

Preclinical models of maternal asthma and progeny outcomes: a scoping review protocol

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ABSTRACT

Objective: This scoping review will describe the methodology, phenotype, and characteristics of maternal asthma models used in preclinical studies and the outcomes that have been measured in the mother and progeny. The review This will identify gaps in knowledge of maternal and progeny outcomes following maternal asthma in pregnancy.

Introduction: Maternal asthma affects up to 17% of pregnancies worldwide and is associated with adverse perinatal outcomes in mothers and babies, including pre-eclampsia, gestational diabetes, cesarean section, preterm birth, small for gestational age, nursery admission, and neonatal death. While the associations are well established, the mechanisms linking maternal asthma and adverse perinatal outcomes are largely unknown due to the difficulties of human mechanistic studies. The appropriate selection of animal models is vital to understanding the mechanisms underlying associations between human maternal asthma and adverse perinatal outcomes.

Inclusion criteria: This review will include primary studies published in English where outcomes have been studied in vivo in non-human mammalian species.

Methods: This review will follow the JBI methodology for scoping reviews. We will search MEDLINE (PubMed), Embase, and Web of Science to identify papers published before the end of 2022. Initial keywords will include *pregnancy, gestation, asthma, and wheeze*, as well as validated search strings to identify papers that describe animal models. Extracted data will include information on methods used to induce maternal asthma; asthmatic phenotypes and characteristics; and maternal, pregnancy, placental, and progeny outcomes. The characteristics of each study will be presented in summary tables and a core outcome list to assist researchers in developing, reporting, and comparing future animal studies of maternal asthma.

Review registration: Open Science Framework osf.io/trwk5

Keywords: animal models; asthma; gestation; pregnancy; scoping review protocol

JBI Evid Synth 2023; 21(10):2115–2126.

Introduction

The prevalence of asthma during human pregnancy continues to grow, with estimates of up to 17%.¹ Maternal asthma is associated with increased risks of adverse perinatal outcomes, including gestational diabetes, pre-eclampsia, placenta previa or abruption, preterm birth, cesarean section, small for

gestational age, nursery admission, transient tachypnea, respiratory distress syndrome, and neonatal death.^{2–4} The impact of maternal asthma extends into childhood, where it is associated with increased risk of wheezing, childhood asthma, pneumonia, and general respiratory disease.^{5,6} Maternal asthma is also associated with a persistently low lung function from childhood to age 32,⁷ demonstrating long-term adverse respiratory impacts on progeny.

There is evidence that the in utero environment contributes to these associations in addition to genetic

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The authors declare no conflict of interest.

DOI: 10.11124/JBIES-23-00006

risk. For example, childhood asthma is more strongly associated with maternal than paternal asthma,⁸ suggesting programming effects of the in utero environment. Furthermore, good maternal asthma control during pregnancy reduces the risk of adverse perinatal and childhood outcomes,^{9,10} demonstrating that an optimal maternal environment improves perinatal outcomes. The use of inhaled corticosteroids to manage asthma during pregnancy reduces the risk of childhood asthma in offspring (OR 0.19; 95% CI 0.06–0.56).¹⁰ Although the association between maternal asthma and adverse perinatal outcomes is well established, the mechanisms are largely unclear. Current mechanistic evidence relies heavily on rodent models in which a larger proportion of development occurs after birth compared with humans.¹¹

Animal models are vital to understand the mechanisms that link maternal asthma to poor offspring outcomes. They allow confounders and variability due to genetics, comorbidities to be removed and interventions tested.^{11,12} This is important as comorbidities may occur in asthmatic women but can be controlled for in animal models. For example, asthmatic mothers are more likely to have a high body mass index, proteinuria, essential hypertension, cardiac disease, contract urinary tract infections, and smoke compared with non-asthmatic mothers.^{9,13} Some women also cease asthma control medication during pregnancy due to concerns about impacts on the fetus,¹⁴ which may further confound associations. The complex physiology of maternal–placental–fetal interactions means that in vitro, ex vivo, and in silico models are not sufficient to understand the mechanisms by which maternal asthma leads to adverse perinatal outcomes.

As a result, animal models of asthma have been developed in species such as mice, rats, guinea pigs, rabbits, sheep, monkeys, and horses.¹⁵ To maximize the potential for translation, these models of maternal asthma should have similar features to human asthma in pregnancy. Established animal models of asthma during pregnancy include allergic maternal asthma in mice and sheep, which display elevated eosinophils, airway remodeling, and increased breathing effort,¹⁶ similar to the characteristics of asthma in pregnant women.¹⁷ However, as the timing of fetal organ development differs between species, it is likely that the impacts of maternal asthma on progeny will also differ across species, which may impact potential clinical translation.¹¹

Evidence from animal models supports the hypothesis that effects of maternal asthma are mediated by the in utero environment, in addition to genetics. In mice, experimental maternal asthma impairs embryo quality (morphology, size, and fragmentation) and embryo quantity, followed by reduced periconceptional growth.¹⁸ At 12–14 days old, the offspring of asthmatic dams have more responsive airways than offspring of control dams.¹⁹ Interestingly, offspring airway hyper-responsiveness was induced by another allergen, casein, whereas maternal allergy was induced by ovalbumin, indicating that the maternal effect may be allergen independent.¹⁹ In this model, reduced maternal ovalbumin exposure pre-mating or blocking interleukin 4 (IL-4) by anti-mouse IL-4 antibody prevented adverse respiratory outcomes for the offspring of asthmatic mothers.¹⁹ Further evidence of immune programming of T cells comes from another murine model of maternal asthma where asthmatic offspring exhibited a moderate to severe T_H1/T_H17 inflammatory signature in response to allergen challenge, compared with the milder T_H2 signature of their mothers.²⁰ In sheep, near-term fetuses from asthmatic mothers had lower lung surfactant expression, lower type II alveolar epithelial cell density, and higher proportions of CD44 positive lymphocytes in the thymus,^{21,22} which could lead to poorer neonatal lung function and greater inflammatory response, respectively. This evidence from preclinical models suggests that the in utero environment of an asthmatic mother alters lung and immune development of progeny.

This scoping review will describe preclinical models of maternal asthma and their perinatal outcomes. In addition to defining the outcomes studied to date, we will evaluate the strengths and weaknesses of each model and the methodological rigor of each study using the Animal Research: Reporting of In Vivo Experiments (ARRIVE) guidelines.²³ We will develop a core outcome set for animal models of maternal asthma to improve comparability and translation by enabling evidence synthesis of preclinical studies.²⁴ Although multiple systematic reviews have been performed on clinical outcomes of human asthma in pregnancy and in children,^{3,4} a similar synthesis of preclinical data has not been conducted. It is unknown whether preclinical studies report similar outcomes to human data, and which outcomes have been measured in preclinical studies. A preliminary search

of PROSPERO and MEDLINE (PubMed) found no current scoping reviews or systematic reviews on this topic. To the best of our knowledge, this scoping review is the first to evaluate the literature on animal models of maternal asthma. A scoping review will clarify the breadth and gaps in animal models of maternal asthma in the current literature and will be used to better inform the design of preclinical studies on maternal asthma. Given the likely heterogeneity in study design and outcomes, a systematic review was not considered appropriate to answer this question.

Review questions

- i) What are the methods used to induce maternal asthma and what are the phenotype and outcomes of the mother and progeny in published preclinical studies?
- ii) What is the methodological rigor of existing studies using preclinical models of maternal asthma?

Inclusion criteria

Participants

This review will consider studies that include in vivo studies of maternal asthma from any non-human mammal. Studies in humans will be excluded as our focus is on use of preclinical studies to reduce confounding and understand mechanisms.

Concept

This review will include studies using animal models where the mother has asthma during her current pregnancy with or without a comparator. When included, the comparator will be a healthy non-asthmatic mother and her progeny will be drawn from the same population. Included studies must describe how maternal asthma was induced and measures of maternal, pregnancy, and progeny outcomes. All reported maternal, pregnancy, placental, and progeny outcomes will be extracted. Maternal outcomes of interest will include airway function and immune responses. Pregnancy outcomes will include litter size and viability. Placental outcomes will include gross, histological, and molecular phenotype. Progeny outcomes will include fetal and postnatal measures, such as growth, survival, and immune and airway responses to allergen challenge. Outcomes analyzed by progeny sex will be reported where available.

Types of sources

We will include studies that report in vivo outcomes of maternal asthma conducted in non-human mammalian species. Only primary studies containing original research will be included. Conference abstracts will be excluded since they do not contain enough methodological information for evaluation.

Methods

The scoping review will be conducted in accordance with the JBI methodology for scoping reviews²⁵ and will comply with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) guidelines,²⁶ a set of preferred reporting items for scoping reviews. Any protocol amendments will be reported in the final review.

Search strategy

The search strategy will include the 3 most relevant databases for identifying animal studies²⁷: MEDLINE (PubMed), Embase, and Web of Science. An initial search of MEDLINE (PubMed) to identify articles on the topic was conducted. A search strategy was devised for MEDLINE using keywords in the titles, abstracts, and index terms (Appendix I). Keywords included *asthma*, *pregnancy*, *maternal*, *gestation*, *animal*, and *model*, as well as names of mammalian species adapted from a validated search string of animal studies.^{28,29} SRA Polyglot Search Translator (SRA; Bond University, Robina, Australia) will be used to adapt the search string for different databases.³⁰ The reference lists of included studies and identified reviews will be screened to locate additional studies. The location of 10 studies identified as eligible in our initial searches of MEDLINE (PubMed) will be used as a quality control for each search.

Only studies published in English will be included due to resource constraints. Studies that are published at any time up to the end of 2022, when this protocol was submitted, will be included.

Study selection

Following the search, citations will be collated using EndNote v.X9 (Clarivate Analytics, PA, USA) and uploaded to Covidence software (Veritas Health Innovation, Melbourne, Australia). EndNote, 2-week systematic review SRA Deduplicator (SRA; Bond

University, Robina, Australia) with the cautious algorithm³¹ and Covidence will be used to remove duplicates.

Two reviewers will independently screen the titles and abstracts using the inclusion criteria listed previously. The full text of studies included at title and abstract stage will then be screened by 2 independent reviewers. Any disagreements during screening will be resolved by discussion with other members of the review team.

The full text of selected citations will be assessed in detail against the inclusion criteria by 2 independent reviewers. Reasons for exclusion of full-text papers that do not meet the inclusion criteria will be recorded and reported in the scoping review. Any disagreements that arise between the reviewers at each stage of the selection process will be resolved through discussion or with a third reviewer. The results of the search, including exclusion reasons, will be reported in full in a PRISMA flow diagram.³²

Data extraction

A standardized, pre-planned form (Appendix II) will be used to extract data from included studies in Covidence. Extracted data will include details on animal numbers, species, and breed or strain; study design; methods to induce maternal asthma; asthmatic phenotypes and characteristics; and maternal, pregnancy, and progeny outcomes. Two independent reviewers will extract the data. Authors will be contacted up to 2 times, as required, for any missing or additional data. Any disagreements will be solved by discussion with a third independent reviewer.

Eligible studies will be critically appraised by 2 independent reviewers using the ARRIVE guidelines.²³ These guidelines contain a checklist including information on the study design, experimental procedures, animal species and strain, housing, husbandry, numbers, and analysis. Each reviewer will use the 21-question checklist to assess whether the paper includes the information (yes), fails to mention the information (no), or whether it is either “unclear” or “not applicable” Any disagreements will be resolved by discussion with a third independent reviewer. The quality assessment will be reported in a table in the full review.

Data analysis and presentation

Characteristics of each extracted study will be presented in summary tables, accompanied by narrative

discussion. We will initially summarize the characteristics of the available studies, and specifically, the study design, species, and aims. Detailed maternal, pregnancy, placental, and postnatal offspring outcomes will then be reported, with maternal and progeny outcomes grouped according to body system. The prevalence of study characteristics or outcome types in the literature will be reported using descriptive statistics. A summary of core outcomes will be developed based on the included papers to assist researchers in developing, reporting, and comparing future model and outcome selection for animal studies of maternal asthma. The outcomes of this scoping review will be published in a peer-reviewed journal and presented at national and international conferences.

Acknowledgments

Vikki Langton, research librarian at The University of Adelaide, for guidance on the search strategy for this review.

This review will contribute toward a PhD for JLR.

Funding

JLR is supported by an Australian Government Research Training Program Scholarship and a Healthy Development Adelaide/Channel 7 Children's Research Foundation PhD Excellence Supplementary Scholarship.

VLC is supported by a National Health and Medical Research Council Senior Research Fellowship (APP1136100).

Author contributions

All authors contributed to the search strategy, eligibility criteria, research question design, and data analysis strategy. JLR was the primary author for the writing of the protocol. All authors read and approved the final manuscript.

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Appendix I: Search strategy

MEDLINE (PubMed)

Search conducted: September 7, 2022

(Asthma [mh] OR Asthma [tiab] OR “Respiratory hypersensitivity” [tiab] OR Wheez* [tiab])

AND

(Pregnancy [mh] OR Maternal [tiab] OR Gestat* [tiab] OR Pregnant* [tiab])

AND

((“animal experimentation”[MeSH Terms] OR “models, animal”[MeSH Terms] OR “Animals”[Mesh: noexp] OR “animal population groups”[MeSH Terms] OR “chordata”[MeSH Terms:noexp] OR “vertebrates”[MeSH Terms:noexp] OR “mammals”[MeSH Terms:noexp] OR “primates”[MeSH Terms:noexp] OR “artiodactyla”[MeSH Terms] OR “carnivora”[MeSH Terms] OR “cetacea”[MeSH Terms] OR “chiroptera”[MeSH Terms] OR “elephants”[MeSH Terms] OR “hyraxes”[MeSH Terms] OR “lagomorpha”[MeSH Terms] OR “marsupialia”[MeSH Terms] OR “monotremata”[MeSH Terms] OR “perissodactyla”[MeSH Terms] OR “rodentia”[MeSH Terms] OR “scandentia”[MeSH Terms] OR “sirenia”[MeSH Terms] OR “xenarthra”[MeSH Terms] OR “haplorhini”[MeSH Terms:noexp] OR “strepsirhini”[MeSH Terms] OR “platyrrhini”[MeSH Terms] OR “tarsii”[MeSH Terms] OR “catarrhini”[MeSH Terms:noexp] OR “cerco- pithecidae”[MeSH Terms] OR “hylobatidae”[MeSH Terms] OR “hominidae”[MeSH Terms:noexp] OR “gorilla gorilla”[MeSH Terms] OR “pan paniscus”[MeSH Terms] OR “pan troglodytes”[MeSH Terms] OR “pongo pygmaeus”[MeSH Terms])

OR

((animals[tiab] OR animal[tiab] OR mice[Tiab] OR mus[Tiab] OR mouse[Tiab] OR murine[Tiab] OR woodmouse[tiab] OR rats[Tiab] OR rat[Tiab] OR murinae[Tiab] OR muridae[Tiab] OR cottonrat[tiab] OR cottonrats[tiab] OR hamster[tiab] OR hamsters[tiab] OR cricetinae[tiab] OR rodentia[Tiab] OR rodent [Tiab] OR rodents[Tiab] OR pigs[Tiab] OR pig[Tiab] OR swine[tiab] OR swines[tiab] OR piglets[tiab] OR piglet[tiab] OR boar[tiab] OR boars[tiab] OR “sus scrofa”[tiab] OR ferrets[tiab] OR ferret[tiab] OR polecat [tiab] OR polecats[tiab] OR “mustela putorius”[tiab] OR “guinea pigs”[Tiab] OR “guinea pig”[Tiab] OR cavia[Tiab] OR callithrix[Tiab] OR marmoset[Tiab] OR marmosets[Tiab] OR cebuella[Tiab] OR hapale [Tiab] OR octodon[Tiab] OR chinchilla[Tiab] OR chinchillas[Tiab] OR gerbillinae[Tiab] OR gerbil[Tiab] OR gerbils[Tiab] OR jird[Tiab] OR jirds[Tiab] OR merione[Tiab] OR meriones[Tiab] OR rabbits[Tiab] OR rabbit[Tiab] OR hares[Tiab] OR hare[Tiab] OR cats[Tiab] OR cat[Tiab] OR carus[Tiab] OR felis[Tiab] OR dogs[Tiab] OR dog[Tiab] OR canine[Tiab] OR canines[Tiab] OR canis[Tiab] OR sheep[Tiab] OR sheeps [Tiab] OR mouflon[Tiab] OR mouflons[Tiab] OR ovis[Tiab] OR goats[Tiab] OR goat[Tiab] OR capra [Tiab] OR capras[Tiab] OR rupicapra[Tiab] OR rupicapras[Tiab] OR chamois[Tiab] OR haplorhini[Tiab] OR monkey[Tiab] OR monkeys[Tiab] OR anthropoidea[Tiab] OR anthropoids[Tiab] OR saguinus[Tiab] OR tamarin[Tiab] OR tamarins[Tiab] OR leontopithecus[Tiab] OR hominidae[Tiab] OR ape[Tiab] OR apes[Tiab] OR “pan paniscus”[Tiab] OR bonobo[Tiab] OR bonobos[Tiab] OR “pan troglodytes”[Tiab] OR gibbon[Tiab] OR gibbons[Tiab] OR siamang[Tiab] OR siamangs[Tiab] OR nomascus[Tiab] OR symphalangus[Tiab] OR chimpanzee[Tiab] OR chimpanzees[Tiab] OR prosimian[Tiab] OR prosimians [Tiab] OR “bush baby”[Tiab] OR bush babies[Tiab] OR galagos[Tiab] OR galago[Tiab] OR pongidae [Tiab] OR gorilla[Tiab] OR gorillas[Tiab] OR “pongo pygmaeus”[Tiab] OR orangutan[Tiab] OR orangu- tans[Tiab] OR lemur[Tiab] OR lemurs[Tiab] OR lemuridae[Tiab] OR horse[Tiab] OR horses[Tiab] OR equus[Tiab] OR cow[Tiab] OR calf[Tiab] OR bull[Tiab] OR sciuridae[Tiab] OR squirrel[Tiab] OR squirrels [Tiab] OR chipmunk[Tiab] OR chipmunks[Tiab] OR suslik[Tiab] OR susliks[Tiab] OR vole[Tiab] OR voles[Tiab] OR lemming[Tiab] OR lemmings[Tiab] OR muskrat[Tiab] OR muskrats[Tiab] OR lemmus [Tiab] OR otter[Tiab] OR otters[Tiab] OR marten[Tiab] OR martens[Tiab] OR martes[Tiab] OR weasel

[Tiab] OR badger[Tiab] OR badgers[Tiab] OR ermine[Tiab] OR mink[Tiab] OR minks[Tiab] OR sable [Tiab] OR sables[Tiab] OR gulo[Tiab] OR gulos[Tiab] OR wolverine[Tiab] OR wolverines[Tiab] OR mustela[Tiab] OR llama[Tiab] OR llamas[Tiab] OR alpaca[Tiab] OR alpacas[Tiab] OR camelid[Tiab] OR camelids[Tiab] OR guanaco[Tiab] OR guanacos[Tiab] OR chiroptera[Tiab] OR chiropteras[Tiab] OR bat[Tiab] OR bats[Tiab] OR fox[Tiab] OR foxes[Tiab] OR donkey[Tiab] OR donkeys[Tiab] OR mule [Tiab] OR mules[Tiab] OR zebra[Tiab] OR zebras[Tiab] OR shrew[Tiab] OR shrews[Tiab] OR bison[Tiab] OR bisons[Tiab] OR buffalo[Tiab] OR buffaloes[Tiab] OR deer[Tiab] OR deers[Tiab] OR bear[Tiab] OR bears[Tiab] OR panda[Tiab] OR pandas[Tiab] OR “wild hog”[Tiab] OR “wild boar”[Tiab] OR fitchew [Tiab] OR fitch[Tiab] OR beaver[Tiab] OR beavers[Tiab] OR jerboa[Tiab] OR jerboas[Tiab] OR capybara [Tiab] OR capybaras[Tiab] OR canine [tiab] OR bovine [tiab] OR porcine [tiab] OR hog [tiab] OR hogs [tiab]) NOT medline[sb])).

This search identified 860 studies.

Appendix II: Draft data extraction form

General information

Study ID

Covidence ID (#number, author, year)

Free text field

Full citation

Free text field

Lead author name

Free text field

Corresponding author contact details

Free text field

Country of study

Free text field

Study funding sources

Free text field

Possible conflicts of interest for study authors

Free text field

Notes

Free text field

Characteristics of included studies

Methods and model

Aim(s)/hypothesis of study

Free text field

Study design (*select one of the following*)

- ☐ Randomized experimental study
- ☐ Non-randomized experimental study
- ☐ Pilot study
- ☐ Other

Free text field

Species (*select one of the following*)

- ☐ Mouse
- ☐ Rat
- ☐ Guinea pig
- ☐ Sheep
- ☐ Other

Free text field

Strain/breed

Free text field

Normal length of gestation

Free text field

Gestational age(s) of progeny at delivery

Free text field

Overall type of maternal asthma (*select one of the following*)

- ☐ Allergic
- ☐ Non-allergic

Method of inducing asthma (*select one of the following*)

- ☐ House dust mite allergic sensitization
- ☐ Ovalbumin allergic sensitization
- ☐ Other allergen sensitization
- ☐ Non-allergic induction

Full method of maternal asthma induction

Free text field

Timing of inducing maternal asthma (*select one of the following*)

- ☐ Before pregnancy
- ☐ Early pregnancy
- ☐ Mid-pregnancy
- ☐ Late pregnancy

Measured characteristics of maternal asthma phenotype

Free text field

Comparison groups

Group name

Free text field

Type (*select one of the following*)

- ☐ Maternal
- ☐ Prenatal progeny
- ☐ Postnatal progeny

Number of mothers

Free text field

Pregnancy stage/gestational age/offspring age at outcome measures

Free text field

Offspring number in group (broken down by litter size, if relevant)

Free text field

Outcomes overall

Which maternal outcomes have been measured? (*select from the following options*)

- ☐ Immune response
- ☐ Lung function
- ☐ Lung structure (including molecular)
- ☐ Asthma severity
- ☐ Gestation length
- ☐ Fetal loss
- ☐ Ewe weight

☐ Organ weight (eg, placenta)☐ Other

For maternal outcomes: timing of assessment(s) *(select from the following options)*

☐ Before pregnancy☐ Early pregnancy☐ Mid-pregnancy☐ Late pregnancy☐ After pregnancy

Which prenatal progeny outcomes have been measured? *(select from the following options)*

☐ Immune response☐ Lung structure (including molecular)☐ Mortality/viability☐ Fetal growth (length)☐ Fetal weight overall☐ Organ weight (eg, lung, brain)☐ Other

Which postnatal progeny outcomes have been measured? *(select from the following option)*

☐ Immune response☐ Lung function☐ Lung structure (including molecular)☐ Asthma☐ Wheeze☐ Allergy☐ Respiratory infection☐ Other

Individual outcomes

Type *(select one of the following)*

☐ Maternal☐ Prenatal progeny☐ Postnatal progeny

Name the outcome

Does this outcome verify the maternal asthma phenotype? *(select one of the following)*

☐ Yes☐ No

Pregnancy stage/gestational age/offspring age at measurement

Method of assessment (brief)

Full methods of assessment

Free text field

Are outcomes analyzed by sex *(select one of the following)*

- ☐ Male only
- ☐ Female only
- ☐ Both sexes
- ☐ Not analyzed by sex

Outcome summary

Comparison groups	Mean	SD	N	p-value (ref: controls)
Group 1				
Group 2				
Group 3				
Group 4				
Group 5				
Group 6				
Group 7				
Group 8				

Are the outcomes significantly different from control mothers/progeny? *(select one of the following)*

- ☐ Yes
- ☐ No