

## Review

## The impact of maternal asthma on the fetal lung: Outcomes, mechanisms and interventions

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## EDUCATIONAL AIMS

The reader will come to appreciate:

- The association between maternal asthma and neonatal, childhood, and adulthood respiratory morbidities.
- How respiratory outcomes associated with maternal asthma may differ with offspring sex.
- Potential mechanisms underlying how maternal asthma alters *in utero* fetal lung development.
- Interventions that may improve the respiratory health of offspring of asthmatic mothers.

## ABSTRACT

Maternal asthma affects up to 17% of pregnancies and is associated with adverse infant, childhood, and adult respiratory outcomes, including increased risks of neonatal respiratory distress syndrome, childhood wheeze and asthma. In addition to genetics, these poor outcomes are likely due to the mediating influence of maternal asthma on the *in-utero* environment, altering fetal lung and immune development and predisposing the offspring to later lung disease. Maternal asthma may impair glucocorticoid signalling in the fetus, a process critical for lung maturation, and increase fetal exposure to proinflammatory cytokines. Therefore, interventions to control maternal asthma, increase glucocorticoid signalling in the fetal lung, or Vitamin A, C, and D supplementation to improve alveologenesis and surfactant production may be beneficial for later lung function. This review highlights potential mechanisms underlying maternal asthma and offspring respiratory morbidities and describes how pregnancy interventions can promote optimal fetal lung development in babies of asthmatic mothers.

## Introduction

Asthma affects up to 17 % of pregnancies worldwide [1]. In addition to increased risks of pregnancy complications [2,3], maternal asthma in pregnancy increases the risk of neonatal respiratory morbidities including transient tachypnoea of the newborn (TTN), respiratory

distress syndrome (RDS), and reduced lung function at 5–6 weeks (Table 1) [3–5]. These adverse impacts persist, with children of asthmatic mothers more likely to have asthma, wheeze, pneumonia, upper respiratory tract infection, and general respiratory morbidities [6–8]. Further, maternal asthma is associated with poor lung function and asthma in adulthood [6,9,10]. Therefore, prenatal preventative

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interventions to improve lung health are urgently required for babies of asthmatic mothers to prevent lifetime impacts on respiratory health [11].

Some of the effects of maternal asthma on child health are due to *in utero* exposure to maternal asthma and are not explained solely by genetic associations. For instance, maternal asthma is a stronger predictor for childhood asthma than paternal asthma (Table 1) [6]. Preclinical studies provide direct evidence for an environmental effect of *in utero* exposure to maternal asthma, as experimental maternal asthma increases allergic responses to allergen challenges in progeny [12]. Lower risk of childhood asthma when maternal asthma is better controlled in pregnancy, further supports this hypothesis [13].

While the mechanisms underlying these associations are unclear, emerging preclinical evidence suggests altered fetal lung and immune development are significant contributors [14,15]. In an ovine model of maternal asthma, lambs born to asthmatic ewes had immature lungs compared to lambs of non-asthmatic control ewes [15]. In mice, asthmatic offspring of asthmatic mothers have a moderate-severe asthma phenotype compared to a milder phenotype in asthmatic offspring of control mothers [16]. Greater understanding of how maternal asthma modifies *in utero* lung development will inform future interventions and therapies to improve postnatal respiratory health and prevent childhood asthma. This narrative review explores the impact of maternal asthma on newborn and child respiratory outcomes, and the underlying mechanisms, focusing on fetal lung and immune development and potential interventions to improve short- and longer-term respiratory outcomes.

### Maternal asthma in pregnancy and offspring respiratory outcomes

#### Neonatal outcomes

The impact of maternal asthma on newborn respiratory health is observable immediately after delivery (Table 1), suggesting impaired lung maturation. Maternal asthma increases the risk of TTN, RDS, and asphyxia (Table 1) [4]. TTN is caused by retained alveolar lung liquid postnatally, reflecting both immature lung fluid clearance and surfactant insufficiency [17,18] while RDS is a result of surfactant deficiency related to pulmonary immaturity [17,19,20]. TTN and RDS are common complications of prematurity, but in pregnancies complicated by asthma the risk of both is higher in term and preterm infants [4]. Since respiratory morbidities account for 28.8 % of late preterm and 15.6 % of term neonatal intensive care unit (NICU) admissions [21], understanding the mechanisms underlying increased respiratory morbidity in offspring exposed to maternal asthma is crucial.

Not all studies indicate the same respiratory impact of maternal asthma on neonatal respiratory outcomes, which may be due to variable definitions and timing of maternal asthma (Table 1). Both retrospective and prospective cohort studies report no difference in rates of resuscitation at birth [4,22], apnoea [4], or overall respiratory difficulties between babies of non-asthmatic and asthmatic mothers [23]. A systematic review and meta-analysis found an association between maternal asthma and TTN but not RDS (Table 1) [3], although the sample sizes for TTN and RDS were small ( $n = 2033$  and  $n = 2225$  mothers with asthma respectively) [3], while a later, larger study ( $n = 17044$  mothers with asthma), reported increased risks of both [4]. This may suggest that maternal asthma alters *in utero* lung development through pathways specific to TTN and RDS pathologies, rather than more generalised lung immaturity.

The above associations may also be sex-specific, but the data is limited. At 5–6 weeks, male sex alone was not predictive of poor lung function but male sex and maternal asthma combined was associated with poorer lung function [5]. This may partly reflect greater susceptibility to environmental challenges and poorer baseline respiratory function [24]. Compared to females, males have greater risk of requiring respiratory support, TTN, RDS and bronchopulmonary dysplasia, and

lower peripheral oxygen saturation, culminating in a “male disadvantage” [24]. These morbidities have long-term impacts; newborns with poor lung function more likely to have childhood asthma [25]. With male sex and maternal asthma individually increasing the risk of poor respiratory health at birth and beyond, and the additive effect potentially worse, sex-specific effects of maternal asthma on the fetal lung warrant further investigation.

Confounding between maternal asthma and other maternal and neonatal factors makes it impossible to assess the extent to which respiratory outcomes are caused by asthma alone. Fetal growth restriction, small for gestational age, neonatal intensive care unit (NICU) admission, sepsis, and congenital abnormalities are all more common in infants of asthmatic mothers increasing the risks of pulmonary morbidity [3,4,21,22,26–29]. While analyses controlling for some prenatal and pregnancy factors still demonstrate a maternal asthma effect [22], many factors are not adjusted for.

#### Childhood outcomes

Maternal asthma is also associated with increased risk of later childhood respiratory morbidities (Table 1) including wheeze, asthma, and general respiratory morbidities [7,8]. In a systematic review by our group, maternal asthma was associated with greater risks of childhood wheeze and asthma, regardless of whether the maternal asthma diagnosis was specific to the pregnancy [30]. Amongst those with asthma in pregnancy, asthma risk in their children was higher with moderate-severe compared to mild asthma and when asthma was uncontrolled [30]. However, genetics may confound the latter with more severe asthma before pregnancy associated with greater loss of control or asthma exacerbations during pregnancy [31].

Few studies have reported sex-specific childhood outcomes in the presence of maternal asthma. In a prospective US cohort of ~1600 births, maternal asthma was predictive of wheeze in both sexes at 1–9 years old, with paternal asthma more predictive of childhood wheeze in male offspring (Table 1) [32]. In a retrospective US cohort of ~17000 births, maternal asthma was associated with childhood asthma at age 5 in both sexes when analysed separately (Table 1) [33], while male sex is associated with both neonatal respiratory morbidities and asthma in preschool age children [24,34].

The associations between longer-term outcomes and maternal asthma can be confounded by other respiratory diseases, since impaired lung development may both cause and be caused by asthma [35]. Children of asthmatic mothers have an increased risk of respiratory infections, a risk factor for childhood asthma [7,34,36], with a higher prevalence of upper respiratory tract infection and pneumonia compared to children of non-asthmatic mothers (Table 1) [7]. Further, the risk of asthma after 5 years of age is associated with both current maternal asthma (Table 1) and infant respiratory infections (aHR 1.51 95 % CI 1.47–1.54) [36].

#### Long term outcomes

Respiratory outcomes associated with maternal asthma extend into adulthood. In a meta-analysis of four studies, adult asthma was more likely when the mother had asthma (Table 1) [6]. Maternal asthma is also associated with a persistently low lung function trajectory in offspring between 11 and 32 years of age [9]. Retrospective studies, however, report conflicting results. Offspring of mothers purchasing asthma medication during the period after delivery when offspring outcomes were assessed (offspring 0–31 years of age, Table 1) were more likely to have asthma medication themselves from childhood into adulthood [10]. Conversely, offspring of mothers with an asthma medication prescription during the period after delivery when offspring outcomes were assessed (offspring age 25.5–35 years, Table 1) were reported to be no more likely to have an asthma medication prescription themselves, compared to controls (Table 1) [37]. This disparity may

**Table 1**

Maternal asthma in pregnancy and offspring respiratory outcomes in the neonatal period.

Study ID; country	Study design; number of participants	Definition of maternal asthma	Timing of maternal asthma diagnosis	Findings in offspring of asthmatic mothers (ref: controls)
<i>Neonatal outcomes</i>				
de Gouveia Belinelo et al 2021; Switzerland and Australia [5]	Two large birth cohorts combined: n = 619 (n = 426 born to asthmatic mothers)	Both cohorts: Self-reported, doctor-diagnosed asthma. Breathing for Life Trial cohort: current asthma symptoms or inhaled asthma medication use	Breathing for life trial: asthma in current pregnancy Bern Infant Lung Development cohort: asthma in last 12 months	In male infants, poor infant lung function (Estimate −3.48 95 % CI −6.81 to −0.11) measured by time to reach peak expiratory flow as a percentage of total expiratory time (%)
Hodl et al 2014; Australia [22]	Retrospective cohort study; n = 172305 (n = 11512 born to asthmatic mothers)	Asthma medication to prevent or treat asthma or had symptoms of asthma during the current pregnancy	Asthma in current pregnancy	Resuscitation at birth (aOR 0.99 95 % CI 0.81–1.20)
Mendola et al 2014; USA [4]	Retrospective cohort study; n = 223512 (n = 17044 born to asthmatic mothers)	ICD-9 code for asthma in maternal electronic medical record	Asthma ever	Respiratory distress syndrome (aOR 1.09 95 % CI 1.01–1.19) Transient tachypnoea of the newborn (aOR 1.10 95 % CI 1.02–1.19) Asphyxia (aOR 1.34 95 % CI 1.03–1.75) Resuscitation at birth (aOR 1.02 95 % CI 0.91–1.14) Apnoea (aOR 1.02 95 % CI 0.92–1.13)
Murphy et al 2013; N/A [3]	Systematic review and meta-analysis; 21 included studies	Physician-diagnosed (whether confirmed or subject self-report), database-coded asthma diagnosis, or asthma fulfilling American Thoracic Society criteria	Unspecified	Respiratory distress syndrome (2 studies, RR 1.57, 95 % CI 0.88–2.81) Transient tachypnoea of the newborn (2 studies, RR 1.54, 95 % CI 1.09–2.18)
<i>Long term outcomes</i>				
Berry et al 2016; USA [9]	Birth cohort study; n = 589 (n = 64 born to asthmatic mothers)	Questionnaire at the time of enrolment	Asthma ever	Poor lung function trajectory, 11–32 years (offspring of asthmatic mothers: 20.0 % low trajectory vs. 9.9 % normal; (p = 0.02) measured by ratio of forced expiratory volume in 1 min to forced vital capacity (FEV <sub>1</sub> /FVC)
Crump 2011; Sweden [37]	National cohort study; n = 622616 (n = 47818 born to asthmatic mothers)	Prescription of asthma medications ( $\beta$ -2 agonist inhalants, glucocorticoid inhalants, or combination inhalants containing a $\beta$ -2 agonist and other drugs for obstructive airway diseases)	Asthma medication purchases when offspring are 25.5–35 years old	Purchase asthma medication, 25–35 years old (aOR 0.99 95 % CI 0.94–1.04)
Damgaard 2015; Denmark [10]	National cohort study; n = 1790241 (n = 69456 born to asthmatic mothers)	Either a combination of at least one purchase of inhaled selective $\beta$ -2 receptor agonist (R03AC) AND at least two purchases of one of the following other drugs for obstructive airway disease: inhaled glucocorticoids (R03BA), inhaled anticholinergics (R03BB), theophyllines (R03DA), oral leukotriene-receptor antagonists (R03DC), systemic steroid (H02AB), a combination inhaler (R03AK)—or at least two purchases of a combination inhaler containing a long-acting $\beta$ -2 receptor agonist and either glucocorticoids or anticholinergics (R03AK)	Asthma medication purchases when offspring are 0–31 years old	Purchase asthma medication, 0–2 years old (aOR 2.14 95 % CI 1.86–2.47), 3–5 years (aOR 2.92 95 % CI 2.69–3.17), 6–11 years (aOR 3.23 95 % CI 3.02–3.46), 12–17 years (aOR 2.83 95 % CI 2.65–3.02), 18–24 years (aOR 2.40 95 % CI 2.23–2.57), 25–31 years (aOR 2.22 95 % CI 2.06–2.39)
Lim et al 2010; N/A [6]	Meta-analysis; 33 included studies	Self-reported physician diagnosed asthma, self-reported asthma, self-reported recurrent/persistent wheeze, and self-reported recurrent asthma symptoms (or a combination of these), physician diagnosed asthma or asthma symptoms	Asthma in current pregnancy (n = 4), asthma ever (n = 29)	Adult asthma (4 studies, OR 5.33 95 % CI 2.51–11.3)
Pennington et al 2018; USA [33]	Retrospective birth cohort; n = 17075 (n = 2075 born to asthmatic mothers)	One or more diagnosis of asthma (ICD-9 code 493.XX).	Asthma ever	Childhood asthma in males, 5 years (risk difference 13.4 % 95 % CI 8.6–18.2) Childhood asthma in females, 5 years (risk difference 14.0 % 95 % CI 9.1–18.8)
Roff et al 2023; N/A [30]	Systematic review and meta-analysis; 120 studies	Diagnosed by a physician or using clinically-accepted criteria	Asthma in current pregnancy (n = 22), asthma ever (n = 98)	Childhood asthma by maternal asthma ever (61 studies, RR 1.75, 95 % CI 1.55–1.97) Childhood asthma by maternal asthma during the pregnancy with that child (13 studies; RR 1.73; 95 % CI 1.54–1.93) Childhood asthma by moderate-severe maternal asthma during the pregnancy with that child (ref: mild asthma, 5 studies; RR 1.23; 95 % CI 1.12–1.35) Childhood asthma by uncontrolled maternal asthma during the pregnancy with that child (ref: controlled asthma, 4 studies; RR 1.15; 95 % CI 1.07–1.23)

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Table 1 (continued)

Study ID; country	Study design; number of participants	Definition of maternal asthma	Timing of maternal asthma diagnosis	Findings in offspring of asthmatic mothers (ref. controls)
Spiegel et al 2018; Israel [7]	Population based cohort study; n = 253808 (n = 3411 born to asthmatic mothers)	Bronchial asthma as defined in hospital database using ICD-9 codes	Unspecified; asthma in prenatal records	General respiratory morbidities (aOR 1.6 95 % CI 1.4–1.9) Childhood asthma (aOR 2.5 95 % CI 1.9–3.1)
Tse 2016; USA [32]	Prebirth cohort study; n = 1623 (n = 219 born to asthmatic mothers)	Maternal reports at enrolment in the study or at the child's birth	Asthma ever	Wheeze in male offspring (aOR 2.15, 95 % CI 1.74–2.66) Wheeze in female offspring (aOR 1.53, 95 % CI 1.19–1.9)
Venter et al 2021; USA [8]	Longitudinal birth cohort; n = 1261 (n = 107 born to asthmatic mothers)	Maternal history of asthma was considered present if pregnant women answered “yes” to the question, “Has a health professional such as a doctor, physician assistant, or nurse practitioner ever told you that you have asthma?”	Asthma ever	Childhood asthma diagnosis (aHR 1.79 95 % CI 1.25–2.57) Child wheeze (aHR 1.67 95 % CI 1.20–2.31)

reflect limitations in the inability to determine whether the fetus was exposed to maternal asthma *in utero* using retrospective data linkage approaches. Further long-term follow-up studies exploring the impact of maternal asthma in progeny, including sex-specific analyses, are warranted.

### Maternal asthma and the fetal lung: mechanisms

To address confounders and variability in human studies of maternal asthma and progeny health [2,38–40], combining preclinical and clinical findings on asthma in pregnancy may provide critical insights into the immune, genetic, epigenetic, and endocrine mechanisms linking maternal asthma and altered fetal lung development and function (Fig. 1).

#### Lung development

In experimentally induced allergic asthma in sheep, near-term fetuses from asthmatic ewes had fewer surfactant-producing type II alveolar epithelial cells and decreased surfactant protein B (*SFTPB*) gene expression in their lungs compared to lambs of control ewes [15,41]. This suggests that maternal asthma impairs surfactant system development, explaining the increased rates of TTN and RDS in newborns of asthmatic mothers while controlling for the confounder of prematurity [3,4]. In mice, pups of asthmatic mothers had thicker airway basement membranes, respiratory epithelium, and subepithelial airway smooth muscle, compared to offspring of control mothers [42], with thickened basement membranes predictive of future wheeze and asthma in humans [14,43].

#### Pulmonary immune function

Maternal immune responses in asthma, such as elevated interleukin-5 (IL-5) [44], may contribute to altered offspring lung structure. In mice that overexpress IL-5 in the maternal lung epithelium, transplacental passage of IL-5 caused eosinophilia in the fetal lung, greater innervation of the developing airways, increased nerve length and branch points, compared to eosinophil-deficient controls [45]; nerve growth factor, a driver of airway sensory innervation, was also higher in the lung lavage [45]. Furthermore, when offspring underwent an asthma induction protocol, some had fatal bronchoconstriction, which was ameliorated by vagotomy [45]. This suggests that vagal signalling to hyper-innervated airways, rather than increased smooth muscle contractility, is a driver of increased bronchial hyperresponsiveness in offspring of mothers with asthma [45,46].

The underlying inflammatory phenotype may indicate asthma severity and play a role in asthma transmission. The T helper cell type 2 (Th2) phenotype is associated with eosinophilia and allergic asthma, whereas Th1 or Th17 inflammatory phenotypes result in moderate-

severe asthma with neutrophilia resistant to inhaled corticosteroids [47,48]. After undergoing an asthma-inducing protocol, offspring of control dams exhibit a milder Th2 phenotype compared to offspring of asthmatic mothers who exhibit a Th1 or Th17 phenotype [16], suggesting maternal asthma programs the fetal lung immune response. In another mouse study, splenic Th cells (80 % CD4<sup>+</sup>) with ovalbumin-specific cell receptors from a transgenic strain were injected into mothers before ovalbumin aerosol challenges to induce asthma [49]. The offspring of ovalbumin-specific T cell recipient mothers had more hyperresponsive airways, higher airway eosinophilia and Th2 cytokine production (IL-4, IL-5, IL-13) when challenged with aerosolised ovalbumin, compared to offspring of asthmatic mothers who received control T cells [49], suggesting a critical role for maternal T cells in the transmission of allergic asthma risk.

Another potential mechanism for inter-generational asthma transmission is epigenetics. In the offspring of asthmatic mice, there were 40 differentially methylated sites in the splenic dendritic cells that capture and process antigens, increasing the likelihood of a Th2 allergic phenotypic response, compared to the offspring of controls [50]. Further, when naïve murine offspring received an adoptive transfer of splenic dendritic cells from offspring of asthmatic mothers, they had higher rates of airway hyperresponsiveness, eosinophilia, and lung inflammation compared to offspring that received dendritic cells from controls [50]. In humans, T cell developmental arrest was associated with respiratory morbidity [51]. Children born to asthmatic mothers had differentially methylated regions in cord blood mononuclear cells, such as the *SMAD3* promotor [52,53]. *SMAD3* is responsible for the differentiation of T<sub>reg</sub> and Th17 cells and is associated with IL-1 $\beta$  production. With *SMAD3* also the most highly connected gene to other asthma-associated differentially methylated regions in the molecular interaction network (17 connections) [52], epigenetic changes at its promoter may underlie immune programming [52]. In bronchial epithelial cells of children born to asthmatic mothers, expression of genes in CD4<sup>+</sup> T cell signalling and Th17 differentiation pathways was reduced [53], making the response to pathogens less robust while increasing the likelihood of severe asthma.

#### Placental changes, glucocorticoids and fetal lung development

Maternal asthma is associated with sex-specific placental changes resulting in altered glucocorticoid signalling in the fetus, which may impact fetal lung development. Glucocorticoids, particularly cortisol, are essential for fetal lung development, stimulating surfactant-producing cell differentiation and surfactant production, thinning of the alveolar septa, and alveolar duct development [54–56]. These stages of fetal lung development are primarily driven by the surge of circulating cortisol concentration in the third trimester of human pregnancy, leading to parturition [55]. Female placentae of asthmatic women have decreased protein expression of the inhibitory glucocorticoid receptor

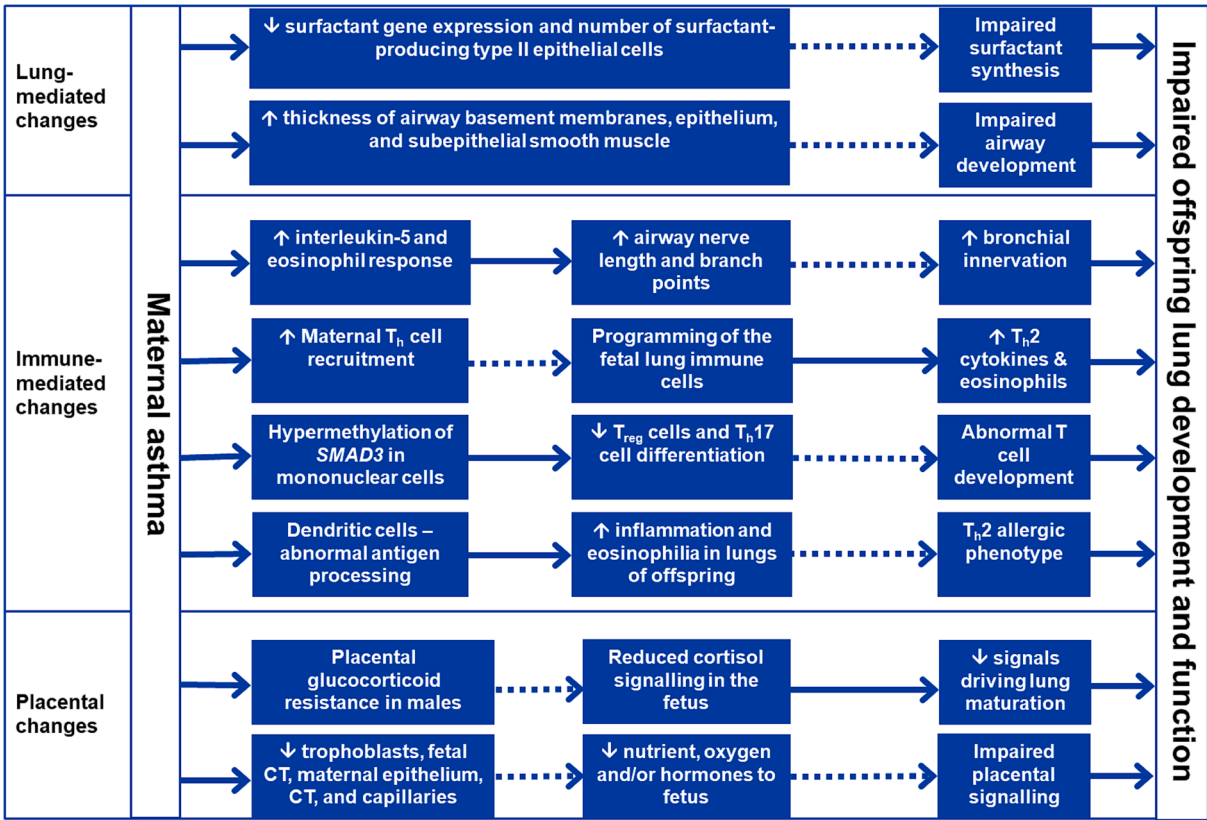


Fig. 1. Known and hypothesised mechanistic links between maternal asthma and fetal lung development and function. CT = connective tissue, Th = T helper cells, T<sub>reg</sub> = T regulatory cells. Dotted lines represent hypothesised mechanisms based on available evidence.

(GR)  $\beta$  isoform and increased expression of the active GR $\alpha$  isoform, resulting in greater cortisol sensitivity [57,58]. Placental responses contributing to hypercortisolaemia, and anti-proliferative growth pathways may therefore explain the reduced weight of female, but not male, offspring of asthmatic women [59]. The higher expression of the GR $\beta$  isoform in male placentae of asthmatic women, potential glucocorticoid resistance [57,58] and reduced glucocorticoid signalling may result in impaired fetal lung development and explain the poor lung function outcomes in male babies born to asthmatic mothers [5].

However, in pregnant sheep with experimental asthma, maternal plasma cortisol concentration is lower but fetal plasma concentration does not change [15]. Further, placentae of asthmatic ewes have a more mature macroscopic phenotype [41], but lower densities of trophoblast, fetal connective tissue, and maternal tissue than controls [60]. This suggests adaptation to placental insufficiency may be driving changes to phenotype and glucocorticoid signalling. Female placentae of asthmatic women have lower placental 11 $\beta$ -hydroxysteroid dehydrogenase type 2 (11 $\beta$ -HSD2) activity, an enzyme that prevents excess maternal cortisol from reaching the fetus, compared to female placentas of non-asthmatic mothers [59]. However, maternal asthma does not impact placental 11 $\beta$ -HSD2 activity in males, and fetal plasma cortisol concentration does not differ with fetal sex [59]. Therefore, while glucocorticoid signalling is likely only one of the mechanisms underlying maternal asthma and poor fetal lung development, the mechanisms may be dependent on sex.

**Interventions to improve fetal lung development when mothers have asthma**

*Asthma control*

Women with well-controlled asthma have similar rates of perinatal complications and their offspring similar rates of childhood asthma as

non-asthmatics (Fig. 2) [2,6]. Conversely, relative to mild controlled asthma, severe uncontrolled maternal asthma during the pregnancy increases the risks of early-onset asthma in offspring [61]. Asthma control in pregnancy is difficult with ~50 % of women losing control. When pregnant women with asthma received asthma management plans and education by Telehealth, their asthma control was better than women receiving standard care [62]. In a trial exploring fraction of exhaled nitric oxide (FENO) guided asthma management in pregnant asthmatic women, FENO based management reduced the risk of asthma exacerbation during pregnancy and improved maternal asthma control [13]. This intervention also lowered offspring childhood asthma risk the (OR 0.19, 95 % CI 0.06–0.56) through changes in maternal use and dosing of inhaled corticosteroids.

*Glucocorticoid agonists*

Antenatal corticosteroids (ACS) are given to women at risk of pre-term labour to promote fetal lung maturation and reduce adverse outcomes associated with prematurity (Fig. 2) [63]. Higher rates of TTN and RDS in children of asthmatic women [3,4], and preclinical evidence for lung immaturity at birth in offspring of sheep with experimental asthma [15], suggest that glucocorticoid agonists would also be efficacious in improving lung function in offspring of asthmatic mothers. ACS increase surfactant synthesis, type II surfactant-producing cell differentiation, and thin the alveolar septa, reducing the risk of TTN and RDS [54,63,64]. While ACS are clinically recommended until 34<sup>+</sup>6 weeks of gestation [65], trials continue to explore their use in late preterm and term populations [66,67]. Interestingly, effects of maternal asthma are particularly evident in babies born at these ages [4]. However, concerns remain regarding potential adverse neurodevelopmental outcomes related to ACS administration [68], with a lower risk of neurodevelopmental impairment in ACS-exposed babies born extremely

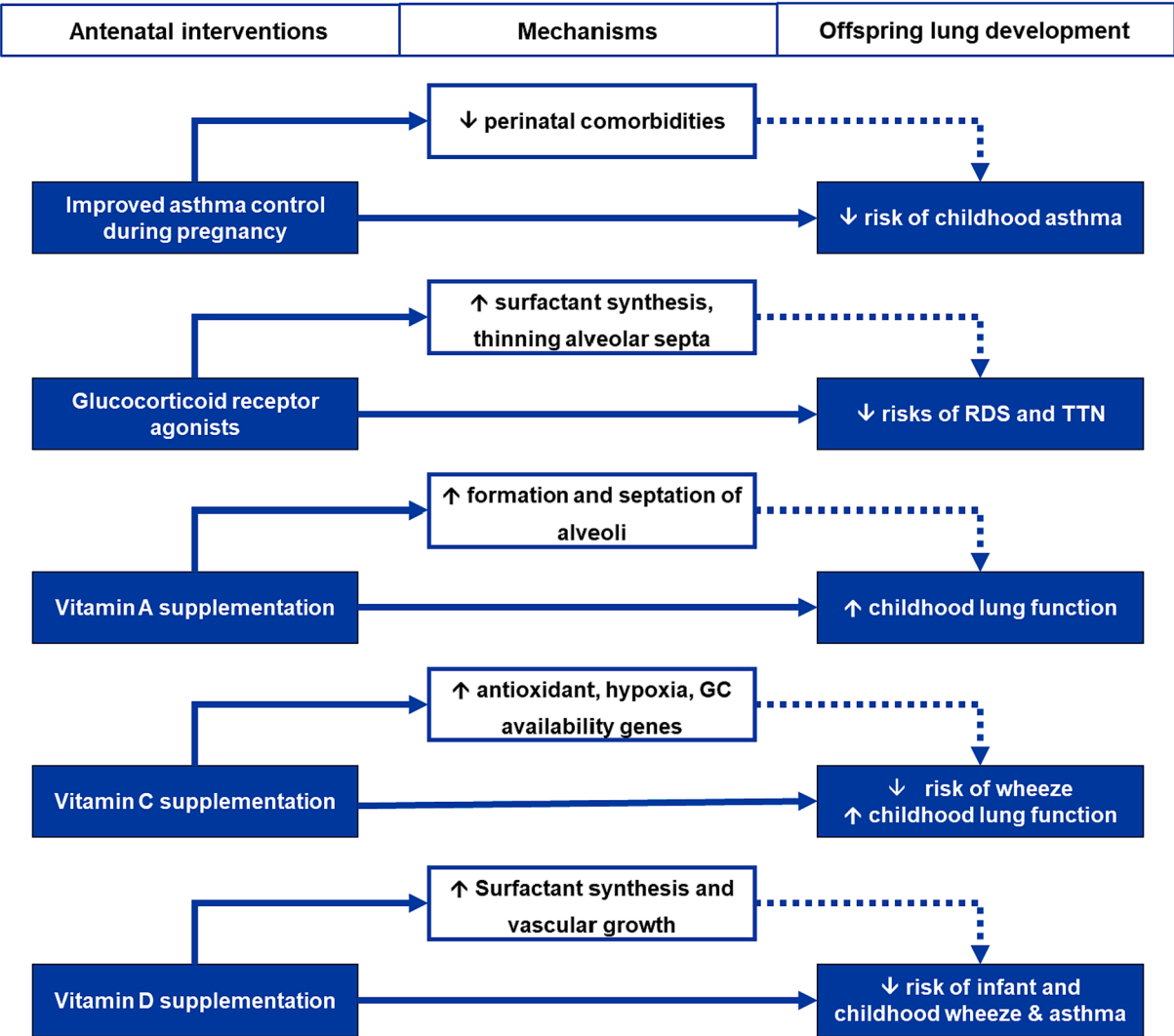


preterm, but a higher risk of neurocognitive disorders in ACS-exposed babies born late preterm or term [69]. Further investigation of alternative glucocorticoid agonists that mature the lungs of babies of asthmatic mothers but do not impact the brain warrants on-going investigation [70].

Vitamin supplementation

Since offspring of asthmatic mothers are at greater risk of respiratory morbidities like wheeze and asthma, maternal vitamin A, C and D supplementation may improve fetal lung development in pregnancies complicated by maternal asthma, by promoting the later stages of alveolarisation and surfactant production (Fig. 2) [71–74]. Some clinical and preclinical evidence demonstrates that supplementation with vitamin A during pregnancy promotes the formation and septation of alveoli [71] and is associated with improved childhood lung function, a finding not limited to undernourished populations [74,76]. However, in the Causal Pathways for Asthma (CASPAR) trial exploring Vitamin A and D intake in pregnancy and asthma development, Vitamin A was associated with a higher risk of offspring asthma whereas Vitamin D was associated with a reduced risk [75]. Nevertheless, maternal asthma was identified as a strong confounder of the effect of Vitamin A

supplementation, necessitating further investigation in this population [75]. In the Vitamin C to Decrease the Effects of Smoking in Pregnancy on Infant Lung Function (VCSIP) trial, maternal asthma did not modify the effect of Vitamin C supplementation to improve lung function in the offspring of pregnant smokers [77]. In a Japanese birth cohort study, antenatal Vitamin C was associated with reduced risk of childhood wheeze [78]. Intravenous Vitamin C supplementation in pregnant sheep upregulated expression of genes for antioxidants (*SOD1*), hypoxia signalling pathways (*EPAS1*, *HIF3A*, *ADM*, *EGLN3*), and glucocorticoid availability (*HSD11B2*) in near-term lamb lungs, an expression profile conducive to lung growth [79]. Further, gene expression of *SFTPB* and the surfactant lipid transporter *ABCA3* in near-term fetal sheep lungs are increased with maternal intravenous vitamin C supplementation [79]. In the Vitamin D Antenatal Asthma Reduction Trial (VDAART), controlling maternal asthma and monitoring vitamin D status were independently associated with prevention of offspring wheeze and asthma [80]. In mice, prenatal vitamin D deficiency reduced lung expression of type II surfactant-producing cell differentiation, surfactant-stimulating (*FOXA1*, *FOXA2*, *TTF1*), and vascular endothelial growth factor genes [72]. Whether Vitamin A, C, and D supplementation independently or together are effective at improving offspring lung health in offspring of mothers with asthma exposure alone, and the underlying mechanisms,



**Fig. 2. Potential mechanisms and outcomes of interventions to improve fetal lung development in babies of asthmatic mothers.** GC = glucocorticoid. RDS = respiratory distress syndrome. TTN = transient tachypnoea of the newborn. Solid lines represent known mechanisms, dotted lines represent hypothesised mechanisms linking the intervention with outcomes.

warrants further investigation.

## Conclusion

Understanding how maternal asthma impacts neonatal health is important due to the high prevalence of asthma in pregnancy and its impact on offspring lifetime respiratory function (Table 1) [3,4,8,9]. However, variability in defining maternal asthma necessitates more harmonisation between future studies. Current evidence suggests that maternal asthma alters fetal lung and immune development, involving a complex interplay of endocrine, immune, neural, and genetic factors, and leading to respiratory morbidities (Fig. 1). Potential interventions to reduce adverse respiratory outcomes associated with maternal asthma include improved maternal asthma control, glucocorticoid receptor agonists, and dietary vitamin A, C, or D supplementation (Fig. 2). Further studies are needed to evaluate whether changes in fetal lung development associated with maternal asthma are observable shortly after birth, explore sex-specific outcomes, fully characterise pathophysiologic mechanisms, and test the efficacy and safety of proposed interventions.

## Future research directions

- Analyse the sex-specific effects of maternal asthma on neonatal, childhood, and adulthood respiratory morbidities.
- Identify mechanisms underlying how maternal asthma impacts *in utero* lung development, independent of confounders.
- Assess the impact of asthma management plans during pregnancy on offspring respiratory health.
- Evaluate the safety and efficacy of interventions to improve respiratory health in offspring of asthmatic mothers.

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## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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