Early-life origins of chronic respiratory diseases: understanding and promoting healthy ageing

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ABSTRACT Chronic obstructive respiratory disorders such as asthma and chronic obstructive pulmonary disease often originate early in life. In addition to a genetic predisposition, prenatal and early-life environmental exposures have a persistent impact on respiratory health. Acting during a critical phase of lung development, these factors may change lung structure and metabolism, and may induce maladaptive responses to harmful agents, which will affect the whole lifespan.

Some environmental factors, such as exposure to cigarette smoke, type of childbirth and diet, may be modifiable, but it is more difficult to influence other factors, such as preterm birth and early exposure to viruses or allergens.

Here, we bring together recent literature to analyse the critical aspects involved in the early stages of lung development, going back to prenatal and perinatal events, and we discuss the mechanisms by which noxious factors encountered early on may have a lifelong impact on respiratory health.

We briefly comment on the need for early disease biomarkers and on the possible role of "-omic" technologies in identifying risk profiles predictive of chronic respiratory conditions. Such profiles could guide the ideation of effective preventive strategies and/or targeted early lifestyle or therapeutic interventions.

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Introduction

Complex chronic respiratory disorders, particularly asthma and chronic obstructive pulmonary disease (COPD), are major noncommunicable diseases that should be studied over the human lifespan so that prevention strategies can be implemented before these diseases become established. Chronic obstructive respiratory diseases, in fact, appear to have their roots in the early stages of life, even though they may become clinically apparent only later on. An international workshop recently analysed data on asthma and allergies from over 130 birth cohorts, shedding more light on the natural history of these conditions and confirming the importance of gene–environment interactions as well as early-life risk factors [1]. There is also growing evidence of a link between early adverse environmental exposures and chronic noncommunicable diseases (obesity, type 2 diabetes, cardiovascular diseases and neurocognitive disorders), but this topic is covered elsewhere in this series.

We used recent literature to analyse the crucial aspects of the early stages of lung development, going back to prenatal and perinatal events, and we discuss how noxious factors encountered early on may have a lifelong impact on respiratory health (fig. 1). We did not intend to perform a systematic review of the literature with evidence grading. Articles were identified from searches of PubMed using Medical Subject Heading. We did not use any selection or rejection criteria. Review articles are cited.

Lung morphogenesis and regeneration/repair

Lung morphogenesis begins at 5 weeks of gestation and comprises five different stages, the last of which, alveolarisation, continues postnatally for at least the first 2–4 years of life [2]. Recent studies on lung growth using hyperpolarised helium-3 magnetic resonance imaging (MRI) suggest that alveolarisation may continue throughout childhood and adolescence, and even into adulthood [3].

Perinatal insults can alter both gene expression and epigenetic determinants with potential long-term consequences that might influence the lung's capacity for repair and thus play a part in the pathogenesis of lung disease in adults [4]. Although other distinctive mechanisms, such as those related to inflammation, are involved as well, studies on lung damage have also demonstrated that lung repair processes reiterate many mechanisms and pathways implicated in the lung's original development [5].

A first aspect crucial to both lung development and lung regeneration/repair is the interaction between the endoderm and mesoderm cell types. Extensive epithelial damage with exposure of the basal lamina gives rise to inflammation and cell apoptosis [6]. If the subsequent regeneration process is ineffective, then remodelling occurs with the aberrant tissue features (*e.g.* fibrosis and emphysema) typical of several chronic respiratory diseases [6, 7].

A second aspect involves a number of pathways mediated by growth factors and cytokines common to both lung development and lung repair processes. An important example concerns transforming growth factor beta (TGF)-β signalling: appropriate levels of TGF-β are crucial to lung development [8] but excessive levels

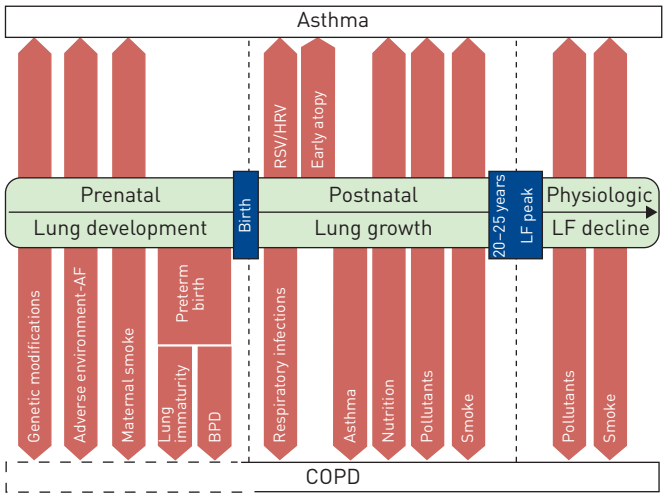

FIGURE 1 Factors involved in asthma and chronic obstructive pulmonary disease (COPD) pathogenesis over the lifespan and their relationship to lung function (LF) trajectory. The green box represents the course and milestones of LF over the lifespan. The red arrows represent the noxae that may contribute to diverting lung health from a physiological to a pathological condition (asthma or COPD). AF: amniotic fluid; BPD: bronchopulmonary dysplasia; RSV: respiratory syncytial virus; HRV: human rhinovirus.

in the adult lung promote progressive fibrosis [9, 10], the hallmark of remodelling. Likewise, the vascular endothelial growth factor (VEGF) has a crucial role in the development of normal lung circulation in the foetus and the newborn [11]. However, VEGF ligands may be involved in the pathogenesis of several lung diseases because the final effect on microvascular endothelial regeneration and repair in response to alveolar hypoxia depends on VEGF ligand balance and relative concentrations [12].

Taken together, these data indicate that lung diseases can be considered in the light of Barker's hypothesis on the ''developmental origins of adult disease'' [13]. Applied to the lung, this hypothesis points to a connection between impaired lung development and chronic lung disease. This connection relates, on the one hand, to long-term changes in lung structure and metabolism due to noxae encountered early in life, with the potential for generating a maladaptive response to harmful agents in adulthood [8]. However, it relates to the reiteration of developmental mechanisms and pathways in the pathogenesis of lung disease [2].

Early immune maturation and respiratory health

Neonates have a peculiar immune system that makes them susceptible to severe infections. This is partly because the neonatal immune system is equipped to be tolerant of novel, harmless environmental antigens. An adaptive immune response is essentially lacking because the newborn immune system has no memory, leaving the newborn dependent on innate immune defence mechanisms. It has long been established that infants are born with a T-helper cell (Th) type 2 bias due to a limited capacity to produce Th1 cytokines [14]. Although most cell types are present in normal concentrations in the newborn's blood, they lack the capacity to mount adult-like Th1 instructive signals, and to produce interleukin (IL)-12^{p70} in particular [15]. Immature immune responses in the neonate are the key obstacle to vaccination with polysaccharide vaccines (such as pneumococcal vaccines) at an early age. Antigen-presenting cells in neonates show weaker responses to innate stimuli than do those in adults, except for Toll-like receptor (TLR)-mediated responses to TLR8 agonists [16]. TLR agonists generally promote Th1 development and have been therapeutically developed to prevent and treat allergic diseases, albeit with conflicting results [17]. The effect of innate immune responses on the onset of allergies depends on the timing, dose and site of stimulation [18]. Experimental and human observational studies have shown that the magnitude of mucosal innate immune stimulation determines whether innate responses prevent or enhance the onset of allergic reactions [19, 20]. Preclinical studies suggest that repeated administration of high-dose TLR agonists in the airways prevents allergic airway inflammation. A natural exposure to TLR agonists in early life, as seen in children born on farms, appears to protect against allergic airway disease [21, 22], and coincides with an increased expression at birth of innate immunity genes such as *TLR2*, *TLR5*, *TLR7* and *TLR8* [23]. A high exposure to innate immunity-stimulating molecules, such as TLR agonists, is probably needed to prompt this beneficial effect [24]. Being conceived and raised in a farming environment appears to have a beneficial effect that persists at least into later childhood [25, 26] and may therefore provide a healthy lifestyle for those at risk of developing allergic asthma. Pharmaceutical agonists of TLR4, TLR7, TLR8 and TLR9 have been developed to treat or prevent allergic disease, and have been tested in clinical studies. In a proof-of-concept study, the TLR9 agonist QbG10 was used with a view to preventing or treating allergic asthma: the condition was controlled in two thirds of the 33 treated adult patients with mild-to-moderate allergic asthma, as opposed to one third of those given a placebo [27]. The further development of these drugs will give us a better understanding of the influence of timing, dose, site of activation and the host's genetic background on the relationship between innate immunity stimulation and the onset of allergic asthma.

New data are also emerging on the relationship between the airway microbiome and the immune system. Neonatal asymptomatic bacterial colonisation (with *Moraxella catarrhalis* and *Haemophilus influenzae*) of the respiratory tract has recently been found to be associated with an inflammatory/immune response of the airway mucosa (with increased levels of inflammatory cytokines) and the onset of asthma in childhood [28, 29].

Early environmental factors influencing the development of asthma and COPD

Factors acting early in life may have profound effects on lifelong respiratory health. These factors may take effect at different times: during intrauterine life (*e.g.* amniotic fluid composition, exposure to nicotine and maternal vitamin intake), in the perinatal period (*e.g.* factors relating to premature delivery and the onset of bronchopulmonary dysplasia (BPD)) and postnatally (*e.g.* exposure to nicotine and environmental chemicals, diet, viral infections, and early allergic sensitisation).

The ''exposome'' concept has recently been proposed as a new paradigm encompassing the totality of human environmental (nongenetic) exposures from conception onwards, complementing the genome [30]. In the following sections, we discuss recent data on the effects of amniotic fluid composition, exposure to nicotine and environmental chemicals, diet, vitamin intake, allergic sensitisation, and viral infection on lifelong respiratory health.

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First lung exposure: the amniotic fluid

The fetal airways are continuously exposed to the amniotic fluid. A shortage of fluid (oligohydramnios) due to abnormal urinary tract development or early rupture of membranes (before the 26th week of gestation) gives rise to lung hypoplasia [31]. One of the crucial markers of lung maturity in prematurely born infants is the amniotic fluid concentration of surfactant proteins, particularly SP-B and SP-C, whereas SP-A and SP-D are considered part of the innate immune system, protecting the fetal and infant lung against microorganisms and facilitating the phagocytosis of apoptotic cells. Animal studies have shown that SP-A and SP-D defects may cause allergic airway disease [32]. To date, there has been little research on how amniotic fluid composition at various times during a pregnancy relates to the development of chronic airway disease. Amniotic fluid is rich in proteins and reaches high concentrations of proinflammatory cytokines, including tumour necrosis factor, by the time of delivery [33]. The concentrations of these cytokines in normal amniotic fluid at birth are on the order of nanograms per millilitre, and therefore higher than that in the synovial fluid of patients with septic arthritis or in the cerebrospinal fluid of patients with bacterial meningitis [34]. In very low birth weight infants (and especially in those with sepsis), perinatal inflammation has been associated with the onset of chronic lung disease [35]. In apparent contrast, chorioamnionitis was found to protect against chronic lung disease in a sample of 798 children born preterm, especially in those with no signs of sepsis [36]. Such studies suggest a complex interplay between normal intrauterine inflammation during pregnancy, incomplete lung maturation and the harmful effects of bacterial infections, for instance.

A recent meta-analysis on 147 000 European infants showed that gestational age, even beyond 37 weeks, correlated inversely with the risk of asthma at school age [37]. This may be explained by higher concentrations in the amniotic fluid of signals such as proinflammatory mediators that would induce fetal lung maturation [37]. Variations in amniotic fluid composition may also help to explain why preterm birth and caesarean section are risk factors for asthma. In a recent study, lower concentrations of matrix metalloproteinases in the amniotic fluid of mothers delivering by scheduled caesarean section were associated with airway disease in their offspring's childhood [38]. When infants are born by scheduled caesarean section, the amniotic fluid has a particular composition [34] with lower concentrations of inflammatory mediators. This may explain their greater risk of airway disease in the long term [39]. In addition, vaginal delivery may protect against the onset of allergic asthma *via* the newborn's acquisition of bacteria such as *Clostridium difficile* at birth [40]. We are convinced that the interaction between fetal airway development and exposure to protein-rich amniotic fluid warrants further study as an essential step to clarifying normal prenatal airway development.

Second-hand smoke exposure

Maternal smoking during pregnancy is a known risk factor for impaired lung function and respiratory disease in children. A pooled analysis of eight birth cohort studies showed that maternal smoking during pregnancy independently resulted in a 39–65% increased risk of wheezing and asthma at 4–6 years of age [41]. Another meta-analysis of 79 cohort studies showed that prenatal maternal smoking caused an increased risk (28–52%) of wheezing in children, depending on the children's age (OR 1.52 in children aged 5–18 years) [42]. Similarly, a retrospective study on lung function data concerning 20 000 children at the age of 6–12 years showed that smoking during pregnancy was independently associated with a lower forced expiratory volume in 1 s (FEV_1) (-1– -6%) [43]. Similar effects on lung function and the presence of respiratory symptoms at school age have been reported for postnatal exposure to tobacco smoke [44, 45]. In a cohort study, passive smoking during the first year of life increased the risk of respiratory symptoms at 5 years of age in children born moderately preterm, with an adjusted odds ratio of 1.8 [45]. The previously mentioned meta-analysis of 79 prospective studies found an 18–70% higher incidence of wheezing in children exposed to postnatal maternal smoking (OR 1.70 in children $\leqslant$2 years of age) [42]. Prospective birth cohort studies following children up to adult age showed a persistence of the harmful effects of prenatal and postnatal tobacco smoke exposure [46–49]. In a birth cohort of 1314 children from Germany, maternal smoking during pregnancy almost doubled the risk of asthma at the age of 20 years [49]. A retrospective study examined lung function in 16 832 young adults from the general population, finding that maternal smoking was associated with a small but significant effect on lung function [50].

A possible mechanism underlying the harmful effects of maternal smoking on fetal lung development could be dysregulated cytokine production [51]. Maternal smoking was associated with a greater risk of lower concentrations of IL-4 and interferon-γ in cord blood, and with wheezing at 6 years old. Earlier studies by SEKHON and co-workers [52, 53] found that, after crossing the placenta, nicotine can interact directly with nicotinic acetylcholine receptors in the lungs of monkeys, thereby altering lung development and resulting in impaired lung function at birth. More recent research has suggested an interaction of *in utero* and early-life smoke exposure with asthma susceptibility genes [54]. This finding highlights the fact that there are still

unresolved questions regarding the mechanisms by which exposure to tobacco smoke impairs lung development and enhances respiratory disease.

Efforts to reduce second-hand smoke (SHS) exposure during and after pregnancy are very important. Various publications have reported the beneficial effects of such efforts on hospitalisation rates and emergency department visits, and on the prevalence of asthma during childhood [55, 56]. Stopping women from smoking before or during pregnancy remains a challenge, however, as illustrated by the conflicting outcomes of intervention studies [55, 57, 58]. A randomised controlled trial (RCT) comparing nicotine patches with placebo in pregnant smokers showed no significant effects on mothers' smoking rate or reported respiratory symptoms in their offspring at 2 years of age [57]. On the other hand, smoke-free legislation might facilitate a reduction in pregnant women's SHS exposure. A recent meta-analysis of 11 studies on the effect of smoke-free legislation in the USA and Europe showed a 10% reduction in emergency department visits for asthma [59].

In the field of tobacco control, further investigations are warranted to ascertain the health effects of so-called ''third-hand smoke'', *i.e.* toxic residues of tobacco smoke remaining on surfaces and in dust, and still circulating in the air after a cigarette has been extinguished [60].

Exposure to environmental chemicals

Several environmental agents, such as airborne pollutants and industrial chemicals related to plastic product manufacturing, are recognised risk factors for chronic obstructive airway diseases.

Two main sources of air pollution have been studied in relation to asthma and COPD, *i.e.* traffic emissions and biomass fuels [61, 62]. A higher risk of asthma was found among subjects exposed to traffic-related pollutants *in utero* and during their first year of life [63]. Exposure to high levels of traffic-related pollutants in childhood has been associated with lung growth impairment, which regresses when children move to areas with cleaner air [64]. Indoor biomass burning for cooking and/or heating represents the main source of indoor air pollution in developing countries. An association has been clearly demonstrated between children's exposure to biomass fuels and their morbidity and mortality from respiratory infections, whereas contradictory results have been reported on the association between indoor biomass fuel exposure and the risk of asthma [62].

Regarding industrial chemicals, some studies have implicated exposure to plastics in the onset of childhood respiratory problems, although it is not clear whether specific plastic components act as specific risk factors [65, 66]. It was recently demonstrated that prenatal and early-life exposure to bisphenol A (BPA), a xeno-oestrogen used to manufacture plastics (*e.g.* for toys and drinking vessels), is associated with an increased risk of wheezing and asthma [67, 68]. The phthalates used in numerous plastic consumer products have also attracted attention and there is converging evidence that exposure to di(2-ethylhexyl)phthalate and benzylbutylphthalate during childhood is associated with the development of allergic disease [69].

Diet

The influence of eating patterns, dietary content and micronutrient intake on respiratory and allergic disease is an intriguing but rather broad topic to review. We therefore focus on the results of intervention studies. So far, 129 clinical trials on nutrition have been undertaken according to the trial register at www.clinicaltrials.gov (fig. 2).

Prenatally, the diet of pregnant women has been studied as a risk factor for childhood asthma. Most birth cohort studies assessing the effect on childhood asthma of maternal food intake during pregnancy (*e.g.* the amount of dairy products, wheat, nuts, fish, fruit and vegetables) and dietary patterns (*e.g.* the Mediterranean diet) found no such association [70–73]. A birth cohort study examining lung function and bronchial responsiveness in children aged 8–9 years also found no association with maternal diet during pregnancy (*e.g.* whether a healthy, vegetarian or ''processed'' diet) [74]. On the other hand, poor maternal nutrition during pregnancy has been associated with an increased prevalence of obstructive airway disease in adulthood [75].

Specific micronutrient intake during pregnancy has also been extensively studied. A cohort study measuring neonatal cord blood folate, homocysteine and vitamin B_{12} levels in a sample of 2001 neonates found no association with asthma at 6 years of age [76]. KALLIOMÄKI *et al.* [77] found that probiotic supplementation during pregnancy was effective in reducing allergic disease (atopic eczema) in children, but two meta-analyses of RCTs assessing the effects of probiotics taken during pregnancy on childhood wheezing, respiratory infections and asthma were unable to confirm any protective effect of probiotics against allergic diseases [78, 79]. One RCT among pregnant Nepalese women showed that vitamin A, but not β-carotene, supplementation improved their children's adjusted FEV_1 and forced vital capacity (FVC) [80]. As for

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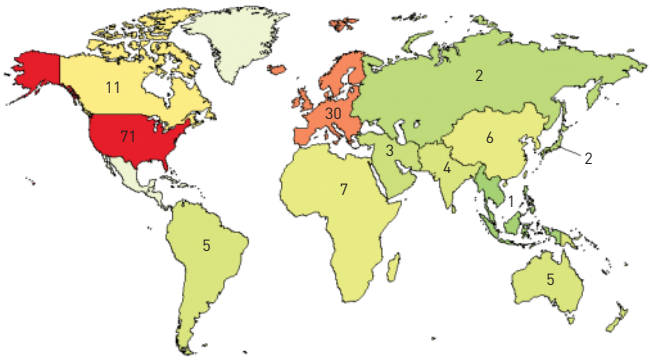

FIGURE 2 Current clinical trials (n=129) on dietary interventions in children with a respiratory outcome. The number of studies per region is shown. Trials with unknown trial status were excluded. Data from www.clinicaltrials.gov (retrieved July 22, 2014).

vitamin E, an RCT among 643 pregnant women found no effects on their children's respiratory outcome at 2 years of age [81]. Studies on folic acid intake during pregnancy and asthma in children have also generally found no association between the two [82–85]. According to several large birth cohort studies, vitamin D intake or plasma levels during pregnancy are generally not associated with childhood asthma or lung function [86–89], and an RCT examining the effects of vitamin D supplementation during pregnancy (n=180) found no significant difference in children's wheezing at 3 years of age [90].

Postnatally, breastfeeding is known to protect against various childhood respiratory diseases, but an extensive discussion of this issue is beyond the scope of this review. In addition to breastfeeding, two recent cohort studies showed that greater food diversity during the first year of life reduced the risk of childhood asthma and food allergies [91, 92]. Vitamin D supplementation might promote healthy lung development but evidence is conflicting. A birth cohort study on 436 children found that their vitamin D plasma levels and vitamin D supplementation were not associated with their lung function at 6–7 years of age [86]. However, an RCT among 744 Mongolian school-age children showed that vitamin D supplementation significantly increased their serum levels of 25-hydroxyvitamin D and halved their risk of acute respiratory infections [93]. The relationship between lower serum 25-hydroxyvitamin D levels and a higher risk of respiratory infection was also confirmed by a Canadian study [94]. The need for high-quality, large-scale food intervention studies was highlighted in a recent review of 87 meta-analyses of vitamin D trials that failed to show any clear benefit of vitamin D supplementation for any medical outcomes [95].

A separate mechanism by which infant diet could lead to asthma is rapid weight gain during infancy. A recent meta-analysis of 31 birth cohort studies (147 252 children) showed that rapid weight gain during infancy was an independent risk factor for preschool wheezing and school-age asthma [37]. This is consistent with numerous reports of an association between obesity and asthma. Hypotheses on the mechanism behind these associations include genetic predisposition, *in utero* exposures, immunomodulatory or endocrine pathways, mechanical changes, and lifestyle factors [96].

Taken together, maternal and childhood diet affect normal lung development but a detailed understanding of the connection is still lacking. Future research will provide insight into the interplay between diet, body composition and lung development.

Allergic sensitisation

Allergic sensitisation in infancy has been seen as a crucial first step in the development of asthma and reduced lung function over time [97, 98]. Synergistic interactions between allergic sensitisation and viral respiratory infections in early life appear to be important in exacerbating the risk [99]. Allergic sensitisation precedes wheezing illness induced by human rhinovirus (HRV) in children who subsequently develop asthma [100]; this typically occurs in children with a genetic predisposition [101]. Trials aimed at preventing the onset of asthma by avoiding contact with allergens have had conflicting results. In a group of 120 non-sensitised, high-risk infants, avoiding house dust mites by using mattress covers proved successful in preventing allergic asthma [102]; at 18 years old, this group still had a lower prevalence of asthma than the control group [103]. In sharp contrast, other trials found that allergen avoidance produced no or even deleterious effects [104–106]. Taken together, these studies fail to support a role for either allergen avoidance or allergen exposure in preventing the inception of allergic airway disease. Nonetheless, a multifaceted approach (mite reduction, breast-feeding and smoking cessation) could have a greater chance

of being successful [103, 107]. For food allergens, however, there is evidence to suggest that early exposure prevents allergic sensitisation [108]. Likewise, delaying the first introduction of hen's eggs to children's diets until after the age of 10 months was associated with a threefold higher risk of allergic sensitisation [109].

Allergen avoidance and exposure have also been considered for the secondary prevention of asthma in already-sensitised individuals, with conflicting results [110]. In patients with allergic rhinitis, large observational and small randomised studies have shown that immunotherapy may prevent progression to asthma. Grass- or birch-specific immunotherapy prevented asthma from developing in 50% of a group of young adults with allergic rhinitis for up to 10 years after treatment [111]. However, large randomised studies are needed to confirm that this form of secondary asthma prevention is safe and effective.

Viral respiratory infections

Respiratory infections during infancy are associated with the onset of childhood asthma. A birth cohort from Sweden consisting of 42 334 children hospitalised for respiratory infections during their first year of life [112] was compared with 211 594 control subjects. It was found that experiencing a viral or bacterial respiratory infection at <12 months old resulted in a 50% higher risk of asthma at 5 years of age; this increased risk of asthma persisted up to 16 years of age. Other (mainly retrospective) studies found respiratory infection during childhood to be a risk factor for COPD [50, 113]. Research has been conducted mainly on viral respiratory infections associated with wheezing, such as respiratory syncytial virus (RSV) and HRV, so in the remainder of this section, we focus on the mechanisms and risks of RSV- and HRV-related chronic respiratory morbidity.

The causative mechanism behind the association between viral respiratory infections and long-term respiratory morbidity has been the subject of much research. It is argued that respiratory pathogens raise an individual's susceptibility to lung impairment and asthma *via* various immunological pathways. However, it may be that an underlying immunological weakness increases the risk of respiratory infection and asthma [114]. A nonrandomised trial among late-preterm infants showed that preventing RSV by means of virus-specific antibody prophylaxis reduced the risk of recurrent wheezing in childhood by 68–80% [115]. This effect was seen only in children with no family history of atopy, however, suggesting that atopy and RSV have distinct roles in the pathophysiology of wheezing illness [115]. A RCT among 429 preterm infants found conclusive evidence of a 61% reduction in the total days of wheezing in the first year of life in infants given RSV prophylaxis as opposed to a placebo; this effect was seen in both atopic and nonatopic children [116]. RSV causes severe disease during infancy. About 1% of all children require hospitalisation for RSV infection in their first year of life [117]. Cohort studies have shown that up to 50% of children who experienced a severe RSV infection during infancy were diagnosed with asthma at school age [118–121]. A meta-analysis estimated an overall odds ratio of 3.84 for asthma [122] in children with a history of RSV infection. That study also showed that the relationship between asthma and a history of RSV infection declined with age, confirming previous reports [123]. A recently published birth cohort study conducted among 1246 children followed up to the age of 29 years showed that RSV infection during childhood alone was not associated with any increased adult asthma, but adult smokers with a history of childhood RSV had a 1.7-fold higher risk of asthma than nonsmokers with a history of RSV infection [124]. The mechanism by which RSV causes recurrent wheezing is not entirely clear. An influx of neutrophils to the airways prompted by the RSV infection may plausibly be associated with damage to the airway architecture, resulting in wheezing and shortness of breath when any subsequent viral infection occurs [125, 126].

The nature of the relationship between HRV and the onset of asthma may be quite different. HRV infection usually causes only mild illness [127]. The authors of the Childhood Origins of Asthma (COAST) birth cohort study among 259 children with an atopic background showed that allergic sensitisation preceded HRV wheezing illness, arguing against a causative role for HRV in the inception of asthma [100]. However, HRV-associated wheezing illness has an even stronger relationship with impaired lung function and asthma at school age (6–8 years) than does RSV infection [128, 129]. In COAST, HRV-induced wheezing illness during the first year of life was associated with a 2.9-fold risk of asthma at the age of 6 years [129]. Other community-based studies confirmed a strong association between HRV-associated wheezing illness and the risk of asthma at school age [130].

In short, RSV infection is causally related to subsequent preschool wheezing, but whether or not this effect extends to the onset of asthma or COPD later in life remains to be seen. HRV-associated wheezing illness during infancy is strongly related to asthma at school age but epidemiological studies have yet to demonstrate a causal relationship.

Finally, genetic variances are believed to have a role in virus-mediated asthma pathogenesis: variants of the 17q21 locus are associated with the onset of asthma. In two cohort studies, these variants were also related to early-life infections and HRV-induced wheezing [101, 131]. A recent study also showed that COPD genes

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are associated with early transient wheezing, pointing to a possible link between COPD and viral respiratory infections during infancy [132].

Long-term consequences of prematurity and BPD

In this section, we discuss the impact on respiratory health of early-life events related to premature birth and lung immaturity, with or without the associated onset of BPD.

The lung develops in five phases: the embryonic period (up to week 6), the pseudoglandular period (weeks 6–16), the canalicular period (weeks 16–24), the saccular period (weeks 24–40) and the alveolarisation period (which takes place mostly after birth) [133]. Preterm babies born before the 32nd week of gestation have lungs in the saccular stage of development at birth. This means that the alveoli are incompletely developed, the air–blood barrier is still too thick to allow efficient gas exchange and the surfactant system is immature [133]. Premature birth interrupts lung development and its subsequent maturation occurs out of phase, resulting in airways that are more compliant, smaller and with fewer alveolar attachments [134]. Most premature newborns are also exposed to intrauterine inflammation [135], which might further interfere with lung development and have a role in BPD, although this issue is still debated. In addition to prenatal factors, a number of early postnatal noxae, such as hyperoxia and volutrauma, may exacerbate the newborn's lung damage, affecting airway growth, alveolarisation and microvascularisation, and leading to BPD [136].

BPD is a chronic obstructive lung disease that occurs in premature infants, especially in those with respiratory distress requiring ventilatory support and oxygen supplementation. BPD is defined as the need for supplemental oxygen for at least 28 days after birth [137]. Advances in neonatal care have modified the characteristics of BPD, prompting a distinction between ''old BPD'' (mainly involving subjects born in the pre-surfactant era) and ''new BPD'' (usually affecting subjects born in the post-surfactant era). From a pathological standpoint, old BPD is characterised mainly by alveolar septal fibrosis and inflammation, and new BPD is characterised by impaired alveolar growth [138, 139].

From a functional standpoint, mid- and long-term follow-up studies conducted in children born prematurely have shown a substantial ''tracking'' of their lung function. This long-term tracking is a general characteristic of lung function, as demonstrated by the strong correlation found between lung function at 2 months and at 11, 16 and 22 years of age in an unselected birth cohort [140]. This suggests that poor airway function shortly after birth is an inescapable risk factor for airflow obstruction in young adults [140].

Although some authors have reported a degree of improvement in airway obstruction as BPD subjects grow older [141, 142], most longitudinal studies have demonstrated a persistently reduced lung function throughout childhood, adolescence and early adulthood [138, 143–145]. Significant functional impairment has also been seen in preterm-born, non-BPD subjects (although less pronounced than in BPD subjects), confirming the important functional impact of prematurity *per se* even beyond the first year of life [143].

Their persistent functional deficit prevents BPD subjects from achieving their full respiratory potential, but the lungs of the prematurely born seem to be more vulnerable too. A steeper than normal decline in FEV_1/FVC has been described in adolescents born preterm, suggesting that their respiratory health deteriorates sooner than it does in their term-born peers [146]. A progressive functional deterioration has also been reported in BPD subjects who experienced a more severe airflow obstruction in infancy, confirming the important long-term effect of perinatal lung injuries [147].

Interestingly, significant impairments of airway function have been reported not only in ''old BPD'' patients, but also in BPD children born in the post-surfactant era [148–151]. This finding underscores the detrimental effect of lung immaturity on respiratory health over the years, even when surfactants and antenatal steroids were used and ventilatory support was less aggressive. Some recent ^{3}He-MRI studies nonetheless suggest that alveolarisation may ''catch up'' in preterm subjects during their first decade of life despite a persistent airway obstruction [152].

From a clinical standpoint, preterm-born subjects (particularly those with BPD) have a higher burden of respiratory symptoms than do healthy control subjects [138, 153, 154]. Although this difference tends to fade with age, data collected in young adults still indicate a greater recurrence of respiratory symptoms in the preterm-born than in the term-born individuals [142]. The higher respiratory morbidity associated with premature birth may be partly due to reduced airway calibre, but it may also be a consequence of neonatal exposure to hyperoxia, which can exacerbate inflammatory responses and lead to changes in key immunoregulatory pathways [150]. It is noteworthy that even late-preterm children (born between the 34th and 36th week of gestation) have a significantly higher than normal respiratory morbidity [45, 155–158], which has been related to lung vulnerability due to immaturity, perinatal factors and a greater susceptibility to RSV infection [158].

It is worth adding that, although children with chronic lung disease after premature birth and children with asthma share some clinical and physiological features (recurrent wheezing and flow limitation on spirometry), there are different underlying mechanisms. In our opinion, the term asthma should be avoided when referring to ex-preterm and BPD children to avoid the risk of them being given ineffective or even unsafe chronic treatments [159].

Finally, it is worth remembering that BPD is frequently associated with other, nonrespiratory conditions relating to preterm birth, such as growth retardation, pulmonary hypertension, neurodevelopmental delay, hearing defects and retinopathy of prematurity [154].

Early origin of COPD

COPD is an umbrella term for a spectrum of diseases characterised by an airflow limitation that is not fully reversible. It is set to become the third most important cause of death globally by 2020 [160]. A growing number of studies suggest that not only cigarette smoke but also several other factors are involved in the pathogenesis of COPD. Alongside those taking effect in adulthood, the role of perinatal and early-infancy factors, including prematurity and BPD, has recently been stressed [161, 162], and an association has been suggested between low birth weight and both airflow limitation in adulthood [163, 164] and death due to COPD [165]. Likewise, it has been demonstrated that some childhood disadvantages (parental asthma, childhood asthma, childhood respiratory infections and maternal smoking) have much the same impact on adult lung function and the risk of COPD as heavy smoking [50], suggesting that COPD can be seen as a disease of childhood that becomes manifest in adults [124, 166].

The hypothesis of an early origin of chronic respiratory diseases supports the theory that noxae acting during periods crucial to lung development may give rise to permanent structural or functional changes in the lung, with potential lifelong consequences [136, 167]. In addition, the modification of genetic pathways involved in lung development and changes to immunoregulatory pathways in response to detrimental conditions may lead to long-term altered lung homeostasis. This might prompt abnormal responses to harmful agents (e.g. cigarette smoke or pollutants), resulting in a faster degeneration of respiratory function [168, 169].

Alongside such an accelerated decline in lung function, a recognised risk factor for COPD is failure to reach the expected peak lung function during early adulthood [138, 160], as often happens after preterm birth. In fact, prematurely born subjects (with or without BPD) may not reach their maximum potential lung function during early adulthood because their lung development is impaired due to the combined effects of prematurity and noxious agents acting early in life (*e.g.* hyperoxia) or later on (*e.g.* smoking). This means that the physiological age-related decline in lung function may predispose these subjects to a COPD-like phenotype, whereas there is no such significant respiratory impairment in healthy individuals thanks to their available reserves [136]. It is noteworthy that a low FEV_1 in adulthood is associated not only with poor respiratory health but also with higher rates of cardiovascular diseases and overall mortality [170].

The hypothesis of an early origin of a COPD-like phenotype related to prematurity and BPD is intriguing but further studies are needed to investigate the biochemical–metabolic processes and pathological changes that lead from BPD to COPD. Pathological data are only available for the early phases of BPD; very little is known about the pathological processes and structural changes occurring in the lungs of BPD and preterm subjects beyond infancy [171].

The likely influence of early-life events on the development of chronic respiratory diseases in adulthood strongly suggests that paediatric and adult respiratory medicine should not be considered separate disciplines, and that adult physicians should be aware of the possible impact of early-life events on an individual's lifelong respiratory health. Interventions to contain negative early-life factors may thus have a significant effect on adult respiratory health and the risk of COPD. Unfortunately, a survey by the British Thoracic Society demonstrated that respiratory physicians rarely ask their adult patients about early-life events [172].

Searching for early biomarkers in chronic respiratory diseases

Chronic respiratory diseases such as asthma or COPD are extremely complex syndromes owing to the large number of cell types and molecular pathways that contribute to their pathogenesis and interact in complex networks [173–175]. Two further aspects add complexity to the picture: 1) there is a partial overlap in the characteristics of the different chronic respiratory diseases; and 2) their onset in adulthood may be the result of harmful early-life events that have made the lungs more vulnerable for the rest of the subject's life. Although analysing single biomarkers and molecular pathways provides useful information, the great complexity of these conditions demands their study using a more global strategy as well, or what is called a systems biology approach [173, 176]. Systems biology is defined as the quantitative analysis of the dynamic

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interactions between different components of a biological system based on a combination of mathematical modelling and experimental biology [177]. Systems biology is considered a key factor in the development of personalised medicine and the "-omic" technologies (genomics, proteomics and metabolomics) have the potential to shift the focus of medicine from the traditional symptom-oriented diagnosis and treatment of diseases (reactive medicine) towards the "P4" medicine, which concentrates on preserving health through the prevention and early diagnosis of disease [178].

The "-omic" technologies are systems biology platforms that are not guided by any *a priori* assumptions. They are used to look into which components are associated with a given pathological condition with a view to shedding light on single phenotypes and new, hitherto unsuspected pathogenic pathways, resulting in a hypothesis-generating approach [179]. Among the "-omics", metabolomics is considered the one that comes closest to phenotype expression, enabling the study of overall metabolic profiles resulting from the joint contribution of genetic information and environmental factors unrelated to the genome [180]. The metabolomic approach has been used successfully to characterise patients who already have asthma [181, 182] or COPD [183]. The next challenge is to apply this novel method very early in life, even before birth, with a view to identifying individuals likely to develop a given chronic respiratory condition. In fact, one of the most promising applications of the metabolomic approach is the early identification of metabolite patterns associated with the subsequent onset of a pathological condition. The potential of such an approach has been demonstrated; for example, in type 1 diabetes, genetically predisposed subjects have a metabolomic profile capable of predicting the onset of the disease before any other immunological or clinical signs become apparent [184]. Similarly, metabolomic analysis of the amniotic fluid has been used to identify subjects at risk of preterm delivery [185, 186]. In the field of respiratory medicine, the feasibility of identifying metabolomic profiles predictive of chronic lung diseases such as asthma or COPD would be particularly appealing, given the assumption of their early origin. Characterising such early predictive metabolomic patterns would have a profound impact on the management of these conditions, potentially enabling the implementation of effective preventive strategies and/or targeted early therapeutic approaches [187, 188].

Conclusions

In this narrative review, we discussed evidence from the recent literature highlighting the need to take a lifespan approach to studying chronic respiratory diseases. A growing body of data supports the conviction that early-life factors play a fundamental part in the later onset of diseases such as asthma and COPD, and the early postnatal period appears to offer a specific window of opportunity for intervention. A better awareness of the close links between early-life lung events and adult respiratory diseases should prompt a greater effort to improve early prevention strategies with a view to ensuring a beneficial impact on both short- and long-term respiratory health.

We have attempted to discuss the most important factors with an impact on long-term respiratory health. Some of them are modifiable, such as SHS exposure, and every effort to prevent maternal smoking during and after pregnancy should be strongly supported. Other factors might be modifiable, such as those related to mothers' and children's diets, but further trials are needed before recommendations can be made relating to specific dietary measures. Finally, there are early factors with a clear negative impact on later respiratory health, such as premature birth, viral respiratory infections and allergic sensitisation, for which further studies are needed to identify effective prevention strategies.

The pathways and mechanisms involved in the relationship between early-life events and chronic respiratory diseases in adulthood warrant further investigation, including novel approaches, such as the high-throughput "-omic" technologies. A better understanding of how these diseases evolve over the lifespan will improve our ability to treat and prevent them. More investment in high-quality paediatric respiratory research in early life is a crucial part of the effort to ensure healthy respiratory ageing.

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