Prenatal Origins of Obstructive Airway Disease: Starting on the Wrong Trajectory?

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ABSTRACT

From the results of well-performed population health studies, we now have excellent data demonstrating that deficits in adult lung function may be present early in life, possibly as a result of developmental disorders, incurring a lifelong risk of obstructive airway diseases such as asthma and chronic obstructive pulmonary disease. Suboptimal fetal development results in intrauterine growth restriction and low birth weight at term (an outcome distinct from preterm complications), which are associated with subsequent obstructive disease. Numerous prenatal exposures and disorders compromise fetal development and these are summarized herein. Various physiological, structural, and mechanical abnormalities may result from prenatal disruption, including changes to airway smooth muscle structure–function, goblet cell biology, airway stiffness, geometry of the bronchial tree, lung parenchymal structure and mechanics, respiratory skeletal muscle contraction, and pulmonary inflammation. The literature therefore supports the need for early life intervention to prevent or correct growth defects, which may include simple nutritional or antioxidant therapy. © 2024 American Physiological Society. *Compr Physiol* 14:5729-5762, 2024.

Didactic Synopsis

Major teaching points

- Lung function trajectories provide compelling evidence that obstructive disease in some patients has a developmental origin.
- Prenatal exposures or disorders (independent of preterm birth) include air pollution, smoke, environmental toxins and allergen, maternal obesity and diet, hypoxia, pregnancy complications, maternal stress, mental well-being, maternal asthma and other illnesses, assisted reproduction technologies, drugs and vitamins, and transgenerational impacts.
- Evidence of prenatal disruption includes intrauterine growth restriction, the study of which may help us identify other physiological changes relevant to the onset of respiratory disease.
- The physiological and structural consequences of prenatal disruption are changes in airway smooth muscle structure–function, goblet cell biology, airway stiffness, geometry of the bronchial tree, lung structure and mechanics, respiratory skeletal muscle contraction, and pulmonary inflammation.
- Treatments to reverse the effects of intrauterine growth restriction should be considered, including antioxidants, vitamins (C, D, and E), and omega-3 polyunsaturated fatty acids.

Introduction

Epidemiological studies have long demonstrated prenatal origins of obstructive airway disease, which supports the developmental origins of health and disease (DOHaD) or fetal origins of adult disease (FOAD) concepts in the respiratory system—that is, there is a prenatal destiny to obstructive airway disease. The inverse relationship between birth weight and risk of asthma and chronic obstructive pulmonary disease (COPD) (81, 246) is likely independent of gestational age (GA), sex, birth duration, and Apgar score (168) but is confounded by shared environmental or genetic influences (370), smaller postnatal body size or poor postnatal growth (73).

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Instead, the relationship between birth weight and obstructive airway disease may be explained by physiological changes that are present from the first days of life, manifesting as early life lung function impairment—that is, *"As the twig is bent, so grows the tree" (Alexander Pope 1732)*. In this review, we first examine lung function trajectories of healthy controls compared with patients diagnosed with asthma or COPD. Lung function longitudinal data can be used to demonstrate the potential consequence of starting life on the wrong trajectory, particularly a future diagnosis of obstructive airway disease. Included in the review is a contextual and necessary description of airway and lung development, and a brief overview of the physiology of airflow. Key outcomes are a comprehensive summary of factors that contribute to an adverse intrauterine environment, and how these affect airway and lung development and respiratory function and health. A broad interpretation of how the various structural and mechanical changes to the respiratory system identified after prenatal complications follows, as well as potential therapeutic approaches for certain conditions.

Lung Function Trajectories

A man walks into a doctor's surgery and says, "*Doctor, I'm short of breath when I try to run*." After a series of questions and responses, blood tests, chest X-ray, electrocardiogram, echocardiogram, exercise test, coronary computed tomography (CT) scan and possibly even a coronary angiogram, the patient's spirometry is measured. Spirometry shows that he has a forced expiratory volume in one second (FEV_1) that is 56% of the predicted value with an FEV_1/forced vital capacity (FVC) ratio of 0.69. After bronchodilator, these values improve minimally to 57% and 0.71. He is diagnosed with moderate ($FEV_1 < 60\%$ predicted) COPD. How did this happen? What does it mean? The patient's absolute FEV_1 (red dot) is shown in Figure 1—he is 63 years old. The solid blue line represents the plot of FEV_1 against age (from 18 years) for a general population of normal males (nonsmokers, no symptoms, and no history of respiratory disease) (143). Why is his FEV_1 below this line? How did he get here? One answer is that he is on a different trajectory (the green line), discussed further below.

Three other trajectories are indicated in Figure 1 (143). The yellow line shows the plot of FEV_1 versus age for people who have a history of doctor-diagnosed asthma and who have never smoked cigarettes. This line is lower than the "normal" solid blue line, from the age of 18 years, but is otherwise almost parallel with the normal trajectory. Our patient (red dot) at age 63 years remains below this as well. These data suggest that asthma by itself does not account for the man's abnormal FEV_1. The red dashed and dotted line in Figure 1 shows the plot for smokers who have no history of asthma. The line starts off the same as the normal line at age 18 years but is steeper than the normal line such that, at age of 63, FEV_1 is on average, lower than the "normal" line, yet higher than the value for

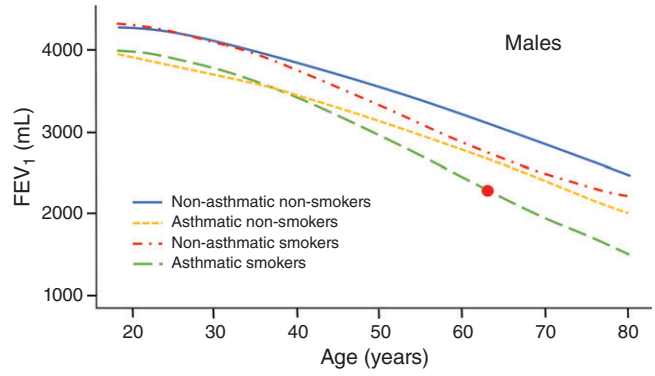

Figure 1 **Hypothetical patient diagnosed (red dot) as having COPD in later life which may have had origins in early life.** The red dot shows the patient's absolute FEV_1. The solid blue line represents the plot of FEV_1 against age (from 18 years) for a general population of normal males (nonsmokers, no symptoms, no history of respiratory disease). The yellow dashed line shows the plot of FEV_1 versus age for people who have a history of doctor-diagnosed asthma and who have never smoked cigarettes. The red dotted and dashed lines show the plot of FEV_1 for smokers who have no history to asthma. The green dashed line shows the plot of FEV_1 for people with a history of asthma AND who have also smoked. FEV_1, forced expiratory volume in 1 s. Adapted, with permission, from James AL, et al., *Am J Respir Crit Care Med*. 2005 (143).

our patient. Finally, the green dashed line in Figure 1 shows the plot of FEV_1 for people with a history of asthma AND who have also smoked. The asthmatic-smokers line passes through the man's FEV_1 at the age of 63 years. Therefore, for this patient, it is possible that asthma (or some other airway disease occurring before the age of 18 years) AND smoking may have combined to leave him with moderate COPD at the age of 63 years.

The next patient is a 65-year-old man who has more severe breathlessness on exertion than the previous patient, his FEV_1 is only 35% of the predicted value and his FEV_1/FVC ratio is 0.45. His lung function does not improve significantly following bronchodilator. He is diagnosed with severe (FEV_1 at 30%) COPD. His FEV_1 is shown in Figure 2 (red dot) (68) with the plot of FEV_1 against age for smokers shown by the protracted dashed line (modified from Ref. 94). We can see that his lung function is lower than this line. How did he get here? In Figure 2, three groups of lines are also shown. These clustered lines show the changes in FEV_1 over 3 to 4 years in patients with mild (top lines), moderate (middle lines), and severe (bottom lines) COPD in two large placebo-controlled trials of treatment in patients with COPD (44, 351). There are three points of interest: (i) the lines are flatter than the plot for smokers. This is because most of the patients in these trials had already stopped smoking and therefore their decline in lung function was closer to normal [as has been seen elsewhere in smokers who quit (307)]; (ii) the decline in lung function is the same for patients on treatment (triangles) as it is for those on placebo (circles); (iii) the slopes of all the sets of lines are roughly the same. These data suggest that the lines of lung function for the

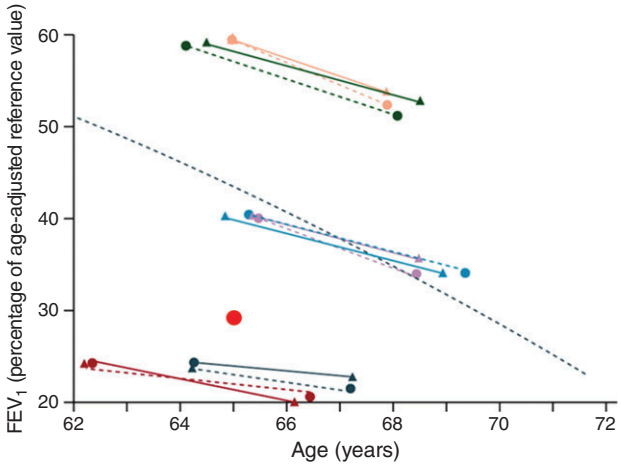

Figure 2 **Hypothetical patient diagnosed as having COPD in later life which may have had origins in early life.** The red dot shows the patient's FEV_1 plotted as a percent of age-adjusted reference value. Changes in FEV_1 over 3 to 4 years in patients with mild (top lines), moderate (middle lines), and severe (bottom lines) COPD. Circles indicate placebo/control and triangles indicate treatment groups. FEV_1, forced expiratory volume in one second. Figure originally published in (68) with the plot of FEV_1 against age for smokers shown by the protracted dashed line. Adapted, with permission, from Decramer M et al., *Lancet*. 2012 (68)/Elsevier; Fletcher C and Peto R, *Br Med J*. 1977 (94).

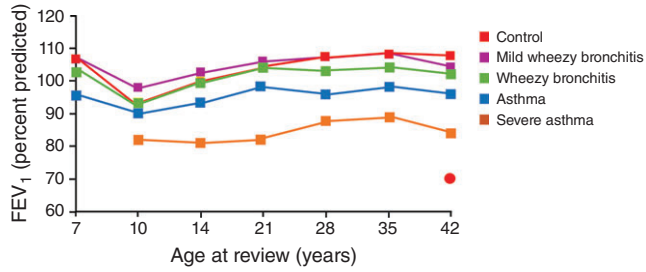

Figure 3 **Hypothetical patient diagnosed as having COPD in later life with origins in early life.** The red dot shows the patient's FEV_1 plotted as a percent of the predicted value. Plots of longitudinal FEV_1 percent predicted versus age for non-asthmatic and nonsmokers (Control; red line), children who were diagnosed with mild wheezy bronchitis (purple line), wheezy bronchitis (green line), or asthma (blue line) at age 7 years and followed to the age of 42 years, and for children who were diagnosed with severe asthma from age 10 (brown line). FEV_1, forced expiratory volume in one second. Adapted, with permission, from Phelan PD, et al., *J Allergy Clin Immunol*. 2002 (279)/Elsevier.

different groups separated at an earlier age, possibly before the patients started smoking.

The next person to come through the door is a 42-year-old woman who is also troubled by breathlessness on exertion and has reduced FEV_1 (70% predicted) and FEV_1/FVC ratio (0.61) without a significant change following bronchodilator. She reports a history of severe asthma from the age of 2 years with multiple hospital admissions but better control of symptoms in recent years. She has never smoked. She is diagnosed with asthma/COPD overlap syndrome (ACOS). In Figure 3, we can see her FEV_1 (red dot) plotted as a percent of the predicted value, along with the plot of FEV_1 percent predicted versus age for non-asthmatic and nonsmokers (control; red line) from a longitudinal study of asthmatic children and controls (279). How did she get here? Figure 3 also shows the plot of the longitudinal lung function for children who were diagnosed with asthma at age 7 years and followed to the age of 42 years (blue line) and for children who were diagnosed with severe asthma from age 10 (brown line). Two features are to be noted: (i) the plots of lung function are roughly parallel; (ii) the patient's FEV_1 is lower than a severe asthmatic and is likely that it was just as abnormal at (and before) the age of 10 years. In fact, we were able to review her medical records at the age of 10 and found that she had abnormal lung function of around 70% predicted even after bronchodilator, with frequent exacerbations of symptoms associated with drops in lung function to less than 50%, and frequent requirements for bronchodilator medication and courses of oral corticosteroids. At the time, her parents said to the doctor, *"How did she get here?."* The doctor might have said, "*I honestly don't know*," and added insightfully, "*it could have been something that happened to her lungs even before she was born*."

So, we have described three patients diagnosed as having COPD (which we will define as irreversible or fixed airflow obstruction) in later life which in two cases may have had origins in early life and in the third an early life origin was confirmed. So, at what age did these patients start having airway disease? Was it in adulthood, teens, childhood, infancy, or *in utero*? You can pick more than one option, and all are possible. To help answer this question we need longitudinal, preferably birth cohort, studies of lung function, symptoms, and risk factors. Fortunately, there are many such cohort studies which have not only answered some questions but also raised a lot more.

A number of longitudinal studies have cast light on the trajectories of lung function, and their risk factors, from early life to mid and late adulthood [summarized in Jordan and McEvoy (153)]. A number of these studies have examined trajectories in a general population (37, 162, 278, 279, 311). Perhaps the most comprehensive are the trajectories derived from the Tasmanian Longitudinal Health Study (37). Six trajectories of lung function (FEV_1) were identified in 2438 individuals followed from 7 to 53 years of age (Figure 4). Three of these trajectories contributed to 75% of the burden of reduced lung function by age 53. Early life predictors of these three trajectories were childhood asthma, bronchitis, pneumonia, allergic rhinitis, eczema, parental asthma, and maternal smoking. Personal smoking and active adult asthma increased the impact of maternal smoking and childhood asthma, respectively, on the early below average, accelerated decline trajectory. Many other longitudinal studies have also shown different trajectories from childhood to adulthood that are associated with reduced lung function in adulthood (20, 22, 162, 311, 359) and summarized in Okyere et al. (260).

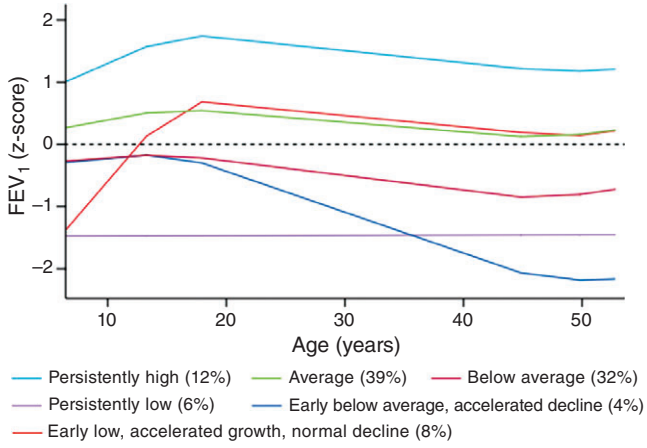

Figure 4 **Six trajectories of lung function identified in 2438 individuals followed from age 7 to 53 years.** The six trajectories are: early below average, accelerated decline (dark blue line); persistently low (purple line); early low, accelerated growth, normal decline (red line); persistently high (light blue line); below average (maroon line); average (green line). FEV_1, forced expiratory volume in one second. Adapted, with permission, from Bui DS, et al., *Lancet Respir Med*. 2018 (37)/Elsevier.

Starting Life on the Wrong Trajectory

Therefore, there are numerous studies that show that abnormalities of lung function associated with airway diseases in childhood and early and later adult life can be tracked back to early childhood. The question arises, do these abnormalities precede or result from disease? To answer this question, a number of general population birth cohort studies (61, 340, 362), with measures of lung function in infancy, were undertaken beginning in the late 1980s. Using techniques to measure lung function (maximal flow at functional residual capacity, "VmaxFRC") within the first month of life (404), these studies have shown that, compared with asymptomatic infants, those with wheeze that persist and who later develop asthma, have abnormal lung function within the first month of life that continues into childhood and adulthood (266, 362). Infants with transient wheeze have a transient reduction in lung function in infancy. These studies show that persistent wheezers and transient wheezers have different risk factors (20).

The presence of abnormal lung function within the first 3 months of life prompts the question, are these abnormalities of lung function present at birth and what are the perinatal and prenatal influences? A study of preterm infants has shown that perinatal events may have effects on infant lung function and the rate of lung growth. Simpson et al. followed the lung function trajectories of 200 very preterm infants with and without bronchopulmonary dysplasia (BPD) and 67 healthy term infants from the age of 4 to 12 years (325). They found that survivors of very preterm birth with BPD, ongoing respiratory symptoms, or CT changes reflecting inflammation had the poorest trajectories of lung function, specifically FEV_1, forced expiratory flow at 25% to 75% of FVC ($FEF_{25\%-75\%}$) and FEV_1/FVC (325). The persistent effects of BPD in preterm infants have been observed in other studies (172).

The genetic determinants of lung function have been studied in genome-wide association studies (140, 350). These studies have shown that a number of genetic polymorphisms are consistently associated with reduced lung function, measured cross-sectionally. Interestingly, some of the genes are related to embryonal development and suggest a mechanism for prenatal effects on lung function that might track throughout life. These genetic variations, however, are not related to respiratory symptoms (409) or the rate of decline in lung function [FEV_1/FVC (151)] during adult life.

Therefore, we can see that our three patients may have arrived at their reduced adult lung function via several different pathways or trajectories with risk factors acting at different points or during different phases of the life span. These might roughly be grouped as follows: pre- and perinatal effects, growth effects, and decline effects. Since the latter possibilities have up until this point received more attention (145), the present review will focus on the first of these groups—specifically the *in utero* origins of obstructive disease. The DOHaD concept is established in many fields and the evidence is mounting in respiratory disease, although there is much work to do!

Airway and Lung Development

Numerous published works provide an in-depth description on the development of airway and lung tissue in humans and its comparison with other species (133, 253, 308). A brief summary is nonetheless necessary to provide context to understand why disruption to fetal development impacts lung function and increases risk of asthma and COPD. We are particularly interested in the development of the airway smooth muscle (ASM) layer due to its importance in obstructive disease.

In humans, lung development comprises the embryonic (4–7 week GA), pseudoglandular (5–17 week GA), canalicular (16–26 week GA), and saccular (24–38 week GA) stages, and in the postnatal period, classical (36 week GA-3 years old) and continued (2–21 years old) alveolarization and microvascular maturation (3–21 years old) (308). Cell types are categorized into epithelial, endothelial, pleural/mesothelial, airway and vascular smooth muscle, pericytes, fibroblasts, neurons, and immune cells such as alveolar macrophages (253). These cell types first appear and mature at different developmental stages such that the timing of a disturbance will impact how respiratory function is affected and in turn the susceptibility to a particular disease.

The formation of the major airways begins in the embryonic period. The bronchial tree and large parts of the respiratory parenchyma begin to form in the pseudoglandular stage with completion of branching morphogenesis in the canalicular stage. The branching morphogenesis of the bronchial tree

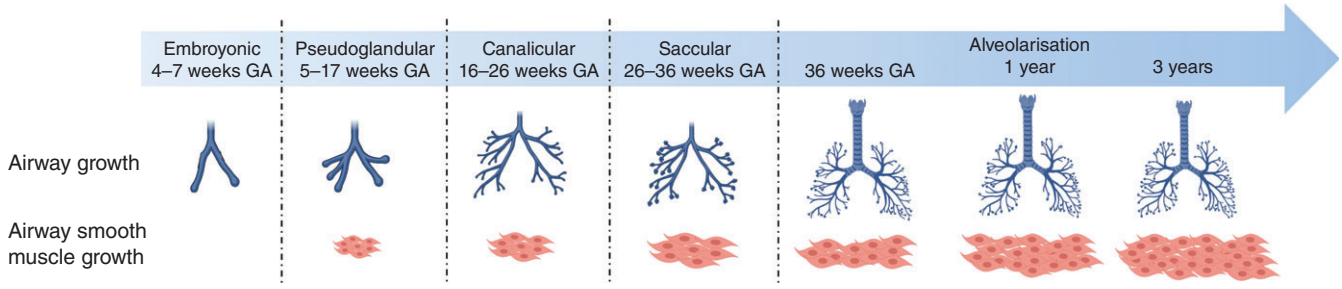

Figure 5 **Human airway and airway smooth muscle growth *in utero* up until 3 years of age.** Formation of the human airway begins in the embroyonic phase, while smooth muscle within the wall appears in the pseudoglandular phase. Airway passages continue to expand and form more complicated branching through the canalicular, saccular, and alveolarisation phases. Airway smooth muscle across the same periods increases in mass. Created with BioRender.com.

is governed by biochemical and mechanical interactions between primordial epithelium and mesenchyme (176, 238, 265). Fibroblast growth factor 10 (FGF10), expressed in the mesenchyme, and its receptor FGF receptor 2, expressed in the distal lung epithelium, drive the branching process (21). Modulating factors include sonic hedgehog (Shh), bone morphogenetic protein (BMP), and fluid pressures within the developing lung buds (25, 176). Under these driving forces, the branching pattern of the lung continues, constrained by the space available and interactions between growing branch tips, in a self-regulated pattern (55), a process predicted some 60 years earlier (357).

Airway smooth muscle refers to smooth muscle tissue that encircles the airways of the lung and its differentiation is initiated in the pseudoglandular stage (335). Mesenchymal cell stretch and tension likely initiates expression of extracellular matrix (ECM) proteins such as laminin (141). The complex interplay of mesenchymal and epithelial cell signaling involving inhibition of Ras homolog family member A and increase in serum response factor likely initiates myogenesis, modulated by FGF10, BMP, and Shh, among others (246). The thickness of the resulting ASM layer increases linearly from 22 week GA until 8 months postnatal age, and then 2- to 4-fold further until early adulthood (134). Postnatally, ASM morphogenesis is characterized by: (i) an increase in the absolute amount of ASM bundles with age, which is correlated with airway length and not diameter; (ii) positive correlation of airway size with ASM bundle size; (iii) greater ASM bundle size in proximal bronchioles than in respiratory bronchioles; (iv) change in the distribution of ASM bundle orientation with age in each airway generation (355); and (v) the thickness of the ASM layer increases via early hypertrophy and subsequent proliferation (376). These findings collectively demonstrate that ASM undergoes marked organizational changes as the airway grows.

Alveolar differentiation is initiated in the canalicular phase by lung inflation (93). Wingless/Int (Wnt) signaling and NKX2.1 (193) determine alveolar epithelial cell type I or II differentiation. Epithelial cell type II begins to synthesis and secrete surfactant protein at 24 weeks GA with adequate amounts of surfactant protein produced by 32 weeks GA, reducing atelectasis (291). The formation of the alveoli occurs during the classical alveolarization phase. The addition of new alveoli to the lungs ceases between 2 and 3 years of age (64, 135, 353) and the alveoli only expand in size thereafter (66, 353). The fact that the infant lung consists of one-third or more of the adult number of alveoli (135) highlights the importance of normal lung growth and maturation *in utero* in determining postnatal respiratory function. Further, as tissue volume does not increase in proportion to lung size (66), individuals born with greater air spaces in larger lungs could therefore be predisposed to COPD in later life.

As shown in Figure 5, airway and ASM development are ongoing processes from pre- to postnatal life, and it is therefore not surprising that preterm infants, where airway and lung development is abruptly interrupted (depending on the magnitude of prematurity), have increased risk of developing asthma or COPD in later life (33, 158). Many reviews have discussed in detail the association between preterm birth and respiratory disease (59, 83, 110); our review will focus more broadly on prenatal determinants of airflow limitation, independent of preterm birth.

Function and Maturation of Airway Smooth Muscle

The functional significance of ASM is unknown and represents an unanswered fundamental question in respiratory biology. In comparison, smooth muscle in other biological systems has a clearly defined role; for instance, contraction of vascular smooth muscle regulates systemic flow and blood pressure, physiological responses necessary for homeostasis (35). No such critically accepted physiological role for ASM has been demonstrated, with some authors even proposing ASM as a vestigial organ, that is, the "appendix of the lung" (241). Such claims may be somewhat overstated, since in fetal life, ASM acts as an active pump, generating phasic (cyclical) mechanical forces, which maintain a positive intraluminal pressure (309) necessary for lung development (337).

A study on isolated ASM strips *in vitro* (104) has reignited the debate surrounding the role of ASM. The study by Gazzola et al. showed that ASM contraction has a greater ability to resist airway expansion during lung inflation than to actively contract the airway lumen (104). These findings provide good support of another theorized role of ASM—reducing anatomical dead space (214, 388). Anatomical dead space describes the volume within the conducting airways which is not involved in gas exchange with the pulmonary circulation (294). Hence, for every breath of air that enters the lungs, not all reaches the alveoli for subsequent gas exchange, and the larger the anatomical dead space, the lower the alveolar ventilation (294) and in turn the lower the capacity to take up oxygen and remove carbon dioxide. Importantly, anatomical dead space is proportional to lung volume (165) as the distending alveoli expand the airway lumen (270). Contraction of ASM which serves to decrease airway distensibility (ease of expansion) may therefore minimize anatomical dead space and optimize alveolar ventilation. As ASM thickness increases, there is a decrease in airway distensibility and anatomical dead space such that alveolar ventilation becomes optimal. However, a more dramatic increase in ASM thickness results in an increase in resistive load opposing airflow, such that alveolar ventilation becomes compromised, thus resulting in airway hyperresponsiveness and subsequently asthma. We have previously discussed several new approaches to target ASM remodeling in asthma (375).

The ASM layer is composed not only of ASM cells but also of ECM. The proportion of ASM cells and ECM within the ASM layer may influence force production and shortening of the ASM around the airways (152, 254). Fetal ASM is mechanically and structurally different from postnatal ASM, which may reflect a shift in function. The developing ASM is myogenic (responding to stretch) and smaller than adult ASM cells (269, 331). Functionally, ASM demonstrates phasic contractions in fetal life, while after birth, ASM produces predominately tonic force, a sustained contractile response (410). Very little data exist on when and to what extent ASM transitions from a phasic to tonic contractile phenotype. Using a developmental sheep model, we showed that ASM phasic activity is suppressed rapidly after birth, although it is still apparent even in the postnatal period, but at a lower intensity from pre-weaning until adulthood (374). To better understand the mechanism for the shift from a phasic to tonic ASM phenotype with advancing age, we developed a computational model, the output of which was compared with experimental observations. The results of the model suggested that reductions in cell–cell coupling was a strong determinant of the apparent reduction in phasic ASM contraction through postnatal life (374). Contractility of immature ASM is also increased compared with mature ASM (336), which parallels the greater airway responsiveness observed in infancy compared with adulthood (386).

It appears that the first year of life is a critical window for ASM growth: mechanisms of growth are early hypertrophy (in the first year of life) followed by late hyperplasia (Figure 6) with proportionate expansion of the ECM within the ASM layer (376). Given that several mechanisms are involved in ASM growth with a myriad of mechanical and biochemical

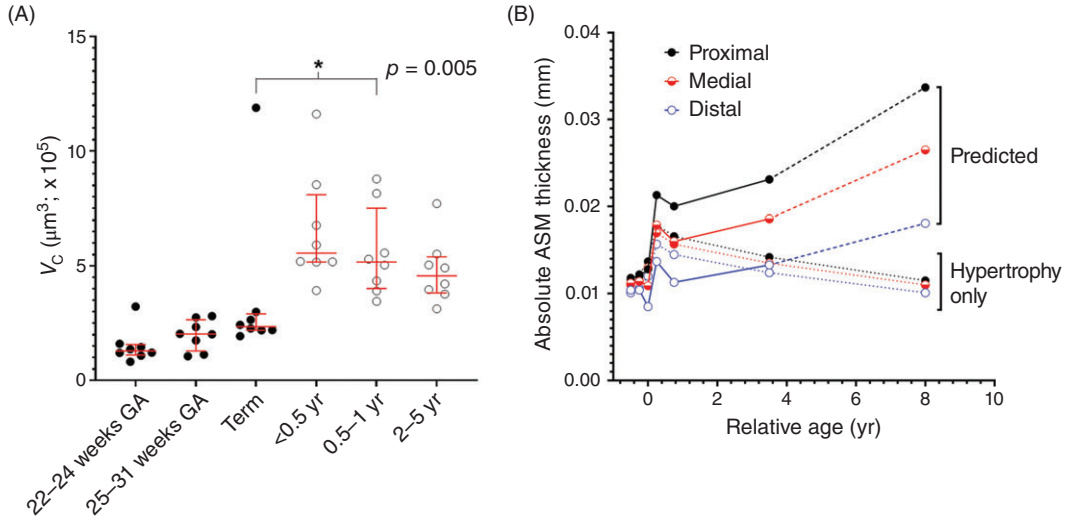

Figure 6 **Growth mechanism of the ASM layer.** Stereological and morphometric assessment of airways collected postmortem at different ages from late gestation to childhood. (A) The ASM cell volume presented in stratified age groups. Data are median (interquartile range). (B) Modeled effects of ASM thickening occurring solely due to isotropic growth of ASM cells without hyperplasia (hypertrophy only; dotted lines) compared with predicted ASM growth. Hypertrophy cannot account for ASM growth beyond 0.5 years. Black circles and lines, proximal airways; red circles and lines, medial airways; blue circles and lines, distal airways. ASM, airway smooth muscle; GA, gestational age; V_C, mean ASM cell volume; yr, year(s). *Significantly different from term ($p < 0.05$). Adapted, with permission, from Wang KCW, et al., *Respirology*. 2022 (376)/John Wiley & Sons/Licensed under CC BY 4.0.

factors that initiate and modulate branching morphogenesis, myogenesis, and subsequent ASM growth, there are plenty of "opportunities" for disruption leading to ASM remodeling. There is evidence in animal studies where an insult was introduced *in utero* while the ASM layer was developing, for example, hypoxia (381) and inflammation (305), that the growth of ASM layer is altered, characterized by an increase in the thickness of the ASM layer in fetal life. The increase in ASM mass in fetal life could potentially contribute to the development of excessive airway narrowing and therefore flow limitation in the postnatal period.

Prenatal Disruption of Lung Function

Many epidemiological studies have demonstrated that intrauterine growth restriction (IUGR) and/or low birth weight are associated with respiratory disease in later life. The first study that reported this relationship is by Professor David Barker and colleagues where they looked at a cohort from Hertfordshire, UK, of more than 5000 men to assess the association between birth and the death rates due to chronic obstructive airway disease (12). The two main findings from this study were: (i) mean FEV_1 fell with decreasing birth weight independent of adverse postnatal growth; and (ii) death from chronic obstructive airway disease in adult life was associated with lower birth weight (12). The same authors later used the Helsinki Birth Cohort where they studied the relationship between body size at birth and asthma (13). This study demonstrated that a slow linear growth *in utero*, potentially from impaired placentation, increases the risk of later asthma. The fact that this relationship is reproduced consistently by other population data (101, 158, 202, 314, 347, 370) with two separate meta-analyses concluding that low birth weight is associated with increased risk of asthma both in children and adults (70, 246) strengthens the "fetal origins hypothesis" proposed by Professor David Barker that an adverse intrauterine environment, resulting in IUGR, may constrain airway growth and peripheral lung development, thus predisposing individuals to COPD in adult life (12). This hypothesis was later extended to asthma (358). Importantly, individuals with low lung function at birth remain at the same low trajectory throughout life, which is a manifestation of their increased predisposition to respiratory disease (22).

Fetal body size data collected through antenatal ultrasound examination in recent years allowed fetal growth trajectory to be tracked throughout gestation. Fetal growth characteristics that were measured between studies vary but include crown-rump length, femur length, biparietal diameter, head circumference, abdominal girth, and estimated fetal weight. The cohort recruited in Southampton, UK, found that a reduced head circumference growth between weeks 10 and 19 and reduced growth in abdominal girth between weeks 19 and 34 were associated with increased wheeze at an age of 3 years (281). Another cohort recruited in Aberdeen, UK, found that a reduced fetal size in the first trimester was associated with increased risk for asthma symptoms at both 5 (361) and 10 years of age (360). Data from the Generation R Study demonstrated that restricted fetal weight growth between the second trimester and birth predispose children to increased airway resistance and risk of wheezing at an age of 6 years (333) and depending on infant weight growth, lower lung function (FEV_1, FVC, FEV_1/FVC, $FEF_{25\%–75\%}$) at an age of 10 years (69). The two take-home messages from these studies are that fetal growth and the timing of the insult are both factors restricting fetal growth and are in turn important determinants of airway and lung function and asthma development throughout life.

Population studies have repeatedly demonstrated the positive association between birth weight and lung function (118, 181, 266), which indicates that intrauterine factors might have a role in lung development. The precise definition of "intrauterine" is the environment in the womb where the fetus resides for 9 months to grow while receiving substrate supply (oxygen, glucose, and other essential nutrients) from the mother via the placenta (120). Any reduction or inappropriate substrate delivery to the fetus may compromise fetal growth leading to IUGR and/or low birth weight. As mentioned previously, the airways and lungs develop during gestation, and it is therefore intuitive that the relation between birth weight and adult FEV_1 may be a consequence of an adverse environment *in utero* which retards growth of the fetus and irrecoverably modifies the development of the airways (12) and their physiological behavior. The underlying mechanism is unknown; however, animal studies have allowed us to investigate changes in airway and lung structure of IUGR and low birth weight offspring compared with healthy offspring (221, 222, 379, 381, 391) which we have discussed in a previous review (378). In human airway samples, we have demonstrated that low birth weight infants born at term, but died at birth, have abnormal structural composition of the ASM layer, characterized by an increased number of ASM cells (hyperplasia) and proportionally greater ECM [Figure 7 (377)]. As these infants were deceased at birth, there was no postnatal exposure impacting airway structure–function, no effect of preterm birth since the gestational period was similar to the control group, suggesting that all of the effects observed must have resulted from some disrupted intrauterine development and provides new data that the problem resides at the level of the ASM layer. Therefore, airway remodeling (accelerated hyperplasia) observed in low birth weight infants precedes postnatal airway inflammation due to airborne exposures such as allergens, which supports an alternative hypothesis that inflammation and remodeling are derived from separate susceptibilities that independently contribute to the severity of obstructive airway disease (375).

The association of birth weight with childhood asthma is also reported to be due to adaptations in airway caliber (70) with supporting evidence that small airway caliber is the most important cause of early infant wheeze (366) and transient wheezing in young children (405) in the absence of

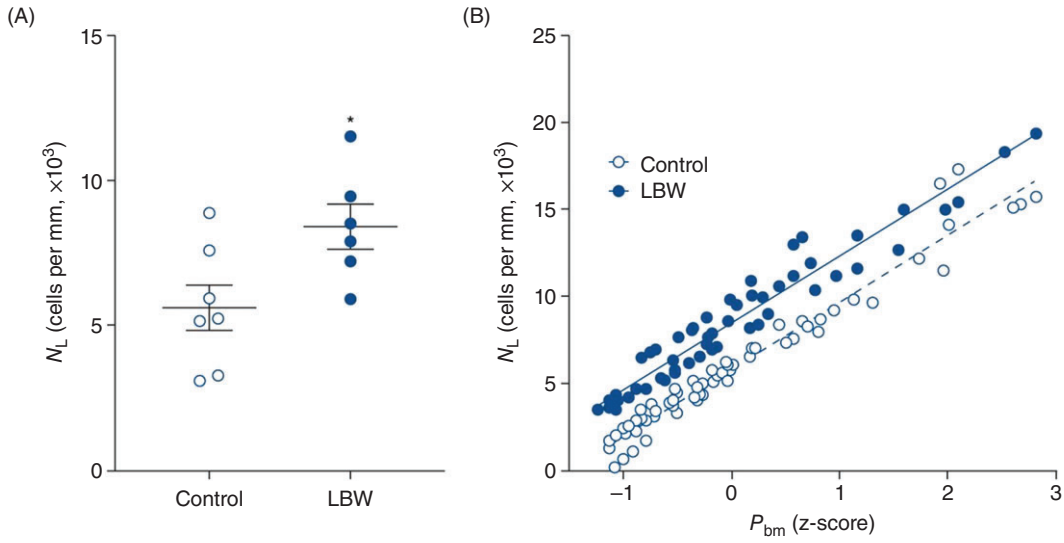

Figure 7 **Low birth weight infants born at term have abnormal structural composition of the ASM layer.** (A) Number of ASM cells. Values are mean ± SEM where each datapoint is a case mean of all airways examined for that subject. *$P < 0.05$, significantly different between the control and the LBW group. (B) A linear mixed effects model examined the association between N_L and the fixed effects of airway size (P_{bm}) and group (control and LBW group). Subject identification was also included as a random effect. Model output is shown demonstrating an increase in N_L with P_{bm} ($P < 0.01$), a relationship that is upward shifted in the LBW group ($P = 0.02$). Line of best-fit is included for visual acuity. LBW, low birth weight; N_L, the number of ASM cells per airway length; P_{bm}, perimeter of basement membrane. Adapted, with permission, from Wang KCW et al., *Eur Respir J.* 2023 (377)/The European Respiratory Society.

inflammation (300). However, a study using monochorionic twin pairs with selective fetal growth restriction whereby only one twin experienced growth restriction reported that the growth-restricted twin exhibited lower large and small airway function in the absence of structural changes (using magnetic resonance imaging) at approximately 18 years of age (302).

External Factors Contributing to an Adverse Intrauterine Environment—Links with Respiratory Health

Intrinsic factors such as chromosomal abnormalities and external factors such as air pollution could contribute to an adverse intrauterine environment. In this review, we will be focusing on the external factors that may modify maternal, placenta, or fetal conditions and subsequent offspring lung health outcomes. Table 1 is a list of prenatal exposures associated with physiological abnormalities and/or onset of respiratory disease.

Air pollution

There is little doubt that air pollution is getting worse across the world and is endangering the health of all individuals, including pregnant women. There is evidence that both outdoor (341) and indoor (100) air pollution lead to IUGR and low birth weight. There is also evidence that low birth weight individuals have increased susceptibility to asthma if they are exposed to perinatal air pollution (306), an effect influenced by socioeconomic status (105). Many studies have attempted to isolate which air pollutant particles are responsible for the damage to the respiratory system.

Ozone (O_3) is mainly formed by nitrogen oxides and volatile organic compounds produced by internal combustion engines and power plants. One study found that maternal O_3 exposures averaged over the entire pregnancy are linked to IUGR and low birth weight (301). In a cohort of greater than 200 subjects of healthy term-born neonates, which included low birth weight subjects, no association between prenatal exposure to O_3 and respiratory outcomes (tidal breathing, multiple-breath washout indices and inflammatory markers) at 5 weeks was detected (179). Although an inverse relationship between pregnancy exposure to O_3 concentration and FEV_1 was observed, exposure to O_3 during pregnancy was not significantly associated with FEV_1 at 6 years of age (364). Exposure to ozone throughout pregnancy increases the risk of asphyxia and respiratory distress syndrome in neonates (313); however, the results of a systematic review showed no effect of prenatal exposure to O_3 on childhood wheezing and asthma (128). Using an ovalbumin (OVA)-induced asthma mouse model where mice were exposed to O_3 during pregnancy, prenatal O_3 exposure exacerbated the severity of OVA-induced allergic disease in offspring by increasing airway and systemic inflammation, mucus production, and the levels of OVA-specific IgE (102). Another mouse study that separated the O_3 effect between different gestational periods found that O_3 exposure in the third trimester of

Table 1 Prenatal Exposures Associated with Physiological Abnormalities and/or Onset of Respiratory Disease

Prenatal exposure	Timing of pregnancy	Human/animal	Structural	Inflammatory	Genetics	Functional/mechanical	Respiratory disease	References
Ozone	Throughout gestation	Human				An inverse relationship between ozone concentration and FEV_1	Asphyxia and respiratory distress syndrome	(313, 364)
		Mouse	↑ goblet proliferation	↑ airway IL-4, IL-17 and TNF-α ↑ airway neutrophils and eosinophils ↑ peribronchial inflammation ↑ OVA-specific IgE	↑ lung IL-4 protein expression			(102, 201)
CO_2	Throughout gestation	Mouse	↑ mean chord length in female offspring ↓ volume of alveolar septa in female offspring ↓ number of alveoli in female offspring			↑ tissue elastance in female offspring ↓ lung compliance in female offspring		(178)
Ultrafine particles	Second or third trimester	Human					Asthma	(180, 400)
	Throughout gestation	Mouse		↑ systemic IL-10	↓ lung IL-13 and IL-17 mRNA expression *Suggest of early window of immunosuppression			(298, 383)
$PM_{2.5}$	First or second trimester	Human					Asthma	(136, 154)
	Throughout gestation and the first three years of life					↓ FEV_1 and FVC * Second to third trimester may be particularly sensitive		(251)
	Third trimester				Hypermethylation of glutathione S-transferase P in DNA isolated from nasal epithelial cells	↓ FEV_1 and FVC		(185)
	Early to mid-gestation	Rat	↑ interstitial proliferation	↑ oxidative stress	↑ α-smooth muscle actin and vimentin mRNA and protein expression ↓ E-cadherin mRNA and protein expression ↑ TGF-β and Smad3 mRNA and protein expression	↓ lung volume parameters, compliance, and airflow during expiration		(349)
	Throughout gestation and postnatal for 90 days	Mouse	↓ alveolar surface to volume ratio					(228)
PM_{10}	Second trimester	Human				AHR	Asthma	(403)
	Third trimester	Human				↑minute ventilation		(179)

(*continued overleaf*)

Table 1 (*Continued*)

Prenatal exposure	Timing of pregnancy	Human/animal	Structural	Inflammatory	Genetics	Functional/mechanical	Respiratory disease	References
NO_3^-	Early gestation	Human				↓ FEV_1 and FVC		(26)
NO_2	Second trimester or throughout	Human				↓ FEV_1 and FEV_1/FVC		(127, 244)
	Throughout gestation	Mouse			Differentiation of Th-2 cells and demethylation of the IL-4 gene	AHR		(406)
Benzene	Second trimester	Human				↓ FEV_1		(244)
Polycyclic aromatic hydrocarbons or diesel exhaust	Throughout gestation	Human					Wheeze Respiratory infection	(146, 148)
	Throughout	Mouse		↑ airway lymphocytes, neutrophils and eosinophils	↑ lung IL-4, IL-5, IL-13, IL-17, IL-6, and TNF-α mRNA expression	↑ airway resistance AHR		(90, 198, 220, 290)
				↑ peribronchial inflammation	Transgenerational impact			
				↑ OVA-specific IgE				
				↑ airway IL-4, IL-5, IL-13, IL-17 and TNF-α				
				↓ airway IFNγ				
1-Nitropyrene	Throughout gestation	Mouse	↑ mucus production	↑ airway eosinophils	↑ lung Muc5ac mRNA expression			(209)
				↑ systemic IL-5				
Nanoparticles	Throughout gestation	Mouse			↓ lung VEGF-α and MMP-9 and FGF-18 mRNA expression			(276)
Cooking smoke	Throughout gestation	Human				↓ ratio of the time to peak tidal expiratory flow to expiratory time	Pneumonia	(184)
						↑ respiratory rate and minute ventilation		
Smoking (direct or second hand)	Second and third trimester	Human				↓ lung volume		(7)
	Throughout gestation				Transgenerational impact	↓ FEV_1, $FEF_{25\%-75\%}$	Asthma	(31, 37, 38, 121, 126, 191, 205, 217, 303, 324, 342, 348)
						↓ lung function trajectory		
	Throughout gestation	Mouse	Perturbation in the alveolar development Impaired differentiation of goblet cells and mucus production	Impaired Th1 response	Dysregulation of 2 genes, SERPINA1A and DNA (cytosine-5)-methyltransferase 3A Transgenerational impact	↓ lung volume ↑ tissue damping and elastance		(177, 258, 326)

Nicotine		Mouse Monkey	↑ branching ↑ airway length ↓ airway diameter		↓ lung SP-A and SP-C mRNA expression	↓ forced expiratory flows		(315, 395, 396, 402)
Vaping	Throughout gestation	Mouse	↓ airspace area ↓ ciliated cells ↑ immature ciliated cells with short cilia Delay thinning of the lung epithelium ↑ proliferation of club cells ↓ alveolarization ↑ pulmonary fibrosis ↑ goblet cell hyperplasia	↑ airway TNF-α and IL-1β ↑ airway neutrophils and lymphocytes	Changes in expression of genes involved lung development—Wnt and Notch signaling pathways ↓ methylation status of the promoter region of IL-10 receptor alpha subunit ↑ of expression of genes involved in inflammation and allergy—TNF-α and IL-1β	↑ lung and alveolar stiffness ↓ baseline compliance ↓ forced expiratory volume in female offspring		(9, 41, 49, 257, 267)
Arsenic	Throughout gestation	Human					Asthma COPD	(327, 328)
		Mouse			↑ of expression of genes involved lung growth - SRY-box containing gene 2 ↑ of expression of genes involved in mucus production — chloride channel calcium activated 3, mucin 5 subtype b, secretoglobin family 3a member 1 ↑ of expression of genes involved innate immunity—regenerating islet-derived 3γ, trefoil factor 2, dynein light chain roadblock-type 2, and long palate, lung, and nasal epithelium clone 1 protein	↑ tissue damping and elastance in male offspring loss of lung compliance ↓ lung volume		(288, 289)
Phenols, phthalates, and bisphenol A	Throughout gestation	Human					Asthma	(96, 103, 368)
		Rat Mouse		↑ airway eosinophils		AHR		(250, 372)
Formaldehyde	Throughout gestation	Rat		↑ airway neutrophils ↑ myeloperoxidase activity		AHR		(218, 219, 323)
Farm animals	Throughout gestation	Human					Asthma	(36, 77, 84, 137)

(*continued overleaf*)

Table 1 (*Continued*)

Prenatal exposure	Timing of pregnancy	Human/animal	Structural	Inflammatory	Genetics	Functional/mechanical	Respiratory disease	References
House dust mite	Throughout gestation	Mouse		↑ airway eosinophils and lymphocytes ↑ HDM-specific IgG_1 and IgG_{2a} ↓ in the phagocytic capacity of pulmonary macrophage populations	↑ lung IL-4, IL-5, and IL-13 protein expression Transgenerational impact	AHR		(182, 292)
High intake of sugar, fructose, artificially sweetened soft drinks, fast-food and high-inflammatory diet	Throughout gestation	Human					Asthma	(19, 51, 227, 371, 399)
High-fat diet	Throughout gestation	Mouse	Delayed structural lung development ↑ cytoplasmic glycogen content ↓ cellular proliferation	↑ total airway inflammatory cells ↑ airway neutrophils ↑ airway IL-6		↑ airway reactivity		(114, 211, 229, 330)
Hypoxia	Throughout gestation	Human	↑ ASM cell proliferation (*in vitro*)				Asthma Respiratory syncytial virus	(52, 124, 166)
	Mid-gestation	Mouse Rat	↑ thickness of ASM layer ↑ heterogeneity in airway caliber	↑ total airway inflammatory cells		↑ airway resistance in juvenile male offspring and adult female offspring ↑ airway wall stiffness impaired diaphragm muscle function		(99, 207, 255, 379–381)
	Throughout gestation	Sheep	↓ surfactant maturation		↓ lung SP-A, SP-B, SP-C, CDC25A and Ki67 mRNA expression ↑ lung PHD2 mRNA and protein expression ↑ lung PHD3, HIF-1α, HIF-1β, GLUT1, JMJD1A, ACE, FLT1, p27, IGF-2 and IGF-1R mRNA expression ↓ lung glucocorticoid receptor-α and -β protein expression ↓ lung GATA-6 protein expression			(263, 264, 334)
	Late-gestation		↑ surfactant maturation					(234)

Preeclampsia/high blood pressure	Throughout gestation	Human				↓ FEV_1/FVC	Asthma Wheezing Eczema Allergy Respiratory morbidity	(39, 203, 215, 343, 394, 414)
Gestational diabetes	Throughout gestation	Human					Asthma Wheezing	(226, 243, 297)
	Throughout gestation and first three weeks of life	Mouse *High-fat diet induced gestational diabetes model	↑ mean linear intercept ↑ airspace to tissue ratio	↑ airway IL-1β, IL-5, CXCL1, TGF-β2, IL-28B, TNF-β, MMP-3 and MMP-8 in female offspring ↑ airway IL-23 and TGF-β2 in male offspring		↑ airway resistance, tissue damping and lung elasticity in female offspring ↑ baseline lung compliance but ↓ baseline lung resistance, airway resistance, tissue damping and tissue elasticity in male offspring		(274)
Stress and mental well-being	Throughout gestation	Human				↓ FEV_1 and FVC	Asthma	(92, 183, 216)
	Mid-gestation	Mouse	↓ extensive terminal sacs ↑mesenchymal tissue thickness	↑ airway eosinophils		AHR		(163, 194, 408)
Maternal asthma	Throughout gestation	Human			↑ pro-inflammatory IgG glycosylation	↓ time to reach peak tidal expiratory flow as a percentage of total expiratory time	Asthma	(60, 197, 199, 225, 261, 332) (65, 195)
Anemia and hyperthyroidism	Throughout gestation	Human					Asthma	(122, 200)
Assisted reproduction technologies	Throughout gestation	Human					Asthma	(46, 86, 159, 392)
Antibiotics	Throughout gestation	Human					Asthma	(164, 206, 243, 344)
Aspirin	Throughout gestation	Human					Asthma	(53)
Vitamin A and folate	Throughout gestation	Human					Asthma	(190, 272)

Abbreviations: ACE, angiotensin-converting enzyme; AHR, airway hyperresponsiveness; ASM, airway smooth muscle; CDC25A, cyclin-dependent kinase A2; FEV_1, forced expiratory volume in one second; FLT1, fms related receptor tyrosine kinase 1; FVC, forced vital capacity; $FEF_{25\%-75\%}$, forced expiratory flow at 25% to 75% of FVC; FGF-18, fibroblast growth factors-18; GLUT1, glucose transporter 1; HDM, house dust mite; HIF, hypoxia-inducible factor; IgE, immunoglobulin E; IgG, immunoglobulin G; IFNγ, interferon gamma; IGF, insulin-like growth factor; IL, interleukin; JMJD1A, Jumonji domain containing 1A; MMP-9, matrix metallopeptidase 9; OVA, ovalbumin; PHD, prolyl hydroxylase domain; p27, *cyclin-dependent kinase inhibitor 1B;* Smad3, mothers against decapentaplegic homolog 3; SP, surfactant protein; TGF-β, transforming growth factor-beta; TNF-α, tumor necrosis factor-alpha; VEGF-α, vascular endothelial growth factor-alpha; Wnt, Wingless/Int.

pregnancy is the most sensitive window for modification with an increase in pulmonary inflammatory cell infiltration, goblet cell proliferation, and OVA-specific IgE levels in serum (201).

Climate change due to increasing atmospheric carbon dioxide (CO_2) is a topical research area. To study the effects of long-term exposure to CO_2 on respiratory structure–function, Larcombe et al. exposed pregnant mice to 890 ppm CO_2 and subsequently offspring until 12 weeks of age, compared with a control group housed under 465 ppm CO_2 (178). Findings demonstrated that the respiratory structure–function of the female, but not male, offspring exposed long-term to elevated levels of CO_2 was affected. The pathophysiology of the female respiratory system included higher lung tissue elastance (lower lung compliance), increased mean chord alveolar length, and decreased volume of alveolar septa and the number of alveoli, but no evidence for changes in airway inflammation (178).

Particulate matter (PM) is extremely small solid particles and liquid droplets suspended in air with their particle size measured in μm. Most particles form in the atmosphere because of complex reactions of chemicals such as sulfur dioxide and nitrogen oxides, which are pollutants emitted from power plants, industries, and automobiles. Other sources include construction sites, unpaved roads, fields, smokestacks, or fires. There are currently three known sizes of PM that contributes to adverse lung health: ultrafine particles (<0.1 μm, UFP) (180), particulate matter that have a diameter of less than 2.5 ($PM_{2.5}$), and 10 μm (PM_{10}). It appears that the second or third trimester UFP (180, 400) and $PM_{2.5}$ exposure in the second trimester (136, 154, 251) in particular result in lower lung function (FEV_1 and FVC) at 6 to 8 years of age and development of asthma during the school period, while data from the Raine Study demonstrated that early-life exposure (aged between 3 and 4 years) to $PM_{2.5}$ was associated with low FEV_1 trajectory between 6 and 22 years of age (303). The Latrobe Early Life Follow-up Study investigated lung function of infants aged less than 5 years who were exposed to smoke 3 years prior and thus $PM_{2.5,}$ in comparison to infants who were not exposed (319). This study was made possible by recruiting subjects born just before, during or just after the Hazelwood coal mine fire incident, an event that led to acute, high-intensity air pollution exposure (319). Results revealed an association between elevated concentrations of $PM_{2.5}$ and worsening peripheral lung mechanics (reactance at a frequency of 5 Hz and the area under the reactance curve) (319) which may be due to increasing vascular stiffness (130). However, when restricted to only children who were exposed to $PM_{2.5}$ *in utero*, there was no detrimental effect on lung function (resistance and reactance) at 7 years old (129). The investigators speculated that the lack of physiological impairment as a result of *in utero* exposure suggests that acute exposure does not lead to permanent damage and/or that any harmful effect on lung structure or function is resolved by longer postnatal timepoints (129). The underlying mechanisms underpinning the relationship between prenatal $PM_{2.5}$ exposure and reduced lung function (FEV_1) appears to be due to an increased glutathione S-transferase P methylation that is associated with oxidative stress in children's nasal cell DNA (185).

Findings from an *in utero* UFP-exposed mouse model showed a reduced pulmonary inflammatory response to allergen challenge during a period of immune maturation, predisposing offspring to respiratory infection and leading to an exacerbated allergic response later in life (298). Similar findings were reported in a separate mouse study (383). In a rat model of early to mid-gestation exposure to $PM_{2.5}$, offspring exhibit structural remodeling and reduced lung volume and compliance, possibly through epithelial–mesenchymal transition upregulation mediated by the TGF-β/Smad3 pathway (349). Altered alveolar structure and elastic properties (smaller surface-to-volume ratio and reduced inspiratory and expiratory volumes at higher levels of transpulmonary pressure) were observed in mice that were exposed to $PM_{2.5}$ throughout gestation until a postnatal age of 90 days, but no structural changes were detected in offspring that were solely exposed to $PM_{2.5}$ in prenatal life (228).

Exposure to PM_{10} in the second trimester and airway hyperresponsiveness in response to a methacholine challenge at 7 years of age showed a combined effect on the new diagnosis of asthma at an age of 11 years (403), while exposure during the third trimester is associated with increased minute ventilation (the product of tidal volume and respiratory rate) in 5 weeks old infants (179). A systematic review from 18 studies confirmed this finding (128). The mechanisms on how prenatal PM_{10} exposure alters offspring lung function remains unclear (and indeed there is variability in whether individuals are affected or not); however, a recent study has suggested that infants carrying more childhood-onset asthma-risk alleles were more susceptible to PM_{10}-associated reduction in functional residual capacity (138).

Nitrate (NO_3^-) and nitrite (NO_2) are nitrogen-containing compounds that can be found in water and soils. Nitrate is a widespread environmental exposure through diet (e.g., leafy vegetables) and drinking water with regulatory limits set as: EU/Australia: 50 mg/liter $NO_3^-$and US: 44 mg/liter NO_3^-. In a Danish birth cohort, low levels of prenatal exposure of NO_3^- (>2–5 mg/liter) were associated with a greater risk of a phenotype described as small for gestational age (odds ratio of 1.04) (147). Early gestation exposure to NO_3^- is associated with reduced FEV_1 and FVC in boys at 7 years of age (26), while the second trimester NO_2 exposure lowers FEV_1 in pre-school-aged children and exposure throughout gestation reduces FEV_1/FVC in adulthood (127, 244). No human or animal studies to date have isolated the mechanisms of the effects of prenatal NO_3^- exposure on lung structure, but the mechanism on how NO_2 leads to asthma is proposed as involving differentiation of Th-2 cells and demethylation of the interleukin (IL)-4 gene (406).

Exposure to benzene in the second trimester, but not early postnatal life (first year of life), is associated with a reduction in FEV_1 of pre-schoolers' at 4.5 years of age (244),

while multiple studies have shown that prenatal exposure to polycyclic aromatic hydrocarbons (PAHs), a component found in diesel exhaust, to be positively associated with childhood wheeze and respiratory infection (146, 148). Mouse models have demonstrated increased IL-4, IL-17, and other pro-inflammatory cytokines as potential mechanisms responsible for the effects elicited by prenatal diesel exhaust exposure (90, 220). 1-Nitropyrene (1-NP) is a by-product of combustion and is the predominant nitrated PAHs emitted in diesel engine. Gestational exposure of 1-NP in a mouse model demonstrated increased airway eosinophil inflammation, mucus production, and systemic IL-5 concentration (209). Nanoparticles are also found in the air due to natural, incidental, and manufactured processes. Prenatal exposure to nanoparticles can induce impairment of lung development and IUGR by decreasing pulmonary expression of vascular endothelial growth factor-α (VEGF-α) and matrix metalloproteinase 9 at the fetal stage, and FGF-18 at the alveolarization stage (276).

Regardless of the specific air pollutant, the broad mechanism for the effect of prenatal exposure to air pollutants on offspring lung function is due to changes in maternal physiology (e.g., hypoxia, oxidative stress, and inflammation) and DNA alterations in the fetus that ultimately affect lung development.

Cooking smoke, cigarette smoking, second-hand smoke, and vaping

The significant impact of smoke is described best in a study that estimated worldwide burden of disease attributable to second-hand smoke (259). Disability-adjusted life-years lost because of exposure to second-hand smoke amounted to 0.7% of the total worldwide burden of diseases in 2004 with asthma as one of the largest disease burdens (259). Smoke may be generated by the burning of biomass fuels for cooking during gestation and cause harm to fetal growth and lungs and therefore increase susceptibility of asthma. For example, indoor wood-fuel smoking exposure leads to carbon monoxide exposure (275) and causes low birth weight (157, 322), while coal smoke produces cadmium which leads to IUGR (14) and may subsequently affect fetus airway and lung development. Recent evidence has demonstrated a link between prenatal cooking smoke (carbon monoxide) exposure and reduced ratio of the time to peak tidal expiratory flow to expiratory time, and increased respiratory rate and minute ventilation of 30-day old infants (184). Gas cooking alone however was not related to any adverse offspring respiratory outcomes but associations became significant in mothers that smoke and consumed below average quantities of fruit and vegetables (87).

There is no doubt that maternal smoking contributes to the development of asthma and COPD in offspring (139). In one study (7), magnetic resonance imaging scans were performed on fetuses from mothers that smoked or did not smoke during their second and third trimesters of pregnancy. The investigators demonstrated that total fetal body and lung volume were smaller in fetuses from mothers that smoke (compared with those who did not), providing clear evidence that maternal smoking directly restricts both body and lung growth (7). The adverse impact on fetal lung development leads to the failure of offspring to reach maximum lung function in childhood with subsequent lifelong decreases in spirometric parameters (e.g., FEV_1 and $FEF_{25\%–75\%}$) (126, 342). Multiple studies tracking lung function trajectories have repeatedly shown that maternal smoking is associated with low lung function throughout life (37, 303, 348). Furthermore, a meta-analysis from over 70 studies examining the incidence of asthma or wheeze in relation to exposure to prenatal, postnatal, or household smoking showed that exposure to prenatal smoking increases the odds ratio of asthma to 1.85 in children less than 2 years of age (38). This effect of prenatal smoking is persistent in older kids with another pooled analysis finding that maternal smoking was associated with an odds ratio of 1.65 for asthma at 4 to 6 years of age (252). The risk of asthma in offspring was further elevated if both parents smoked [odds ratio of 3.7 (121)]. There are also incidents where pregnant women did not smoke but were exposed to smoke (as well as their unborn fetus) through passive or second-hand cigarette smoke, leading to a risk of asthma in offspring (38, 121, 324). Given that both paternal and maternal cessation of smoking has a protective effect against childhood asthma (121), effort to educate expecting parents about the harmful impact of smoking on offspring respiratory health is imperative.

Mouse offspring at 2 weeks of age (juvenile period) that were exposed *in utero* to cigarette smoke from six cigarettes per day had lower lung volumes (suggesting smaller lungs) and increased tissue damping and elastance (suggesting stiffer lungs) (177). Dysregulation of 2 genes, SERPINA1A and DNA (cytosine-5)-methyltransferase 3A (258) along with perturbation in alveolar development (258), impaired differentiation of goblet cells and mucus production and Th1 response (326) were implicated as the underlying mechanism of *in utero* smoking-induced lung damage. Animal studies have repeatedly demonstrated that nicotine is the key mediator of *in utero* smoke exposure on lung development. Together, these studies showed that functionally, prenatal nicotine exposure decreases forced expiratory flows in offspring through α7 nicotinic acetylcholine-mediated signals (315, 396), and structurally, modified airway branching (395, 402) with an increased airway length and decreased diameter (396), accompanied by increased expression of surfactant protein (SP)-A and SP-C mRNAs (402).

Distressingly, e-cigarette use in pregnancy is increasing as it has been plugged as a safe substitute compared with conventional cigarette use during pregnancy (387). A recent human study sampled from the US population found that mothers who vaped had an increased risk of IUGR (384). Mouse studies have further demonstrated that maternal vaping produced smaller offspring (41, 257) due to oxidant and antioxidant imbalances in the uterine/placental

environment (41). In late-gestation mouse fetuses, maternal vaping exposure until 18.5 d GA caused a delay in lung development, characterized by reduced airspace area and fewer ciliated cells and more immature and shorter ciliated cells compared with controls (267). Gene expression related to lung development, for example, Wnt and Notch signaling pathways was also altered (267). At birth, the lung structure of maternal vaping mouse offspring was altered, including delayed thinning of the lung epithelium, increased proliferation of club cells, and reduced alveolarization through epigenetic chromatin modifications, Wnt signaling, and genes related to inflammation (41, 257). At approximately 3 months of age, mouse offspring exposed to maternal vaping had increased levels of pro-inflammatory cytokines [tumor necrosis factor-α (TNF-α) and IL-1β] (49) and various asthma and allergy-related genes (41). One study found that at 5 months of age, mice exposed to e-cigarette vapor *in utero* have impaired lung function (greater lung and alveolar stiffness, reduced baseline compliance, and decreased forced expiratory volume that was only observed in female offspring), pulmonary fibrosis, and increased goblet cell hyperplasia (9). Global DNA methylation was increased in mice exposed to e-cigarette vapor, which suggests epigenetic modifications have also occurred in these offspring (49). Importantly, the same effects were observed in both nicotine-free and nicotine-containing e-vapor-exposed offspring, suggesting the effects are likely due to by-products of vaporization rather than nicotine (9, 49). Furthermore, when mouse offspring from a maternal vaping model were subsequently exposed to house dust mite (HDM) in adulthood, their lung tissue exhibited heightened inflammation and male offspring had increased neutrophils in their bronchoalveolar lavage fluid, while female offspring had increased neutrophilic and lymphocytic inflammatory response compared with the control group (*in utero* air exposure) (41). Many asthma and allergy-related genes were dysregulated in male and female offspring exposed to e-vapor *in utero* and challenged as adults with HDM, for example, thymic stromal lymphopoietin and chemokine ligand 26 (41). Alarmingly, maternal vaping mouse offspring demonstrated epigenetic chromatin modification genes from birth to adulthood and a decrease in the methylation status of the promoter region of IL-10 receptor alpha subunit which correlates with the upregulation of the *IL-10* gene at birth (41), suggesting a fetal epigenetic lung programming origin.

Environmental toxins and allergen

Exposure to environmental toxins *in utero* will also significantly impact growth and organ development and has long-term implications for disease risk (239). For example, arsenic is an environmental pollutant toxic metalloid that people are exposed to mainly through ingestion of contaminated water. The odds ratio for asthma was 2.33 for children that were exposed to arsenic *in utero* and early life (5 years of life) (328). The investigators could not entirely isolate the *in utero* period of exposure to arsenic, as children were most likely drinking from the same sources as their pregnant mothers (328). Given that the standardized mortality rates for COPD were higher in young adults (30–49 years old) that were exposed to arsenic water *in utero* and early life (327), these data suggest that early life exposure to arsenic water is an early life origin of COPD. To isolate exposure to arsenic specifically to the *in utero* period, a mouse study exposed pregnant mice to drinking water containing arsenic from day 8 of gestation until delivery (20 d GA) (289). The authors found that offspring exposed to arsenic had impaired *in utero* somatic growth but exhibited catch-up growth during the first 2 weeks of life. Interestingly, only male offspring exposed to prenatal arsenic displayed increased tissue damping and elastance and a loss of lung compliance, all of which had resolved by 4 weeks of age (289), which may have occurred since offspring had access to uncontaminated water after birth. Further, the authors found lower lung volume, lung surface area and alveolar number, upregulation of expression of genes involved in mucus production (chloride channel calcium activated 3, mucin 5 subtype b, secretoglobin family 3a member 1), innate immunity (regenerating islet-derived 3γ, trefoil factor 2, dynein light chain roadblock-type 2, and long palate, lung, and nasal epithelium clone 1 protein), and lung growth (SRY-box containing gene 2) in the *in utero* arsenic exposed offspring (288). These structural and immune changes are expected to increase susceptibility to future respiratory infections and airway obstruction (288).

Household chemical exposure during pregnancy is also associated with persistent wheeze and lung function abnormalities (reduced FEV_1 and $FEF_{25\%-75\%}$) in offspring up to 7 years of age (131, 320). Toxins that can be found in indoor environments include phenols, phthalates, and bisphenol A; prenatal exposure to these toxins has been shown to increase the risk of asthma in childhood (103, 368) and adulthood (96), with data from rodent models showing evidence of airway hyperresponsiveness and eosinophilic inflammation (250, 372).

Formaldehyde is another common pollutant present in air, furniture, paint, and plastics, and notably an ingredient found in cigarettes and e-cigarettes. Formaldehyde can cross the placenta and enter fetal tissues (280), and it is therefore not surprising that exposure to ambient formaldehyde was associated with low birth weight (100, 223). To examine the underlying mechanism between formaldehyde and fetal lung growth, pregnant rats were exposed to formaldehyde inhalation throughout gestation. The investigators found that low dose of formaldehyde exposure (0.92 mg/m^3) during pregnancy suppresses the development of the allergic lung response in offspring and ASM (tracheal) contraction to a cholinergic stimulus (218) involving modifications to toll-like receptor 4 gene expression as well as nuclear factor kappa-light-chain-enhancer of activated B cells activity and reduced gene expression of IL-6 (pro-inflammatory) and increased gene expression of IL-10 (anti-inflammatory) (323). However, prenatal high-dose exposure to formaldehyde (6.13 mg/m^3) resulted in offspring developing features

of neutrophilic asthma (influx of neutrophils into the lung and increased myeloperoxidase activity) (219).

There are mixed reports in regard to the association between *in utero* exposure to pets and farm animals with asthma on whether it is protective (79) or detrimental (36, 77, 84, 137) to postnatal risk of asthma. A study based on the European study on atopy and asthma in children of farming parents, known as the "Prevention of Allergy—Risk factors for Sensitization in children related to Farming and Anthroposophic Lifestyle study", showed that children with prenatal exposure to farm animals had an odds ratio of 0.65 for developing asthma, potentially due to maternal immune responses to farm exposures priming the developing fetal immune system (79). However, two studies using Mexican American (84), Finnish, and Russian (137) populations found that children with prenatal farm animal exposure had an increased odds ratio for allergic asthma. These conflicting data suggest that the relationship of prenatal exposure to farm animals with the risk of asthma might not be uniform across all populations. The explanations for the discrepancies between studies included: (i) intensity and/or frequency of the exposure; (ii) level of microbial burden already present; (iii) hygiene hypothesis whereby a lack of exposure to microbial organisms in a child's early years contributes to the development of asthma and allergic diseases; and (iv) genetic variables.

The strong association between HDM, allergic sensitization, and asthma in humans has been shown repeatedly (312, 338). Because of this strong association, HDM is a popular agent to induce allergy in mice to study allergic disease; however, the duration and concentration of induction produce different phenotypes of response (62, 397) which is much the same in humans (43). Relevant to our review, maternal HDM exposure during pregnancy has been shown to be sufficient to enhance neonatal sensitivity to HDM as the adult offspring exhibit airway hyperresponsiveness, airway inflammation, Th2 cytokine production, increased immunoglobulin levels, and a modest decrease in the phagocytic capacity of pulmonary macrophage populations following HDM exposure in offspring (292).

Collectively, exposure to environmental pollutants, toxins, or allergens during pregnancy has significant impacts on asthma in offspring. Importantly, the timing of exposure during gestation appears to be an important factor in determining the influence of the insult to subsequent abnormalities in airway/lung structure–function. Even under the most hygienic conditions, or diligent allergen avoidance, limiting any exposure might be difficult in susceptible individuals (131).

Maternal obesity and diet

Mothers who are overweight or obese prior to pregnancy have greater risk of a number of maternal and fetal/neonatal complications, and specifically relevant to this review, wheezing and asthma (67, 123, 186, 212, 282, 286, 414). The relationship between maternal overweight and obese phenotypes and asthma is not mediated by lower cortisol levels (67), postnatal growth, and infectious or atopic mechanisms (186). On the other hand, extreme low or high gestational weight gain are risk factors for low birth weight (187) and childhood asthma (98, 123, 186, 261, 283). Considering that fetal immune development commences mid-gestation (85) and the airways and lungs develop throughout gestation (Figure 5), what a pregnant woman consumes during pregnancy is expected to be important to respiratory system development and risk of obstructive disease (71). For example, maternal undernutrition (208), overweight or obesity (123, 310), or specific diet such as high-fiber intake (352), which are all associated with offspring somatic growth and susceptibility to asthma.

It is known that there are multidirectional effects of maternal pre-pregnancy obesity on fetal growth: pre-pregnancy obesity has a high association with IUGR, low birth weight, and macrosomia (187), but our focus is on the association among pre-pregnancy obesity, IUGR, and low birth weight and subsequent risk on obstructive airway diseases. Examples of an imbalanced diet-related increased risk of offspring asthma include high intake of sugar (19), fructose (399), artificially sweetened soft drinks (227, 399), fast-food (371), and high-inflammatory diet (51). The above foods have overlapping ingredients and it is therefore critical to isolate the exact causal agent, in particular fructose, which is the sugar component present in many unhealthy diets.

Animal studies are important to isolate the specific impact of various food components consumed during pregnancy. In a mouse model of high-fat diet during pregnancy, placental inflammation was observed, resulting in placental insufficiency and IUGR (229). Maternal high-fat diet exposure delayed structural lung development where fetuses at 18 d GA exhibited lung morphology more comparable to 15 to 16 d GA, and less overall lung maturation, reflected by increased cytoplasmic glycogen content and reduced cellular proliferation (229). At 2 weeks of age (juvenile period) mice, there was no impact of maternal high-fat diet on offspring lung function (resistance, tissue damping, or elastance) or inflammation (330). However, offspring of a maternal high-fat diet mouse model in adulthood exhibited airway inflammation (increased airway neutrophils and IL-6) and increased airway reactivity post-methacholine challenge (114, 211). In general, it appears that consumption of these foods causes allergic disease by interfering with the developing immune system and shifting the Th1/Th2 immune response balance toward a Th2 profile. Further, the offspring's diet quality was positively associated with their mother's antenatal diet quality (24), therefore, demonstrating that intergenerational influences and maternal biology and behavior can affect the intrauterine environment and the developing fetus, which will enhance or reduce the risk for developing asthma or COPD in later life.

The obese-asthmatic phenotype is highly heterogenous and is less responsive to treatment [see review for further

details (373)]. Given that transference of maternal obesity to offspring may increase the risk of asthma, education, and guidance to women of reproductive age on the need to consume a healthy diet to improve their own health before, during, and after pregnancy is also important to optimize the health of their infants (224).

Hypoxia

The fetus solely depends on the mother to receive oxygen and the amount of oxygen received is directly related to fetal growth (30), which explains why any suboptimal oxygen delivery will impact fetal, airway, and lung growth. There are many reasons that could contribute to a reduction in oxygen delivery from the mother to the fetus, including placental insufficiency, preeclampsia that reduces blood flow, maternal smoking, or living at high altitude, which reduces the amount of oxygen in circulation. Children that were born and continued to stay at high altitude face an enhanced risk of hospitalization for asthma (166). Furthermore, data from children born at high altitude in Colorado suggest that birth at high altitude increases rehospitalization following infection with respiratory syncytial virus (52). We and others have shown that hypoxia could stimulate ASM growth via proliferation (58, 124, 381). To isolate the role of hypoxia on airway development, we have utilized a rodent model of maternal hypoxia-induced IUGR to show that when hypoxia was introduced during the pseudoglandular-canalicular phase of airway growth, functionally, IUGR offspring exhibited changes in airway responsiveness to methacholine in a sex- and age-dependent manner: male offspring exhibited airway hyperresponsiveness during the juvenile period while female offspring exhibited airway hyperresponsiveness during adulthood (379). Both male and female mice had stiffer airways (trachea) (255) and longer half-relaxation times after twitch contractions of the diaphragm muscle, postulated to be due to changes in the actions of the sarcoendoplasmic reticulum Ca^{2+}-ATPase pump (99). Structurally, we found that hypoxia can indeed increase ASM thickness when the fetus is still exposed to hypoxic conditions (381); however, the effect is not permanent as the thickness of the ASM layer observed in IUGR offspring was normalized once normoxia was restored (379, 381).

Male rat offspring after maternal hypoxia have increased heterogeneity in airway caliber in adulthood compared with control (380), which was mathematically predicted to favor the onset of airway hyperresponsiveness, supporting direct measurements in mice after maternal hypoxia (379). Additionally, maternal hypoxia-induced-IUGR offspring have higher airway inflammation as demonstrated by increased inflammatory cell count (macrophages) in the bronchoalveolar lavage fluid in the absence of systemic inflammation (207, 380). Thus, the exposure to hypoxia during gestation can adversely impact airway function, structure, and heighten inflammation that increases susceptibility to asthma or COPD.

Given that allergy remains the strongest risk factor for the development asthma, and in practice, an individual would repeatedly be exposed to allergens from the environment throughout life, it is safe to hypothesize that when IUGR-affected offspring are sensitized and challenged to an allergen throughout life, they would experience airway hyperresponsiveness. We have therefore further characterized the separate and combined effect of IUGR and allergic inflammation on airway responsiveness (160). We found that IUGR and allergic inflammation can independently lead to airway hyperresponsiveness, but there was no greater effect when exposures were combined. Hence, it appears that IUGR itself might be associated with asthma by affecting baseline airway responsiveness rather than susceptibility to allergen (160).

Sheep studies that generate IUGR offspring via placental restriction (hypoxia throughout gestation) have shown delayed surfactant protein maturation (263) due to an increased lung prolyl hydroxylase domain (PHD) and decreased glucocorticoid receptor (264) in the fetuses that persisted into postnatal life (334). However, when IUGR fetuses were generated via housing of ewes in hypoxic conditions for a month in late gestation, there was increased surfactant maturation at the molecular level without any changes in the numerical density of surfactant-positive cells in lung tissue of hypoxic offspring (234). When interventions were administered to these IUGR fetuses *in utero* (PHD inhibitor and recombinant human VEGF), it appears that there was limited responsiveness of the IUGR lungs, which could be due to a biochemical limit or reduced plasticity to respond to changes in the regulation of hypoxia signaling following exposure to hypoxia conditions *in utero* (236, 237). Differences between studies reinforce the importance of the timing of hypoxia insult on the fetuses as airways and lungs do not grow linearly during gestation.

Pregnancy complications—preeclampsia and diabetes

Preeclampsia is a pregnancy complication characterized by high blood pressure and dysfunction in other organs, most often the liver or kidneys. Preeclampsia begins before 20 weeks of gestation with angiogenic biomarkers of preeclampsia detectable as early as 10 weeks of gestation. Preeclampsia leads to reduced uterine blood flow and contributes to fetal hypoxia, which results in IUGR (354). In terms of a potential positive association between preeclampsia and offspring asthma, eczema, allergy, lower lung function, and respiratory morbidity, there are conflicting data, with some supporting such associations (39, 203, 215, 343, 414) and others reporting no correlation (8, 40, 318, 343), which may be related to geographic differences or differences in asthma phenotype (8). Any association between prenatal disorders and postnatal respiratory health may be trimester specific (early and late pregnancy) (203, 394) and also depend on the severity of the preeclampsia condition (severe but not mild/moderate) (39). There are some pregnant women who

experience gestational hypertension without any signs of damage to other organs with conflicting data as to whether higher blood pressure in pregnant women is associated with lower lung function (FEV_1/FVC) and increased risks of current wheezing and current asthma in children (394, 414) or not (318). The potential mechanisms include Th2-mediated inflammation and overproduction of anti-angiogenic factors in amniotic fluid.

Gestational diabetes, defined as hyperglycemia identified during pregnancy, increases the risk of a range of adverse maternal and perinatal outcomes that are critical in the relationship with wheezing and asthma, including preeclampsia and obesity. There are again conflicting results on the association between maternal gestational diabetes and type 2 diabetes during pregnancy with risk of offspring asthma, with some studies showing increased risk (226, 243, 297) and others not (407, 414). Discrepancies in findings could be due to differences in the age of the children included in the studies. Diabetes in pregnancy was not associated with offspring wheezing from birth to 24 months of age (414). However, after evaluation of persistent wheezing in children aged 6 to 7 years of age, there was greater risk associated with diabetes in pregnancy (297). A mouse model of diet-induced gestational diabetes reported sex differences in offspring respiratory health where female offspring exhibited increased airway inflammation and matrix metalloproteinases, airway resistance, tissue damping, and lung elasticity in response to methacholine, while male offspring had increased baseline lung compliance (274). Data therefore demonstrate that multiple *in utero* factors are at play when determining offspring respiratory health.

Maternal stress and mental well-being

Maternal stress is related to impaired fetal growth (188) and childhood asthma (216) and decline in lung function [FEV_1, FVC, and $FEF_{25\%-75\%}$] (183). In children at 7 years of age, prenatal exposure to high levels of stress was associated with symmetric reductions in FEV_1 and FVC which may predispose these children to future COPD and asthma (183). It appears that exposure to anxiety and depression had the strongest effect compared with other stressors and exposure during the third trimester had the greatest impact compared with the first and second trimesters (92). Animal studies showed that pathways by which stress predisposes children to asthma are not clear, but could be due to delayed prenatal lung maturation (less extensive terminal sacs, surrounded by thicker mesenchymal tissue) and airway hyperresponsiveness in female offspring (408), disruption in immune (eosinophilic inflammation) (194, 408), and neuroendocrine function (163). Paternal psychosocial stress though was not associated with offspring asthma at 7 years of age (216).

Maternal asthma and other illnesses

Maternal asthma during pregnancy is associated with reduced fetal growth (247) independent of preterm birth (56) that may be due to altered placental glucocorticoid metabolism (57). Maternal asthma is a known risk factor for asthma development in children (197, 261) with one study showing a significant increase in asthma risk among children whose mothers had poor control and increased severity of asthma during pregnancy (225). The potential mechanism could be due to increased pro-inflammatory IgG glycosylation patterns in mothers and offspring (332), hypoxia as maternal asthma exacerbations reduce fetal oxygen (60) or genetics (199). Paternal asthma does impose a risk on offspring asthma, however, maternal asthma conferred a greater risk of disease than paternal asthma (odds ratio of 3.04 vs. 2.44) (195, 197). Interestingly, maternal asthma is associated with lower lung function (time to reach peak tidal expiratory flow as a percentage of total expiratory time) in male, but not female, 5 to 6-week-old infants (65). Healthy pre-pregnancy dietary patterns (113) and regular monitoring (295) to control obesity, control of anxiety/depression (115), and smoking cessation (295) could be good interventions for maternal asthma control. A randomized controlled trial has suggested that inhaled corticosteroid step-down therapy could be considered when eosinophilic inflammation or symptoms are low for pregnant asthmatic women to minimize medication exposure during pregnancy (248). Other maternal illnesses during pregnancy that were associated with increased risk of offspring asthma include anemia (122) and hyperthyroidism (200).

Assisted reproduction technologies, drugs, vitamin A, and folate

There are conflicting results as to whether individuals born using assisted reproduction technologies will have a higher risk of asthma in later life (46, 86, 159) or not (47, 170, 392). A meta-analysis has suggested a trend toward a significantly increased risk of asthma (risk ratio of 1.28), but not allergies, in offspring conceived after assisted reproduction technologies (393). Maternal use of antibiotics during pregnancy has been associated with low birth weight and altered DNA methylation that controls growth (369), which may explain the association between maternal antibiotics with increased risk of childhood wheeze (164) and asthma (206, 243, 344) regardless on which trimester the antibiotics were consumed (206). The effect also appeared to be dose dependent (206, 344). Low-dose aspirin is commonly prescribed to prevent recurrent pregnancy loss associated with antiphospholipid syndrome and preeclampsia and is often used throughout pregnancy. However, *in utero* exposure to aspirin was associated with an increased risk of childhood asthma (adjusted odds ratio = 1.3) (53). There are also some vitamins, specifically vitamin A (272) and folate (190), that when taken at levels higher than recommended during pregnancy are associated with asthma.

Transgenerational impact

Population studies show that transgenerational transmission of birth weight persists across three generations whereby

females born with low birth weight have a high risk of producing low birth weight infants (171). There is also evidence that smoke exposure during pregnancy can lead to multigenerational transmission of asthma whereby maternal grandmother smoking is associated with an increased risk of asthma and lower lung function (FEV_1/FVC) for the grandchildren (31, 191, 205, 217). In mouse models, F0 exposure to smoke or diesel exhaust particles induces asthma phenotypes and epigenetic alterations in dendritic cells and gonads in subsequent generations (198, 290), which may contribute to known sex differences in asthma. In another mouse model where F0 was exposed to allergen sensitization during pregnancy, adult F2 offspring exhibit airway hyperreactivity but no changes to airway inflammation or airway sensory nerve density (182). In addition, there were significant epigenetic changes to the airway epithelium and vagal ganglion sensory neurons that regulate lung development and inflammation such as Wnt and platelet-derived growth factor signaling pathways (182). It is not known whether IUGR alone, independent of environmental toxins, exhibits a similar transgenerational risk of asthma.

Physiological Mechanisms for Postnatal Respiratory Impairment

The previous sections have described structural and mechanical changes accompanying an adverse intrauterine environment. Based on our contemporary knowledge of airway and lung physiology, we can propose a framework for how these early life abnormalities contribute to respiratory impairment and hence a future diagnosis of asthma or COPD. To set the scene, a basic overview of the physiology of airflow is first provided; other more focused reviews are recommended (125, 210, 245).

A brief commentary on the physiology of airflow

Obstructive disease is generally identified by expiratory flow limitation, conventionally through a maximal forced spirometric maneuver, and is distinct from restrictive disease, characterized by difficulty in lung inflation. Both disease processes can however occur simultaneously (74, 116). Forced expiratory volume in the first second is reduced in obstructive disease, more than FVC which is not rate dependent, but can fall if pulmonary spaces are no longer patent, such that there is incomplete emptying (34). Forced oscillometry and plethysmography may also reveal defects at or near normal tidal volume, most notably an increase in airway resistance (or reduced conductance) (155, 156, 363). The latter plethysmographic approach detects changes in absolute lung volume (385) which reflects gas trapping or changes in elastic recoil pressure.

Focusing on the determinants of airflow, fundamentally, at least at the level of the individual airway, driving pressure-producing flow is opposed by resistance. During a forced expiratory maneuver, driving pressure is the summation of pressures generated by expiratory skeletal muscle contraction (internal intercoastal and abdominal muscles) and lung elastic recoil pressure, that is dependent on tissue compliance/elastance. Resistance is inversely related to lumen radius to the fourth power, a mathematical confirmation that any factor reducing lumen size will significantly increase airway resistance.

Activation of circumferentially distributed ASM by exogenous or endogenous stimuli (including neural innervation) shortens each muscle cell and tensions the entire ASM layer. "Active tension" is proportional to the thickness of the ASM layer (174, 213) due to a greater number of contractile units working in parallel. According to the law of Laplace, an increase in wall tension generates a collapse pressure that favors lumen narrowing, that is, bronchoconstriction ensues which in turn increases resistance. The magnitude of ASM tension generated is influenced by the dose of stimulus and density/affinity of receptors (17, 111, 132) and the position of the ASM on its length–tension curve (339). The length–tension curve can however be modified by a process known as length adaptation, wherein contractile response is optimized by prolonged exposure to a particular muscle length (10, 249, 382). Force adaptation has also been documented, whereby the muscle's mechanical response is optimized after prolonged activation to low levels of contractile stimuli (28, 273).

There has been some consideration of ASM contractile phenotype in the normal and abnormal airway. A broad definition is the mechanical capacity of ASM for a given thickness or cross-sectional area. Most often, contractile phenotype is the amount of force the ASM layer produces for per cross-sectional area (contractile stress). The debate as to whether contractile phenotype changes in disease remains alive (117, 271), although transient increases in contractility are very likely with the inflammatory milieu (321, 346, 411) present in patients with asthma and COPD.

Contraction of ASM is opposed by mechanical after-loads that limit airway narrowing. Mechanical loads arise from within the airway wall, such as the compressibility of the inner mucosa (316, 390) and external cartilaginous constraints (150, 256), or parenchymal elastic after-loads that develop as the outer surface of the airway pulls away from surrounding alveoli (173, 304). When modeling airway narrowing, it is often assumed that airways narrow according to their pressure–volume curve (213) which emphasizes the importance of airway wall compliance.

In addition to ASM contraction, the lumen of conducting airways can be obstructed by mucus deposition and released from submucosal glands or epithelial goblet cells. Mucosal glands are more proximally distributed, compared with goblet cells which extend further down the bronchial tree (296, 389). Mucus release can result in partial obstruction of the lumen, or complete occlusion, referred to as a "mucus plug" (48, 76).

Finally, it is oversimplistic to consider airflow at the level of a single airway. Flow in and out of the lung is an

amalgamation of contributions from interconnected proximal and distal airways and interdependence forces exerted by surrounding parenchyma (6, 367). That is to say, changes to the caliber of airways in one region of the lung will impact another and importantly the final global signal measured at the mouth during spirometry. Ventilation heterogeneity measured by multiple breath nitrogen washout is positively correlated to an excessive fall in FEV_1 induced by methacholine (80).

A physiological explanation for risk of disease after prenatal complications

While preclinical animal models have been essential in identifying the biological consequences of prenatal exposures, we choose to reinterpret all findings (humans or otherwise) in the context of how they affect human lung function. The collective evidence indicates that an adverse intrauterine environment is related to obstructive disease through changes in: (i) ASM structure–function; (ii) goblet cell biology; (iii) airway stiffness; (iv) geometry of the bronchial tree; (v) lung structure and mechanics; (vi) respiratory skeletal muscle contraction; and (vii) pulmonary inflammation. While we feel that discussing these concepts as a general summary of the experimental evidence generated will be more helpful to the reader, it is recognized that specific exposures may set the individual along different trajectories.

There is little doubt about the important role of ASM remodeling in asthma (45, 144) and to a lesser extent in COPD (27, 144). Thickening of the ASM layer is implicated in the onset of airway hyperresponsiveness (174, 254). There is however variability between patients in terms of the amount of ASM remodeling, with some patients expressing prodigious remodeling throughout the bronchial tree, and others very little (142). It is expected that "structural" phenotypes may be important when considering the choice of therapy (78) and even predicting patient response. An excellent example of the relationship between patient response and the presence of ASM remodeling is the study by Stoltz et al., in which patients with COPD who had higher amounts of ASM in biopsy reported a greater response to inhaled corticosteroids compared with those who had low amounts of ASM (345).

Prenatal complications are associated with changes in ASM proliferation (124), ASM thickness (305, 381), number of cells per length of airway and volume fraction of ECM within the ASM layer (377), and contractility (255). The significance of an increase in ASM proliferation is intuitive, potentially leading to an increase in ASM thickness and therefore airway narrowing, resistance, and airflow limitation. An increase in the number of ASM cells is again expected to upregulate force generation as this represents a greater number of contractile units. Changes to ECM within the ASM are perhaps less intuitive, but there is evidence that ECM-related stiffening increases ASM contractility (5). A disproportionate increase in ECM is a feature of COPD (152) and is accompanied by an increase in acetylcholine-induced narrowing of bronchial segments (42). It is important to acknowledge that it remains unclear to what degree neonatal ASM remodeling persists into later life, for example, in one study, remodeling was identified only 7 days after delivery in a sheep model of preterm birth and lipopolysaccharide exposure (305). In another study, abnormalities in ASM structure were resolved completely once the prenatal disturbance (hypoxia) was removed in fetal mice (381). Whether changes in ASM cell number and ECM proportion within the ASM layer in low birth weight infants (377) also persists into adulthood is again unclear. Regardless, it is reasonable to assume that ASM is malleable *in utero* and even if it appears macroscopically normal, enhanced contractility will contribute to airway hyperresponsiveness.

A signal for abnormal goblet cell development after prenatal insult is highly relevant to obstructive disease. Mucus cell hyperplasia is a feature of asthma (3, 262) and COPD (167, 299). As discussed, excessive mucus production may lead to plugs that partially or completely obstruct the lumen (268). Hence, exposures that enhance goblet cell hyperplasia (9, 201) are very likely to contribute to airflow limitation. It is somewhat paradoxical that in a mouse model of prenatal second-hand smoke, there was inhibition of allergen-induced goblet cell differentiation and mucus production (326). An effective mucociliary clearance system is of course important for the removal of toxins, such that any deficiency may leave the airway vulnerable to injury (89).

Increased airway stiffness has been documented in asthma (32) and COPD (75). For a given distending pressure (transmural pressure), lumen radius will be reduced, and resistance will be increased in stiffer airways. Tracheal stiffness was dramatically increased (~70%) in a mouse model of IUGR (255). While there will be reasonable questions over the applicability of findings in a trachea to the lower bronchial tree, the most important aspect of the study was that changes in airway mechanics were observed at 8 weeks of age, that is, into the mature stage of the mouse. These findings show clearly that *in utero* complications may produce life-long abnormalities in airway mechanics that seem directly relevant to patients with obstructive disease.

A consequence of an adverse intrauterine environment is disrupted morphology or geometry of the bronchial tree. Reduced diameter or increased length of airways (396) will increase resistance as stated by Poiseuille's equation, while the addition of points of branching (396) causes turbulent airflow, requiring a greater driving pressure and therefore work of breathing (277). There is a more heterogenous distribution of airway caliber (cross-sectional area) in 7-week-old rats that were previously subject to IUGR (380). The importance of heterogeneity in structure and function to obstructive disease is now well recognized but may be particularly relevant in asthma. Ventilation heterogeneity is associated with airway hyperresponsiveness in patients with asthma, but not COPD (119). Using data obtained from the rat model (heterogenous airway caliber), a mathematical simulation predicted greater resistance in response to a theoretical agonist, an effect driven by variable airway compliance (380).

The conclusion from the simulation was that the developmental consequence of variable airway caliber may contribute to airway hyperresponsiveness.

Structural and mechanical changes to lung parenchyma are a prominent feature of COPD. Emphysematous disease involves the destruction of alveoli and increases lung compliance, manifesting as a fall in elastic recoil pressure. While perhaps less well appreciated, loss of elastic recoil pressure has also been documented in chronic persistent asthma (108) with histological evidence of emphysema in nonsmoking subjects (106, 107). Loss of elastic recoil pressure contributes to airflow limitation through a reduction in driving pressure. However, the collective evidence from animal studies is that prenatal disturbances increase lung stiffness (9), a measurement that may be affected by reductions in lung volume (9, 258) which has also been documented. Reported histological changes that potentially affect lung compliance include modification of alveolarisation (41, 258) and fibrotic disease (9). A reduction in surfactant production and maturation (263, 402) could also account for greater lung stiffness, although under some scenarios, there is an increase in surfactant maturation (234).

When considering diagnostic detection of obstructive disease, the other important element is respiratory muscle strength that is required for an effective maximal forced expiratory maneuver in the measurement of FEV_1. Outside the scenario of preterm birth (63), there is no substantial amount of information to support respiratory skeletal muscle dysfunction as a consequence of a suboptimal *in utero* environment. Prenatal disturbances can affect diaphragm function (the muscle chosen for study in an organ bath system) including reduced force production, impaired fatigue resistance, and longer relaxation times (99). Together these observations indicate that prenatal disturbances result in a weaker diaphragm and disease that is likely more susceptible to failure under high respiratory loads. However, extrapolation of these findings to other muscle types is dangerous due to differences in fiber type. Intercoastal muscles have a greater proportion of slow-twitch fibers compared with diaphragm and abdominal muscles (242, 284). If all respiratory muscles are affected in a manner similar to the diaphragm, pressures generated during expiration are expected to be lower and that will in turn affect volumes recorded during spirometry.

Airway inflammation is a substantial determinant of morbidity in obstructive disease and includes eosinophilic and neutrophilic infiltrates (109). The inflammatory cascade increases ASM contractility (321, 346, 411) and airway hyperresponsiveness (169, 285), stimulates mucus release (88), activates irritant receptors contributing to symptoms such as cough (54), and is still widely regarded as the chief cause of remodeling (375). The implications of inflammation to respiratory health are demonstrated by improved disease control after nonspecific (16) and specific (161) pharmacological resolution of inflammation in patients with asthma. In comparison, anti-inflammatory therapy is much less effective in COPD (82). It stands to reason that a defective inflammatory response from the beginning of life increases susceptibility to obstructive disease. There are numerous documented changes to the inflammatory response after prenatal disturbances in the absence of any allergens or environmental triggers as evident by an increase in airway, lung, and systemic pro-inflammatory cytokines levels, for example, IL-4, IL-17, TNF-α, and inflammatory cells (eosinophils, neutrophils, and lymphocytes). Many of these inflammatory biomarkers are adversely expressed in obstructive airway disease (15). Intrauterine growth restriction is associated with altered epigenetic mechanisms in the lung which are important in the control of inflammation (41, 406), which may explain why there was no additional effect of allergy on airway responsiveness in maternal hypoxia-induced IUGR offspring (160). As discussed in a previous review (378), other prenatal insults which also induced IUGR did exhibit a heightened inflammatory response when subsequently exposed to allergen.

What the above serves to outline is that the respiratory system is complicated (with many working parts) and that there is a considerable opportunity for any developmental disorder to produce changes that compromise function in the postnatal period. There may not be one consistent change and we acknowledge again that the nature of the insult is expected to be important. Much more research on the physiological consequences of prenatal disorders is required before clear patterns can be identified. The diversity of pathology developed as a result of an adverse intrauterine environment is certainly problematic for treatment strategies. Below, we use IUGR, regardless of its specific cause, as a scenario where an interventional approach may be feasible.

Potential Treatments to Reverse the Effects of IUGR on Respiratory Health

There has been an ongoing effort to "rescue" fetuses that are at an increased risk of IUGR and low birth weight to prevent them from developing disease in later life. For example, aspirin has been prescribed to expectant mothers to prevent preeclampsia and IUGR, however, there are conflicting reports on how aspirin affects offspring health. Aspirin has been shown to improve neurodevelopment up to the age of 18 months (175) but increases the risk of childhood asthma at 6 years of age (53). Another drug prescribed to expecting mothers at risk of preeclampsia and IUGR is oral L-arginine that helps in regulating blood pressure through vasodilation (112). Other studies show that oral L-arginine supplementation in severe asthmatics leads to low fractional exhaled nitric oxide (reflecting eosinophilic disease) but does not reduce asthma exacerbation rates (192). The potential benefits of prenatal oral L-arginine on offspring respiratory health should be further assessed. Resveratrol is an antioxidant and anti-inflammatory agent which have been shown in population, cell culture, and animal studies to have a protective role against respiratory disease (398). Resveratrol

has also been considered as a potential therapeutic agent in several pregnancy-related disorders, such as preeclampsia and IUGR as it improves fetal development *in utero* (287). Postnatally, one study in maternal high-fat diet-induced obese mice showed that treatment with resveratrol during pregnancy was able to reduce retroperitoneal adiposity in offspring (356). Animal studies have also demonstrated the benefits of maternal resveratrol intervention on offspring cardiovascular and metabolic health (317) but there were concerning alterations in fetal pancreatic development (293). MitoQ, another antioxidant that targets the mitochondria and enhances nitric oxide signaling, has been shown in animal studies to improve the cardiovascular health of IUGR offspring exposed to hypoxic conditions during gestation (4, 29). The balance between pro-oxidants and antioxidants is important to prevent harmful effects of oxidative stress on lung maturation *in utero*; therefore, the impact of both resveratrol and MitoQ (see below) on the respiratory health of offspring affected by IUGR requires investigation.

Keeping in line with the antioxidant theme, data from the Vitamin C to Decrease the Effects of Smoking in Pregnancy on Infant Lung Function (VCSIP) study have demonstrated promising results using an oral vitamin C supplementation for pregnant smokers (230–233). In this randomized clinical trial, individuals aged 15 years or older who self-reported as female and had a singleton gestation between 13 and 22 weeks and were current cigarette smokers (≥1 cigarette in the last week) were randomized to vitamin C (500 mg/d) or a similar placebo, stratified by GA (≤18 vs. >18 weeks). Although the average birth weight of the offspring from this cohort was not considered as low birth weight, 10.7% were IUGR-affected infants and 11.3% preterm (230). Airway function and respiratory outcomes of wheeze in offspring born to pregnant smokers randomized to vitamin C were improved at birth (230), 3 months (233), 12 months (232), and 5 years of age (231). Initiation of the vitamin C intervention before 18 week GA may have had a greater effect on the occurrence of wheeze compared with treatment initiated after 18 week GA (231). No serious adverse events were related to the intervention; therefore, a simple and low-risk supplemental vitamin C appears to be a favorable treatment.

Evidence from animal studies show that maternal daily vitamin C treatment (200 mg/kg, intravenously) for a month in the late gestation in sheep increases the expression of gene (but not protein) regulating pathways that are essential for normal lung maturation development, suggesting that maternal vitamin C treatment helps to prepare the fetuses for exposure to the air-breathing environment after birth (235). As mentioned by the VCSIP investigators, future follow-up studies in this cohort that acquire additional airway function and structure data may provide more insights on the effect of supplemental vitamin C on airway development and therefore postnatal structure–function. If the beneficial effects observed persist throughout life, then this may be a useful approach to reduce the health burden of airway pathophysiology due to IUGR that increases susceptibility to obstructive airway disease.

Although the VCSIP study shows promising results for vitamin C, vitamin C is a relatively weak antioxidant. Therefore, studies have started to focus on antioxidants that have greater antioxidant capacity or more targeted effects on the oxidative stress pathway at the cellular level. Since mitochondria are a major site of reactive oxygen species production, mitochondria-targeted antioxidant therapy may provide a more focused therapeutic strategy. MitoQ is a promising candidate as it is a mitochondria-targeted antioxidant that blocks lipid peroxidation but does not directly affect mitochondrial superoxide production or react to any substantial extent with superoxide (329). In a sheep study at 105 d GA, pregnant sheep were randomly assigned to one of four treatment groups: normoxic saline, normoxic MitoQ, hypoxic saline, or hypoxic MitoQ (204). There was no significant effect of MitoQ treatment on either fetal body or total or relative lung weight. However, maternal treatment with MitoQ during late gestation promoted fetal pulmonary surfactant maturation, which is important to prepare the fetal lung for air breathing, and an increase in the expression of lung mitochondrial complexes III and V independent of oxygenation. Maternal treatment with MitoQ in hypoxic pregnancy also increased the expression of genes regulating liquid reabsorption in the fetal lung that is important to enable the lung to function as the primary organ of gas exchange at birth (204). These data suggest that MitoQ as an antenatal targeted antioxidant treatment may improve lung maturation in the late gestation sheep fetus.

Meta-analyses have repeatedly identified higher maternal vitamin D and E intake during pregnancy to be associated with a reduced likelihood of wheezing illness or asthma in children (18, 91, 401). Maternal vitamin D status was not associated with alterations in somatic growth (fetal or postnatal) in human and mouse studies, therefore suggesting that vitamin D deficiency does not alter airway function/structure through IUGR (412, 413). Increased maternal vitamin D has an impact on airway epithelial cell secretory function; airway epithelial cells of human neonates that were exposed to maternal dietary vitamin D and stimulated with IL-1β/TNF-α were associated with decreased IL-3 (pro-inflammatory cytokine) but increased IL-10 (anti-inflammatory cytokine) release (240). Using a mouse model of maternal vitamin D deficiency, data demonstrated that vitamin D deficiency results in increased airway resistance, airway remodeling (smaller lung volume, volume of parenchyma, and alveolar septa), and inflammation in the offspring (95, 97, 412). Genes involved in embryonic organ development, pattern formation, branching morphogenesis, Wnt signaling, and inflammation were altered in vitamin D-deficient offspring that were evident in adulthood (95), but not during prenatal life (50). Interestingly, the association between low maternal vitamin D and E stops after 15 years of age with the authors suggesting that other postnatal exposures predominate in the etiology of incident asthma as children transition through puberty into adulthood (72).

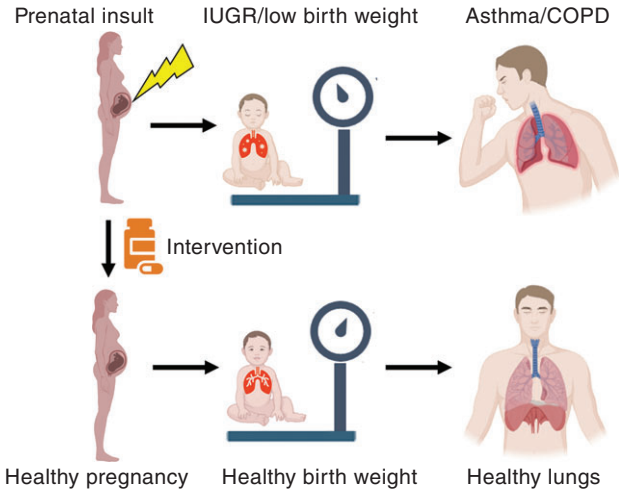

Figure 8 **Prenatal environment and respiratory health in later life.** Prenatal exposures can disrupt body growth which may be a symptom of other biological changes, including those to the respiratory system that subsequently increase the risk of obstructive diseases such as asthma and COPD. Treatments to reverse the effects of prenatal insults should be considered to promote fetal growth and ultimately healthy lungs. COPD, chronic obstructive pulmonary disease; IUGR, intrauterine growth restriction. Created with BioRender.com.

Maternal omega-3 polyunsaturated fatty acids supplementation has been shown to increase offspring body weight (1, 189) and could be due to increasing gestational period (1). However, there were mixed results on its effect in reducing the risk of childhood asthma. Two systematic reviews and a meta-analysis of randomized controlled clinical trials concluded that data on the effects (beneficial or not) of long-chain n-3 fatty acid supplements during pregnancy on offspring asthma is limited and requires further research (11, 23, 365). Nevertheless, it appears that sub-analysis to tease out dose (≥1200 mg) (149, 196) and GA (>22 weeks) (149) of omega-3 polyunsaturated fatty acids intake might demonstrate beneficial effects of maternal omega-3 polyunsaturated fatty acids on offspring respiratory health.

Conclusion

This review highlights very important population health data that establish normal and abnormal lung function trajectories. These studies demonstrate presentation of the obstructive disease phenotype early in postnatal life, often a diagnostic challenge to the treating physician. The onset of IUGR is a clear signal that fetal development has been perturbed and associations with asthma and COPD demonstrate that this disorder is worthy of further examination. There are many unknowns. How do we get from IUGR to obstructive disease? A primary goal of this literature review was to start to assemble the evidence for structural and mechanical change after prenatal disruption in terms of how this affects airflow measured in the lung function laboratory. Understanding the mechanism for any postnatal respiratory impairment with an *in utero* origin is important for disease modification. If the association between IUGR and asthma is due to ASM impairment, therapy in early life may be more effective if targeted at this tissue, compared with an association mediated by inflammatory pathways, which would of course require different (anti-inflammatory) pharmaceutical approaches that resolve cellular infiltrates.

We note that there may have been a bias toward asthma in discussing the impact of prenatal disorders, particularly when interpreting the results of animal studies. Yet many observations may equally apply to COPD, and this paradigm shift is evidenced by the 2023 GOLD guidelines which have expanded COPD classification to nonsmoking disorders, including abnormal lung development (2). Future directions are now to concentrate on changing the disease trajectory or to minimize the extent of the damage caused by a suboptimal *in utero* environment, whether it be by behavioral change, environmental national and international strategies, or administration of properly tested therapeutics (Figure 8).

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Related Articles

Development and Growth of the Human Lung
Development, Growth, and Aging of the Lung
Mechanical Properties of Airway Smooth Muscle
Morphometry of Airways
Lung Mechanics in Disease

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