

Maternal asthma during pregnancy and risks of allergy and asthma in progeny: a systematic review protocol

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ABSTRACT

Objective: The primary objective of this systematic review is to synthesize the best available evidence on the relationship between *in utero* exposure to maternal asthma and postnatal allergy. Secondary objectives are to investigate the impact of asthma loss of control, asthma exacerbation, and asthma severity during pregnancy on risks of allergy and asthma in progeny.

Introduction: Maternal asthma is a well-known risk factor for childhood asthma, with recent evidence suggesting that children of asthmatic mothers are also at increased risk of allergic diseases. Importantly, these do not appear to be purely genetic associations, since maternal asthma is more strongly associated with childhood asthma than paternal asthma. In addition, experimentally induced allergic asthma during pregnancy increases allergic responses to sensitization in mice. The strength of the relationships between exposure to maternal asthma or severity of maternal asthma, and progeny asthma and allergy, are unknown.

Inclusion criteria: This review will include primary studies that report incidence of physician-diagnosed asthma or allergic disease in human progeny who were exposed *in utero* to maternal asthma, in comparison to progeny not exposed to maternal asthma.

Methods: Initial search terms include (pregnan* OR gestat*) AND asthma* AND allerg*. We will search the following electronic databases for published and unpublished evidence: PubMed, Embase, MEDLINE (Ovid), Web of Science, Cochrane Library, CINAHL, Scopus, Informit Health, MedNar, ProQuest, and Trove. There will be no restrictions on publication date. Only studies available as a full-text English publication will be considered for inclusion.

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Keywords: asthma; atopic disease; gestation; *in utero*; offspring

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Introduction

Asthma is the most common respiratory condition affecting pregnancy and is increasing in prevalence.¹ It is a complex chronic inflammatory disease syndrome affecting the airways, key characteristics of which are airway hyper-responsiveness and progressive airway remodeling resulting in airflow obstruction, which may have allergic or non-allergic underlying pathophysiology.² The

prevalence of asthma during pregnancy was estimated at between 3.7% and 8.4% in the United States of America from 1997 to 2001, compared to an estimated prevalence of 3.2% in 1988 to 1994.³ A similar prevalence of asthma in the first trimester of pregnancy (3.8%) was reported in a data linkage study of ~500,000 women from Norway, Wales, and Denmark from 2000 to 2010.⁴ Higher rates of asthma in pregnancy have been reported in other populations, including 9.4% in a whole-of-population study of Swedish women from 2006 to 2009,⁵ and 12% in singleton pregnancies delivered in Newcastle, Australia, from 1995 to 1999.⁶

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Asthma during pregnancy increases risks of complications during pregnancy, labor, and for the neonate.¹ For example, in a meta-analysis of data from >1.6 million women, risks of low birthweight, pre-term delivery and pre-eclampsia were each 40% to 50% higher in the presence of maternal asthma.⁷ Risks of neonatal death and neonatal hospitalization were ~50% higher in the presence of maternal asthma in a separate meta-analysis.⁸ The adverse effects of maternal asthma persist, including increased risks of developing asthma and common allergic diseases in the offspring. Children from mothers with asthma have ~10% lower lung function,⁹ a three-fold greater risk of developing asthma,¹⁰ and an 11% higher risk of atopic dermatitis by age 10,¹¹ compared to children of non-asthmatic mothers. Atopic dermatitis, where inflammation of the skin is induced by cutaneous exposure to allergens in sensitized individuals,¹² is one of the earliest allergic diseases to develop postnatally, along with food allergies, with peak rates in the first two years of life.¹³

Allergic rhinitis (hayfever), is another common allergic disease that emerges later in childhood and is characterized by Immunoglobulin E (IgE)-mediated inflammation of the nasal mucosa with symptoms including watery eyes, runny nose, and sneezing.¹² Interestingly, risks of allergic rhinitis were similar in children of asthmatic and non-asthmatic women.¹¹ Food allergy, following ingestion, inhalation, or contact with food substances (most commonly milk, eggs, peanuts, tree nuts, wheat, soy, fish, or crustacean shellfish), may involve both IgE-mediated and non-IgE-mediated responses, including skin and mucosal, respiratory, and gastrointestinal symptoms.¹² Food allergens are also the most common trigger for allergic anaphylaxis, which is characterized by acute, severe, and systemic responses to an allergen, such as skin and mucosal inflammation, respiratory compromise, decreased blood pressure, and/or gastrointestinal symptoms.¹² A maternal history of allergy, eczema, or asthma was not associated with allergic sensitization to food allergens (hazelnut, cashew, peanut, or peach) in 10-year-old Dutch children,¹⁴ although food allergy was not directly tested through food challenge in this study. To the best of our knowledge, associations between maternal asthma during pregnancy and food allergy or anaphylaxis in their offspring have not been reported. Importantly, evidence regarding the

association between *in utero* exposure to maternal asthma and offspring asthma or allergy has not been systematically reviewed, and the strength of these associations is therefore unclear.

It is less clear whether maternal asthma control or the severity of the maternal asthma phenotype have differential impacts on offspring allergic outcomes, although there is evidence that perinatal outcomes differ according to asthma control or severity and not only between women with and without asthma. Exacerbations of asthma occur during pregnancy in ~20% of women and increase the risk for a low birthweight baby.¹⁵ In a large data linkage study in Sweden, more severe maternal asthma did not increase risks of pre-term birth above the risk due to asthma itself, but fetal growth was impaired to a greater extent in women with moderate to severe asthma compared to those with mild asthma.⁵ The impact of maternal asthma control and severity on childhood asthma and allergic outcomes is less studied. In a study of >8000 children of asthmatic mothers in Quebec, children of mothers with moderate-to-severe uncontrolled asthma had 27% higher risk of asthma within the first 10 years of life, but similar risk of allergic rhinitis and atopic dermatitis, as children of mothers with mild controlled asthma.^{11,16} Similarly, in a more recent data linkage study in Denmark comprising >7000 singleton-born children of asthmatic mothers, early-onset persistent asthma in children was more prevalent in mothers with mild uncontrolled asthma (19%), moderate to severe controlled asthma (33%), or moderate to severe uncontrolled asthma (37%) than in children whose mothers had mild controlled asthma.¹⁷

Several lines of evidence implicate environmental as well as genetic pathways in the increased risk of asthma and allergic disease after *in utero* exposure to maternal asthma. In mice, experimental maternal allergic asthma increases allergen-induced airway remodeling and immune responses in progeny, regardless of whether progeny are exposed to the same allergen as used to sensitize their mothers or a different allergen.¹⁸ In humans, maternal asthma confers a greater risk of offspring asthma than paternal asthma,¹⁰ and in a randomized controlled trial of more rigorous asthma management guided by exhaled nitric oxide concentrations, the risks of doctor-diagnosed asthma were 25.9% in the intervention arm compared to 43.2% in the control arm (OR 0.46, 0.22–0.96), demonstrating that improved

maternal asthma control is protective for childhood asthma.¹⁹ Associations between prenatal exposures and later asthma risk have previously been reported in systematic reviews of cesarean section delivery, first trimester antibiotic use, and paracetamol use during pregnancy, each of which are associated with increased risk of asthma in children, although there are some limitations in the evidence underlying these meta-analyses.²⁰⁻²² We have previously reported that risks of childhood food allergy and eczema increase with increasing birthweight relative to gestational age,²³ likewise supporting the concept that prenatal exposures can program susceptibility to allergic diseases in later life.

We therefore, sought to determine the extent to which exposure to maternal asthma *in utero* during human pregnancy increases risks of asthma and allergic diseases including eczema (atopic dermatitis), hayfever (allergic rhinitis), and food allergy or anaphylaxis, as well as the impact of maternal asthma severity and control on these outcomes. A preliminary search of PROSPERO, MEDLINE, the Cochrane Database of Systematic Reviews, and the *JBIR Database of Systematic Reviews and Implementation Reports* was conducted and no current or in-progress systematic reviews on the topic were identified.

Review question

Is maternal asthma during human pregnancy associated with risks of allergy and asthma in progeny? Secondary aims are to investigate the impact of asthma loss of control, asthma exacerbation, and asthma severity during pregnancy on risks of allergy and asthma in progeny.

Inclusion criteria

Population

We will include studies that contain data from pregnant women with a diagnosis of asthma, and a control group of pregnant women without asthma. Maternal asthma will be defined based on physician diagnosis or database-recorded use of asthma-specific medication, or diagnosis during pregnancy. Included studies must report one or more outcomes of interest (asthma and/or allergic disease) in progeny of exposed pregnancies.

Exposure of interest

The main exposure to review will be maternal asthma during pregnancy, including asthma that is

diagnosed prior to or during pregnancy. Other exposures that we will review include incidence of loss of asthma control and exacerbations occurring during pregnancy, and asthma severity (mild, moderate, severe).

Comparator

Outcomes will be compared between offspring of women with and without asthma during pregnancy. We will also compare outcomes within women with asthma based on asthma control, asthma exacerbations, and asthma severity (mild, moderate, severe).

Outcomes

This review will consider studies that include the following outcomes in offspring: asthma or allergic disease (allergic dermatitis or eczema, food allergy or anaphylaxis, allergic rhinitis or hayfever, urticaria, and asthma). These outcomes will be measured by self, parent, or clinical report of clinical diagnosis of allergic disease; registered use of medication or other intervention requiring clinical diagnosis; or clinically acceptable criteria based on defined allergy symptoms.

Types of studies

Studies published in English will be included. We will include studies that include data for women with asthma during pregnancy and women without asthma during pregnancy. There are no restrictions on study type. There will be no date limitations for inclusion in the review.

Methods

The proposed systematic review will be conducted in accordance with JBI methodology for systematic reviews of etiology and risk.²⁴ Any important protocol amendments will be documented in the final review and updated in PROSPERO.

Search strategy

The search strategy will aim to locate both published and unpublished studies. An initial limited search of PubMed and Web of Science was undertaken to identify articles on the topic. The text words contained in the titles and abstracts of relevant articles, and the index terms used to describe the articles were used to develop a full search strategy for PubMed (see Appendix I). The search strategy, including all identified keywords and index terms, will be adapted

for each included information source. The reference list of all studies selected for critical appraisal, as well as relevant review manuscripts identified during searching, will be screened for additional studies.

The databases to be searched include MEDLINE (PubMed), Embase (Elsevier), Web of Science, Informa Health, the Cochrane Library, CINAHL (EBSCOhost), MedNar (Deep Web Technologies), ProQuest Theses and Dissertations, Scopus (Elsevier), and Trove. If necessary, additional information will be sought from authors of studies selected for critical appraisal.

Study selection

Following the search, all identified citations will be collated and uploaded into Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia) via Endnote v.X9 (Clarivate Analytics, PA, USA) and duplicates removed. Titles and abstracts will then be screened independently by two reviewers (any of the listed review authors) and assessed against the inclusion criteria for the review. Potentially relevant studies will be retrieved in full and their citation details imported into the JBI System for the Unified Management, Assessment and Review of Information (JBI SUMARI; JBI, Adelaide, Australia).²⁵ The full text of selected citations will be assessed in detail against the inclusion criteria by two independent reviewers (any of the listed review authors). Reasons for exclusion of full text studies that do not meet the inclusion criteria will be recorded and reported in the systematic review. Any disagreements that arise between the reviewers at each stage of the study selection process will be resolved through discussion with at least one additional member of the review author team. The results of the search will be reported in full in the final systematic review and presented in a Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram.²⁶

Assessment of methodological quality

Eligible studies will be critically appraised by two independent reviewers at the study level for methodological quality using standardized critical appraisal instruments from JBI for cohort, case-control, and cross-sectional studies. Authors of papers will be contacted to request missing or additional data for clarification, where required. Any disagreements that arise will be resolved through discussion,

or with a third reviewer. The results of critical appraisal will be reported in narrative form and in a table. All eligible studies, regardless of the results of their methodological quality, will undergo data extraction and synthesis (where possible).

Data extraction

Data will be extracted from papers included in the review by two independent reviewers using the standardized data extraction tools in JBI SUMARI. The data extracted will include specific details about the exposure of interest, including sub-categories related to asthma control and severity where applicable, populations, study design, methods of ascertainment for exposures and outcomes of interest, and outcomes of significance to the review question and specific objectives. Any disagreements that arise between the reviewers will be resolved through discussion, or with a third reviewer. Authors of papers will be contacted to request missing or additional data where required.

Data synthesis

Quantitative data will, wherever possible, be pooled in statistical meta-analysis, using JBI SUMARI. All results will be subject to double data entry. Effect sizes expressed as odds ratios, relative risk, or other measures of association and their 95% confidence intervals will be calculated for analysis. In a random effects model, untransformed effect-size estimates will be used in calculating the weighted mean correlation coefficient. The choice of model (random or fixed effects) and method for meta-analysis will be based on the guidance by Moola *et al.*²⁴ Subgroup analyses will be conducted where there is sufficient data to investigate outcomes in progeny of women with and without loss of asthma control or asthma exacerbation, and with differing severity of asthma, and to assess asthma and allergic disease outcomes in different progeny age groups.

To determine whether statistical meta-analyses are appropriate, we will consider clinical heterogeneity (ie, clinical populations, outcome definitions, and ascertainment), design heterogeneity (ie, study design, analytical approach, extent of control for confounding factors), as well as statistical heterogeneity. The latter will be quantified with the χ^2 and I^2 statistics. A funnel plot will be generated within JBI SUMARI to assess publication bias if there are 10 or more studies included in a meta-analysis. Statistical tests for funnel

plot asymmetry (Egger test, Begg test, Harbord test) will be performed where appropriate. Where statistical pooling is not possible, the findings will be presented in narrative form including tables and figures to aid in data presentation where appropriate.

Assessing certainty in the findings

The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach for grading the certainty of evidence will be followed,²⁷ as described for prognostic factors,²⁸ and a Summary of Findings will be created using GRADEPro GDT 2015 (McMaster University, ON, Canada). The Summary of Findings will include the absolute risk for exposed and non-exposed offspring, relative risk estimate, and a ranking of the quality of the evidence. Assessment of bias and quality will be conducted by two independent assessors (any of the review authors). Any disagreements that arise between the reviewers will be resolved through discussion or with a third reviewer. A narrative summary will be provided of the overall methodological quality of the included studies.

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Author contributions

All authors contributed to the search strategy, eligibility criteria, research question design, and data analysis strategy. AJR and KLG were the primary authors involved in the writing of the protocol. KLG will be the guarantor of the final review. All authors read and approved the final manuscript.

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Appendix I: Search strategy

MEDLINE (PubMed)

Date searched: April 20, 2020.

Terms describing exposure of interest are identified in *italics* and terms identifying outcomes of interest are identified in **bold**:

(*“Asthma”* [mh] OR *Asthma* [tiab] OR *Respiratory hypersensitivity* [tiab] OR *Wheez** [tiab]) AND (*“Pregnancy”* [mh] OR *Maternal* [tiab] OR *Gestat** [tiab] OR *Pregnan** [tiab]) AND (**Hypersensitivity** [mh:noexp] OR **“Hypersensitivity,Immediate”** [mh] OR **“Hypersensitivity, Delayed”** [mh:noexp] OR **Asthma** [tiab] OR **Allergic** [tiab] OR **Allergy** [tiab] OR **Allergies** [tiab] OR **Allergic Reaction** [tiab] OR **Hypersensitiv*** [tiab] OR **Dermatitis, Allergic Contact** [mh:noexp] OR **Atopic** [tiab] OR **Airway Hyper-responsiveness** [tiab] OR **Respiratory Hyperresponsiveness** [tiab] OR **Hay Fever** [tiab] OR **Hayfever** [tiab] OR **Allergic Rhinitis** [tiab] OR **Eczema** [tiab] OR **Urticaria*** [tiab] OR **Anaphyla*** [tiab] OR **IgE** [tiab] OR **Eosinophilic** [tiab] OR **Wheez*** [tiab]) AND (**Childhood** [tiab] OR **Child*** [tiab] OR **Progeny** [tw] OR **Offspring** [tw])

This search retrieved 4701 records.