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## The Role of Lung Function in Determining which Children Develop Asthma

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### Abstract

Longitudinal studies have demonstrated that altered indices of airway function, assessed shortly after birth, are a risk factor for the subsequent development of wheezing illnesses and asthma, and that these indices predict airway size and airway wall thickness in adult life. Pre- and post-natal factors that directly alter early airway function such as extreme prematurity and cigarette smoke may continue to affect airway function and hence the risks for wheeze and asthma. Early airway function and an associated asthma risk may also be indirectly influenced by immune system responses, respiratory viruses, the airway microbiome, genetics and epigenetics, especially if they affect airway epithelial dysfunction. Few if any interventions, apart from smoking avoidance, have been proven to alter the risks of developing asthma, but vitamin C supplementation to pregnant smokers may help decrease the effects of *in utero* smoke on offspring lung function. We conclude that airway size and the factors influencing this play an important role in determining the risk for asthma across the lifetime. Progress in asthma prevention is long overdue and this may benefit from carefully designed interventions in well phenotyped longitudinal birth cohorts with early airway function assessments monitored through to adulthood.

### Keywords

lung function; airway function; prenatal determinants; asthma; wheeze

### Introduction

The origins of many of the phenotypes of asthma occur during the fetal and early childhood period and children who develop asthma by age seven have been shown to have deficits in lung function as neonates (1). This commentary will summarize the role of lung function, as an index of airway functional size, as a risk factor for the subsequent development of

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wheezing illnesses and asthma. The commentary will also present the prenatal and the early postnatal factors important in determining early airway size and also factors that continue to influence airway function and the subsequent development of asthma. It will also present an example of potential primary prevention with vitamin C supplementation to pregnant smokers to mitigate the adverse effect of *in utero* smoke on lung development and function.

## Prenatal Determinants of Lung Function in Relation to Asthma

Airway disease begins early, through prenatal and early postnatal influences, and through transgenerational effects due to epigenetic changes. This early focus is a paradigm switch for many practitioners who, when seeing a wheezing child often ask about trigger factors and medical compliance, all very important, but not about early life factors such as prematurity and pregnancy exposures, which are key to prevention of asthma. There are multiple prenatal factors that can adversely affect lung development and place the infant on a lower lung function trajectory. This can impact the attainment of maximal lung function plateau in early adulthood and in turn impact their ability to achieve lifelong lung health (2–5). These factors can be broadly classified into often overlapping categories including: maternal environmental exposures/toxins and pregnancy complications, preterm birth with or without bronchopulmonary dysplasia (BPD), maternal nutrition and lifestyle. Early lung function is important in investigating these prenatal factors.

### Prenatal Environmental Exposures/Toxins

Prenatal environmental exposures that have been shown to be associated with lung development and lung function in term and preterm infants include exposure to nicotine and tobacco smoke, indoor and outdoor pollution, medication or drug exposure during pregnancy, antenatal inflammation, delivery mode, early postnatal oxygen supplementation and exposure to positive pressure ventilation (3;5). Exposure during pregnancy to various pollutants has been associated with early decreases in the offspring's spirometry (6;7). Household air pollution during pregnancy was associated with decreased lung function at one month of age and increased risk of pneumonia before one year of age (8).

Pulmonary and airway function testing has demonstrated the significant adverse effect of prenatal tobacco products exposure on lung/airway development and have linked these changes to subsequent childhood respiratory disease (9). This is one of the most potentially preventable insults to the developing lung and can impact lung development from multiple standpoints: pre-clinical data indicates prenatal nicotine exposure increases collagen deposition throughout the lung and airways (10) and increases airway branching among other effects (11); while smoking in pregnancy increases preterm delivery, low birth weight, and intrauterine growth restriction (IUGR) (12). All of the latter are also important factors of altered lung function as shown by lung function testing. Unfortunately, the prevalence of smoking during pregnancy continues to be about 10–12% in the United States and is still high throughout the world (13). World-wide over 50% of pregnant smokers continue during pregnancy (14). These findings are of particular concern with the increasing use of electronic cigarettes (9).

Cohort studies have reported that adverse respiratory outcomes related to *in utero* smoke exposure track into child and adulthood, with early and persistent decreases in offspring lung function (15–22). Infants (term and preterm) exposed to *in utero* smoke have decreased pulmonary function at birth that supports anatomic changes, including changes in flow volume characteristics, respiratory system compliance (Crs), and forced expiratory flows (FEFs), even before postnatal smoke exposure (20;23;24). Young children exposed to *in utero* smoke had 7–10% decreases in forced expiratory volume in one second (FEV<sub>1</sub>) (19) and infants exposed to *in utero* smoke had a lower maximal expiratory flow at functional residual capacity ( $\dot{V}_{maxFRC}$ ) than those not exposed (15). A prospective study of 2400 patients demonstrated decreased FEV<sub>1</sub> and other forced expiratory flows to 21 years of age after *in utero* smoke exposure, the *in utero* effect being much greater than that of post-natal exposure (22).

### Preterm Delivery

Prematurity (birth at < 37 weeks gestation) is the most common cause of altered lung and airway development, as maturation occurs postnatally under altered mechanical and environmental conditions, including active tidal breathing with strain and stretch of immature intrathoracic structures, and a state of relative hyperoxia, even with room air(3;5). Extremely preterm infants born at <28 weeks gestation are at high risk for BPD which is characterized by alveolar hypoplasia and obstructive airway disease (25;26). In addition to prematurity, other prenatal factors such as chorioamnionitis, preeclampsia, pre-existing hypertensive disorders, gestational diabetes, and maternal obesity are associated with an increased risk for BPD (12;27). For instance, a prospective, longitudinal study of 587 preterm infants demonstrated that maternal smoking during pregnancy and maternal hypertension each was associated with a significant two-fold increase in the odds of BPD after preterm birth (12). In infants with severe BPD studied at 55 weeks of postmenstrual age (PMA), three distinct phenotypes of lung function were identified, but 91% of the infants had airway obstruction (28). Serial measurements in BPD have also demonstrated significant reductions in expiratory flows into adulthood that tend to track along the same lung function percentile (29–32).

Lung function testing has demonstrated that healthy infants born only a few weeks prematurely also demonstrate altered lung development compared to term reference infants, with decreased Crs when measured at term PMA (33), and FEFs that remain decreased into childhood (34). This gives a physiologic basis for the increased asthma symptoms these infants demonstrate as a whole as they age, and offers the opportunity for potentially early identification of at risk children. Infants with tidal breathing measurements that were below the median shortly after birth were significantly more likely at 10 years of age to have a history of asthma (35). Lower  $\dot{V}_{maxFRC}$  in the first year of life was associated with increased risk of wheezing, as well as an increased risk for active asthma up to age 36 years (36).

### Maternal Nutrition/Supplements/Lifestyle

Maternal malnutrition, obesity, and micronutrient intake have all been shown to affect lung development and function. IUGR is a risk factor for decreased lung function in

infancy, childhood, and adulthood and although multi-factorial can be associated with poor nutrition. Several studies have demonstrated that term infants with IUGR had lower FEV<sub>1</sub> than normally grown age-matched school-aged peers (37;38). An obesogenic intra-uterine environment with increased oxidative stress and increased cytokine production has been associated with increased bronchodilator and steroid dispensing in early childhood (39). Maternal micronutrient intake (including supplemental vitamins A, C, D, and E) play a role in fetal lung development, protect against oxidant damage, are pro-angiogenic factors, and can modulate the inflammatory response that may impact lung development (40). In a double blind, randomized controlled trial (RCT), maternal vitamin A supplementation before, during, and after pregnancy in a malnourished Nepali population was shown to significantly improve the offspring's spirometry measurements at 9 to 13-years of age (41).

### Primary Prevention: Within our Grasp?

As outlined, antenatal events have a significant effect on lung development and therefore childhood asthma. This makes early intervention, at least as early as during prenatal care, a paramount priority if the incidence of asthma is to be decreased. An example of potential primary prevention is vitamin C supplementation in the face of *in utero* smoke to promote normal lung development.

Based on pre-clinical results in a pregnant primate model, two separate RCTs of vitamin C (500 mg/day) versus placebo to pregnant women unable to quit smoking cigarettes, have demonstrated improved lung/airway function in the offspring of the vitamin C supplemented smokers (23;42;43). The first study randomized 159 pregnant smokers at < 22 weeks gestation, and the vitamin C supplemented offspring had a significant increase in their neonatal tidal breathing parameters and Crs, and a 48% decrease in wheeze through 1-year of age (23). The second RCT randomized 252 pregnant smokers. The offspring of the vitamin C compared to the placebo group had significantly higher FEFs (FEF<sub>25-75</sub>, FEF<sub>50</sub>, FEF<sub>75</sub>) and FEV<sub>0.5</sub> by repeated measures analysis at 3 and 12-months of age (42;43). Follow-up through 5-years of age demonstrated sustained effects with higher FEFs and decreased wheeze at 4–6 years of age in the offspring of the vitamin C supplemented group (Figure 1A and 1B) (44). Vitamin C may be a safe and inexpensive intervention to mitigate the effects of smoking during pregnancy, in addition to continued cessation counseling.

**Fetal origins of asthma in children born at term**—As a group, patients with asthma have lower level of airway function than those without asthma. This is particularly true for asthma patients in the severe end of the spectrum, but also, to a lesser extent, for those with mild disease (45). Longitudinal studies have shown decreased growth in airway function in children (46;47) and increased lung function decline in adults with asthma, especially among those with recurrent exacerbations (48). The steepest deficits have been observed during the first years of life (Figure 2). A potential explanation for this association is that chronic airway inflammation, especially of the eosinophilic type, induces airway remodeling and, by this mechanism, causes airflow limitation. Cross-sectional studies showed that patients with asthma who had evidence of airflow limitation have increased proportion of sputum eosinophils as compared with those without airflow limitation (45). In a recent longitudinal study of asthma patients, Tang et al (49) reported that worsening of mucus

plugs in computed tomography (CT) lung scans after three years of follow up was associated with increase in airflow obstruction, and the presence of mucus plugs correlated with sputum eosinophilia. Taken together, these findings suggest that airflow limitation in asthma can be caused by the disease process itself, especially during the first years of life.

If alterations in airway function and, presumably, airway structure, may precede the development of asthma and predispose for its subsequent incidence has been the matter of intense scrutiny. Since in a high proportion of cases of asthma, the first symptoms occur during early life (50), testing such hypothesis requires long-term prospective studies in which airway function is assessed before the development of any symptoms, preferably during infancy. Results for several such studies are now available.

Haland et al (35) first reported that Norwegian children whose fraction of expiratory time to peak tidal expiratory flow to total expiratory time [tPTEF/tE] obtained from tidal breathing flow-time loops shortly after birth was at or below the median were more likely to have a history of asthma by 10 years of age than those whose tPTEF/tE was above the median. The tPTEF/tE ratio measured during the first months of life had been previously shown to predict wheezing lower respiratory illnesses by age one in the Tucson Children's Respiratory Study (TCRS) (51) and is an indirect index of airway obstruction (52). Subsequently, Hallas et al (53) showed in Danish children that airway function, as assessed by maximal mid-expiratory flows (MMEF), was significantly diminished from birth up to age 13 years in children who had asthma by that age. Using data from the Perth Infant Asthma Follow up study, Owens et al (54) showed that infants who had a  $\dot{V}_{maxFRC}$  at age 1 month that was below the median were 3.5–4 times more likely to have active asthma at ages 18 and 24 years than those who had  $\dot{V}_{maxFRC}$  above the median. More recently, Guerra et al. assessed the association of both tPTEF/tE and  $\dot{V}_{maxFRC}$  measured during the first months of life in the TCRS and the subsequent development of asthma (36). They reported that one standard deviation decreases in infant tPTEF/tE and  $\dot{V}_{maxFRC}$  were associated with a 70% and 55% increased risk of active asthma between the ages of 6 and 36 years, respectively. These effects were partly independent from each other, and two out of three infants who were in the lowest tertile for both tPTEF/tE and  $\dot{V}_{maxFRC}$  developed active asthma by mid-adult life. These results suggest that tPTEF/tE and  $\dot{V}_{maxFRC}$  sense different functional characteristics of the infant airway, which can separately contribute to subsequent asthma risk.

To determine if physical characteristics of the airway could be related to lower levels of tPTEF/tE or  $\dot{V}_{maxFRC}$  in infancy, Guerra et al correlated these indices with measurements obtained at age 26 years from high resolution computed tomography (HRCT) of airway generations 0 to 10, ranging in size from approximately 14 to 2 mm in diameter (36). No consistent associations were observed between  $\dot{V}_{maxFRC}$  in infancy and HRCT-derived measurements. In contrast, low infant tPTEF/tE in infancy was associated with significant reductions in inner diameter, outer diameter, total area, luminal area, and wall area measured at functional residual capacity, but not at total lung capacity, indicating smaller, thinner airways.

These results suggest that tPTEF/tE senses a physical airway feature, namely, potentially more collapsible large and mid-size bronchi, and it can be assumed that this feature could

derive in clinical manifestations of airway obstruction if associated, for example, with acute respiratory illnesses. Interestingly, Pekka Malmberg et al (55) found no significant decrease in tPTEF/tE after methacholine inhalation in infancy, suggesting that this measurement is not sensitive to changes induced by airway smooth muscle contraction. On the other hand, given that no consistent anatomical changes were observed in large/mid-size airways of adults who had low  $\dot{V}_{maxFRC}$  in infancy, it is plausible to speculate that these individuals have either an inflammatory phenotype or perhaps functional (e.g., bronchial hyperresponsiveness) and/or anatomical changes in their smaller airways, which at present cannot be assessed by use of HRCT. In support of these contentions, Chawes et al (56) reported that neonates enrolled in the Danish birth cohort quoted earlier and who had diminished maximal flows at birth had elevated serum markers of systemic inflammation, including IL-6 and C-reactive protein, during the first year of life. In addition, Pekka Malmberg et al (55) found a strong reduction in  $\dot{V}_{maxFRC}$  after methacholine inhalation, and Kotaniemi-Syrjänen et al (57) reported significant correlations between baseline  $\dot{V}_{maxFRC}$  and the degree of bronchial hyperresponsiveness observed in infants.

Taken together, these findings suggest that structural and functional characteristics of both large and small airways already present at birth can predispose for the development of asthma symptoms at least up to mid adult life. They also question the assumption that excessive airway inflammation is the only determining factor in all patients with asthma.

**The role of the immune system in determining early airway function and subsequent asthma**—Immune responses are involved both pre- and postnatally in determining the intensity and direction of inflammation in the developing respiratory system (58;59). Based on the results of early airway functions studies, these responses can be expected to influence ongoing airway function and the development of asthma in children. Distinct differences in immune system responses have long been recognized between those who develop asthma and those that don't. Early observations that eosinophilia was commonly associated with asthma in children (60) led to the view that atopy was a causal factor for developing airway disease and asthma. Later, atopy was found to be due to over-production of IgE (61) resulting from increased T helper 2 (Th2) responses.

More recent studies have shown that increases in Th2 responses in atopics are commonly associated with decreases in Th1 and innate immune responses that result in reduced interferon responses (62). The relative roles of these T helper responses in determining airway function and asthma in children is still unclear. On one hand, the increased IgE levels in children with increased Th2 responses are plausibly associated with long-term, antigen-induced, IgE-mediated inflammation of the airway wall beginning at an early age (63). However, interferon responses are crucial for protection against respiratory viruses, so the associated decrease in Th1 responses is likely to explain why respiratory virus infections are the main cause of acute respiratory exacerbations associated with wheezing from early in life and in asthmatics (64;65). Curiously, the Th2 system is not known to have an important role in protection from viral infections, but treatment with an anti-IgE antibody such as omalizumab has been shown to decrease acute virus-induced asthma exacerbations (66). This may be because respiratory viruses such as rhinovirus take advantage of the presence of IgE bound to IgE receptors (67) to produce an increase in acute airway inflammation.



These observations lead to the question of whether repeated acute respiratory viral infections in early life cause long-term airway inflammation and damage that predisposes to the reduced airway function associated with asthma and may indeed predispose to asthma. This question has proven remarkably difficult to settle, as associations are common, but proven mechanisms are not. In the Childhood Origins of Asthma (COAST) cohort, the odds ratio of developing asthma by 6 years in children who had a rhinovirus-induced wheezing episode before 3 years of age was 9.8 which was over 3 times higher than the odds ratio for early RSV infection in at-risk children (68). The greatly increased association between early rhinovirus infection versus early respiratory syncytial virus (RSV) infection has been confirmed in a recent meta-analysis (69). Atopy interacts with respiratory virus infections to increase the risk of asthma, (70) but the mechanism of this interaction is still unclear. There is evidence that rhinovirus infection in early life can alter subsequent Th1 and Th2 responses. For example, mice exposed to early-life infection with rhinovirus show augmented IL-25-driven Th2 responses (71). Also, recent evidence has shown that acute infections with RSV reprogram the airway epithelium to alter the response to subsequent infections, (72) but whether this results in on-going airway damage is still not clear. Taken collectively, the data on respiratory viruses suggests that repeated infections may compromise the airway and contribute to asthma, but the absence of well-defined mechanisms and the many potential confounders leave the question of causality unanswered.

### **The role of the airway microbiome in determining airway function and disease**

The role of the airway microbiome in airway function and the development of asthma has not been established despite the observation that bacteria are more common in the airway of neonates who later develop asthma being made 15 years ago (73). The question is whether these bacteria themselves cause airway inflammation leading to asthma (74) or they are simply bystanders due to the known immune system differences between asthmatics and non-asthmatics. In infants who had a nasopharyngeal sample taken during the first year of life, most were colonized with staphylococcus or corynebacterium but subsequent asymptomatic colonization with streptococcus predicted later asthma (75). Azithromycin given to children at-risk of severe lower respiratory infections may reduce the severity of exacerbations, (76) but whether this is due to the known anti-inflammatory action of this drug or its action as an antibiotic has not been ascertained. In children sampled at the time of an acute asthma exacerbation compared with controls, minimal differences were found in the airway microbiome (77). Finally, rhinovirus infections can promote pathogen-dominated airway microbiota that may increase the risk for wheezing (63;78). Overall, the question regarding causality of the airway microbiome in producing sufficient airway inflammation to alter respiratory function or produce asthma has not been resolved.

### **Genetic and epigenetic causes of airway dysfunction and asthma**

Pre- and post-natal airway growth and development is influenced by a wide range of genetic and epigenetic factors involved in innate and adaptive immunity (58;79). For example, airway dysfunction in asthma may involve asthma susceptibility alleles in bronchial epithelial cells (80). Risk alleles in *IL1RL1*, *IL33*, *TSLP*, *CDHR3*, *MUC5AC*, *KIF3A*, *EFHC1* and *GSDMB* have been implicated and suggest a central role of the airway epithelium in reduced pulmonary function and the genesis of asthma (80). Epigenetic

changes are also involved in airway epithelial dysfunction in asthmatics (80) and these are likely to be highly responsive to environmental exposures. A recent study showed that more than half of the asthma-associated alleles in the airway epithelium showed evidence of CpG methylation(81)including *CDHR3* in children (82).

Glutathione S-transferase (GST) genes are involved in detoxification and this explains their role in the *in utero* susceptibility to the products of cigarette smoke (83;84). In the Perth Infant Asthma Follow-up birth cohort study, in infants exposed to *in utero* smoke, infant and/or maternal GSTT1 null was associated with increased airway responsiveness and decreased  $\dot{V}$  maxFRC at 1 month of age and maternal GSTP1 Val/Val or Ile/Val was associated with increased  $\dot{V}$  maxFRC at 6 months of age (85). At 24 years of age, GSTM1-null homozygosity was associated with lower FEV1 and FVC in those with versus those without *in utero* tobacco exposure (86). These data show that genetically inactive GST genes in the mother or child are risk factors for reduced pulmonary function throughout childhood into adulthood. The GST null genotypes are also associated with an increased risk of asthma in childhood but not in adults (87). Collectively these studies and many others (83;84;88;89) show that GST genes are required for protection from the toxic effects of tobacco products and when they are genetically dysfunctional, children's airways are compromised and the risk of asthma is increased.

## Conclusion

There is now strong evidence suggesting that airway size plays an important role in determining the risk for the development of asthma across the lifetime. Continued advancement in the prevention of asthma is likely to require interdisciplinary collaboration including basic science to define mechanisms and translational research to test hypotheses arising from this. Future interventional clinical translation studies will benefit from being done in well-phenotyped longitudinal birth cohorts following lung function trajectories from soon after birth to adulthood.

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## Abbreviations:

<b>IUGR</b>	intrauterine growth restriction
<b>RCTs</b>	randomized controlled trials
<b>Cr<sub>s</sub></b>	respiratory system compliance
<b>FEFs</b>	forced expiratory flows
<b>V<sub>max</sub>FRC</b>	maximal expiratory flow at functional residual capacity



**FEV<sub>1</sub>** forced expiratory volume in one second**Reference List**

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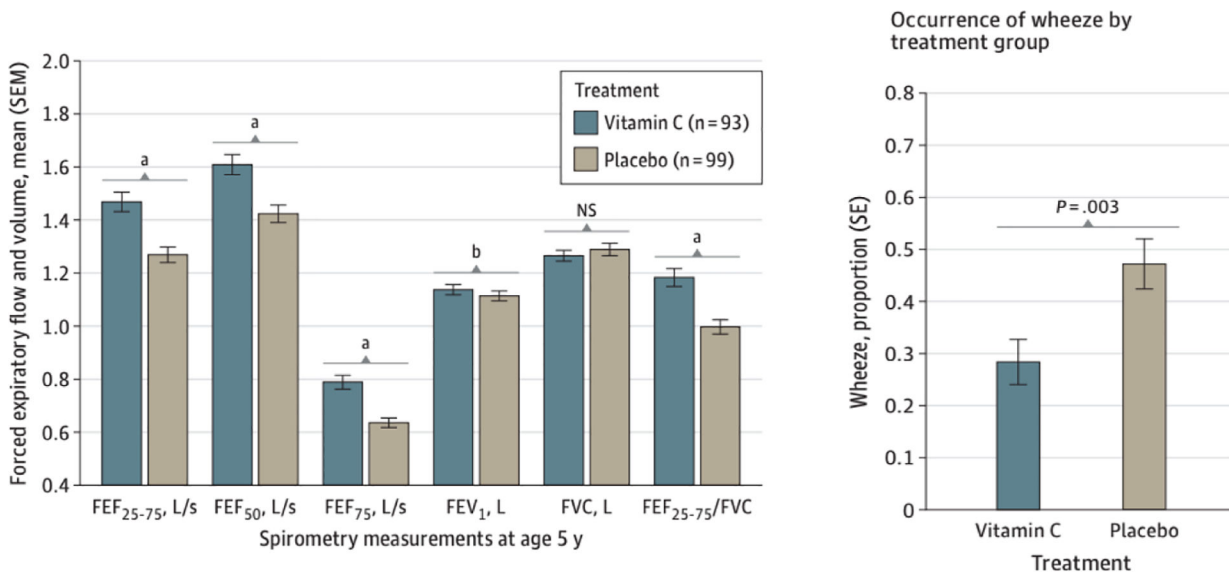
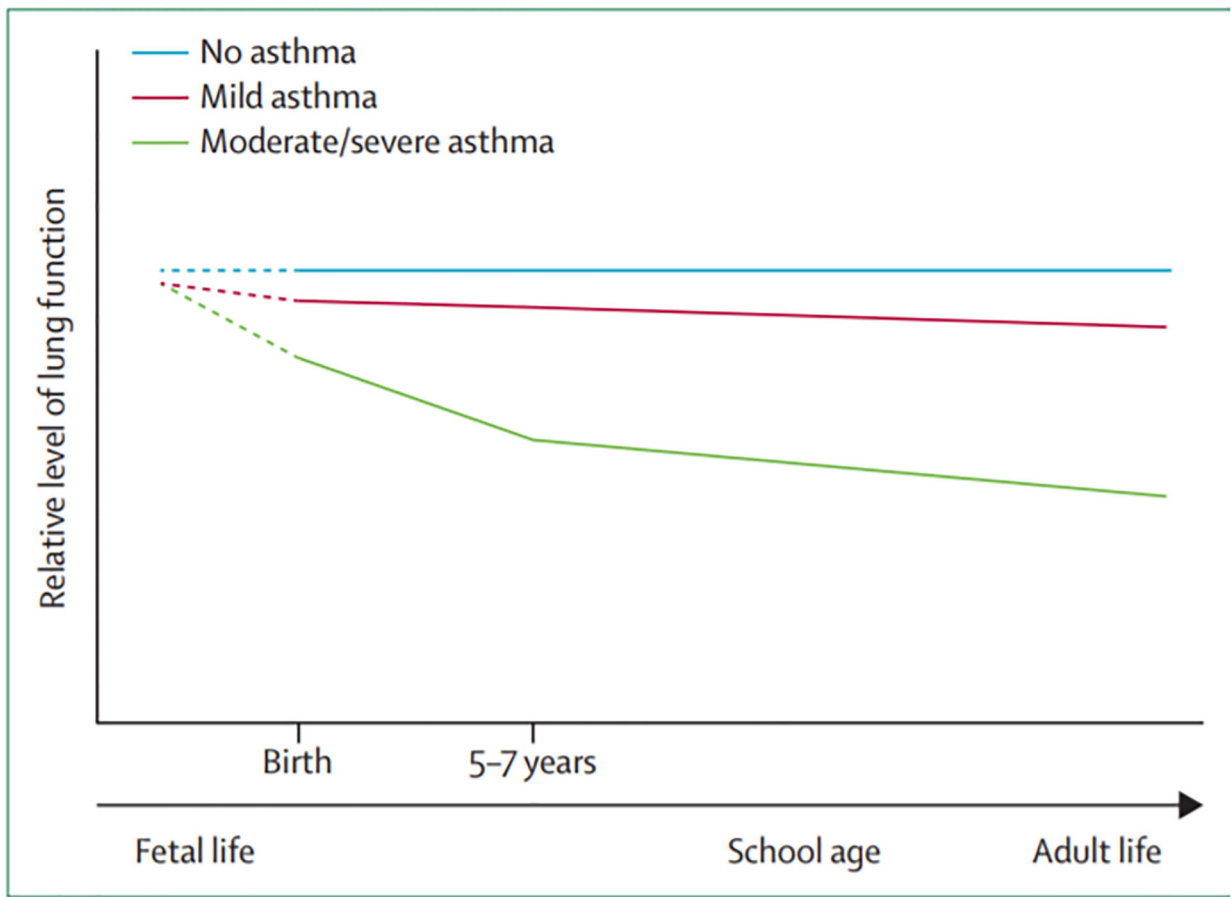


Figure 1A. Airway Function Test Results Obtained by Spirometry Measurements at Age 5 Years in Children Born to Pregnant Smokers Randomized to Vitamin C Supplementation (500mg/d) vs Placebo

Spirometry measurements are shown for offspring of 93 and 99 pregnant smokers in the vitamin C and placebo treatment groups, respectively. *P* values were adjusted for trial stratification variables of study site and gestational age at randomization, sex, race and ethnicity, and height at testing. All forced expiratory flow (FEF) and forced expiratory volume in 1 second (FEV1) measurements increased significantly in offspring of vitamin C–treated pregnant smokers. FEF25–75 indicates FEF between 25% and 75% expired volume; FEF50 indicates FEF at 50% of expiration; FEF75, FEF at 75% of expiration; and NS, not significant. <sup>a</sup> *P* < .01; <sup>b</sup> *P* < .05.

Figure 1B. Any Occurrence of Wheeze between the Fourth and Sixth Birthday in Offspring of Pregnant Smokers Randomized to Vitamin C versus Placebo during Pregnancy  
 Multiple logistic regression was used to compare the occurrence of wheeze between the vitamin C and placebo groups adjusting for study trial design factors of study site and gestational age at randomization, and covariates of race, and sex, and significant two-way interactions of all of these variables. 212 children were included (106 vitamin C and 106 placebo treated). The children born to the vitamin C treated pregnant smokers had a significant decrease in current wheeze at 28% versus 47% (estimated OR of 0.41; 95% CI: 0.23–0.74; *P* = 0.0032). (Reproduced from *Jama Pediatr.* 2023;177(1):16–24 with permission).





**Figure 2. Changes in Lung Function During the Course of Mild and Moderate Asthma**

Schematic representation of airway function trajectories for children without asthma, with asthma and mild or no airflow limitation, and for children with persistent asthma and airflow limitation. As a group, the latter show impaired airways function growth especially during the preschool years. These deficits extend, albeit in a less evident way, to the school age and, as steeper decline in airway function, to adulthood (Reproduced from Lancet 2013 Oct 19;382(9901):1360–72 with permission).