Does Prenatal Anxiety or Depression Symptoms Associate With Asthma or Atopic Diseases Throughout the Offspring's Childhood? An Updated Systematic Review and Meta-analysis

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Abstract

Background:

Asthma is the most common respiratory disease among children, while atopic disease such as atopic dermatitis affects about 20% infants under 2 years old. Recently, the investigators found that they may all be related to prenatal depression or anxiety, but further research and analysis are needed. This study aimed to explore the association between prenatal psychiatric disorder and childhood asthma or atopic disease in a systematic review and meta-analysis of nine studies.

Methods:

We searched PubMed, Embase, and Cochrane library up to May 2020. The primary outcome was the childhood asthma and childhood atopic dermatitis. We used random-effects model because of high heterogeneity indicated by I^2 >50% and P<0.10.

Results:

A total of 598 studies were initially entered the PRISMA flow process, after selection, there had 9 studies met our inclusion criteria. Prenatal mental disorder is associated with childhood asthma (ES=1.146, 95%CI: 1.054-1.245, P=0.001; I^2=93.5%, $P_{heterogeneity}$<0.001) whereas no statistically significant had been found on childhood atopic dermatitis (ES=1.211, 95%CI: 0.982-1.494, P=0.073; I^2=78.5%, $P_{heterogeneity}$<0.001). The childhood asthma seems to be related more to depression (ES=1.170, 95%CI: 1.061-1.291, P=0.002) and anxiety/depression (ES=1.157, 95%CI: 1.050-1.275, P=0.073; I^2=95.3%, $P_{heterogeneity}$<0.001).

Conclusion:

This present meta-analysis demonstrated that prenatal mental disorder increased the risk of childhood asthma. We limited the included samples to pregnant women to investigate the association between prenatal psychological factors and offspring's physical health. Future study should include large high-quality cohort studies to investigate behavior, environmental and genetic causes for this association

Background

In terms of the developmental origins of health and disease, there is evidence that adverse early-life exposure associated with the maternal psychiatric disease can alter the immune system and exacerbate the risk of asthma and atopic diseases such as atopic dermatitis[1-4]. Asthma is one of the most common respiratory diseases that seriously affects children's physical and mental health which was recognized by the World Health Organization [5, 6]. Recent investigations paid more attention to investigate the nature and mechanism of disease at the earliest stage in the first few years [7-9]. Psychological and emotional factors are considered to trigger the exacerbation of asthma, and emotional stimulation has been proved to lead to the increase of respiratory resistance in asthma [10]. Atopic dermatitis is also called atopic eczema, it affects a large proportion of children especially infants under 2 years old. Some studies investigated that the prevalence of atopic dermatitis in children under 2 years old is as high as 20%, and had reported a twofold to threefold increase in the last 30 years [11]. There has evidence to show a causal link between maternal mental disorder and atopic dermatitis (AD), and a shared genetic pathway had contributed to this familial liability [12].

In a meta-analysis carried out in 2019, a combination of 41 studies had declared that there has a significant influence between parental psychotic disease and childhood asthma whereas an insignificant association with atopic dermatitis. The evidence was limited to fewer literatures on researching the influences of offspring asthma was made by father mental disorder than postnatal depression in mothers. Besides that, there has a new study was published in 2019 reported maternal mental disorder isn't associated with offspring asthma significantly, whereas low job control shows a more relevant risk factor [13]. Despite the association was significant, the odds of environmental effects on the periods between delivery and diagnose of asthma or AD still cannot be ignored. Therefore, it is unclear to demonstrate that childhood asthma or AD is related to the maternal psychotic disease. Given the uncertainty and the publication of several additional trials. We sought to undertake an updated meta-analysis and systematic review of all studies investigating the prenatal impact of anxiety and depression on childhood asthma and atopic dermatitis to see the differences from the previous study.

Methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline was implemented for this systematic review and meta-analysis [14]. We initially start to search relevant articles by PICOS principle, followed by screening based on inclusion and exclusion criteria.

Eligibility Criteria

We included observational studies that satisfy associations between prenatal psychotic diseases (depression and anxiety) and asthma and atopic dermatitis with language limited to English. The participants that met this review eligibility criterion were children and their biological mothers who were willing to undertake an intentional study, and the medical records were also permitted to access. We included an intervention group that was mother with prenatal anxiety or depression whereas a control group which was mother without prenatal anxiety or depression to see the different outcomes.

Search Strategy:

For this systematic review and meta-analysis, we searched PubMed, Embase, and Cochrane library up to May 2020 with restriction of language and article type. The following terms were used during the search strategy: (children) AND (asthma) AND (depression) AND (maternal), as well as relevant keywords.

Data extraction:

The information was extracted independently by the two investigators. The study characteristics (authors, year of publication, the country where the study performed, type of study design, sample size), treatment parameters (exposure of the mother during pregnancy, questionnaire for the diagnosis of exposure, age of children when the study was taken, the effect size of outcome measurements, covariates in the multivariate analysis), and primary outcome (symptoms of wither asthma or atopic dermatitis) were extracted from the included studies. Disagreements were resolved by discussion.

Data synthesis

In this meta-analysis, we extracted adjusted odds ratios that were associated with most of the covariates reported in the study, unless we determined any additional variables in the causal relationship between exposure and outcome. When studies showed multiple exposures with multiple impact sizes, we reported only those exposures that the investigator considered the most severe and chronic. When a study reported multiple results separately, we extracted two results for different analyses. When a study reported only analyses of different types of asthma, such as early or late-onset transient asthma, we treated the effect size as two independent outcomes.

Quality of the evidence

We assessed the cohort or case-control studies using the Newcastle-Ottawa Scale (NOS) [15]. Quality assessment was evaluated independently by two reviewers. The discrepancy in the assessment was resolved through discussion until a consensus was reached.

Statistical analysis

STATA SE 14.0 software (StataCord, College Station, Texas, USA) was applied for all analyses. Studies were grouped by type of outcomes. The comparison between results was employed effect and corresponding 95% confidence interval (CI) for each group.

We used Cochran's Q test and I^2 index to calculate statistical heterogeneity for which high heterogeneity was defined as I^2 ≥50%, P≤0.1 in Q test [16]. A random-effect model was chosen for high heterogeneity which was emerged from various studies. P-values <0.05 were considered statistically significant. We planned to conduct two sensitivity analyses including removed the poor-quality studies we ranked by determining the robustness of the meta-analysis; including the estimated comparison between the type of exposure, study design, and sample collection continent. For sensitivity analysis, we didn't estimate potential publication bias with funnel plots because the number of studies included in the meta-analysis was less than 10. As for outcome with less than 10 studies, the funnel plots and Egger's test could yield misleading results and were not recommended [17].

Results

Study Selection

Figure 1 shows the study selection procedure, and the reasons for the exclusion of excluded studies were also shown in the same place. A total of 598 studies were retrieved from PubMed (302), Embase (265), and Cochrane (31). After removing duplicate articles, 432 articles were left. 10 articles were excluded because of notes/reports. 109 articles were excluded because of a conference abstract. 25 articles were excluded because of reviews. And 15 articles were excluded because of language restriction. Of these, 273 articles were left for full-text screening and 264 were excluded because of not accessible (n=10), study aim/design (n=54), population (n=100), outcome (n=28), intervention (n=63), animal (n=9). Since no additional records identified through other sources, giving a total of 9 observational studies entered our final model[10, 12, 13, 18-23].

Characteristics of the included studies

Table 1 presents the included studies[10, 12, 13, 18-23]. There were 4 prospective cohort studies [7,18-20], 4 retrospective cohort studies [12, 13, 21, 22] [11,13,21,22] and 1 case-control study [23]. The majority of included studies came from Europe, and the rest of them were from America. The sample size which was included in this meta-analysis was 982, 942. The included studies investigated based on different exposure including depression, anxiety, depression or anxiety, mental health service use, prenatal postpartum distress, and negative life events. Studies were grouped into the categories according to their outcomes which had 5 asthma[10, 12, 13, 18, 21], 3 AD[19, 20, 23], and 1 asthma and AD[22]. To ensure the reliability and quality control of this meta-analysis, we scored each of the included studies by using NOS criteria, studies with more than five stars can be included in the research. After evaluation, there were 6 studies scored 9 [10, 12, 18, 20, 22, 23], and 3 studies scored 8 [13, 19, 21] (Supplementary Table 1a). The outcome of Letourneau et al., 2017 was measured when the infants were only 18-months old which contribute to an insufficient follow-up period for outcome occurrence [19]. The outcome of Liu et al., 2019 was measured when the children age 0 to 6 years old, not long enough follow-up period to see the outcome occurrence [13]. For Radhakrishnan et al., 2018, the exposure in this study was defined as any use of mental health service which may include mental illness [21].

The effect of prenatal depression on childhood asthma

Six studies (eight databases) [10, 12, 13, 18, 21, 22] could be included for the meta-analysis of prenatal depression on childhood asthma. To compare with control group (maternal without depression), the results showed that prenatal depression had influences on childhood asthma (ES=1.146, 95%CI: 1.054-1.245, P=0.001; I^2=93.5%, $P_{heterogeneity}$<0.001) (Figure 2A and Table 2a).

The effect of prenatal depression on childhood AD

Four studies (eight databases) [19, 20, 22, 23] could be included for the meta-analysis of prenatal depression on childhood AD. The result indicated that there has no statistically significant between the control group and treatment group, which means prenatal depression may not bring influences on childhood AD (ES=1.211, 95%CI: 0.982-1.494, P=0.073; I^2=78.5%, $P_{heterogeneity}$<0.001) (Figure 2B and Table 2b).

Subgroup analyses of childhood asthma

There had only one study [10] examined the association between prenatal anxiety and childhood asthma were ambiguous (ES=1.03, 95%CI: 0.86-1.23, P=0.746) whereas prenatal depression [18] (ES=1.17, 95%CI: 1.06-1.29, P=0.002) and prenatal depression or anxiety [12, 13, 21, 22] (ES=1.16, 95%CI: 1.05-1.27, P=0.003; I^2=95.3%, $P_{heterogeneity}$<0.001) had a significant causal link to childhood asthma (Figure 3A and Table 2a).

There had two prospective studies [10, 18] (ES=1.123, 95%CI: 1.000-1.262, P=0.051; I^2=33.2, $P_{heterogeneity}$=0.221) showed inconspicuous correlation between prenatal mental disorder and childhood asthma whereas four retrospective studies [12, 13, 21, 22] (ES=1.157, 95%CI: 1.050-1.275, P=0.003; I^2=95.3, $P_{heterogeneity}$<0.001) indicated childhood asthma is associated with prenatal mental disorder (Figure 3B and Table 2a).

Four studies whose sample collection were taken at Europe [10, 12, 13, 18] (ES=1.106, 95%CI: 1.001-1.221, P=0.047; I^2=93.5, $P_{heterogeneity}$<0.001) examined that childhood asthma is correlated with prenatal mental disorder, however, two studies which were taken at North America [21, 22] (ES=1.328, 95%CI: 0.989-1.784, P=0.059; I^2=88.7, $P_{heterogeneity}$=0.003). suggested opposite conclusion (Figure 3C and Table 2a).

Subgroup analyses of childhood AD

Two studies indicated that there had no association between prenatal anxiety and childhood AD [19, 20] (ES=1.31, 95%CI: 0.58-2.96, P=0.523; I^2=68, $P_{heterogeneity}$=0.044), as well as other two studies, demonstrated that there has no significant causal link between prenatal depression and childhood AD [20, 23] (ES=1.14, 95%CI: 0.85-1.53, P=0.391; I^2=84.3, $P_{heterogeneity}$<0.001). However, one study showed that childhood AD is associated with prenatal depression or anxiety [22] (ES=1.27, 95%CI: 1.11-1.46, P=0.001) (Figure 3D and Table 2b).

Both two prospective studies [19, 20] (ES=1.329, 95%CI: 0.816-2.164, P=0.253; I^2=72.1, $P_{heterogeneity}$=0.006) and one case-control study [23] (ES=1.010, 95%CI: 0.824-1.237, P=0.927; I^2=75.5, $P_{heterogeneity}$=0.043) showed a negative association between prenatal mental disorder and childhood AD, whereas only one retrospective cohort study [22] (ES=1.27, 95%CI: 1.11-1.46, P=0.391; I^2=84.3, $P_{heterogeneity}$<0.001) stands reversely (Figure 3E and Table 2b).

Both two studies came from Europe [20, 23] (ES=1.144, 95%CI: 0.876-1.494, P=0.322; I^2=80.3, $P_{heterogeneity}$<0.001) and two studies were from North America [19, 22] (ES=1.607, 95%CI: 0.795-3.248, P=0.187; I^2=58.4, $P_{heterogeneity}$=0.121) suggested that there has no correlation between childhood AD and prenatal mental disorder (Figure 3F and Table 2a).

Sensitivity Analyses

The sensitivity analyses indicated publication bias was not significant since there has no study affected the observed result for childhood asthma (Supplementary Figure 1A) and childhood AD (Supplementary Figure 1B).

Discussion

The present study is a systematic review and meta-analysis regarding prenatal anxiety or depression symptoms and childhood asthma or atopic dermatitis. In the final analysis of nine studies, the relationship between prenatal mental disorder and childhood asthma was statistically significant compared with childhood AD. The result of the present study is in consistent with the previous meta-analysis which further confirms the prenatal mental disorder is associated with childhood asthma. Some studies had reported that anxiety/stress during pregnancy can aggravate the activation of hypothalamic-pituitary-adrenal (HPA) axis, leading to the release of cortisol; besides, the cortisol of pregnant women cannot be completely metabolized by the placenta, and may even promote the release of placental glucocorticoids, and crosses to the fetus which can bring influences to the fetal brain development and may result in airway inflammation and hyperresponsiveness [24, 25]. Maternal stress-induced changes in cortisol levels may affect fetal immune regulation and TH2 lymphocyte dominance by directly affecting cytokine production [26]. In human subjects, the prenatal psychotic disease was associated with changes in the inherent and adaptive immune responses in the umbilical cord blood of infants at high risk for atopic disease [27]. β_2-adrenoreceptors [28] expressed throughout the body was stimulated by the stress hormone adrenaline [29, 30]. The investigators had identified that maternal psychotic disease during pregnancy might affect fetal growth especially low-birth-weight infants with smaller lungs and the airway experiencing high risks of asthma [31-33]. Given this wealth of researches, having a focus on the association between maternal mental disorder during pregnancy and childhood asthma would be more meaningful.

The main focus of the previous meta-analysis is to explore the effects of parental mental illness on children's physical health, after the research, they revealed that prenatal mental disorder had contributed to the poor fetal growth which further suggested that the impact of the maternal psychotic disease during pregnancy on children [34]. To compare with the previous study, more attention is being paid to the impact of maternal mental health during pregnancy on childhood systemic autoimmune diseases by the present meta-analysis. Even though the number of included studies was different from the previous meta-analysis, the included sample size which entered the final analysis was similar to each other could explain the consistency of the results obtained.

The association between prenatal maternal depression and childhood asthma seems more significant which we only included one study [18] because this is the only one that meets the inclusion criteria. In theory, prospective study is more reliable than retrospective study. Albeit not statistically significant in

prospective studies [10, 18], our findings pointed to statistically significant may occur in the trend of prospective studies if new studies are conducted in the future and the sample size is expanded. Therefore, this result is generally reliable and the concerns could be eliminated. The results showed that asthma was significantly associated with maternal preconception mental status in included patients in Europe [10, 12, 13, 18]. Although the combined overall aOR value was statistically significant (P=0.001), the association was not statistically significant for the North American studies (P=0.059) [21, 22]. This difference may be due to the large confidence intervals in some studies and the conservative estimates of the North American subgroups by the random-effects model.

Limitations

All identified studies come from observational settings and are therefore subject to confounding bias. Moreover, there were several retrospective studies in our analysis. Factors such as selection bias, recall bias, and information bias were inevitably inherent in our analysis. Despite we extracted the adjusted effect sizes for analysis, the covariates of each model were different. Some studies may be subject to over-adjustment, where analyses adjust for variables on the causal pathway between the exposure and the outcome. Although we actively tried to include unpublished research, all the identified studies were from the published literature. Therefore, it might well be that some positive findings are the result of publication bias.

Conclusions

In conclusion, this present meta-analysis supported that prenatal mental disorder increased the risk of childhood asthma whereas no significant association had been found on childhood AD. Although the result of this updated meta-analysis is consistent with previous study, we limited the included samples to pregnant women to investigate the association between prenatal psychological factors and offspring's physical health. Future studies should explore behavior, environmental and genetic causes for this association. If future research is to be able to deepen our understanding of when and how these vulnerable children are at risk of preventable illnesses, large high-quality cohorts must be identified.

List Of Abbreviations

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) ; the Newcastle-Ottawa Scale (NOS); confidence interval (CI)

Declarations

Ethics approval and consent to participate: Not applicable.

Consent for publication: Not applicable.

Availability of data and materials: The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests: The authors declare that they have no competing interests.

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Authors' contributions: SGC: study design, data collection and analysis, statistical analysis, and manuscript drafting; SC: study design and critical revision of the manuscript. All authors have read and approved the manuscript

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Tables

Table 1. Literature search and study characteristic

Author, Year	Country	Study Design	N	Exposure (age measured)	Diagnosis of exposure	Outcome and age measured of the outcome	Effect measure	Covariates
Cookson, 2009	UK, Europe	Prospective cohort study	5810	Anxiety symptom (32 weeks of gestation)	Crown-Crisp index	Asthma (7.5-y)	aOR=1.03 (0.86,1.23)	Partner's self-reported anxiety symptom scores during pregnancy
Magnus, 2017	Norway, Europe	Prospective cohort study	63626	Major depression (30 weeks pregnancy)	SCL-5	Asthma (7-y)	aOR=1.17 (1.06,1.29)	Maternal age, parity, education, pregnancy body mass index, smoking during pregnancy, and history of asthma
Letourneau, 2017	Canada, North America	Prospective cohort study	242	Anxiety (32-40 weeks of gestation)	EDS, SCL-90-R	AD (18-month)	aOR=2.78 (1.04,7.39)	Maternal unresponsiveness and controlling, postnatal depression, social support and anxiety, pregnancy specific anxiety, maternal asthma
Elbert, 2017	Netherlands, Europe	Prospective cohort study	5205	Depression (2nd trimester of pregnancy)	Brief Symptom Inventory	AD (9-10y)	1. inhalant aOR=2.07 (1.43,2.97) 2. food aOR=0.75 (0.29,0.97)	Maternal age at enrollment, education, ethnic origin, parity, pet keeping, BMI at enrollment, smoking and history of allergy eczema or asthma, and child's sex, gestational age, birth weight, child's ever breastfeeding and day care attendance
Brew, 2018	Sweden, Europe	Retrospective cohort study	360526	Depression or anxiety (continuously through preconception, pregnancy)	SCARED, SMFQ	Asthma (5-y)	aOR=1.44 (1.34,1.56)	Sex, gestational age, birthweight, maternal age, parental country of birth, atopic status of twin 2
Liu, 2019	Denmar, Europe	Retrospective cohort study	547533	Negative life events (1 year before conception until delivery)	ICD (10th revision)	Asthma (0 to 6-year)	1. Early-onset transient asthma aPR=1.02 (0.99,1.06) 2. Early-onset persistent asthma aPR=1.04 (0.99,1.08) 3. Late-onset asthma aPR=0.99 (0.93-1.05)	Maternal age at delivery, education at conception, smoking during pregnancy, parity comorbidity before delivery, parental atopic status, calendar year of birth, negative life events, job demands, and job control
Radhakrishnan,2018	Canada, North America	Retrospective cohort study	122333	Mental health service use (during pregnancy)	NA	Asthma (12-y)	aOR=1.16 (1.12,1.20)	Maternal history of asthma, the child's socioeconomic status using neighborhood income quintile as a proxy, urban versus rural residence at birth sex, low birthweight, and the presence of childhood comorbid illnesses

van der leek, 2020	Canada, North America	Retrospective cohort study	9995	Maternal distress (both pre and postnatal)	ICD (9th revision)	AD, Asthma (5-, 7-year)	1. AD: aOR=1.27 (1.11 1.46) 2.Asthma: aOR=1.57 (1.29,1.91)	Preterm birth, maternal age, atopy status, urban residence, infant sex and antibiotic treatment
Hamann, 2018	Denmark, Europe	Case-control	94622	Depression (during pregnancy)	HAMD	AD (before 5-y)	1. Compared to general population: aOR=1.12 (0.97, 1.29) 2. Compared to pediatric hospital/clinic population: aOR=0.91 (0.79, 1.05)	Age, sex, parenta AD, and socioeconomic position

ICD: International Classification of Disease; SCL-5: 5-item symptom checklist; SCARED: Screen for Child Anxiety Related Emotional Disorders; SMFQ: Shortened Mood and Feelings. EDS: Edinburgh depression scale; aOR: adjusted odds ratio; AD: Atopic dermatitis

Table 2a. Treatment vs. Control for Asthma.

	N	ES (95%CI)	P	I-square, %	P (Heterogeneity)
Asthma	8	1.146(1.054,1.245)	0.001	93.5	<0.001
Anxiety	1	1.030(0.861,1.232)	0.746	.	.
Depression	1	1.170(1.061,1.291)	0.002	.	.
Anxiety/depression	6	1.157(1.050,1.275)	0.003	95.3	<0.001
Prospective cohort	2	1.123(1.000,1.262)	0.051	33.2	0.221
Retrospective cohort	6	1.157(1.050,1.275)	0.003	95.3	<0.001
Europe	6	1.106(1.001,1.221)	0.047	93.5	<0.001
North America	2	1.328(0.989,1.784)	0.059	88.7	0.003

Table 2b. Treatment vs. Control for AD.

	N	ES (95%CI)	P	I-square, %	P (Heterogeneity)
AD	8	1.211(0.982,1.494)	0.073	78.5	<0.001
Anxiety	3	1.305(0.576,2.959)	0.523	68	0.044
Depression	4	1.138(0.847,1.528)	0.391	84.3	<0.001
Anxiety/depression	1	1.270(1.107,1.457)	0.001	.	
Prospective cohort	5	1.329(0.816,2.164)	0.253	72.1	0.006
Retrospective cohort	1	1.270(1.107,1.457)	0.001	.	.
Case-control	2	1.010(0.824,1.237)	0.927	75.5	0.043
Europe	2	1.144(0.876,1.494)	0.322	80.3	<0.001
North America	6	1.607(0.795,3.248)	0.187	58.4	0.121

Figures

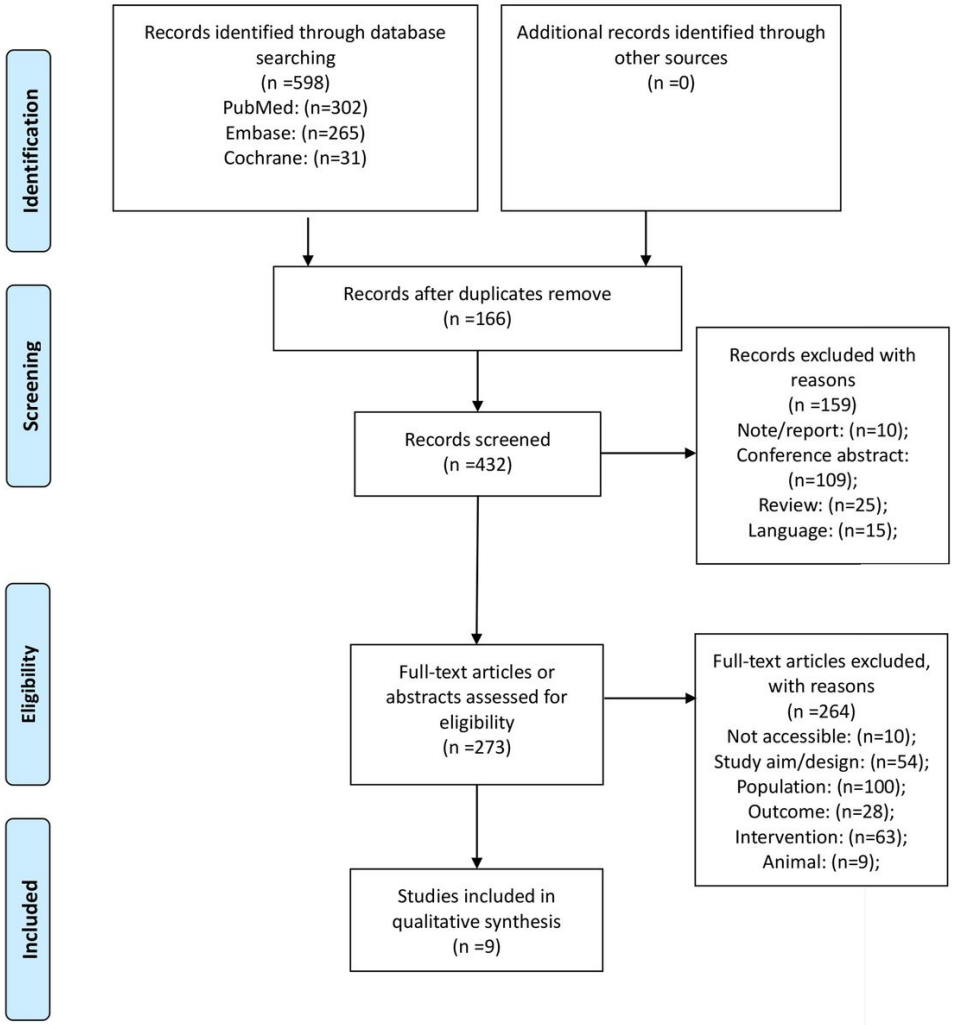

Figure 1

Flow chart of the study selection.

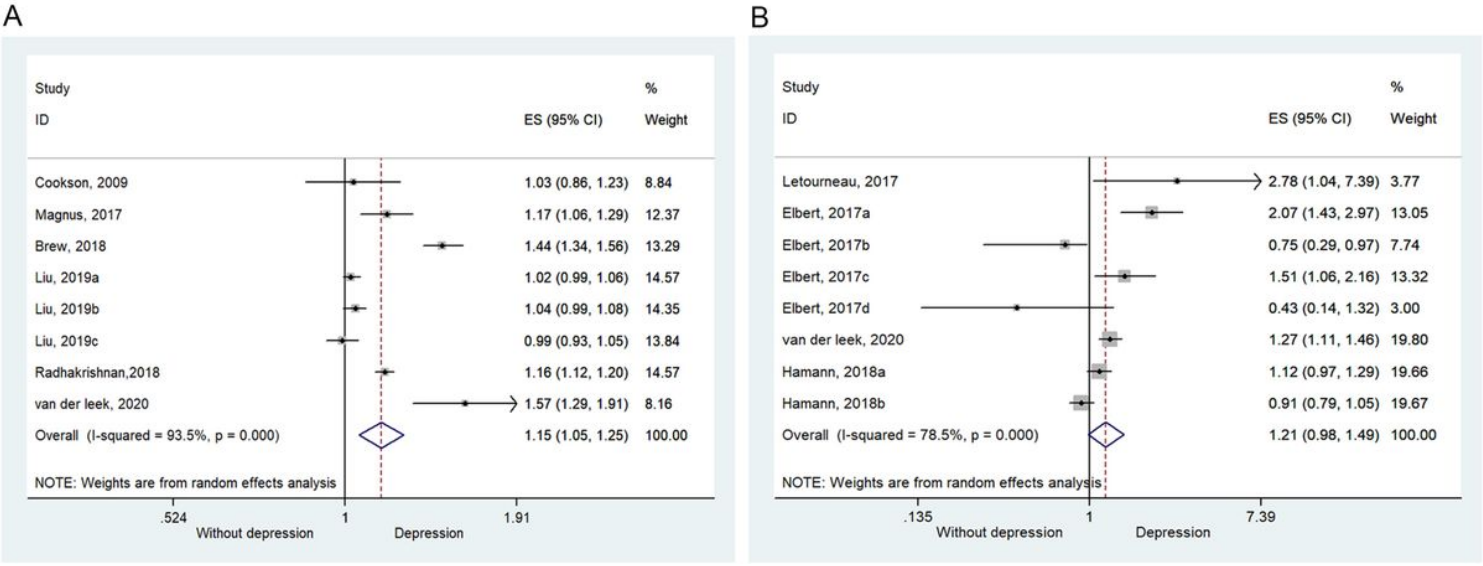

Figure 2

A) Forest plot of asthma. Children who were born to mothers with prenatal mental illness had increased odds of developing asthma. B). Forest plot of AD. The impact of prenatal mental illness was not significant for childhood AD

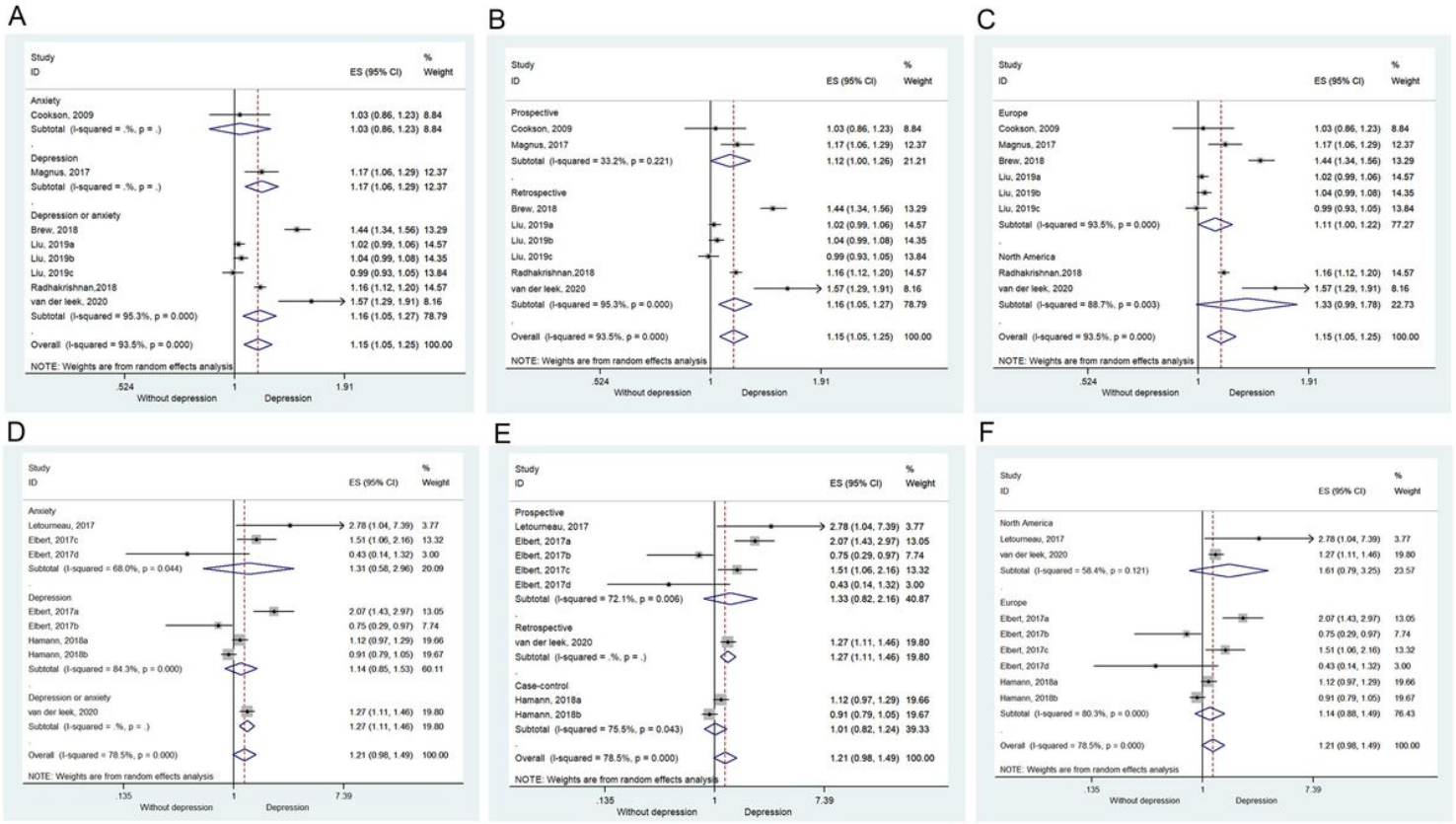

Figure 3

A). Forest plot of asthma by type of exposure. The association between prenatal anxiety and childhood asthma were ambiguous. But clear evidence for the link between prenatal depression, as well as anxiety/depression, with asthma. B). Forest plot of AD by type of exposure. C). Forest plot of asthma by type of study design. Retrospective study concluded the significant association between prenatal mental illness and childhood asthma, whereas prospective cohort study stands reversely (P=0.051). D). Forest plot of AD by type of study design. Only a retrospective cohort study stands for a positive association between prenatal mental illness and childhood AD, whereas others not. E). Forest plot of asthma by where the sample was collected. F). Forest plot of AD by where the sample was collected

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- PRISMA2009checklist.doc
- SupplementaryTable.docx
- SupplementaryFigure1.tif