

Relationship between birth weight or fetal growth rate and postnatal allergy: a systematic review protocol

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Review question/objective: The objective of this systematic review is to synthesize the best available evidence on the relationship between size at birth or fetal growth and postnatal allergy. Specifically, this review aims to assess evidence regarding relationships between absolute birth weight at term, birth weight corrected for gestational age, expressed as relative to population or customized growth data, or fetal growth measures and physician-diagnosed or parent- and self-reported postnatal clinical allergic disease (eczema/atopic dermatitis, hay fever/rhinitis, allergic asthma or anaphylaxis).

The specific review question is: what is the association between the absolute birth weight at full-term or birth weight relative to population or customized data and corrected for gestational age or direct measures of fetal growth, and physician-diagnosed or parent- and self-reported clinical allergic disease (eczema/atopic dermatitis, hay fever/rhinitis, allergic asthma or anaphylaxis)?

Keywords allergy; anaphylaxis; eczema; fetal growth; hay fever

Background

Description of the conditions of interest

Allergy is a common non-communicable disease worldwide that is estimated to affect 30-40% of the world's population¹ and is increasing in prevalence, particularly in young children.² Allergic conditions, including anaphylaxis and asthma, can become life-threatening if not well-managed. Common allergic conditions include eczema (atopic dermatitis), hay fever (allergic rhinitis), allergic asthma and anaphylaxis.

Eczema, also known as atopic dermatitis, is an inflammatory skin condition induced by sensitization and subsequent cutaneous exposure to allergen/s.¹ Hay fever, also known as allergic rhinitis, is an allergic condition resulting from IgE-mediated inflammation of the nasal mucosa and produces symptoms including: watery eyes, a runny nose and sneezing.¹ The term asthma is used to describe a complex chronic inflammatory disease syndrome affecting the airways, characterized by bronchial hyperresponsiveness and progressive airway remodeling and loss of function.³ Allergy is one of the

causes of asthma;⁴ this review addresses allergic asthma but not asthma or wheezing that are because of other causes such as exercise-induced asthma or non-specified causes. Anaphylaxis is a severe, potentially fatal, systemic allergic reaction, which is rapid in onset and occurs suddenly after contact with an allergy-causing substance.⁵

Description of the epidemiological relationship of interest

Recent evidence suggests that the risk of allergy in older life is highly influenced by exposures in early life, including prenatal growth and gestational age at delivery, mode of delivery, maternal pregnancy diet and family size.⁶ Epigenetic changes and altered microbiome development have been suggested as potential mechanisms for lasting effects of some perinatal exposures on susceptibility.⁷⁻⁹ Growth before birth and size at birth have been associated with risks of allergy in a number of human cohort studies,⁶ including in twin studies, where siblings share a common postnatal environment and genetic similarities.^{10,11} Experimental models of manipulated fetal growth have also induced altered allergy susceptibility in progeny. In rats, maternal under-nutrition throughout gestation reduced birth weight by approximately 30% and reduced antigen-specific circulating IgE and airway allergic responses to acute

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ovalbumin challenge after sensitization to ovalbumin.^{12,13} It has been shown that intrauterine growth restriction (IUGR) in sheep, induced by placental restriction, decreased cutaneous inflammatory responses to intradermal ovalbumin, also following sensitization and despite normal IgE responses.¹⁴ Together, these are consistent with protection against allergy by restricted fetal growth. In contrast, maternal under-nutrition throughout gestation in a second study of rats resulted in increased eosinophilia and endothelin-1 expression in the lung in response to systemic sensitization and airway exposure to ovalbumin.¹⁵ The mechanisms for the effects of altered fetal growth on later allergic susceptibility are largely unknown, although epigenetic mechanisms have been suggested.

In humans, IUGR affects 6–12% of pregnancies in developed countries and a greater percentage of pregnancies within poorer populations.¹⁶ These infants are unable to reach their genetic growth potentials *in utero*. Intrauterine growth restriction may be caused by fetal genetic conditions, maternal factors such as low maternal body weight, age or parity, maternal under-nutrition, alcohol consumption or smoking and other causes such as preeclampsia, intrauterine infections and placental dysfunction.¹⁷ The majority of IUGR in developed countries is associated with poor placental development and/or function.¹⁷

Infants born at a weight below the 10th percentile for gestational age are classified as being born at a small size for their gestational age. This group may include those who are genetically small and is not limited to those who are also exposed to the pathological environment of IUGR.¹⁸ Human cohort studies often also categorize neonates as low birth weight (LBW: <2500 g).¹⁹ This descriptor is more useful where gestational age is taken into account or the cohort is restricted to term-born individuals, but also fails to fully differentiate IUGR from individuals who are born at appropriate size for gestational age. Ideally, “true” IUGR is classified on the basis of decreasing centiles of fetal size with advancing gestation and/or other markers of fetal constraint, including umbilical and uterine artery Doppler patterns, requiring detailed and/or serial ultrasound measures.¹⁸

At the other end of the fetal growth spectrum, fetal overgrowth is also associated with postnatal health, with strong evidence that this increases the

risk of being overweight in later life.²⁰ Large size at birth may reflect oversupply of nutrients to the fetus, for example in gestational diabetes, elevated maternal glucose and maternal obesity.^{21,22} These exposures may result in individuals who are born large for gestational age or of high birth weight (HBW: >4500 g). As noted above for IUGR, these classifications do not completely define or identify all neonates who have undergone a period of accelerated growth *in utero*.

Why this review is important

Given the increasing prevalence of allergy, it is important to define *in utero* pathways and mechanisms behind the developmental influence of susceptibility to allergic disease to then identify targets for interventions. It is also unclear whether relationships between birth weight or fetal growth and later allergy in humans are consistent between different allergic diseases, populations and ages. No recent or underway systematic reviews of this topic were found when searching the *JB I Database of Systematic Reviews and Implementation Reports*, Cochrane Library, PubMed, CINAHL and Prospero. Some detailed literature review articles describing the association between size at birth and allergic disease exist. However, no reviews published on this topic have used systematic review methodology, except for one meta-analysis of the relationship between categories of absolute birth weight, uncorrected for gestational age (LBW compared with normal birth weight [NBW], and HBW compared with NBW) and atopic dermatitis.²³ The final meta-analysis included 10 studies of a total of ~111,000 study participants.²³ Based on this set of evidence, the authors concluded that LBW is protective against occurrence of atopic dermatitis when compared with study participants of NBW [I^2 85.90, 95% confidence interval (CI) 75.93–91.74] and that HBW represents a risk factor for atopic dermatitis (I^2 58.38, 95% CI 0–83.1).²³ It is not considered that this meta-analysis identified all the relevant literature, as the databases searched were limited to PubMed, Cochrane Library and Web of Knowledge only, and eczema was not included as a search term.²³ In addition, the analysis may be confounded by a lack of precision in the outcome measure, as studies where outcomes were parent- and patient-reported allergy were included in addition to studies reporting clinical diagnosis.²³

This may have been exacerbated by a lack of stratification of outcomes by age, with outcomes in infants, children and adolescents grouped together and potential recall bias.²³ Furthermore, no correction was made for gestational age, included in analysis of data from very LBW cohorts, where low birth weight probably reflect prematurity,²⁴ and the authors acknowledge the need for additional studies of this relationship that take gestational age into account.²³ Finally, because of poor figure quality in the published manuscript,²³ interpretation of results is difficult. It is therefore considered that a more comprehensive analysis of the relationship between birth weight or fetal growth, reflecting fetal under and overgrowth, is required, in addition to the analysis of relationships between these exposures and other atopic diseases. Studies from this previous meta-analysis²³ will be included in data evaluation for the present review.

This systematic review will accurately assess studies and provide clarity on the relationship between birth weight or fetal growth rate and postnatal allergic disease.

Inclusion criteria

Types of participants

This review will consider studies that include individuals who were born full term (37–42 weeks gestation). Studies that include preterm-born individuals (<37 weeks gestation) will be considered only where gestational age has been corrected for (use of birth weight centiles that are either customized or expressed relative to population means or stratification by gestational age or inclusion of gestational age as a factor in statistical models), to investigate effects of fetal growth independent of effects of gestational age. Outcomes in all age groups will be included and will be stratified according to postnatal age because of the differing prevalence and changes in phenotypes of allergic diseases with age.^{25–27} As gender may affect the prevalence of allergy,²⁸ outcomes will also be separately stratified by gender where it is reported.

Exposures of interest

The exposures of interest are size at birth or fetal growth, measured either as continuous variables or grouped into categories. Defined birth weight categories include those based on absolute birth weights of infants born at term (LBW, <2500 g and HBW, >4500 g) and categories based on birth

weights relative to population means and gestational age (small size at birth for gestational age, lowest 10th percentile of birth weight within population; large size at birth for gestational age, highest 10th percentile of birth weight within population). Fetal growth is based on direct measures by ultrasonography at multiple points during gestation.

Outcomes

The review will consider studies that include the following outcome measures: physician-diagnosed or parent- and self-reported clinical allergic disease (eczema/atopic dermatitis, hay fever/allergic rhinitis, allergic asthma or anaphylaxis). Inclusion of parent- and self-reported allergic disease will be restricted to those studies where outcome is prior physician diagnosis or of defined clinical symptoms allowing specific diagnosis.

The review will address allergic asthma but not asthma or wheezing that is because of other causes such as exercise-induced asthma or non-specified causes.

Types of studies

The review will consider for inclusion analytical epidemiological study designs, including prospective and retrospective cohort studies, case-control studies and analytical cross-sectional studies, where these studies include the exposures and outcomes of interest.

Search strategy

The search strategy aims to find both published and unpublished studies. A three-step search strategy will be utilized in this review. An initial limited search of PubMed and EMBASE using keywords listed below will be undertaken followed by analysis of the text words contained in the title and abstract and the index terms used to describe the articles. A second search using all identified keywords and index terms will then be undertaken across all included databases. Third, the reference list of all identified reports and articles will be searched for additional studies. Only publications in English will be considered. There will be no date limitations for inclusion in the review.

The databases to be searched include: PubMed, EMBASE, Web of Science, Cochrane library, CINAHL, Scopus.

The search for unpublished studies will include: Informit Health databases, MedNar, ProQuest, Australian Digital Thesis Program.

Initial keywords to be used will be: fetal growth, intrauterine growth, birth weight, size for gestational age, allergy, allergic, atopy, eczema, hay fever, rhinitis, anaphylaxis.

Assessment of methodological quality

Studies selected for retrieval will be assessed by two independent reviewers for methodological validity prior to inclusion in the review using a customized critical appraisal instrument modified from the standard Joanna Briggs Institute Meta-analysis of Statistics Assessment and Review Instrument (JBI-MASARI) (Appendix I). Any disagreements that arise between the reviewers will be resolved through discussion or with a third reviewer.

Data extraction

Data will be extracted from studies included in the review initially using a customized data extraction tool (Appendix II) based on the standardized data extraction tool from JBI-SUMARI. It will be piloted and refined early in the data extraction phase to accurately capture all of the data that we require for analysis. The data extracted will include specific details about the populations, study methods and outcomes of significance to the review question and specific objectives.

Data synthesis

Quantitative data will, wherever possible, be pooled in statistical meta-analysis. All results will be subject to double data entry. Effect sizes will be stratified by study design and expressed as relative risk for cohort studies, odds ratio for case-control studies and prevalence odds ratio for analytical cross-sectional studies and their 95% CIs will be calculated for analysis. To determine whether statistical meta-analyses are appropriate, we will consider clinical heterogeneity (i.e. clinical populations, outcome definitions and ascertainment), design heterogeneity (i.e. study design, analytical approach, extent of control for confounding factors including gestational age) as well as statistical heterogeneity. The latter will be quantified with the I^2 statistic. Where statistical pooling is not possible, the findings will be presented in narrative form, including tables and figures to aid in data presentation, wherever appropriate.

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Appendix I: Appraisal instruments

MAStARI appraisal instrument

JBIC Critical Appraisal Checklist for Comparable Cohort/ Case Control

Reviewer Date

Author Year Record Number

	Yes	No	Unclear	Not Applicable
1. Is sample representative of patients in the population as a whole?	☐	☐	☐	☐
2. Are the patients at a similar point in the course of their condition/illness?	☐	☐	☐	☐
3. Has bias been minimised in relation to selection of cases and of controls?	☐	☐	☐	☐
4. Are confounding factors identified and strategies to deal with them stated?	☐	☐	☐	☐
5. Are outcomes assessed using objective criteria?	☐	☐	☐	☐
6. Was follow up carried out over a sufficient time period?	☐	☐	☐	☐
7. Were the outcomes of people who withdrew described and included in the analysis?	☐	☐	☐	☐
8. Were outcomes measured in a reliable way?	☐	☐	☐	☐
9. Was appropriate statistical analysis used?	☐	☐	☐	☐

Overall appraisal: Include ☐ Exclude ☐ Seek further info. ☐

Comments (Including reason for exclusion)

JBI Critical Appraisal Checklist for Analytical Cross Sectional Studies

Reviewer _____ Date _____
 Author _____ Year _____ Record Number _____
 Yes No Unclear Not applicable

- | | | | | |
|---|--------------------------|--------------------------|--------------------------|--------------------------|
| 1. Were the criteria for inclusion in the sample clearly defined? | ☐ | ☐ | ☐ | ☐ |
| 2. Were the study subjects and the setting described in detail? | ☐ | ☐ | ☐ | ☐ |
| 3. Was the exposure measured in a valid and reliable way? | ☐ | ☐ | ☐ | ☐ |
| 4. Were objective, standard criteria used for measurement of the condition? | ☐ | ☐ | ☐ | ☐ |
| 5. Were confounding factors identified? | ☐ | ☐ | ☐ | ☐ |
| 6. Were strategies to deal with confounding factors stated? | ☐ | ☐ | ☐ | ☐ |
| 7. Were the outcomes measured in a valid and reliable way? | ☐ | ☐ | ☐ | ☐ |
| 8. Was appropriate statistical analysis used? | ☐ | ☐ | ☐ | ☐ |

Overall appraisal: Include ☐ Exclude ☐ Seek further info ☐

Comments (Including reason for exclusion)

Appendix II: Data extraction instruments

Customized data extraction instrument based on JBI data extraction form

Customized Data Extraction Tool for Descriptive and Case-Control Studies

For reviewing the relationship between birth weight or fetal growth rate and postnatal allergy

Study Details

Record ID #: _____ Date: _____

Author: _____ Reviewer: _____

Year: _____ Study title: _____

Journal: _____

Study aim: _____

Study Method

Setting:	Study design ☐ Longitudinal ☐ Cross-sectional ☐ Retrospective observational ☐ Prospective observational
Follow-up or study duration:	
Subject characteristics (including specified inclusion/exclusion criteria):	
Dependent variables: ☐ Fetal growth (direct measurement) ☐ Birth weight – as a <u>continuous</u> variable ☐ Birth weight – as a <u>categorical</u> variable Further detail:	Ethical approval ☐ Yes ☐ No/unclear ☐ Not required
Confounding variables:	
Age category (tick all that apply): ☐ Infancy (0-2 y) ☐ Adolescence (13-18 y) ☐ Childhood (3-12 y) ☐ Adulthood (≥19 y)	

Method of data analysis:

Outcomes reported

	Eczema (atopic dermatitis)	Hay fever (allergic rhinitis)	Allergic asthma	Anaphylaxis
Assessment method (tick all that apply)				
<i>Physician diagnosis (direct)</i>	☐	☐	☐	☐
<i>Physician diagnosis (parental-reported)</i>	☐	☐	☐	☐
<i>Questions for clinical allergy symptoms</i>	☐	☐	☐	☐

Method of controlling for gestational age

- ☐ Term born only
- ☐ Twin study (ie. heavier vs. lower birth-weight twin)
- ☐ Statistical models corrected for gestational age
- ☐ Exposures reported are already corrected for gestational age (eg. Z-score, 10th/90th percentiles)

Results

Eczema / hay fever / allergic asthma / anaphylaxis (circle) or exposure: _____, reported by category

Category	Number of events (n, N)			Ratio	95% CI
	M	F	Total		
<i>Example: LBW <2500 g</i>	45 allergic, 100	15 allergic, 100	60 allergic, 100	###	###-###
<i>Example: Eczema</i>	48 LBW, 100	23 LBW, 50	71 LBW, 150	###	###-###

*Note M, F and total ratios and 95% confidence intervals

Exposure, reported for those with eczema / hay fever / allergic asthma / anaphylaxis (circle)

Continuous exposure	Allergic individuals (mean, SD (SE), N)			Non-allergic individuals (mean, SD (SE), N)		
	M	F	Total	M	F	Total
<i>Example: Birth weight</i>			3.21, 0.3 (0.2) kg, 23			3.62, 0.3 (0.2) kg, 23

Other notes about results: _____

Authors' comments: _____

Reviewer comments (including notes/ critiques/limitations of the study): _____