

ARE INFANT WHEEZING AND CHILDHOOD ASTHMA RISK FACTORS FOR THE DEVELOPMENT OF COPD?

Julie L Morrison | FCP (Paeds)

Robert P Gie | FCP (Paeds)

Department of Paediatrics and Child Health, Faculty of Medicine and Health Sciences, Stellenbosch University, Tygerberg, Cape Town, South Africa

Email | morrison@sun.ac.za

ABSTRACT

Wheezing in childhood and chronic obstructive pulmonary disease (COPD) in adults are both common clinical problems associated with tobacco smoking. This therefore raises the question whether childhood wheezing is also a risk factor for the development of COPD. The programming of lung development occurs in utero, with foetal exposure to maternal smoking resulting in decreased lung function at birth. Decreased lung function at birth tracks through life, resulting in decreased lung function in adulthood. Not only tobacco smoking and exposure but also indoor and outdoor atmospheric pollution influence foetal lung development. Adults with decreased lung function are at risk of developing COPD in the fourth and fifth decades of life. The data from cohorts followed up from childhood have confirmed that viral associated wheezing (wheezy bronchitis) and severe asthma in childhood are risk factors for developing COPD. These risk factors are independent of tobacco smoking during adulthood. Although many factors other than tobacco smoke influence the development of COPD, it is estimated that 33 per cent of South African mothers smoke during pregnancy. This results in decreased lung function in early life and an increased risk of COPD. Maternal smoke cessation programmes are urgently needed in South Africa.

Keywords: infant wheezing; childhood factors; COPD; risk factors; lung function tracking

INTRODUCTION

In 2016 chronic obstructive pulmonary disease (COPD) was the sixth leading cause of death globally, with approximately 250 million people suffering from the disease worldwide.¹ With childhood wheezing being a common clinical problem, it is understandable that parents are concerned that their children will develop COPD as adults. Previously, the opinion was that their concerns were misplaced as there was the misconception that COPD was attributable solely to tobacco smoking in adulthood. COPD diagnosis is based on spirometric criteria, where the FEV_1 :FVC ratio is less than 0.7 post bronchodilator.

The limitation of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) definition is that it takes into account neither the spirometric changes related to age and sex nor the different phenotypes of COPD and early-life events contributing to the disease. Recently, it has estimated that the percentage of COPD cases attributable to smoking is approximately 54% of male and 24% of female patients.² In industrialised countries the association is higher than in developing countries.² Although COPD becomes clinically evident at around 40–50 years of age, it is clear that in many patients it has its origins early in

life. There is now sufficient evidence that antenatal exposures result in decreased lung growth. Infants born with decreased lung function have an increased risk of developing COPD as an adult.³ The magnitude of this effect is so large that it has been suggested that certain exposures in childhood pose a risk for developing COPD that is as high as heavy smoking during adulthood.⁴ The aim of this article is to consider the available evidence that early-life insults and exposures which contribute to wheezing in early childhood increase the risk of developing COPD in later life.

SEARCH STRATEGY

This article is based on publications in the English scientific literature over the past 20 years. It is not a comprehensive review or a meta-analysis article. The literature was searched using Pubmed and Google Scholar. The search words and terms used were COPD, infant wheezing, early origins of COPD, early-onset COPD, lung development and COPD, childhood environmental exposures and COPD, foetal tobacco exposure and COPD, risk factor for development of COPD. From the articles recovered, the references were used to identify additional articles. Articles found to be relevant to the subject were included.

LUNG GROWTH AND COPD

The interaction of lung growth and the development of COPD is complex. An individual's lung function is programmed in early life. To be able to understand the interaction between lung growth and the development of COPD one needs to understand the factors that influence development. Three phases are identified in lung development: lung growth, lung plateau and lung decline.

LUNG GROWTH

Lung growth is best divided into airway and alveolar development. Previously, it was thought that alveolar development continued until two years of age and after this no new alveoli developed. This concept has recently been challenged and it is now thought that alveoli develop throughout somatic growth.⁵ In contrast, more is known about lung-function (airway) development. Lung function increases, reaching a maximum at approximately 22 years of age,³ with the lung volumes increasing approximately thirty-fold from infancy. Most of the structural changes in lung development occur in utero and the first years of life.³

Risk factors that influence the in utero lung development include maternal smoking, maternal asthma and atopy, a low birth weight, prematurity, diet, environmental factors including indoor pollution and genetics.⁶ These factors result in decreased lung function early in life (see Figure 1).

In a sentinel study, it was demonstrated that decreased lung function at birth was associated with wheezing during infancy.⁷ In this study, the main risk factors for decreased lung development were antenatal maternal smoking and being born small for gestational age. Data from this cohort demonstrate that approximately 10% of healthy individuals have decreased lung function at birth which tracks its centile into adulthood, resulting in decreased lung function in the third decade of life.⁸ Many studies following birth or childhood cohorts have demonstrated similar findings. An interesting hypothesis suggested that 40% of airway bronchial hyperactivity (ABH) is acquired in utero and 60% in early childhood.⁹

Epidemiological studies demonstrate that antenatal factors (maternal smoking, genetics, intrauterine growth restriction, maternal atopy, etc) lead to a modification in airway and alveolar development and maladaptive response in the newborn lung. In early childhood, exposure to tobacco smoke and environmental pollution are risk factors for asthma and recurrent lower airway tract.

In the period after birth, lung growth continues to be negatively influenced by maternal and environmental tobacco exposure in addition to respiratory viral infections, indoor and outdoor pollution, malnutrition, asthma and multiple atopic sensitisations; all of these exposures are associated with a decrease in lung growth.¹⁰

The COPDGene study showed that childhood pneumonia was associated with increased chronic bronchitis, more frequent and severe COPD exacerbations and an increased frequency of cardiovascular disease.¹¹ In a cohort recruited in Hertfordshire a

reduction in adult FEV₁ after bronchitis or pneumonia in infancy was reported, with an increased odds ratio of wheezing and persistent sputum production in adult life independent of birth weight, smoking habit and social class.¹² Whooping cough in infancy was associated with a 0–2.2 L (0.02–0.42 L) reduction in adult FEV₁.¹² In addition to the above, the development of bronchopulmonary dysplasia (BPD) in premature babies – defined as oxygen dependency at 36 weeks' gestational age – is also associated with decreased lung function. Survivors of BPD have been shown to have increased airway wall thickening that is compatible with airway obstruction.³

LUNG FUNCTION PLATEAU

Between 20 and 25 years of age the lung growth reaches a plateau, after which there is no further growth or decline in lung function. Lower lung function in childhood leads to lower peak lung function in early adulthood; this is known as 'tracking': lung function tracks the percentile from early childhood into adulthood; decreased lung growth in childhood results in a lower lung-function plateau. The factors that influence the lung-function plateau are largely unknown, although tobacco smoking shortens the plateau phase.¹³

LUNG FUNCTION DECLINE

After the plateau phase, lung function steadily decreases, with the forced vital capacity in 1 second (FEV₁) decreasing at approximately 20 mL/year in non-smokers. Smokers lose lung function at approximately twice the rate (40 mL/year) of non-smokers.¹³ This decrease continues throughout life, probably as a result of a loss of lung elastance.² Tobacco smoking results in an increased loss of lung function annually, with approximately 50% of smokers reaching the lung function threshold when they become symptomatic, usually in the fourth or fifth decade.¹³ Whereas tobacco smoking is the most important cause of accelerated lung function loss, other causes include indoor and outdoor pollution, occupational exposures and acute exacerbations of bacterial infections.

EARLY CHILDHOOD WHEEZING AND COPD

Children who have transient wheezing in the first three years of life have decreased lung function, recorded soon after birth; the decreased lung function manifests prior to developing wheezing, which tracks over the first three decades of life. There is some evidence that three connecting genes present in patients with transient wheezing are also present in patients with COPD.¹⁴ It is postulated that maternal tobacco smoking interferes with these genes, which are needed for normal lung development in utero and are also responsible for airway inflammation later in life.¹⁴

Because both viral associated wheezing (VAW) and wheezy bronchitis (WB) are closely associated with decreased lung function early in life, it is not surprising that these children have an increased risk of developing COPD.^{15,16} Data supporting this observation comes from cohorts in Australia and Scotland who have been followed up on for more than 50 years. In both cohorts, the participants were recruited as children and followed up on for decades, with their lung function measured at regular

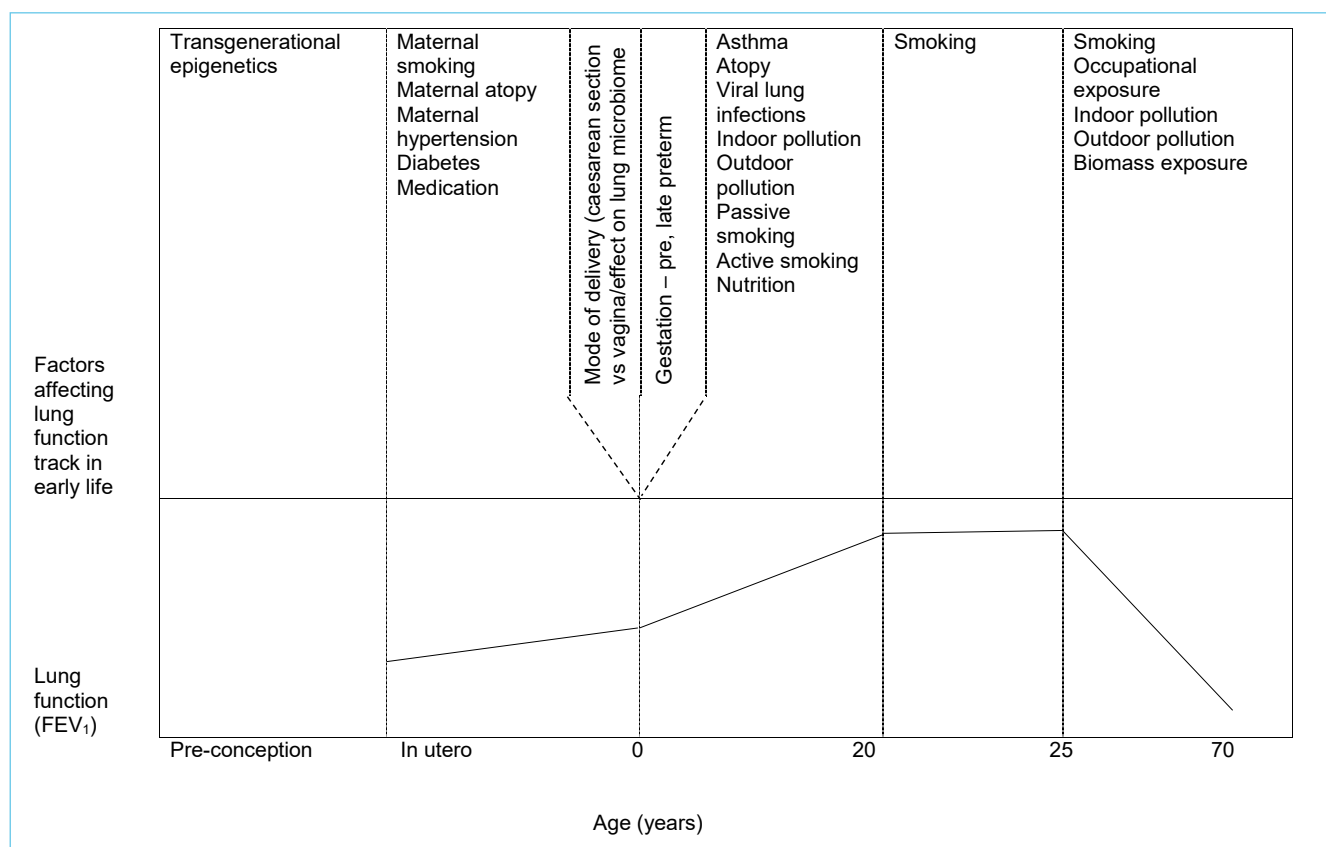


Figure 1: Factors affecting lung function track throughout life

intervals. In both studies the participants with WB/VAW had an increased risk of developing COPD (OR 181 95th CI 1.12–2.91 and OR 3.5 95th CI 0.4–35.2 respectively).^{15,16} The diagnosis of COPD (GOLD criteria) became evident only from the fifth decade of life onwards.¹⁵ Of interest was that those at risk of developing COPD had a lower lung function (FEV_1) in early life, which tracked with time and was not the result of an accelerated loss of lung function as seen in smokers.¹⁵ This emphasises the fact that decreased lung function in childhood is an important risk factor for the development of COPD.

Adults who develop wheezing later in life have increased lung function loss that results in their developing COPD.¹⁵ These two different mechanisms of developing COPD suggest that there might be different phenotypes of COPD.

CHILDHOOD ASTHMA AND COPD

Numerous studies demonstrate that severe asthma is associated with the development of COPD. It is estimated that the history of asthma increases the risk of developing COPD by 10–30-fold.¹⁷ There are, however, not many cohorts that have been followed up from childhood into the sixth and seventh decades of life.¹⁷ This long-term follow-up is essential because COPD usually becomes evident only later in life, as has been demonstrated in long-term follow-up trials.^{15,16} From these studies it is evident that children suffering from severe asthma have a 32-fold (95th CI 3.4–269) increased risk of developing COPD by the sixth decade of life.¹⁸ Asthmatic children with an increased risk of

developing COPD are characterised by a low baseline FEV_1 , early onset of symptoms and persistent wheezing.² In contrast, children with intermittent and persistent non-severe asthma do not have an increased risk of developing COPD.¹⁸

Similarly, in the Scotland cohort referred to above, childhood asthma was associated with an increased risk of developing COPD (OR = 6.37 95th CI 3.73–10.94). In this study, asthmatic children between the ages of 10 and 15 years with obstructive spirometry were more likely to develop COPD in the fourth decade of life.¹⁸ In a US study of 1 041 asthmatic children (5–14 years of age) 11% of them had developed COPD by 30 years of age. The diagnosis of COPD was based on spirometric criteria that demonstrated a post-bronchodilator response, which indicated irreversible or partially reversible airway obstruction ($FEV_1/FVC < 0.70$). Those most likely to develop COPD had low FEV_1 lung-function measurements and/or an early decline in their FEV_1 .¹⁹

The development of decreased lung function that increases the risk of developing childhood asthma is programmed in utero. In a meta-analysis of 24 938 children, reported in 24 birth cohorts, gestational age and decreased weight for gestational age (small for gestational age) were associated with decreased lung function and increased risk of developing childhood asthma.²⁰ In this article, median analysis suggests that the decrease in lung function might explain between 7% (2–10%) and 45% (15–81%) of the association between early growth characteristics

and childhood asthma.²⁰ This once more suggests that in utero programming increases the risk of developing childhood asthma and COPD in later life.

It has been suggested that the diagnosis of chronic childhood asthma adds 20 years to the lung age or the equivalent of 60 pack years of smoking, suggesting that chronic childhood asthma might be as large a risk factor for the development of COPD as is adult tobacco smoking.²¹

LIMITATIONS IN THE STUDIES

The first limitation concerns the diagnosis of COPD. The GOLD guidelines for the diagnosis of COPD suggest that COPD is characterised by partially irreversible airway obstruction. COPD is diagnosed when the forced vital capacity in 1 sec (FEV₁) to forced vital capacity (FVC) ratio (FEV₁/FVC) is less than 0.7 following an inhaled bronchodilator. Unfortunately, the FEV₁/FVC is influenced by age and sex. In younger adults, the ratio would underdiagnose COPD, whereas in older patients it could lead to an overdiagnosis.⁵

The second limitation is that the diagnosis of COPD is based on spirometric criteria and does not necessarily reflect the different phenotypical forms of COPD. Will the outcome of COPD associated with decreased lung function in childhood be similar to COPD which develops in adults who have an accelerated decrease in lung function and become symptomatic at an earlier age?

Another uncertainty is whether the COPD that follows WB/VAW in childhood has the same pathogenesis that follows severe childhood asthma where ongoing airway inflammation is present.

Furthermore, these studies all indicate that the known risk factors in childhood for the development of COPD apply to the group of children or adults investigated and not to the individual patient. If a clinician is discussing the risk of developing COPD with a parent, this weakness needs to be borne in mind.

RELEVANCE TO THE SOUTH AFRICAN CONTEXT

The prevalence of COPD in two suburbs of Cape Town has been reported to be higher than in 11 other large cities in the world.²² This was true for both men and women.²² With maternal tobacco smoking being associated with a decrease of in utero foetal lung growth, a sobering report, recently published by Vanker et al, is worth bearing in mind.²³ In this study of more than 1 000 mother–infant pairs conducted in two suburbs (Drakenstein) in the Western Cape, they report that 77% of pregnant mothers either actively smoked or were exposed to tobacco smoke during pregnancy.²³ Of even greater concern was that at birth 18% of the babies had urine cotinine levels equivalent to those of an active smoker and 38% had cotinine levels that indicated recent exposure to tobacco smoke.²⁴ In addition, these two studies indicated that antenatal exposures to maternal tobacco smoking and other indoor pollutants had a far greater impact on their infants' lung health than postnatal exposures.^{23,24} We would postulate that if this is true for other regions of South Africa,

the country will experience an unprecedented increase in the prevalence of COPD in the future.

Furthermore, the effect of maternal tobacco smoking has been shown also to have a transgenerational effect. If a grandmother smokes, her grandchild has an increased risk of developing childhood asthma, even if the child's mother does not smoke.⁵ This epigenetic effect is thought to be the result of gene methylation.⁵ This suggests that the effects of maternal smoking on infant lung health are going to be present in future generations even if smoking cessation programmes are successfully introduced. In southern Africa, there are other important risk factors for the development of COPD that require attention. These include pulmonary tuberculosis, HIV infection and poverty.²⁵

CONCLUSION

Dozens of studies demonstrate that in utero and early-life lung development are influenced by many risk factors, of which maternal smoking is the most important. Infants with decreased lung development have a greater risk of developing VAW and childhood asthma. Moreover, the decreased lung-function centile tracks into adulthood, resulting in a reduced lung-function centile in adulthood that is associated with the development of COPD. Smoke-cessation programmes, especially those that focus on pregnant women, need urgent attention if the long-lasting effects of smoking on the lung health of children and adults are to be prevented.

DECLARATION OF CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

This article has been peer reviewed.

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