China	PC	Self-Rating Anxiety Scale and Center for Epidemiologic Studies–Depression Scale at 32-36 weeks of gestation	ISAAC core questionnaires	2 years	4178	28.9	A: 6.7 D: 7.3	3.2	Maternal age at delivery, socioeconomic status, maternal parity, exposure to second-hand smoke during pregnancy, family history of asthma, child's birth weight, gestational age	7
Alcala et al[24] 2022	Programming Research in Obesity, Growth, Environment and Social Stressors study, Mexico	PC	Edinburgh Depression Scale questionnaire at 2nd or 3rd trimester. Depression defined as score of > 12	ISAAC core questionnaires	2-3 years	601	27	D: 17	4	Child's sex, mother's age and education at enrollment, parity, report of a smoker in the home during the second or third t rimesters, and average PM2.5 exposure during pregnancy, and average PM2.5 at first year postpartum	7
Meel et al[26] 2020	Generation R Study, Netherlands	PC	Global Severity Index and anxiety depression symptom scale in 2nd trimester	ISAAC core questionnaires or any asthma medication use in the past 12 months	10 years	4231	30.9	A: 9.3 D: 8.2	5.9	Maternal age, parity, education level, smoking during pregnancy, body mass index at enrolment, history of asthma or atopy and pet keeping, and child's sex, gestational age at birth, birth weight, ethnicity, breastfeeding and daycare attendance	8

Continued

Table I *(Continued)*. Details of included studies.

Study	Database	Type	Measurement of exposure	Measurement of outcome	Age of diagnosis of asthma	Sample size	Maternal age (years)	% with anxiety (A) depression (D)	% with asthma	Covariates adjusted	NOS score
Leek et al[25] 2020	Manitoba Population Research Data Repository, Canada	RC	One health care contact or prescription of medications for depression or anxiety	Asthma hospitalization, 2 physician visits or 2 prescription medications for asthma	7 years	12587	NR	A&D: 14	7.1	Sex, mode of delivery, low birth weight, preterm birth, newborn respiratory distress, maternal age, first pregnancy, maternal asthma and atopy, maternal smoking during pregnancy, urban location, low household income, and infant antibiotic use	8
Magnus et al[23] 2018	Norwegian Mother and Child Cohort Study, Norway	RC	5-item symptom checklist at 30 weeks of gestation	Maternal report of physician-diagnosed asthma	7 years	47619	30.1	NR	4.2	Maternal age, parity, education, pre-pregnancy body mass index, smoking during pregnancy, and history of asthma	7
Zhou e al[22] 2017	EDEN mother child cohort study, France	RC	Centre for Epidemiological Studies-Depression scale (score > 16) at 24-28 weeks of gestation	ISAAC core questionnaires	5 years	1139	31.1	D: 13.8	21	Study center; maternal educational attainment; maternal smoking during pregnancy; maternal age at recruitment; maternal pre-pregnancy body mass index; siblings; gender of the newborn; and family history of asthma, eczema, allergic rhinitis, or food allergy	7
Brew et al[21] 2017	Swedish national register, Sweden	RC	Using ICD codes for diagnosis or prescription of medication	Using ICD codes for diagnosis or prescription of medication	4 years	360526	NR	A& D: 3.3	8.7	Maternal education, maternal asthma, number of siblings, gender	6
Cookson et al[20] 2009	Avon Longitudinal Study of Parents and Children, UK	PC	Crown-Crisp Experiential Index at 18-32 weeks of gestation	Physician diagnosis	5.5 years	5810	NR	A: 19.5	15.4	Sex, preterm delivery, multiple birth, number of siblings, maternal age, maternal education, maternal history of asthma and allergy, prenatal tobacco smoke exposure and problems during pregnancy (diabetes, hypertension, steroid intake)	7

PC, prospective cohort; RC, retrospective cohort; ISAAC, International Study of Asthma and Allergies in Childhood; NOS, Newcastle Ottawa scale.

Values of $p<0.05$ were considered to be statistically significant. Any publication bias was graphically checked with a funnel plot. A subgroup was also conducted for the combined association of maternal anxiety/depression and risk of childhood asthma based on the variables: study type, location, identification of anxiety/depression, identification of asthma, timing of asthma diagnosis, sample size, percentage with asthma, and NOS score.

Results

The total number of records retrieved from all databases was 3,272. Of these, unique articles were 1,286. 1,261 records were not relevant to the review. 25 underwent full-text analysis, and nine[9,17,20-26] were selected for the meta-analysis (Figure 1).

Study Characteristics

Individual study characteristics can be found in Table I. Studies were from the UK, China, the Netherlands, Mexico, Canada, Norway, France, and Sweden. Four were prospective, while the remaining were retrospective. The articles were published between 2009-2023. Different standardized scales were used by the studies for the assessment of anxiety and depression during pregnancy. The scales included The Self-Rating Anxiety Scale and Center for Epidemiologic Studies-Depression Scale, the Edinburgh Depression Scale, the Global Se-

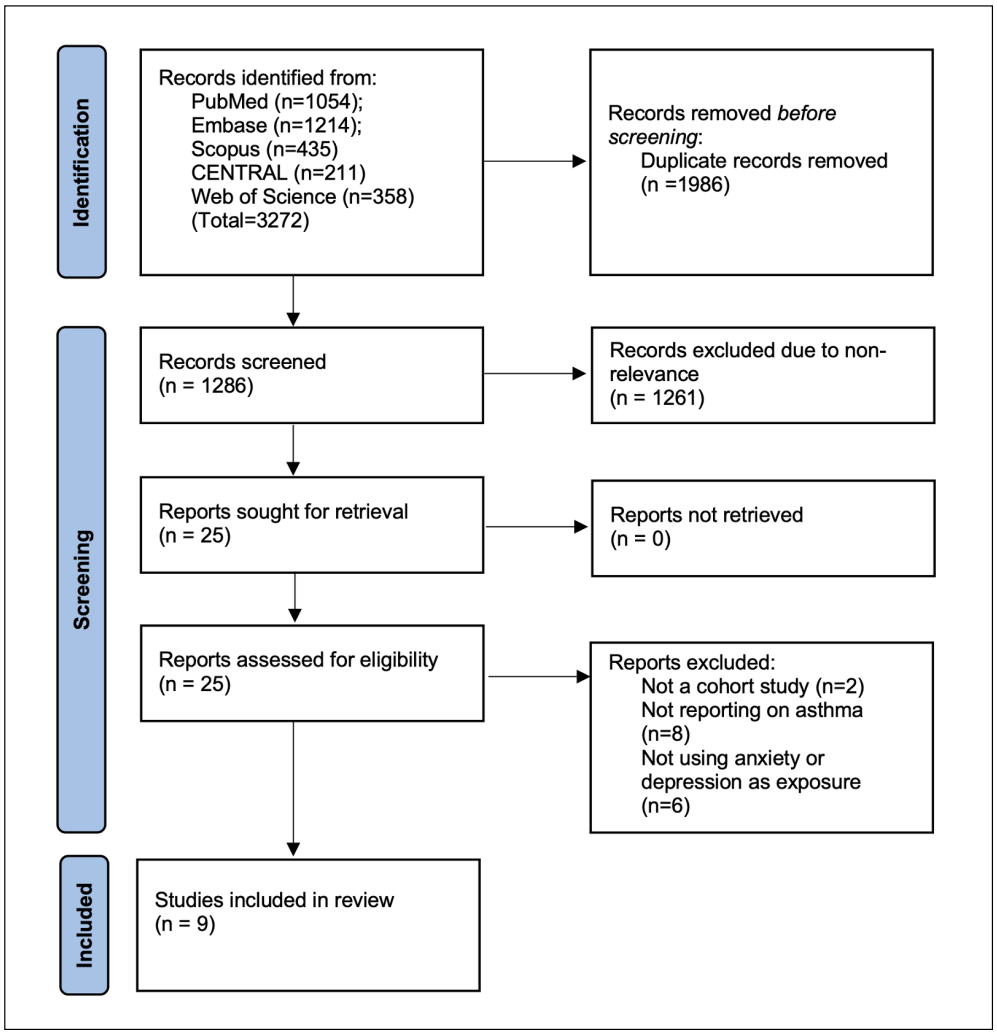

Figure 1. Flowchart denoting the selection of studies.

verity Index and anxiety depression symptom scale, the Centre for Epidemiological Studies-Depression Scale, and the Crown-Crisp Experiential Index. Some studies also used medical records to identify mothers with anxiety/depression. The International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire was most commonly used by studies to identify asthma in childhood. Other methods included medical records, physician diagnosis, and maternal reporting of physician diagnosis. The age of diagnosis varied considerably and ranged from 2 to 18 years. A total of 1,027,469 mother-child pairs were included in the nine studies. Three studies[21,25,27] reported combined data on anxiety and depression. The number of children with asthma ranged from 3.2 to 21% in the studies. The covariates adjusted in the analysis were dissimilar across studies. Three studies[25-27] recorded a NOS score of 8, five[9,20,22-24] had a score of 7, and one study[21] had a score of 6.

Quantitative Synthesis

The forest plot in Figure 2 shows the results of the meta-analysis. Maternal anxiety reported by three studies[9,20,26] was found to significantly increase the risk of asthma in childhood (OR: 1.61 95% CI: 1.29, 2.01 I^2=0%). Maternal depression reported by five studies also significantly increased the risk of asthma in childhood (OR: 1.25 95% CI: 1.07, 1.45 I^2=12%). Combined data was reported by three studies. Maternal anxiety or depression was associated with a significantly increased risk of asthma in childhood (OR: 1.28 95% CI: 1.16, 1.41 I^2=93%). Overall, the pooled analysis showed that maternal anxiety or depression significantly increased the risk of asthma in childhood by 30% (OR: 1.30 95% CI: 1.20, 1.40 I^2=75%). The funnel plot did not show any publication bias (Figure 3).

Subgroup Analysis

Data on all subgroup analyses for the combined association between maternal anxiety or depres-

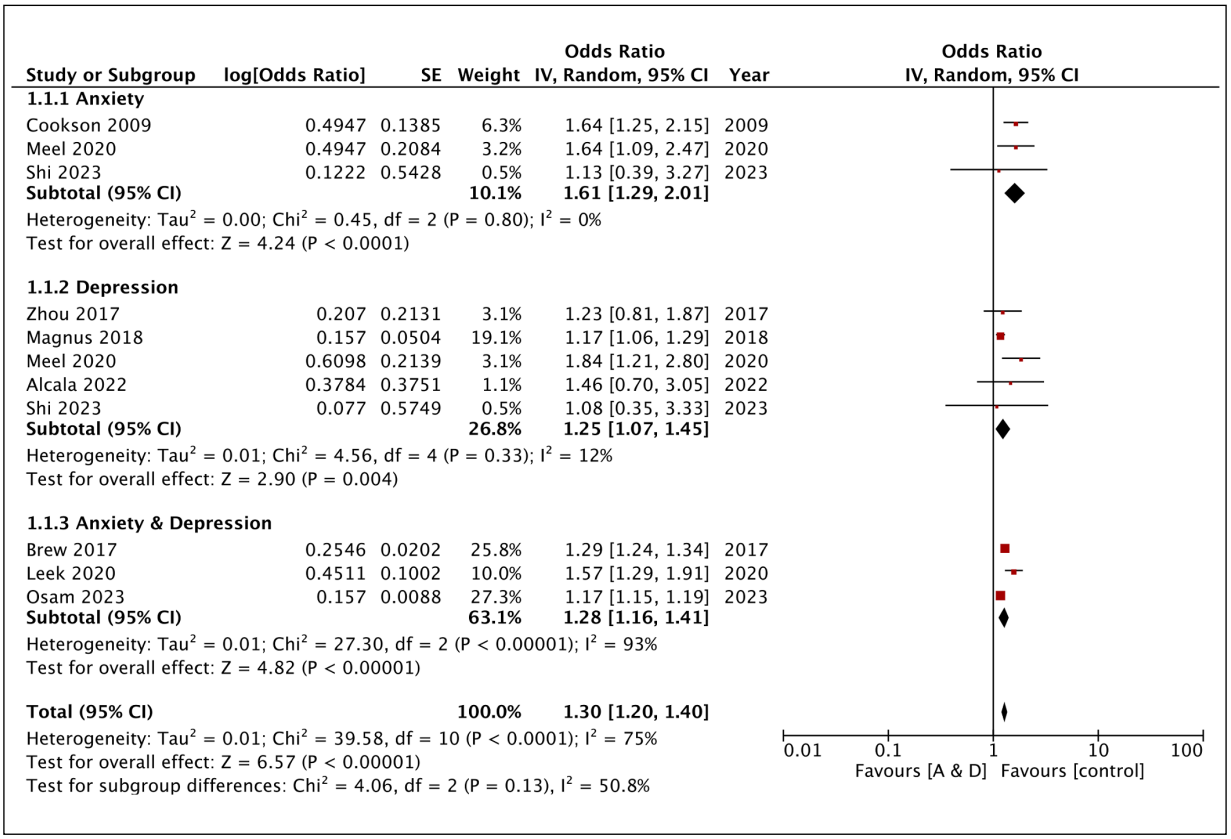

Figure 2. Meta-analysis analyzing the association between maternal anxiety only, depression only, or both anxiety and depression with subsequent risk of asthma in offspring.

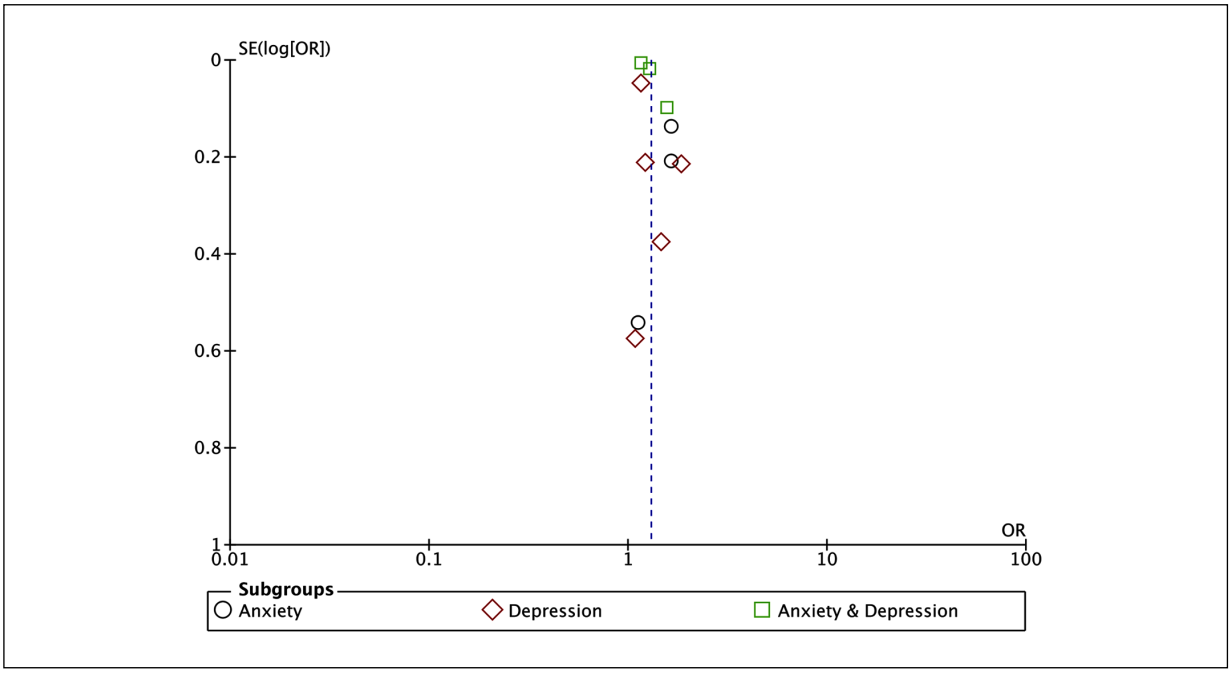

Figure 3. Funnel plot to graphically assess publication bias.

sion and the risk of childhood asthma is presented in Table II. Results still showed a significant association between maternal anxiety or depression and risk of childhood asthma based on subgroup analysis with all variables except two. Sub-group analysis of studies with physician-diagnosed asthma did not show a significant outcome (2 studies). Similarly, studies sub-group analysis of studies diagnosing asthma between 2-3 years of age also did not present significant results.

Table II. Subgroup analysis.

Variable	Groups	Studies	Odds ratio [95% confidence intervals]	I^2 (%)
Study type	Prospective	4	1.63 [1.35, 1.96]	0
	Retrospective	5	1.25 [1.15, 1.35]	85
Location	European	6	1.27 [1.17, 1.37	81
	Non-European	3	1.53 [1.27, 1.84]	0
Identification of anxiety or depression	Standard indices	6	1.39 [1.18, 1.64]	35
	Others	3	1.28 [1.16, 1.41]	93
Identification of asthma	ISAAC core questionnaires	4	1.50 [1.21, 1.87]	0
	Physician diagnosed	2	1.35 [0.97, 1.87]	81
	Other	3	1.28 [1.16, 1.41]	93
Timing of asthma diagnosis	2-3 years	2	1.28 [0.75, 2.18]	0
	4-5.5 years	3	1.35 [1.17, 1.55]	33
	7-10 years	3	1.46 [1.16, 1.85]	74
Sample size	> 10,000	4	1.25 [1.15, 1.35]	89
	< 10,000	5	1.55 [1.31, 1.84]	0
Percentage with asthma	< 8%	5	1.42 [1.18, 1.71]	50
	> 8%	4	1.26 [1.15, 1.39]	88
NOS score	8	3	1.47 [1.15, 1.87]	81
	< 8	6	1.27 [1.20, 1.35]	12

ISAAC, International Study of Asthma and Allergies in Childhood; NOS, Newcastle Ottawa scale.

Discussion

This updated systematic review and meta-analysis aimed to examine the association between maternal anxiety and depression and the risk of asthma in childhood. After a comprehensive literature search, nine studies were available for inclusion. The results demonstrated that maternal anxiety and depression were significant risk factors for asthma in childhood.

While we aimed to study the role of anxiety and depression separately, the included studies presented data on either anxiety or depression or both anxiety and depression as a single component. Hence, a pooled analysis of both anxiety and depression was conducted in our review. Indeed, both anxiety and depression are highly prevalent psychiatric illnesses and commonly comorbid with each other[27]. Together, they belong to a wider category of internalizing disorders. The coexistence of both anxiety and depression is commonly seen in the same period. In one study, around 41.6% of patients with depression seen in 12 months had the presence of one or more anxiety disorders at the same time. For anxiety disorders, the lifetime prevalence of comorbid depression ranged from 20% to 70%[28]. The Sequenced Treatment Alternatives to Relieve Depression study has shown that around 53% of individuals with major depression had significant comorbid anxiety and were deemed to have anxious depression[29]. Anxiety and depression also share the largest number of genetic risk factors among all internalizing disorders. Amongst non-genetic risk factors, previous life adversity (like trauma or neglect), parenting style, and stress exposure are commonly seen with the development of both anxiety and depression[27].

Anxiety and depression are also noted in new expectant parents. The prevalence of perinatal maternal anxiety can be as high as 13%, while about 11% of mothers experience depression during pregnancy[30,31]. In the included studies, the prevalence of anxiety and depression varied widely from just 3.3% to as high as 38.6%. Such major variation could be due to the difference in patient populations, study locations, and the measures used to diagnose anxiety and depression. Our meta-analysis found that maternal anxiety and depression, when analyzed separately, significantly increased the risk of asthma in childhood by 61% and 25%, respectively. On combined results of three studies[21,25,27] which reported anxiety and depression as a single exposure variable, the meta-analysis noted a statistically significant 28% increased risk of asthma. Overall, the review showed that maternal anxiety or depression significantly increased the risk of childhood asthma by 30%. Our results are in agreement with the previous review of Chen et al[16], who noted a statistically significant association between prenatal anxiety and depression and the risk of childhood asthma (Effect size: 1.146, 95% CI: 1.054-1.245 I^2=93.5%). However, out of the six studies included in their review, two were not focused on anxiety and depression alone. One of the studies by Radhakrishnan et al[32], examined the association between the use of maternal mental health services and the risk of childhood asthma. The authors noted a significant association between the two, but maternal mental health services were utilized not only for anxiety and depression but also for psychoses, substance abuse problems, other mood disorders, and social issues. Liu et al[33] examined the association between negative life events and job stressors and the risk of asthma in offspring. The study found that maternal stressors were not associated with childhood asthma, but low job control increased the risk of early-onset transient asthma. These two studies provide important information on the role of maternal mental health in increasing the risk of childhood asthma but include a heterogeneous population and hence were excluded from this review. With our updated literature search, we were able to include five new studies to present the most updated evidence on the clinical question.

The high heterogeneity in our meta-analysis is an important limitation. Methodological variations in the studies, differences in assessment tools, study population, etc., could have been important factors contributing to such heterogeneity. Nevertheless, multiple subgroup analyses failed to alter the significance of the results. Non-significant results were noted only for studies with physician-diagnosed asthma and those diagnosing asthma at 2-3 years. One possible reason is that only two studies were available for each of these analyses, which could have led to a non-significant outcome. However, the consistency of significant outcomes across multiple subgroups adds credibility to the outcome of this review.

The pathophysiological relationship between maternal anxiety and depression and childhood asthma is still under research, and several mechanisms have been proposed. Studies[34,35] show that maternal anxiety can trigger the hypothalam-

ic-pituitary-adrenal (HPA) axis and cause large quantities of cortisol secretion. The placenta is unable to metabolize such large quantities of cortisol, leading to the release of placental steroids, which cross onto the fetus, where it can influence brain development and cause airway inflammation and hyperresponsiveness[34,35]. High levels of maternal cortisol also affect immune regulation in the fetus by affecting TH2 lymphocyte response. The immunomodulatory property of steroids tilts the TH1/TH2 balance towards the TH2 response, which can cause asthma in genetically susceptible children[36]. Maternal anxiety and depression also affect fetal growth and cause reduced fetal weight gain, and head and abdominal growth. Smaller lungs and airway volumes in low-birth-weight infants can increase asthma risk[37,38]. Maternal stress levels have been shown to alter fetal intestinal microbiota. The intestinal microbiota has a major role in the development of the fetal immune system and the regulation of immune response. Reduced bacterial diversity in the fetus can cause the development of allergic diseases like asthma[39,40]. Nevertheless, all these possible mechanisms still need further validation to establish the role of maternal anxiety or depression as a risk factor for childhood asthma.

The results of the review must be weighed against the following limitations. As randomized controlled trials are impossible, the best evidence on the review question can only be obtained *via* well-designed cohort studies. However, such studies still have confounding bias, selection bias, recall bias, and information bias. We attempted to reduce errors due to confounding by pooling only adjusted data. However, the confounders adjusted by the studies were not exactly similar. Several known and unknown confounders were missed due to the lack of availability of data in the medical records. Such missed confounders could alter the effect size. One possible way of reducing such unknown confounding is by sibling-comparison analysis. However, these types of studies omit non-shared risk factors and are still prone to bias[41]. Secondly, the identification of exposure and outcome was dissimilar across studies. Several different assessment scales are available for anxiety and depression and not all of them have high discriminative ability[42]. The lack of a common assessment scale in the studies may have underestimated or overestimated the prevalence of anxiety and depression. Also, due to the combined presentation of data from several studies[21,25,27], this review had to combine anxiety and depression as a single exposure variable. Limited studies were available for separate analyses of anxiety and depression. Similarly, the dissimilarity in the identification of asthma and the variation of age of diagnosis is a major cause of concern. Lastly, data was available mostly from high-income countries, predominantly from Europe. Environmental factors play a major role in asthma development, and hence, the results cannot be generalized to the world population.

Strengths and Limitations

The strength of the study is the updated literature search, adding five new studies to the previous meta-analysis and omitting heterogeneous studies not focusing on anxiety and depression. To the best of our knowledge, this review provides the highest quality of evidence on the association between maternal anxiety and depression and the risk of asthma in childhood by analyzing only cohort studies. Case-control and cross-sectional studies, which have a high risk of bias, were omitted. The results have important clinical implications. Offspring of mothers diagnosed with anxiety or depression in pregnancy should undergo early and regular screening for childhood asthma. Mothers should also be counseled during pregnancy regarding the risk of asthma in the child. Research should be conducted on interventions to reduce such increased risk.

Conclusions

Maternal anxiety and depression can increase the risk of asthma in childhood. The observational nature of studies, differences in adjusted founders, methodological variations, and predominance of European data are important limitations. Further prospective research taking into account present limitations is needed for improved evidence.

Conflict of Interest

The authors declare that they have no conflict of interests.

Funding

No funding was received.

Availability of Data and Materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' Contribution

YS conceived and designed the study. YS and QH collected the data and performed the literature search. YS was involved in the writing of the manuscript. All authors have read and approved the final manuscript.

Ethics Approval

Not applicable.

Informed Consent

Not applicable.

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