Early origins of chronic obstructive pulmonary disease

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SUMMARY

Chronic obstructive pulmonary disease (COPD) is a major cause of morbidity and mortality worldwide and a significant challenge for adult physicians. However, there is a misconception that COPD is a disease of only adult smokers. There is a growing body of evidence to support the hypothesis that chronic respiratory diseases such as COPD have their origins in early life. In particular, adverse maternal factors will interact with the environment in a susceptible host promoting altered lung growth and development antenatally and in early childhood. Subsequent lung injury and further gene–environment interactions may result in permanent lung injury manifest by airway obstruction predisposing to COPD. This review will discuss the currently available data regarding risk factors in early life and their role in determining the COPD phenotype.

1. Introduction

1.1. Chronic obstructive pulmonary disease

Chronic obstructive pulmonary disease (COPD) is a major cause of morbidity and mortality worldwide.1 COPD is usually defined by chronic airflow obstruction with a forced expired volume in one second/forced vital capacity (FEV1/FVC) ratio of <0.7 following a bronchodilator challenge.2 However, making a diagnosis of COPD purely on obstructive spirometry may be inaccurate as obstructive lung disease in adulthood can be caused by diseases such as cystic fibrosis (CF), non-CF bronchiectasis and asthma.3

More than 50 years ago, it was documented that cigarette smoking is a causal factor for developing COPD.4 However, in the past decade, results from a growing number of population-based studies suggest that the risk of COPD from cigarette smoking was ~50% and that the burden of non-smoking COPD is much higher than previously believed.5 Alternate risk factors implicated in the non-smoking COPD phenotype include indoor and outdoor air pollution, specifically biomass fuel, occupational exposures to dust and fumes6 and the interaction of the environment with candidate genes. Less attention has been given to the ‘fetal origins hypothesis’ that is, the origins of many chronic adult diseases such as COPD may be found in early life. Early observations by Barker et al.7 concluded that low birth weight and respiratory infections in infancy reduced lung function in adulthood. Consistent with this, death from COPD was associated with lower birth weight.7

This review summarises the current and emerging evidence that many factors, both genetic and environmental, influence antenatal and postnatal lung growth, connecting early life events with COPD. Important concepts at the core of this review are: (i) knowledge of normal lung development; (ii) antenatal programming; and (iii) tracking of lung function.

1.2. Normal lung development

Lung growth starts in utero and continues to early adolescence going through different phases. The embryonic phase, between the 4th and 7th weeks of gestation, begins with the formation of a groove in the ventral lower pharynx and a bud at the lower part of the groove. After further elongation and subdivision of the bud, the two main bronchi are formed. Between the 7th and 16th weeks, known as the pseudoglandular phase, the future bronchial trees continue to subdivide to form the terminal bronchioles. During the canalicular phase, from the 17th to the 26th week of gestation, airway branching is complete with the formation of the primitive saccules. The airway lumen enlarges and walls thin as connective tissue components are reduced. It is also during this phase that the cuboidal epithelium lining the saccules differentiates into type I and type II pneumocytes with concomitant increases in peripheral mesenchyme vascularization. From 27 weeks onwards in the saccular phase, the pre-acinar airways grow, additional respiratory
bronchioles develop and acini are formed. Airway growth continues after birth with the airway diameter and length at least doubling until adulthood. Secondary septation subdividing the sacculi into smaller subunits or alveoli occurs although alveolar development is predominantly a postnatal process.\textsuperscript{8,9} Alveoli continue to increase in number until and beyond birth. At 29 weeks’ gestation, there are \~30 million alveoli and this increases to some 150 million alveoli by term, one-third to half the adult number.\textsuperscript{8,9} Moreover, the molecular phases of lung development are not confined within these specific stages and rather represent a continuous dynamic process.\textsuperscript{10} With regards to the natural course of lung function from birth to adulthood, FEV\textsubscript{1} and FVC will increase from childhood and plateau in early adulthood (20\textendash25 years of age). There is then a steady decline in both FEV\textsubscript{1} and FVC until \~40 years of age, following which there is a more rapid decline in these values.\textsuperscript{11} Changes in FEV\textsubscript{1}/FVC ratio thus occur with age and a ratio of 0.7 is attained at \~50 years of age in men and a few years later in women.\textsuperscript{11} Adult lung function may be influenced by a number of abnormal patterns of airway growth which include: (i) abnormal lung function at birth; (ii) normal childhood lung growth and function but accelerated decline as an adult; or (iii) failure to achieve a plateau in lung function followed by a normal or abnormal rate of decline of lung function in mid-adulthood.

### 1.3. Antenatal programming

The ‘fetal origins hypothesis’ encompasses the concept of programming. This concept is well established in developmental biology and encapsulates the idea that stimuli or insults during critical or sensitive periods in early life will result in developmental adaptations that will produce permanent structural, physiological and epigenetic changes that may have lifetime consequences. For example, maternal smoking, inadequate maternal nutrition and maternal hypertension will contribute to placental insufficiency leading to low birth weight. There is now a wealth of data showing that low birth weight is associated with increased cardiovascular and respiratory morbidity in adulthood including systemic hypertension, ischaemic heart disease and COPD.\textsuperscript{7,12}

### 1.4. Tracking of lung function

Tracking is defined as following a particular centile so that there is no deviation from that centile over time. For lung function, tracking would imply that there is no centile change from birth to childhood to adulthood. Longitudinal studies from childhood to adolescence demonstrate a high degree of tracking.\textsuperscript{13} In one of the first studies to track airway function from birth to early adult life, the Tucson Children’s Respiratory Study suggested that adult airway function is established very early in life, probably in utero in term babies.\textsuperscript{14} Infants with the lowest maximal expired flow rates at functional residual capacity ($V_{\text{max FRC}}$) had persistently low lung function at 6, 11, 16 and 22 years of age, although there was no further deterioration in lung function after 6 of age. Similarly in the Melbourne asthma cohort, lung function centiles at 50 years of age were established by 7 years of age.\textsuperscript{15} Even small lung function deficits result in premature airflow obstruction with lung aging, and this effect is magnified if there is an accelerated decline in lung function. For example, environmental stimuli such as pollution or a personal history of smoking may lead to accelerated loss of lung function even if a normal plateau is reached. An important general principle is that minor effects on lung function are magnified by lung aging.

### 2. Antenatal risk factors for COPD

Some of the risk factors summarized here are discussed in detail in earlier reviews in this series. Although the specific ante- and postnatal risk factors predisposing to alterations in fetal development are summarized individually, interactions between these factors are important in predisposing to COPD (Fig. 1).

![Fig. 1. Early origins of COPD.](image-url)
2.1. Exposure to cigarette smoke

Clinical and epidemiological data from subjects whose mothers smoked tobacco have collectively provided strong evidence that in-utero smoke exposure has multiple effects and is linked to low birth weight, changes in maturation of the developing lung and interference with the control of respiration with blunted ventilatory responses to hypoxia. Elliott et al. described increased inner airway wall thickness, increased airway smooth muscle and increased distance in alveolar attachment points in victims of sudden infant death syndrome (SIDS) whose mothers smoked during pregnancy, although it is unclear whether these changes were a result of maternal smoking or of secondary factors associated with SIDS. Moreover, in animal studies, rat pups whose mothers were exposed to environmental tobacco smoke (ETS) during pregnancy had lung hypoplasia with fewer, larger saccules. Pregnant monkeys injected with nicotine led to the activation of nicotinic receptors thereby increasing the production of mucin in the airways.

Gene–environment interactions may further modify fetal airway development. The effects of in-utero exposure to maternal smoking on asthma and wheezing occurrence were largely restricted to children with Glutathione S-Transferase M1 (GSTM1) null genotype. Similarly, polymorphisms of the enzymes which are involved in metabolism of nicotine and detoxification processes of nicotine, free radicals and xenobiotics, the CY1P1A1 Aa/aa and GSTT1 null genotypes, in smoking mothers conferred the greatest risk for reduced birth weight and IUGR in their infants. Thus gene–environment interactions not only modify fetal lung development but contribute to low birth weight (reviewed below) which is an independent risk for adult COPD.

Physiological correlates include dose-dependent reduced tidal flows in babies born to smoking mothers within the first 3 days of life. Low Lmax FRC in term babies born to mothers who smoked during pregnancy persisted for at least the first 18 months of life. In cohorts extending to 18 years of age, in-utero smoke exposure resulted in reduced mid-expiratory flows. Specifically, these results could not be attributed to smoke exposure after birth. These data are particularly relevant with the current evidence that the long term effects of maternal smoking and personal smoking act synergistically to increase airflow limitation and thus increase the risk for development of COPD. Additionally, maternal smoking may predispose to airway hyper-responsive (AHR) in the newborn, especially in those with a maternal history of asthma, with AHR still evident in early adulthood, again suggesting that effects of smoke exposure are permanent. The role of tobacco smoke on life-long programming has recently been reviewed.

2.2. Birth weight

There is a clear association between low birth weight, airway function and respiratory morbidity in children, adolescents and adults. In one study, 825 Caucasian adults aged between 59 and 70 years completed a questionnaire and performed spirometry. For each pound (454 g) decrease in birth weight, the mean FEV1 fell by 60 ml, independent of smoking habit, social class and respiratory tract infections in infancy and childhood. A recent meta-analysis confirmed that there was an increase in FEV1 of 48 ml (95% confidence interval: 26–70) per 1 kg in birth weight after adjustment for age, smoking and height. In school-aged children, small for gestational age (SGA), defined as birth weight <10th percentile, was associated with deficits in spirometry compared with age-matched normal birth weight children and in adult subjects birth weight in SGA subjects predicted forced mid-expired flows between 25 and 75% of the FVC (FEF25–75) Z-scores in mid-childhood and adulthood. Although birth weight effects are small, it is clear that they impact on long-term lung growth and development. The mechanisms mediating these effects remain unclear.

2.3. Maternal nutrition

The direct effects of maternal malnutrition on neonatal lung growth have been studied in rats. Pregnant rats who were subjected to varying degrees of food deprivation had offspring with smaller lungs in proportion to their body weight when compared with controls. Pregnant guinea-pigs starved during their second trimester had pups whose lungs showed reductions in the alveolar–capillary surface area compared with normally fed guinea-pigs. Despite normal postnatal feeding for 128 days, the changes in alveolar–capillary surface area persisted.

In humans, 912 people with a mean age of 50 years, born between 1943 and 1947 in Amsterdam, were examined. The prevalence of obstructive airways disease was increased in people exposed to the Dutch famine (1944–1945) in mid-gestation [odds ratio (OR: 1.7)] and tended to be higher in those starved in early gestation (OR: 1.5). Thus maternal nutrition during pregnancy may permanently affect airway growth and increase the likelihood of COPD. Whether these effects are mediated directly or indirectly through low birth weight has not been established.

2.4. Genotype

Genes associated with lung development are also implicated in COPD. A disintegrin and metalloprotease 33 (ADAM33) gene is of putative interest for COPD and is the subject of a recent comprehensive review. ADAM33, first identified as a susceptibility gene for asthma and AHR, is expressed in the airway smooth muscle cells in the developing lung during branching morphogenesis, increases throughout gestation, and persists into adult life. In one birth cohort study, the single nucleotide polymorphism (SNP) F1–1 in ADAM33 was a determinant of both infant wheezing and specific airway resistance at 3 and 5 years of age. Four SNPs in ADAM33 were associated with specific airway resistance and FEV1 independent of smoking exposure. Consistent with these data, in adulthood SNPs in ADAM33 predicted a more rapid decline in lung function in individuals with chronic asthma followed over 20 years. The same authors subsequently demonstrated that SNPs in ADAM33 contributed to accelerated lung function decline in the general population and that SNPs play a role in the development and severity of COPD.

Another gene linking early lung function and COPD is the beta-receptor. Beta-2 adrenergic receptors (β2AR) are cell surface receptors on airway smooth muscle. Polymorphisms of the β2AR, particularly involving the amino acid substitutions at positions 16 (arginine to glycine, Arg/Gly 16) and 27 (glutamine to glutamic acid Gln/Glu 27), have been shown to alter both receptor function in vivo and asthma susceptibility. An unselected cohort was reviewed at 1 month, 6 months, 12 months, 6 years and 11 years of age. Vmax FRC was not related to β2AR polymorphisms in the first year of life, but, by childhood, Arg16/Gln27 was associated with increased AHR at 6 years of age and lower FEV1 and FVC at 11 years of age. Further, in >1000 randomly selected older adults, Arg16/Gln27 haplotype was associated with current asthma, COPD and respiratory symptoms suggesting that β2AR may be an important modulating factor in COPD.

Fibroblast growth factors (FGFs) and receptors (FGFRs) are expressed in the developing lung and appear to be major regulators of lung growth and differentiation. Specifically, the FGFR1 signaling pathway is critical for lung development, and adults
heterozygous for FGF10 demonstrated lower expired flows and FEV1/FVC ratios.\textsuperscript{48} Thus polymorphisms of genes involved in lung growth and development are crucial areas for further research not only for the early origins of COPD but also for targeted early interventions for this disease.

2.5. Additional maternal factors affecting antenatal lung development

Many additional factors have been postulated as causal in alterations in lung growth and development with subsequent respiratory consequences. These include, among others, the use of maternal paracetamol (Tylenol) during pregnancy, vitamin D deficiency,\textsuperscript{49} vitamin C intake during pregnancy and duration of breastfeeding.\textsuperscript{50–52} More recently, a prospective cohort study observed that a high minute ventilation and elevation in exhaled nitric oxide in newborns correlated with maternal exposure to environmental pollution.\textsuperscript{53} The effects of postnatal exposure to pollutants are reviewed below.

3. Postnatal risk factors for COPD

3.1. Postnatal tobacco smoke exposure

The risk of lower respiratory illness, wheezing and asthma is increased in young children whose mothers smoke.\textsuperscript{54,55} In the European Community Respiratory Health Survey, intrauterine and environmental exposure to parental smoking resulted in lower lung function and increased respiratory symptoms in adulthood; the risk increased in males.\textsuperscript{56} In a meta-analysis involving >20,000 children, an alarming 60% of all children had been exposed to ETS; 20% of this exposure was in utero. Pooled data demonstrated that smoking during pregnancy and passive smoking during childhood were associated with reduced respiratory flows.\textsuperscript{57} Longitudinal studies during childhood have shown a decrease in FEV1/FVC in boys of smoking parents; this ratio was reduced further in asthmatic children.\textsuperscript{58}

3.2. Environmental pollution

3.2.1. Indoor air pollutants

Globally, COPD is linked to exposure to biomass fuels such as coal, straw, animal dung, crop residues and wood, which are used to heat and cook in poorly ventilated homes. The World Health Organization estimates that, in countries of low and middle income, 35% of people with COPD developed its exposure to indoor smoke from biomass fuels.\textsuperscript{59} Babies born to Guatemalan women exposed to biomass fuel had lower birth weight than those exposed either to ETS or to other pollutants\textsuperscript{60} and school children (birth weight not obtained) in rural India, where biomass fuel use was prevalent, had a significantly lower FVC and FEV1 and an increased incidence of asthma.\textsuperscript{61} Of note, in adulthood, chronic exposure to biomass fuel is associated with onset of COPD.\textsuperscript{62} A diagnosis of COPD is also associated with worksite exposures to gases, dusts, vapours, or fumes,\textsuperscript{8} which may be a particular threat to children and adults in developing countries where not only are laws less stringent but child labour is prevalent.

3.2.2. Outdoor air pollutants

The risk attributable to outdoor compared with indoor pollutants in the development of COPD is much smaller. Outdoor pollution includes particle matter (PM), ground-level ozone (O3), and sulfur dioxide from vehicle traffic and fuel combustion, which are the most common outdoor pollutants associated with respiratory ill-health.\textsuperscript{63} In one longitudinal study, children living within 500 m of a freeway in southern California had a mean deficit of 81 ml in FEV1 at 8-year follow-up when compared with children who lived at least 1500 m from a freeway.\textsuperscript{64} Specifically, reduced lung function was associated with increased PM\textsubscript{10} exposure, and children from the cohort who moved to areas of lower PM\textsubscript{10} levels showed improved lung function following the move.\textsuperscript{65} Higher PM\textsubscript{10} levels in one large industrialized city in the UK were associated with a higher carbon content of airway macrophages in induced sputum samples in school children, which correlated with significantly lower FEV\textsubscript{1}, FVC and FEF\textsubscript{25–75}.\textsuperscript{66} Likewise, Galizia et al. observed significantly lower lung function and an increase in respiratory symptoms such as cough, sputum production and wheeze in a group of college students who never smoked and lived in areas of high O3 exposure for ≥4 years.\textsuperscript{67} In summary, attenuation of lung growth due to air pollution in childhood is a risk factor for adult-onset respiratory disease.

3.3. Childhood respiratory infections, wheeze and asthma

How do childhood respiratory illnesses and asthma impact long-term lung development and function? Two hypotheses have been proposed: (i) a viral infection in early life alters the course of lung growth and development and switches the host to airway obstruction or (ii) lung development is altered in utero or in early life due to antenatal insults and predisposes the ‘primed host’ to early respiratory illnesses and subsequent chronic airway obstruction.

In 1977 Burrows et al.\textsuperscript{68} suggested that childhood respiratory infections represent an important risk factor for COPD. Barker et al.\textsuperscript{7} concluded that COPD morbidity (reduced lung function) and mortality was more strongly influenced by respiratory infections in childhood than that for cigarette smoking in their cross-sectional study. However, cross-sectional data without pre-morbid lung function cannot determine whether airway abnormalities predate early respiratory infections. Both a history of bronchiolitis and wheezing illness have been subsequently associated with lower lung function in infancy.\textsuperscript{58,60} In one longitudinal cohort study of infants recruited soon after birth without any preceding illness, early wheezing was transient in most children by 6 years of age. However, persistent wheezers (wheeze before 3 years and wheeze at 6 years of age) had lower levels of \textit{V}_{\text{max}} FRC than both transient early wheezers (wheeze before 3 years of age and no wheeze at 6 years of age) and late onset wheezers (wheeze after 3 years of age and wheezing at 6 years of age).\textsuperscript{70} The transient early wheezers still had lower levels of lung function at 6 years of age compared with children who either had never wheezed or had late onset of wheeze, and was strongly associated with maternal smoking. Late onset and persistent wheeze were both more likely to be associated with maternal asthma and atopy. In adolescence these transient wheezers had lower levels of lung function with no further deterioration of lung function observed after 6 years of age. Similarly, the persistent wheezers had significantly lower forced expiratory flows by age 6 years and up to age 16 years with lower and tracking FEV\textsubscript{1}/FVC ratios at ages 11 and 16 years.\textsuperscript{71} In the follow-up study at 22 years of age, infants in the lowest quartile for \textit{V}_{\text{max}} FRC had the lowest FEV\textsubscript{1}/FVC ratios, FEF\textsubscript{25–75} and FEV\textsubscript{1} in adulthood. Moreover, late onset and persistent wheezing during the first 6 years of life and low \textit{V}_{\text{max}} FRC at 6 years of age was associated with both a new and chronic diagnosis of asthma, with the asthmatic subjects additionally demonstrating lower FEV\textsubscript{1}/FVC ratios than those with no asthma.\textsuperscript{72} In the Dunedin cohort, ~1100 children were enrolled at birth in 1972 to 1973 and followed prospectively.\textsuperscript{72} History of asthma-like symptoms and lung function were assessed at 2–5-year intervals between ages 9 and 26 years. Persistent wheeze and intermittent wheeze (if wheeze was absent on one or more assessment) was associated with tracking of lower FEV\textsubscript{1}/FVC ratios.
starting at age 9 years, with no further deterioration within the asthma group. In a study extending to 50 years of age, the Melbourne Asthma Study originally recruited 300 children into three randomly selected groups: mild wheezy bronchitis, moderate wheezy bronchitis, and asthma; and these were compared with a control group. Throughout adolescence and adult life, important findings were that: (i) lower FEV1/FVC ratios were observed in children who were originally diagnosed with asthma; (ii) lung function tracked in all three groups in late adulthood with lower levels already established by age 7 years; (iii) lung function did not decline further in adulthood even in the severe asthmatics; and (iv) nearly half of the children with severe persistent asthma had COPD at 50 years of age, and these children had the lowest lung function of the whole cohort at age 10.15,24 In a separate study, the additive effects of maternal, paternal or childhood asthma, childhood respiratory infections and maternal history of smoking was further associated with lower lung function with no catch-up growth, a faster rate of decline in lung function and a greater risk of COPD.75 The effects of early childhood disadvantage were at least as great as those of adult smoking. Physiological evidence to support the hypothesis of the impact of early life events on respiratory morbidity includes changes in cord blood cytokine responses linked to the frequency of moderate to severe perinatal morbidity in the first year of life,76 and an increase in adiposity in the first year of life predisposing to wheeze before 3 years of age.77 Structurally, airway remodeling has been described by Saglani et al.78 with a thickened reticular basement membrane and eosinophilia in current wheezy children aged <24 months when compared with their age-matched controls. These pathological changes were not seen in wheezy children <1 year of age, but, by school age, structural airway changes were similar but less severe than those of adults with asthma.79

Notwithstanding the methodological differences between these studies, collectively, these functional and structural data suggest that airway abnormalities are determined very early in life, some even in utero, and these will increase the risk of subsequent wheezy illnesses and asthma in early childhood, predisposing to a lifetime of lower lung function. Whether these changes represent either abnormal inflammatory responses or persistent airway inflammation or both remains to be established. Since airway function is very likely established by school age, the pre-school years represent a critical time for intervention to minimize lung injury and chronic airway obstruction.

### 3.4. Childhood nutrition

A thorough review of the impact of nutritional factors on childhood lung disease can be found elsewhere.80 Briefly, dietary factors and nutritional status play an important role in the respiratory health of children.80 In a cross-sectional study of 2650 school children aged 8–11 years from the UK, Cook et al.81 reported that children who never ate any fruit had an FEV1 of 79 ml (4.3%) lower than that of children who ate fruit more than once per day; potential mechanisms include fruit promoting lung antioxidant defenses. Whether continued consumption of fruit will result in cumulative effects over a period of time from childhood to adulthood, perhaps to minimize or even counteract the risk for COPD, is unclear. However, a deficient diet may also exert its effects on the lung by increase in susceptibility to pollutants such as tobacco smoke, ozone and allergens.80 Obesity, currently described as the commonest form of ‘malnutrition’ in children, has increased rapidly worldwide with 32% of children in the USA described as overweight or obese and >300 million obese individuals (children and adults) worldwide.82 The results of lung function in obese children (aged ≥9 years) are conflicting, with FEV1 and FVC decreasing with increasing proportions of body fat83 in one small study but normal values demonstrated in another smaller study.84 However, the duration of obesity (comparisons <5 years and >15 years) in both children and adults was significantly associated with a lower FVC, FEV1 and FEV1/FVC ratio. Although the effect of obesity on lung function is not clear, these findings would suggest that an obese child with normal pulmonary function is at risk for developing abnormal lung function with prolonged obesity. Since there is clear evidence that childhood obesity tracks into adulthood,52 the combined effects of obesity and COPD may be additive with respect to airway obstruction as FEV1 declines as both conditions worsen.

### 3.5. Chronic lung disease of prematurity (CLDP)

CLDP [also commonly referred to as bronchopulmonary dysplasia (BPD)] is a result of acute lung injury secondary to prematurity and its treatments, the most significant of which include mechanical ventilation and oxygen therapy.85 Ex-preterm survivors with and without CLDP have excess respiratory morbidity, including airway obstruction in infancy, childhood and adulthood.32,36,86,87 (described in detail in earlier reviews in this series). Limited studies have evaluated CLDP and subsequent pulmonary function in adults. Northway et al.88 found that 68% of CLDP subjects (subjects with the old form of BPD) had significantly lower FEV1, FVC and FEF25−75 when compared with the preterm group with no CLDP and term controls. In one of the largest longitudinal follow-up studies, airway obstruction was evident in ex-preterm children aged 7–9 years82 but in adult life there were no significant differences between FEV1, FVC and FEF25−75 when compared with controls, implying some catch-up growth.36 However, there was evidence of tracking, with mid-childhood Z-scores for FEV1 in childhood predictive of adult FEV1 Z-scores (P < 0.001 and r² = 0.34).36 Indeed, the low incidence of CLDP and maternal smokers compared with the Northway cohort88 may have created a bias towards improved airway function in adulthood. It is also plausible that the methods used to measure airway function were insensitive more subtle, persistent abnormalities. Future studies will be necessary to determine: (i) the relevance of these findings in the newer era of extremely immature survivors of preterm birth; and (ii) whether in ex-CLDP subjects, impaired pulmonary function in adulthood, whether latent or overt, results in an accelerated decline in ventilatory reserve that could further increase the risk of premature airflow obstruction in later life. Of significance, loss of pulmonary function may be further accelerated in smokers; alarmingly, up to 50% of preterm survivors have been reported to smoke in adulthood.36 It should be noted that the term ‘new COPD’ should be applied cautiously if at all to adult survivors of CLDP with premature airflow obstruction; there is no evidence that any inflammatory component of the disease is the same as in heavy smokers with COPD.

### 4. Summary: early origins of COPD

The perception of COPD as a disease of only adult smokers cannot be upheld. Epidemiological findings provide a wealth of evidence that antenatal programming, genes and the environment in early life play etiologic roles in chronic adult diseases such as COPD. The argument is compelling; antenatal factors, especially maternal smoking, lead to modifications in airway and alveolar development and maladaptive responses of the newborn lung. This ‘altered host lung’ may act as a precursor for subsequent lung injury, due to ETS, environmental pollutants and childhood respiratory infections, resulting in further disruption to the growing
lung. By early childhood, repeated lung injury and gene–environment interaction manifest with lower lung function and airway obstruction in susceptible children. As lung function tracks into adult life, these individuals will enter adulthood with lower lung function than expected. Even if these individuals were to show normal lung function decline during adult life, they would reach the threshold of FEV1 and FEV1/FVC ratio at an earlier age than their peers, increasing their risk of a COPD phenotype. Thus, it is evident that there is a need to elucidate the mechanisms involved in early life predisposition to chronic diseases of adulthood. Current knowledge should provide the impetus for research to decipher the exact biological mechanisms in lung developmental processes and complex gene–host–environment interactions believed to be at the root of COPD.

5. Conclusion

COPD is the result of a complex interplay between environmental exposure and host susceptibility that begins in early intrauterine life. COPD prevention strategies must focus on these early origins if we are truly to halt the rising prevalence of children who will become ‘respiratory cripples’ in adulthood. Urgent epidemiological and biological research is needed to better understand the COPD phenotype. Finally, since comprehensive smoke-free legislation is an effective strategy to decrease respiratory illness, further stringent legislation must play a key role in the prevention of chronic respiratory diseases.

Practice points

- Prevention and cessation of smoking at all ages but most importantly and immediately in pregnant women.
- Strategies include: legislation to minimize access to cigarettes legislation to minimize images of smoking; protecting children from tobacco smoke at home; improving indoor and outdoor air quality especially in the developing world.
- Enhance obstetric care to: minimize premature birth improve maternal nutrition optimize birth weight of newborns; optimize neonatal care to improve lung protective strategies and minimize CLDP.
- Prevent childhood obesity.

Conflict of interest statement

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References


