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Association between Hypertensive Disorders of Pregnancy and the Risk of Asthma, Eczema and Allergies in Offspring: A Systematic Review and Meta-analysis

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Author contribution statement

NC, ASK and GMM were involved in the planning of the study. NC, SAK and GMM were involved in the search, selection and quality appraisal of included studies. NC and GMM performed the analysis, and drafted the manuscript. ASK, FPM and GMM were involved in the interpretation of results. All authors provided critical revision of the manuscript for important intellectual content.

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Abstract

Objective: Conduct a systematic review and meta-analysis examining the association between hypertensive disorders of pregnancy (HDP) and risk of asthma, eczema, food allergies and allergic rhinitis in the offspring.

Design: A systematic review and random effects meta-analyses were used to synthesise the published literature. PRISMA guidelines were followed throughout. Two independent reviewers carried out data extraction and quality assessment of included studies. Grading of Recommendations Assessment, Development and Evaluation (GRADE) was used to assess certainty of findings.

Data Sources: A systematic search of PubMed, Embase, Web of Science and CINAHL was performed from inception of databases-April 21, 2020, supplemented by hand-searching reference lists of included articles.

Eligibility Criteria: Two reviewers independently reviewed titles, abstracts, and full-text articles. English-language, cohort, case-control and cross-sectional published studies examining the association between HDP (primary exposure: preeclampsia; secondary exposures: all other HDP) and asthma, eczema, food allergies and allergic rhinitis were included.

Results: Of the 2,833 studies retrieved, 14 studies met inclusion criteria. Of these, 11 studies reported evidence of association between HDP and atopic disorders. Thirteen studies reported estimates for asthma. Seven of these included adjusted estimates (including 3,645,773 participants) for a preeclampsia-asthma relationship resulting in a pooled odds ratio (OR) of 1.14 (95% CI: 1.04, 1.26) (I^2=62%). However, this OR was reduced to 1.08 (95% CI: (0.78, 1.48) when the large registry based cohort studies were excluded, and only studies using parent-reported measures to determine a diagnosis of asthma were included. Four studies included adjusted estimates (including 254,998 participants) for other HDP and asthma (pooled OR: 1.02, 95% CI: 0.96, 1.09) (I^2=0%). Two studies provided adjusted estimates (including 1,699,663 participants) for a preeclampsia-eczema relationship (pooled OR: 1.06, 95% CI: 0.98, 1.14) (I^2=0%). One study including preeclampsia-food allergies was identified (OR: 1.28, 95% CI: 1.11, 1.46). Three studies examined a HDP (including preeclampsia) and allergic rhinitis relationship, with effect estimates ranging from 1.14 to 2.10. Studies were classified as low or low-moderate risk of bias, while GRADE certainty of findings were low to very low.

Conclusions: While preeclampsia was associated with a possible increased risk of asthma in offspring, there was no evidence for a relationship between other HDP and asthma. There is a lack of published literature examining the association between HDP and eczema, food allergy and allergic rhinitis. Further primary research is warranted to gain a better understanding of the association between HDP and the risk of childhood atopic disease.

Systematic review registration: Review protocol in appendix.

Introduction

Hypertensive disorders of pregnancy (HDP) are estimated to affect up to 10% of all pregnancies, and are a recognised risk factor for maternal and prenatal morbidity and mortality[1-3]. The International Society for the Study of Hypertension in Pregnancy (ISSHP) categorises HDP as: "chronic hypertension", "white-coat hypertension", "masked hypertension", "gestational hypertension", and "preeclampsia" (*de novo*/superimposed on chronic hypertension[4]. Hypertensive disorders of pregnancy are associated with maternal inflammation, oxidative stress and disruption of blood flow to the placenta, all of which can impact fetal development[5].

It is well established that pregnancy and early childhood are critical time periods for the development of airways and the immune system, and genetic and environmental factors play important roles in determining the development of atopic disorders in offspring[6-8]. Childhood atopic disorders include asthma, eczema (also known as atopic dermatitis), food allergies and allergic rhinitis, and are characterised by the development of an allergen-specific T helper type 2 (Th_2) response which often (but not always) includes the development of specific immunoglobulin (IgE) targeted against the allergen[9]. The presence of these specific antibodies is detected using a skin prick test or a blood test[8].

Previous epidemiological research has indicated an association between HDP and atopic disorders in offspring[10, 11]. For example, a population-based registry cohort with data on over 1.5 million people suggested an association between preeclampsia and asthma after controlling for several potential confounders[10] However, results are conflicting as some relatively smaller studies do not suggest an association[12, 13]. Furthermore, all studies on this topic were original studies, with no systematic review conducted, to date.

Given that HDP are among the most common adverse prenatal conditions[3], and the lack of general consensus on this topic, collating existing evidence examining a HDP-atopic disorder association is timely. Therefore, the aim of this study was to synthesise the available published literature on the relationship between HDP and atopic disorders in the offspring in the form of a systematic review and meta-analysis.

Methods

The systematic review was based on the following requirements:

Population: Pregnant women and their children

Intervention/Exposure: HDP (primary exposure: preeclampsia; secondary exposures: other HDP)

Comparison: No preeclampsia/no HDP

Outcomes: Atopic disorders (outcome 1: asthma; outcome 2: eczema; outcome 3: food allergies; outcome 4: allergic rhinitis)

Data Sources and Search Strategy

Based on a pre-prepared protocol (**Appendix 1**), and in accordance with the Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA) guidelines[14], two reviewers (NC and GMM) conducted a systematic literature search of four electronic databases: PubMed, Embase, Web of Science and CINAHL, from inception through to April 21, 2020.

Search terms associated with HDP and asthma, eczema, food allergy and allergic rhinitis were combined according to the principles of Boolean Logic (AND/OR/NOT) and using Medical Subject Headings (MeSH). For example, ("Pre-eclampsia" OR "hypertensive disorders of pregnancy") AND ("asthma" OR "eczema" OR "food allergy" OR "allergic rhinitis"). The full search strategy is included in Appendix 2. Results were limited to human studies, published in the English language. No restrictions were placed on publication date, location of study or age of participants. Searches of the electronic databases were supplemented by hand-searching the reference lists of included studies for further potentially eligible studies, and contact with authors was made when a conference proceeding only was located to identify if the relevant full-text paper had been published. A post-hoc search of PubMed was also conducted adding the keywords "bronchial spasm" OR "bronchial hyperreactivity" OR "respiratory hypersensitivity" to the search strategy.

Study Selection

Titles and abstracts of studies retrieved from each database search were stored and managed in Endnote reference manager©. Two review authors (NC, GMM) independently reviewed the titles and abstracts of all studies, removing duplicates and obtaining full texts where necessary. Where

consensus on eligibility could not be achieved, a third review author (ASK) was involved in the discussion. Eligibility criteria for inclusion in the systematic review included:

- English language cohort, case-control or cross-sectional published studies where a HDP diagnosis was reported, and the outcome of interest was a childhood atopic disorder (asthma, eczema, food allergy and/or allergic rhinitis).
- Where the outcome of interest was asthma, this must be clearly defined (i.e. not wheezing).
- Peer-reviewed, epidemiological studies containing original data only.
- Examining the association between HDP and atopic disease in the offspring was part of the main objective of the study.
- Diagnosis of HDP could be confirmed through self-reporting (following doctor diagnosis) and/or medical records.
- Diagnosis of asthma, eczema, food allergies and allergic rhinitis could be confirmed through maternal-reporting/self-reporting (following doctor diagnosis) and/or medical records and/or clinical diagnosis and/or skin prick/blood test.
- Among studies conducted on the same population with overlapping time-periods, we chose the study covering the longest time-period for inclusion in the meta-analysis to avoid using the same population more than once.
- Conference abstracts were excluded.

Data Extraction

Two reviewers (NC, SAK) independently extracted data from all studies deemed eligible for inclusion, using a standardized data collection form. The extracted data included: the first author, publication year, data source, study design, region, study period, sample size, how both exposure and outcome were diagnosed, any confounders adjusted for (if any), matching factors (if any) and the overall result. Any discrepancies were resolved by consensus with a third reviewer (GMM). Authors of six studies were contacted to provide crude estimates and 95% confidence intervals (or raw data to allow us to compute effect estimates). A reply was received from four authors, of which, three could provide us with the additional information.

Bias and Quality Assessment

A funnel plot was used to visually assess the presence of publication bias for preeclampsia-asthma studies only. Quality assessment of included studies was carried out by two reviewers (NC, SAK) independently using an appropriate quality assessment tool described by McDonald et al.[15], while any discrepancies were resolved by a third reviewer (GMM) if necessary. The bias classification tool assesses the six most common types of bias associated with observational studies. For each eligible study, selection bias, exposure bias, outcome bias, confounding bias, analytic bias and attrition bias were rated as minimal, low, moderate or high. An overall likelihood of bias based on the total of the six types of bias was then reported. For example, risk of attrition bias was deemed minimal if there was "none or <10% attrition, and reasons for loss of follow up [were] explained", while conversely risk of attrition bias was deemed as high if there was ">20% attrition, and reasons for loss of follow up [was] not explained". The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach was used to rate the certainty of findings. In the GRADE approach, observational studies start as low-quality evidence. Five factors (risk of bias, imprecision, inconsistency, indirectness, and publication bias) may lead to rating down the quality of evidence and three factors (large effect, dose response, and if residual confounding is likely to decrease rather than increase the magnitude of effect) may lead to rating up[16].

Statistical Analysis

Where data permitted, Review Manager 5.3 was used to conduct meta-analyses. Using the generic inverse variance method, the overall pooled estimate between preeclampsia and asthma was calculated. The studies that adjusted for potential confounders during the analysis stage were referred to as adjusted estimates. Crude estimates and adjusted estimates were analysed separately. The overall pooled estimate between other HDP and asthma was also calculated using the generic inverse variance method (with both crude and adjusted estimates analysed separately). Similarly, the overall pooled estimate between preeclampsia and eczema was also calculated using the same method (adjusted estimates only due to lack of data).

A random-effects model was used to calculate pooled odds ratios with 95% confidence intervals. The random-effects model was selected to allow for differences in the 'exposure effect' from study to study[17]. Forest plots were used to present the results. Heterogeneity was measured using the I^2, and was categorized as: 0-40% - might not be important; 30-60% - may represent moderate heterogeneity; 50-90% - may represent substantial heterogeneity and 75-100% indicating

considerable heterogeneity, according to the Cochrane Handbook criteria[18]. Where data did not allow for meta-analyses to be conducted, a narrative synthesis was conducted to present results.

Subgroup/sensitivity analysis: Subgroup/sensitivity analyses according to study design and location were decided *a priori.*

Post hoc sensitivity analyses: Among asthma studies, three population-based registry studies with overlapping time-periods were conducted in Denmark[10, 19, 20], while this occurred among two eczema studies[10, 20]. Therefore, while the main analyses included Stokholm et al[10] (as this study covered the longest time-period), we also conducted a sensitivity analysis including one Danish cohort study at a time. In order to determine if a wide range of follow-up (i.e from early childhood to >18 years) had an impact on findings, we conducted post-hoc sensitivity analyses excluding (adjusted) studies with follow-up over 18 years of age[21].

To explore clinical/methodological sources of heterogeneity among preeclampsia-asthma studies, we excluded the large registry based cohort studies, therefore examining a preeclampsia-asthma relationship among studies that used parent-reported measures to determine a diagnosis of asthma.

Results

Search Results

The initial search produced 2,833 results prior to the removal of duplicates. Once duplicates were removed, 1,978 studies remained. Following the screening of titles and abstracts, 38 full text

articles were reviewed. Twenty-six articles were excluded for reasons outlined in **Figure 1**, resulting in the identification of 11 eligible studies. Following review of the reference lists of each eligible study, three further eligible studies were identified. Therefore, a total of 14 unique studies were included in the systematic review; 13 of which included data on asthma, five on eczema, one on food allergies, and three on allergic rhinitis.

Characteristics of Eligible Studies

Of the 13 studies that included data on asthma, there were 12 cohort studies[7, 10-13, 20-26] and one case-control study[19]. Range of follow-up was between age <1 year and 13 years for the majority of studies[7, 10, 12, 13, 22-26], while four studies followed participants up to adulthood (up to 27 years)[11, 19-21]. The average sample size among asthma studies was 537,198, with a minimum of 806[23] and a maximum of 1,698,638 participants[10].

Of the five studies that include data on eczema, four were cohort studies[10, 20, 22, 26] and one was cross-sectional with a retrospective cohort analysis[27]. Range of follow-up was between age 3 years and 14 years for four studies[10, 22, 26, 27], while one study followed participants up to 27 years[20]. The average sample size was 654,718, with a minimum of 1,025[22] and a maximum of 1,698,638[10].

One cohort study examined food allergies (n=1,698,638) up to seven years of age[10], and three cohort studies examined allergic rhinitis (age ranges 3-14 years)[10, 21, 22] with an average sample size of 1,702,986, a minimum of 1,025[22] and a maximum of 1,698,638[10].

Ascertainment of HDP was determined using medical records in 11 studies[7, 10-12, 19, 20, 22-26], measured directly in one study[13] and was self-reported in two studies[21, 27]. Asthma diagnosis was determined using medical records in eight studies[7, 10-12, 19, 20, 24, 26], while parental reporting was used in five studies[13, 21-23, 25]. A diagnosis of eczema was determined using medical records in three studies[10, 20, 26], and parental reporting in two studies[22, 27]. Food allergy data was obtained from the Danish National Patient Register[10], while data on allergic rhinitis was parental reported in two studies[21, 22], and obtained from the Danish National Patient Register in one study[10].

The confounders that were adjusted for included, amongst others: offspring gender, mode of delivery, gestational age, birthweight, parity, maternal age, smoking during pregnancy, maternal body mass index, maternal asthma, maternal education and allergen exposure. A summary of the eligible studies (including a full list of confounding factors) examining the association between HDP and asthma, eczema, food allergy and allergic rhinitis can be found in Appendices 3-6.

Meta-Analysis Results

Asthma: Thirteen studies investigating the association between HDP and asthma were identified[7, 10-13, 19-26]. Of these, 11 studies reported crude estimates[7, 10-12, 19, 21-26], and 11 studies reported adjusted estimates[7, 10, 12, 13, 19-25]. Effect estimates ranged from 1.03-1.89 among the 11 studies reporting crude estimates, and from 0.80-1.34 among the 11 studies reporting adjusted estimates.

Eight studies (conducted on different populations without overlapping time-periods) included crude estimates for a preeclampsia-asthma relationship[7, 10, 11, 22-26], while seven studies included adjusted estimates on preeclampsia-asthma[7, 10, 13, 22-25]. Crude pooled estimates (including 3,919,377 participants) for preeclampsia resulted in an odds ratio (OR) of 1.22 (95% CI: 1.12, 1.33) (I^2=69%) (**Figure 2**). Adjusted estimates (including 3,645,773 participants) reduced the preeclampsia-asthma OR to 1.14 (95% CI: 1.04, 1.26) (I^2=62%) (**Figure 3**).

Three studies included crudes estimates for other HPD-asthma[12, 21, 25], while four studies included adjusted estimates[12, 13, 21, 25]. The crude pooled result (including 250,104 participants) for other HDP-asthma was 1.09 (95% CI: 1.02, 1.16) (I^2=0%) (**Figure 4**), while the adjusted pooled result (including 254,998 participants) was 1.02 (0.96, 1.09) (I^2=0%) (**Figure 5**).

Eczema: Five studies were identified that investigated the association between all HDP and eczema (atopic dermatitis) with effect estimates ranging from 0.96-1.14 among studies providing crude estimates, and from 0.90-1.84 among studies providing adjusted estimates[10, 20, 22, 26, 27].

Two studies (conducted on different populations without overlapping time-periods) provided adjusted estimates (including 1,699,663 participants) for the association between preeclampsia and eczema[10, 22] resulting in a pooled OR of 1.06 (95% CI: 0.98, 1.14) (I^2=0%) (**Figure 6**). One Danish based study[20] (n=1,545,443) could not be included in the meta-analysis as it was conducted on a similar population with overlapping time-periods to Stokholm et al[10]: 1.04, (95% CI: 0.79, 1.38). One study provided a crude estimate only (n=24,690) for the relationship between eclampsia and eczema: 0.96, (95% CI: 0.73, 1.27)[26]. Finally, one study provided an adjusted estimate only (n=3,794) for the relationship between other HDP and eczema: 1.08, (95% CI: 0.71, 1.64)[27].

Subgroup/sensitivity analysis:

Study design: All seven cohort studies included in the meta-analysis[7, 10, 13, 22-25] (with adjusted estimates) examining a preeclampsia-asthma association were cohort studies. All four studies (with adjusted estimates) examining other HDP-asthma were cohort studies[12, 13, 21, 25]. Similarly,

both studies (with adjusted estimates) examining a preeclampsia-eczema relationship were cohort studies[10, 22].

Location: Six adjusted preeclampsia-asthma studies were conducted in Europe[7, 10, 13, 22, 24, 25] (pooled OR: 1.14, 95% CI: 1.03, 1.26), while one adjusted preeclampsia study was conducted in the United States[23] (OR: 1.21, 95% CI: 0.51, 2.87). Three adjusted studies examining other HDP-asthma were conducted in Europe[13, 21, 25] (pooled OR: 1.04, 95% CI: 0.88, 1.23), while one study was conducted in Australia[12] (OR: 1.02, 95% CI: 0.95, 1.10). Both studies (with adjusted estimates) examining a preeclampsia-eczema relationship were conducted in Europe[10, 22] (Table 1).

Post hoc sensitivity analysis: Including one Danish cohort study with overlapping time-periods at a time did not materially change results. Adjusted OR for preeclampsia-asthma including Stokholm et al[10]: 1.14 (95% CI: 1.04, 1.26 - I^2=62%), including Wu et al[20]: 1.15 (95% CI: 1.03, 1.29 - I^2=38%), and including Liu et al[19]: 1.19 (95% CI: 1.12, 1.26 - I^2=31%). Adjusted OR for preeclampsia-eczema including Stokholm et al[10]: 1.06 (95% CI: 0.98, 1.14 - I^2=0%), and including Wu et al[20]: 1.01 (95% CI: 0.80, 1.27 - I^2=0%).

Excluding the other HDP-asthma study with follow-up over 18 years of age did not materially change results[21]: (other HDP-asthma: OR 1.02, 95% CI: 0.96, 1.09 - (I^2=0%)). All other studies included in the meta-analyses were followed-up for <18 years (preeclampsia-asthma: OR 1.14, 95% CI: 1.04, 1.26 - (I^2=62%)), (preeclampsia-eczema: OR 1.06, 95% CI: 0.98, 1.14 - (I^2=0%)) (see Table 1 for a summary of results).

Excluding the large registry based cohort studies among preeclampsia-asthma studies[7, 10, 24] (and therefore examining a preeclampsia-asthma relationship among studies that used parent-reported measures to determine a diagnosis of asthma[13, 22, 23, 25]) resulted in an OR of 1.08 (95% CI: 0.78, 1.48) (Table 1 and Appendix 7, eFigure 1).

Narrative Synthesis Results

Food allergies and allergic rhinitis: As the systematic search identified only one study exploring the association between HDP and food allergies[10] and three studies exploring the association between HDP and allergic rhinitis[10, 21, 22], meta-analyses were not conducted for these outcomes. The one identified study that investigated food allergies[10] reported a positive association between

preeclampsia and food allergies in offspring: adjusted estimate 1.21 (95% CI: 1.05, 1.39). This same study[10] also examined allergic rhinitis and reported a positive association between preeclampsia and allergic rhinitis: adjusted estimate 1.14 (95% CI, 1.05, 1.24). A second study which examined preeclampsia-allergic rhinitis (stratified by mild/moderate and severe preeclampsia)[22] reported an adjusted OR of 1.21 (95% CI: 0.70, 2.07) for mild/moderate preeclampsia and 2.10 (95% CI: 0.86, 5.11) for severe preeclampsia. Finally, one study examined other HDP-allergic rhinitis[21], resulting in an adjusted OR of 1.42 (95% CI: 0.84, 2.40). A summary of these studies can be found in Appendices 5 and 6.

Bias and Heterogeneity

Visual assessment of the funnel plot did not indicate presence of publication bias (Appendix 8, eFigure 2). There was substantial heterogeneity among preeclampsia-asthma studies (I^2=62%) and low heterogeneity among studies that include other HDP and asthma (I^2=0%) based on adjusted estimates. Similarly, there was low heterogeneity among preeclampsia-eczema studies (I^2=0%). Heterogeneity between preeclampsia-asthma studies was possibly due to the larger registry based cohort studies as heterogeneity was reduced to 0% these were excluded[7, 10, 24] (Appendix 7, eFigure 1). In addition to this, it is possible that varying methods of exposure and outcomes measures (as outlined in Appendix 3) may have resulted in clinical/methodological sources of heterogeneity. For example, the I^2 among preeclampsia-asthma studies that use parent-reported measures[13, 22, 23, 25] to determine a diagnosis of asthma was 0% (Appendix 7, eFigure 1). The majority of studies were classified as 'low' or 'low-moderate' risk of bias (Appendices 9-12). GRADE certainty of findings were low to very low (Appendix 13).

Discussion

The objective of this systematic review and meta-analysis was to investigate the association between HDP and asthma, eczema, food allergy and allergic rhinitis in offspring, yielding three principal findings.

First, the adjusted pooled estimate suggested that preeclampsia was associated with a 14% increase in the likelihood of asthma compared to those unexposed to preeclampsia (OR: 1.14, 95% CI: (1.04, 1.26), while the adjusted pooled estimate examining the other HDP-asthma relationship produced an OR of 1.02 (95% CI: 0.96, 1.09). It was proposed by Stokholm et al[10] that the *in utero* exposure to excessive inflammation associated with preeclampsia could be leading to the preeclampsia-asthma association, proposing that the skewed distribution of T cells in preeclamptic women could increase IgE levels in offspring, thus increasing the risk of asthma[10]. This may partly explain why an association was observed between preeclampsia-asthma, and not other HDP-asthma. Furthermore, fetal growth restriction, which is now included in the definition of preeclampsia, as per ISSHP guidelines[4], may also play a role and has been linked to an increased risk of asthma in previous literature[28].

Second, the adjusted pooled estimate examining a preeclampsia-eczema relationship produced an OR of 1.06 (95% CI: 0.98, 1.14). However, only two studies (conducted on different populations without overlapping time-periods) were identified for inclusion in the meta-analysis[10, 20, 22], highlighting the paucity of research measuring this association.

Third, there was a dearth of literature supporting an association between HDP and food allergies and HDP and allergic rhinitis. Only one publication was identified exploring the relationship between preeclampsia and food allergy[10]. This study reported an OR of 1.21 (95% CI: 1.05, 1.39) and proposed that the risk of food allergy increased as the duration of exposure to preeclampsia was extended[10]. Given the increasing prevalence of childhood onset food allergies[29], it is timely that further research in this area is initiated. Finally, only three studies were identified exploring the association between HDP and allergic rhinitis[10, 21, 22]. All three studies reported a positive association between HDP and allergic rhinitis (with effect estimates ranging from 1.14 to 2.10, and results of two of these studies spanning the null value[21, 22]) citing the involvement of an inflammatory response involving a skewed distribution of T cells in the preeclamptic women as the potential biological mechanism[10, 22]. However, further research is warranted to further investigate if such an association exists, and if so, what biological mechanisms are involved.

Strengths and Limitations

This systematic review contains several strengths. A thorough search of four relevant electronic databases was conducted, supplemented by manually reviewing the reference lists of the eligible studies for further suitable studies. Each process of the systematic review was carried out by two independent reviewers and PRISMA guidelines were followed throughout[14]. Finally, we attempted to contact several authors for further information to ensure data contained within the meta-analysis was as comprehensive as possible.

However, this systematic review also contains several limitations. We included English-language studies only, potentially overlooking relevant, non-English language studies. We only included published, full-text articles, therefore excluding data from grey literature or conference proceedings. Furthermore, as the full search strategy may have been lacking in keywords such as "bronchial spasm" OR "bronchial hyperreactivity" OR "respiratory hypersensitivity", we conducted a post-hoc search of PubMed, adding these words to the search strategy. While this increased the number of hits retrieved, no new relevant studies were identified in the process. The small number of published studies also limited this review. While visual assessment of the funnel plot of preeclampsia-asthma studies did not indicate the presence of publication bias, it was not feasible to generate a funnel plot for other HDP-asthma or preeclampsia-eczema due to the limited number of published studies. In addition, it is important to note that the reported positive association between preeclampsia and asthma should be considered with caution given that only

seven studies were included in the meta-analysis, and a high degree of heterogeneity was reported (I^2 =62%).

Studies included in this systematic review also contain some limitations. For example, while the majority of studies were classified as 'low' or 'low-moderate' risk of bias, GRADE certainty of findings were low to very low, indicating that the true effect may be different from the estimated effect[16]. Furthermore, while the majority of studies attempted to control for confounding in their analysis phase, residual or unmeasured confounding cannot be ruled out in observational studies[30]. Selection of potential confounders varied in each study and were identified from existing literature or the research team's knowledge of the subject, however only one study appears to have aided the selection of confounders using a directed acyclic graph[25]. It is important to acknowledge that some of the factors controlled for, as potential confounders, could in fact be potential mediators of the HDP-atopic disorder association. For example, eight studies controlled for a combination of mode of delivery, gestational age and birthweight, which may have biased results towards the null and thus, should be interpreted with caution[10-12, 20-23, 25, 31].

All studies with adjusted estimates considered maternal age and infant sex as potential confounders. Seven of the 13 eligible asthma studies recognised the potential confounding role of maternal asthma[7, 10, 19, 21, 22, 24, 25], while maternal smoking was also identified as a potential confounder in seven studies[7, 10, 13, 19, 21, 22, 25], with the majority of these studies attenuating towards the null when adjusted[7, 10, 13, 19, 21, 22]. However, exposure to certain environmental factors during pregnancy, which may be associated with asthma development could also be considered as potential confounders. Such factors include exposure to traffic pollution, antibiotic use and viral infection[32]. The former was not considered in any of the included studies, while antibiotic use was adjusted for in two studies[10, 21], and viral infection was considered as a confounder in only one study[24].

Additionally, few studies included data on severity of preeclampsia or other HDP[11, 20, 22], and were limited by small sample sizes (as fewer than ten cases of asthma were exposed to severe preeclampsia in one study)[22], and residual confounding (as confounders were not adjusted for when examining preeclampsia-asthma specifically in a separate study)[11]. Finally, the role of antihypertensive medication used during pregnancy should be explored in order to determine its potential impact on the development of atopic disorders in offspring[33].

Conclusion

This systematic review and meta-analysis indicates that preeclampsia may be associated with an increased risk of asthma in the offspring, while there was no evidence for a relationship between other HDP and asthma. Further research is warranted to validate these findings and to determine if the observed relationship is causal. Insufficient published literature was available to substantiate whether an association exists between HDP and eczema, food allergy and/or allergic rhinitis. Further primary research is needed to explore these associations.

Appendices

Refer to web version for appendices.

Conflict of Interest: No conflicts of interest, including financial interest.

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Flowchart of Study Selection

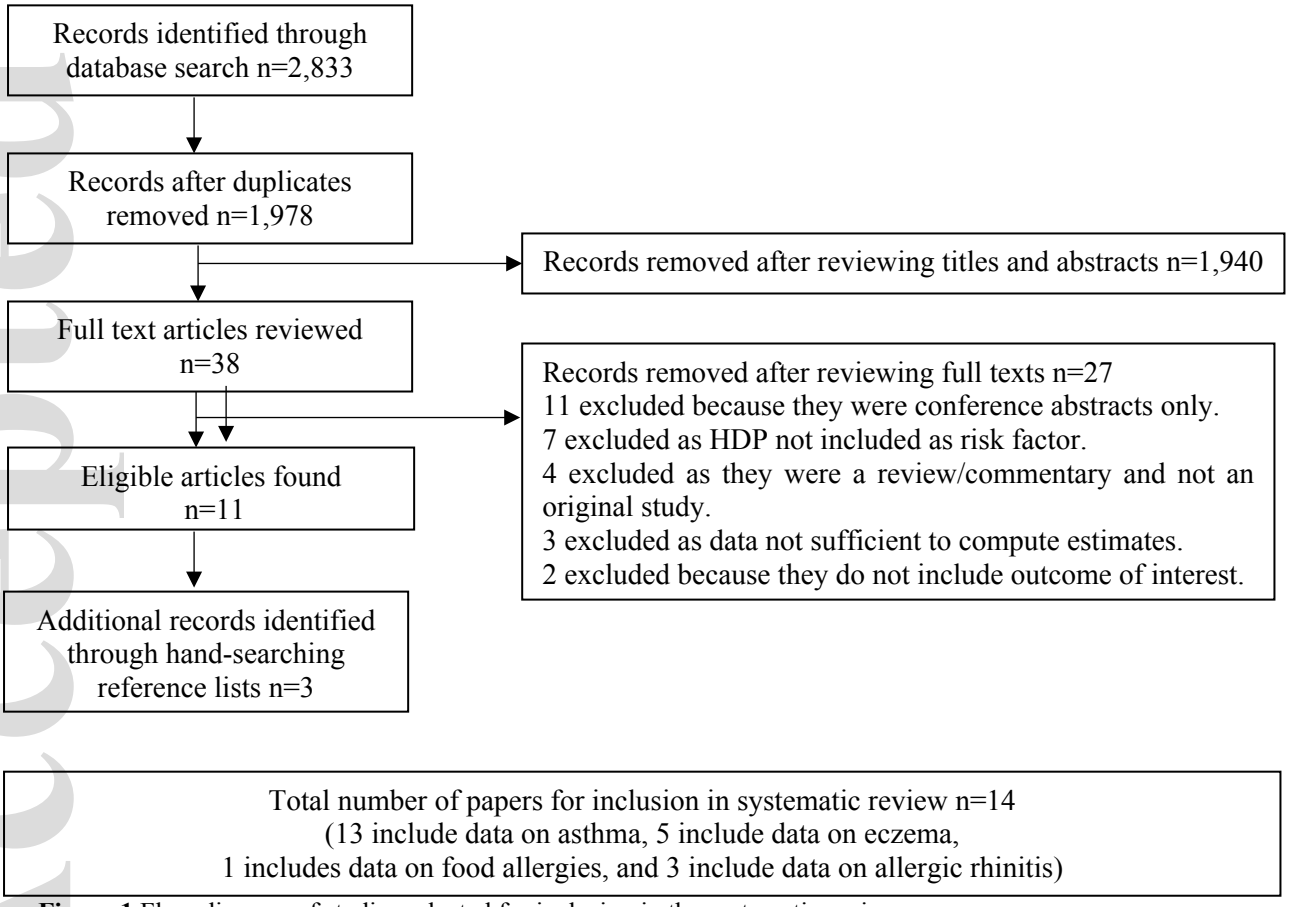

Figure 1 Flow diagram of studies selected for inclusion in the systematic review.

Forest Plots for Studies of the Association between Preeclampsia and Asthma

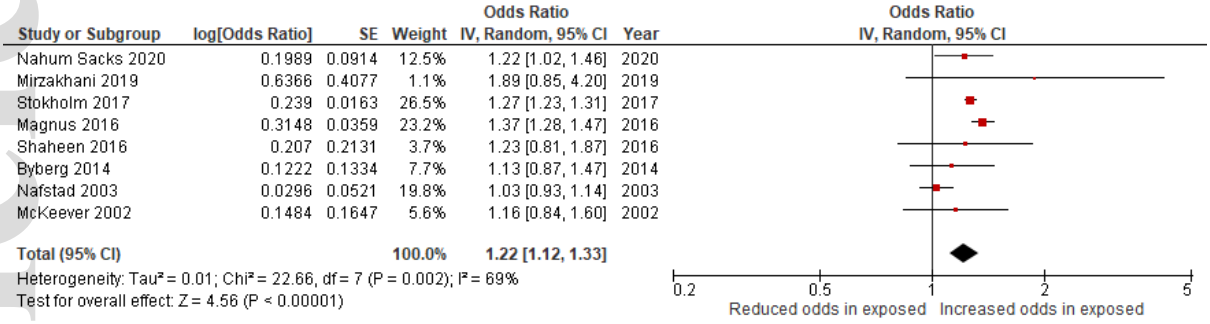

Figure 2 Forest Plot for the Association of Preeclampsia with Asthma (crude estimates).

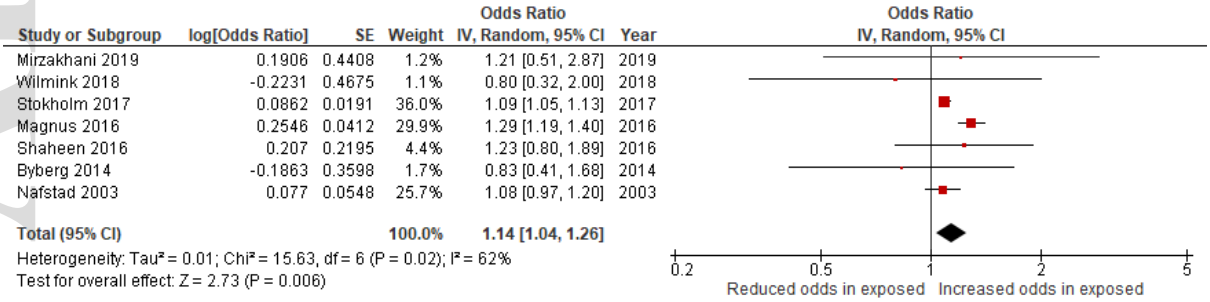

Figure 3 Forest Plot for the Association of Preeclampsia with Asthma (adjusted estimates).

Forest Plots for Studies of the Association between other Hypertensive Disorders of Pregnancy (HDP) and Asthma

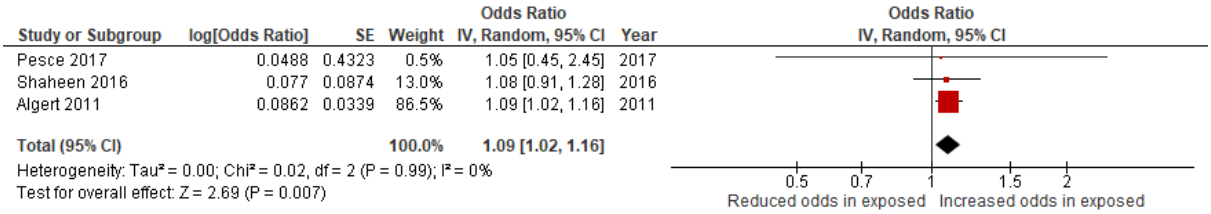

Figure 4 Forest Plot for the Association of other HDP with Asthma (crude estimates).

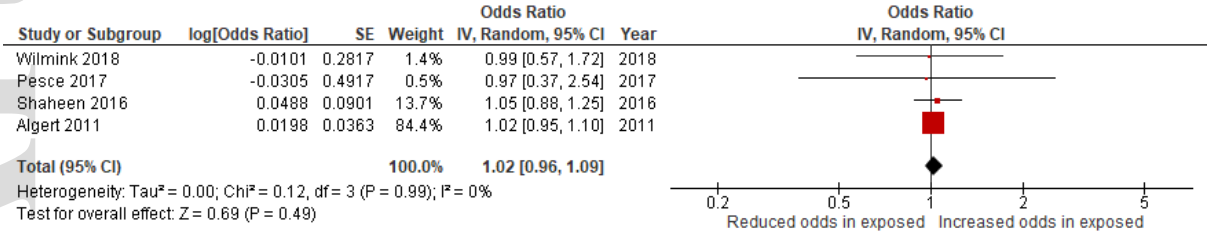

Figure 5 Forest Plot for the Association of other HDP with Asthma (adjusted estimates).

Forest Plot for Studies of the Association between Preeclampsia and Eczema

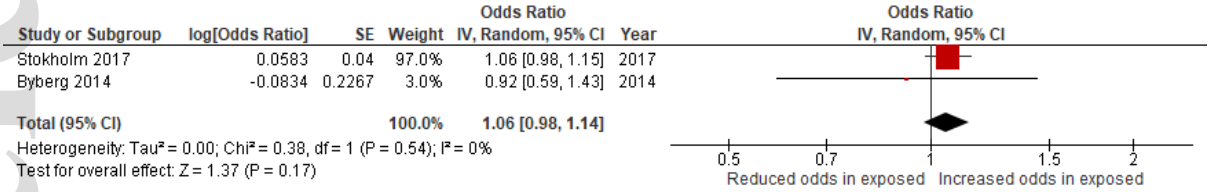

Figure 6 Forest Plot for the Association of Preeclampsia with Eczema (adjusted estimates)

Table 1: Meta-analyses for HDP-Asthma and HDP-Eczema					
Asthma	**Number of studies**	**N**	**OR**	**95% CI**	**I^2**
Preeclampsia (crude)	8	3919377	1.22	(1.12, 1.33)	69%
Preeclampsia (adjusted)	7	3645773	1.14	(1.04, 1.26)	62%
Other HDP (crude)	3	250104	1.09	(1.02, 1.16)	0%
Other HDP (adjusted)	4	254998	1.02	(0.96, 1.09)	0%
Study design[a]					
Cohort (preeclampsia)	7	3645773	1.14	(1.04, 1.26)	62%
Cohort (other HDP)	4	254998	1.02	(0.96, 1.09)	0%
Location[a]					
Europe (preeclampsia)	6	3644967	1.14	(1.03, 1.26)	68%
United States (preeclampsia)	1	806	1.21	(0.51, 2.87)	NA
Europe (other HDP)	3	14487	1.04	(0.88, 1.23)	0%
Australia (other HDP)	1	240511	1.02	(0.95, 1.10)	NA
Including one Danish cohort study at a time[a]					
Preeclampsia	7	3645773	1.14	(1.04, 1.26)	62%
Preeclampsia	7	3492578	1.15	(1.03, 1.29)	38%
Preeclampsia	7	3217867	1.19	(1.12, 1.26)	31%
Excluding studies with >18 years of follow-up[a]					
Preeclampsia	7	3645773	1.14	(1.04, 1.26)	62%
Other HDP	3	252379	1.02	(0.96, 1.09)	0%
Excluding the large registry based cohort studies[a]					
Preeclampsia	4	13699	1.08	(0.78, 1.48)	0%
Eczema	**Number of studies**	**N**	**OR**	**95% CI**	**I^2**
Preeclampsia (adjusted)	2	1699663	1.06	(0.98, 1.14)	0%
Study design[a]					
Cohort (preeclampsia)	2	1699663	1.06	(0.98, 1.14)	0%
Location[a]					
Europe (preeclampsia)	2	1699663	1.06	(0.98, 1.14)	0%
Including one Danish cohort study at a time[a]					
Preeclampsia	2	1699663	1.06	(0.98, 1.14)	0%
Preeclampsia	2	1546468	1.01	(0.80, 1.27)	0%
Excluding studies with >18 years of follow-up[a]					
Preeclampsia	2	1699663	1.06	(0.98, 1.14)	0%
[a]Includes all studies that adjusted for confounders in the analysis phase.					