Early life exposures and the development of COPD across the life course.


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**Introduction**

There is growing recognition that various forms of deprivation, in particular adverse antenatal or early life exposures, increase the risk of lung disease, in particular COPD, across the life course(1-7). These influences manifest in three broad ways. The first is processes that prevent an individual's lung development and growth from achieving its full potential. The second is processes that prime the lungs to be more sensitive to subsequent insults, which contributes to the third; early, then ongoing lung damage caused by exposure to inhaled toxic materials including tobacco smoke, environmental and indoor pollution, occupational hazards and infections as well as other stressors. Such insults are particularly prevalent in low and middle income country contexts (LMICs), often exacerbated by social deprivation and poverty.

The "life course" approach to disease development, appreciating the accumulating and potentially interacting influence of genetics, environment, vulnerability to exposures by age, and ageing itself, on the development of lung disease has been formally championed by epidemiologists since the 1990s(8, 9). A recent conceptual framework introduced the term "GETomics", highlighting the potentially different, cumulative and interacting gene (G) – environment (E) interactions acting across time (T) to influence epigenetic changes and/or immune responses, and ultimately the development of health and disease(10) (Figure 1).

It is virtually impossible to disentangle the precise contributions of different adverse social determinants of health, because they tend to co-exist and act in synergy(3, 11). Poverty, traffic pollution, poor nutrition and an adverse microbiome, occupational stress and exposure to dust, fumes and chemicals, limited access to healthcare, lower respiratory tract infections, low rates of breast feeding and high rates of smoking, for example, cluster together(12, 13). Compounding these influences, pandemics and other catastrophes bear down most heavily on those who are already deprived. A study of more than a million Dutch children born in the 1980s defined three forms of childhood adversity(14). These were material poverty, threat or actual family loss, and family effects such as maternal separation. Each was associated with increased mortality, and the three together were associated with a more than 4-fold risk of early death. This "syndemic"- synergistically interacting epidemics that occur in a particular context with shared drivers(15), has been proposed as a key explanation for the simultaneous occurrence of COPD and multimorbid diseases(16).

Life course approaches to health disparities include two key perspectives – developmental and structural(9). The developmental perspective focuses on critical or sensitive periods where healthy development can be impaired and future maladaptive physiological responses are primed. Structural perspectives focus on socially patterned exposures to cumulative harms across the life course. A recent review sets out how COPD can be considered as a manifestation of structural violence, categorised into five domains; (i) avoidable lung harms, (ii) diagnostic delay, (iii) inadequate COPD care, (iv) low status of COPD, and (v) lack of support for people living with COPD(3, 11). A comprehensive assessment of the broad issues of social justice and hierarchies of power and privilege that influence who does or does not develop COPD and the severity of disease, access to and affordability of care, is outside the scope of this paper. Nevertheless, it is apparent that these processes impact on individuals to a varying extent depending in part on a range of social factors related to wealth and social class, ethnicity and gender(3, 17). Advocacy and action to address these injustices and their lethal intersections(18) at source is an essential role for anyone promoting lung health. It is also important to acknowledge the effects of global heating and climate disruption, both directly on lung health and indirectly through disruption to food and healthcare systems.

Further understanding of the processes and the mechanisms underpinning the development of COPD across the life course opens the opportunity both to change the way in which the condition is viewed, and potentially to develop targeted interventions to prevent, arrest or reverse lung disease.

**The concept of lung function tracking**

During in utero lung development, airway branching is complete by around 17 weeks of gestation, after which acinar structures start to form. Surfactant protein synthesis commences towards the end of the second trimester, with true alveoli appearing from 28 weeks onwards. Post-natally, vital capacity reaches a peak at age 20-25 years and steadily declines thereafter. The ideal study to track lung function across the life course would recruit women of childbearing age, follow them through pregnancy and measure their children's lung function until death in old age, with extensive complementary environmental /exposure data, and biological sampling.

Although this has not yet been achieved, there are studies that are reaching the seventh decade of life having recruited at school age(4, 5), whereas those recruiting antenatally, for example the Tucson study(19), have not yet reached the fifth decade. The study of overlapping cohorts can allow increasingly robust conclusions to be drawn, and this is the goal of CADSET, a clinical research collaboration promoted by the European Respiratory Society that includes more than 40 research groups across Europe with access to many general population, birth cohorts and clinical cohorts(20). Importantly, there is a paucity of cohorts from LMICs, despite the many adverse environmental exposures, and high prevalence of COPD and severe disease these populations experience(1, 21).

The "first 1000 days" – 9 antenatal months and the first two years of life - underpin the developmental origins of health and disease (DOHaD) and are crucial for lifetime lung health(21-23). For the vast majority, the lung function centile that individuals occupy during their pre-school years appears to track through to the seventh decade of life(24) a fraction of this tracking being attributable to the effect of polygenic inheritance(25) . However, there are exceptions to this pattern and both catch-up growth and growth failure with a decline to a lower centile are well described(4, 26, 27). "Catch-up" lung function growth is most likely in those with lower first-year prevalence of bronchitis, less exposure to maternal smoking in pregnancy and less post-natal parental smoking(24), and is also associated with less personal smoking during adolescence(27), delayed puberty(28), and an absence of childhood/adolescent asthma(4). Thus, alongside early childhood, the peripubertal and adolescent years are a further vulnerable period. Starting to smoke before puberty is linked to increased risk of lung cancer and developing COPD(29, 30), even accounting for pack year history and other childhood exposures.

The level of lung function ultimately achieved in adulthood has consequences beyond the lungs; low forced expired volume in one second ($FEV_1$) is a marker for cardiovascular and all cause premature morbidity and mortality, not just for poor respiratory outcomes(31). It is clear that (a) antenatal and early life factors are crucial in lifetime lung health; (b) we might be able to modulate lung growth if we better understood the pathways of catch-up; and, (c) careful monitoring of lung function during infancy and adolescence is important to identify unfavourable lung function trajectories (32).

In early life where airflow obstruction, emphysema and MUC gene over-expression can already be identified, the stage has been set for early systemic multi-morbidity, all hallmarks of COPD(16). Systemic inflammation is recognised as a feature of adult lung disease(33), and this may also start early. High-sensitivity C-reactive protein is elevated especially in mothers who smoke and are of low socioeconomic status, and maternal and child levels are correlated(34).

**Transgenerational effects**

Around 30% of the variance in child spirometry is related to parental spirometry(31) and there is increasing realisation that the health of the child is determined even many years before their parents first meet, let alone conceive(35). The most important of these exposures is tobacco. If a grandmother smokes, irrespective of whether her daughter smokes, her grandchildren are at increased risk of asthma(36, 37). Whereas it used to be thought that the ill effects of paternal smoking were confined to passive exposure of the infant, in fact the signal is greater for early onset of paternal smoking, long before the child or adolescent becomes a father, and this effect is even greater than maternal smoking in pregnancy(38). The extent to which these mechanisms are epigenetic in nature requires further exploration(39, 40). The effects of preconception parental exposure to outdoor pollution, as well as occupational exposures, socioeconomic factors, paternal obesity, maternal use of oral contraceptives and parental infections are also likely important. Here and elsewhere, it must be acknowledged that these associations do not necessarily mean causation; so for example, underlying poverty may drive both obesity and long term adverse outcomes.

**Unsafe in the womb: antenatal adverse effects**

The biological readout of adverse in utero effects is summarised in Box 1 and a recent review(41). Maternal stress, including neighbourhood factors and intimate partner violence are also important, as is maternal atopy and exposure to indoor and outdoor pollution. Of note, tobacco legislation has been associated with reduction in the prevalence of preterm birth(42).

Epigenetic and protein studies of fetal lung tissue at different stages of development, show that methylation patterns linked to intrauterine smoke exposure resemble those seen in adult lung tissue from former smokers with COPD, thus establishing a link with the early life exposures(43), as well as identifying protein interaction pathways such as AGE-RAGE and focal adhesion that may contribute to the lung development abnormalities and link to COPD(44).

In addition to other toxic effects of tobacco smoke, adverse effects of nicotine in animal studies, including structural and functional abnormalities, have been identified even without exposure to any other chemicals. The mechanism may be related to dysregulation of siRNAs(45). Intrauterine growth restriction, and/or being small for gestational age, may in part be related to correct placentation and have a relationship with lung function later in life(46, 47). Maternal obesity in pregnancy is associated with an increased incidence of childhood wheeze, and therefore presumably impaired lung function(33). Uncontrolled maternal HIV in pregnancy is associated with lung function impairment in offspring who are HIV-exposed but uninfected(23, 48).

**Box 1: Impact of adverse effects in utero on adult lung health**

- Prematurity and low birth weight; both impair lung function, and even early term delivery (37-38 weeks) is associated with increased respiratory symptoms.
- Altered lung structure, including dysanaptic airway growth, airway instability through reduction in alveolar tethering, increased MUC gene expression, neonatal bronchial responsiveness and failure of alveolar development leading to early emphysema.
- Increased sensitization to later adult adverse stimuli, including smoking and occupational exposures.
- Altered immune function (as shown in cord blood studies), leading to greater vulnerability to pre-school wheeze.
- Telomere shortening, a marker of premature aging.
- Epigenetic fetal lung tissue modifications resembling those in ex-smokers with COPD.

**The most dangerous journey: birth**

Although prematurity occurs across all social classes, it is commoner in the context of deprivation and in some ethnic groups, as well as in low-middle income countries (LMICs)(49). Increasing environmental temperatures also increase the risk of premature birth(50). Many adult survivors of preterm birth now meet spirometric criteria for COPD(51), although whether the molecular pathology is the same as in other pathways to airflow obstruction is not clear. Today's graduates from Neonatal Intensive Care, born more prematurely with lower birth weights (300-400 gm), are very different from their historical counterparts, and are more likely to have an emphysema-like disease due to pulmonary hypoplasia. Surfactant treatment, 'soft' resuscitation and low pressure, faster rate ventilation, are all associated with improved outcomes. Very low birth weight survivors are a very small minority of those who are delivered before term, with approximately 85% of infants born prematurely globally being moderate to late preterm births (gestational age of 32-37 weeks)(49). However even moderate to late preterm birth is associated with subsequent long term impairment in lung function(52) and childhood morbidity(53-55). A full review of the many factors which affect respiratory outcomes in premature delivery can be found elsewhere(56). Finally, the level of lung function of pre-term survivors at 5 years, has been linked to the enrichment in COPD polygenic risk score (PRS), again showing the value of a GETomics approach to the disease(25).

Mode of delivery may also have long term consequences. Caesarean section delivery will mean reduced or no exposure of the baby to the vaginal microbiome which may increase the risk of later atopic disease(57). Birth cohort studies have shown that airway hyper-responsiveness in the first few weeks of life, before any respiratory infection or airway inflammation has supervened, and with only minimal allergen exposure, is associated with adverse long term respiratory outcomes(58-60). The likely basis for airway responsiveness is abnormal airway growth, based on animal studies(61). Breast feeding is an important protective measure, but all too often, support for mothers is lacking, especially in those of low socioeconomic status.

**The pre-school years**

During childhood, the growing lung continues to be susceptible to the adverse effects of passive smoking and other pollutants. Early rapid weight gain is associated with dysanapsis, where non-proportional growth of airways and lung result in relatively small airways for lung size, which is associated with adverse long term respiratory outcomes(62). Lower respiratory infection in the first two years of life is associated with an almost two-fold risk of premature death in adult life(7), as well as impairment in lung function including higher resistance and lower compliance and structural lung abnormalities including gas trapping(63). Importantly, each LRTI has an additional effect on lung function, and although severe disease, as reflected by hospitalisation, leads to the largest impairment of lung function, even mild disease has long term adverse effects on lung function(21, 64), with RSV-LRTI associated with the development of airflow obstruction. Whether infections are causative, or a marker of an underlying predisposition is unclear, and this may vary between different populations. Causality can be inferred from the finding that some of these effects are mediated through a lower level of lung function during adulthood(7), and through the findings from the Drakenstein child health study where impairment in lung function at 5 years due to LRTI was independent of baseline lung function measured at 4-6 weeks of age (21). Whatever the mechanism, what is clear is that an early lower respiratory tract infection should be considered as a red flag, a marker of future adverse outcomes, and this should provoke a focused response to intervene with health improvement measures, including attention to the environment, something that is not recognised in international bronchiolitis and childhood pneumonia guidelines.

It may well be that the benefit of immunisations against influenza and RSV in preventing infection is of more than short-term advantage(7). Recently 2 new interventions to prevent RSV-LRTI in infants have become available in high income countries – a pre-F maternal vaccine and a long-acting monoclonal antibody given to infants prior to or during the RSV season. Trials have shown high efficacy and implementation studies confirm very high effectiveness(65). While these interventions are now available in many HICs, they are not yet licensed or available in LMIC settings despite the predominant burden of severe RSV-LRTI and mortality occurring in these areas. It is crucial that these effective interventions are available and affordable to children in low- and middle-income countries. A further issue is that early life exposures, including to infections, can impact on TH1/TH2 immune responses and influence the risk of developing asthma, as reviewed here(66).

Tuberculosis, which is highly prevalent in some LMICs, is increasingly recognised to have a detrimental impact on long term health and is associated with COPD-like disease(67). Data from the Drakenstein cohort show that early life TB disease is associated with increased risk of wheezing and lung function impairment, at least to 5 years of age(21, 68).

**Childhood and adolescence**

The effects of indoor and outdoor pollution continue to manifest in childhood. Notably, lung growth improves where legislation ensures cleaner air(69). Childhood nurture is important; physical, sexual, and emotional abuse, and physical and emotional neglect all lead to premature telomere shortening, especially if there are multiple abuse factors(33, 70). Both insufficient nutrition and obesogenic diets impact on lung development, while low levels of physical activity have been consistently associated with a more rapid rate of lung function decline(71). Most people who smoke start during their teens and smoking is a highly transmissible habit within families and peer groups(72, 73). Lower respiratory tract infections including tuberculosis can also continue to impact on healthy lung development.

**Beyond age 25: the ageing lung**

Various paths may lead to COPD, combinations of (a) failure to achieve a normal peak lung function, resulting from the pre-utero, childhood and adolescent factors discussed; and (b) accelerated decline of lung function, either from a normal or reduced peak lung function(74). The major factor identified as triggering the accelerated loss of lung function during adulthood remains personal tobacco smoking, though pollution and occupational exposures may also make important contributions. As in childhood, the likelihood of encountering these adverse adult exposures is socially patterned, with intersectional effects of race, class and gender(3).

Studies seeking a direct link between adverse early-life exposures and subsequent susceptibility to adult exposures, specifically to the rate of lung function decline during adulthood have delivered conflicting results. Some studies have suggested a link to season of birth and to markers of childhood social disadvantage(75, 76), although this has not been confirmed in studies where childhood social disadvantage data have been collected prospectively(27, 77). Differences between prospectively and retrospectively collected data highlight the value

of life-spanning studies. Certainly, an association between childhood asthma and adult lung function decline, perhaps mediated by ongoing asthma-like disease activity, would seem plausible. In patients with asthma and multiple acute wheeze attacks, treatment with inhaled corticosteroids ameliorates impaired lung growth in children and might set a better trajectory in adulthood, including less rapid decline in lung function in adults.

Ageing is characterized as a progressive impairment of tissue/organ/organism function, resulting in increased vulnerability to environmental challenges and a growing risk of disease and death(78). Lopez-Otin *et al* described nine hallmarks of aging(79), that have been now expanded(80). The hallmarks of aging include *molecular* (telomere attrition, genomic instability, epigenetic alterations, and loss of proteostasis), *organelle* (disabled autophagy, mitochondrial dysfunction), *cellular* (senescence), *supracellular* (stem cell exhaustion), *organ* (chronic inflammation), *organ systems* (deregulated nutrient-sensing), *systemic circuitries* (altered intercellular communication) and *meta-organism* (dysbiosis)(81). Most of these hallmarks of aging have been linked to lung aging specifically, and interestingly some of them have also been observed in young individuals with low lung function. Recent comprehensive reviews of lung aging are available(82), but we in particular highlight here the contributions of: (i) Telomere attrition - telomere attrition during somatic cell division relates to chronological aging(83) and telomere shortening induces cell senescence(79). Associations between telomere attrition and low lung function have been identified across the lifespan, and telomere attrition is associated with replicative senescence, another hallmark of aging. The accumulation of senescent cells has been reported in chronic respiratory diseases including COPD and IPF, and is a topic that deserves further research in pre-term children(84). (ii) Genomic instability - instability of both the nuclear and mitochondrial DNA is a key hallmark of aging, since DNA damage may lead to apoptosis or cell senescence and stem-cell exhaustion, compromising tissue homeostasis and renewal(80). Linked to this, epigenetic drift, referring to the observation that epigenetic differences in monozygotic twins increase with age(85), and the accumulation of epigenetic modifications that occur during the lifespan, is a key component of the GETomic approach to health and disease(86). Specifically, the most comprehensively studied epigenetic modification is the addition of a methyl group to cytosines next to guanines in the DNA molecule (i.e., DNA methylation in CpG sites). Both active and passive smoking produce extensive DNA methylation changes, some of which do not revert after quitting smoking. Similarly, maternal

smoking during pregnancy is associated with DNA methylation in cord blood DNA at birth and, importantly, these changes persist at least up to adolescence(87) and are associated with low lung function(88). Further, as introduced above, epigenetic markers identified in *fetal* lung tissue may increase the risk of developing COPD later in life(89), as co-methylation analysis has revealed highly preserved features with enrichment in developmental and inflammatory pathways, including Hippo, Wnt, TGFB and PI3K/AKT pathways. Adverse childhood experiences and other social determinants of health as well as tobacco smoke exposure are also associated with increased epigenetic markers of aging in later life(90, 91). (iii) Loss of proteostasis, the term referring to the regulation of *de novo* protein synthesis, folding, assembly, as well as protein export, breakdown, and degradation(80). Several works have now identified proteomic biomarkers associated to low lung function across the lifespan(92, 93). (iv) Altered cellular communication - cellular communication is achieved by small molecules, acting as chemokines, and in turn an altered production of chemokines, is associated with low level inflammation as the immune system ages (also known as 'inflammeaging')(94). In COPD, the effect of inflammeaging both in the airways, and in the systemic compartment is well documented, and is associated with the chronic inflammatory response to tobacco smoke, altered antioxidant imbalance, accumulation of senescent cells (an additional hallmark of aging) and the presence of multimorbidity(95). Interestingly, a persisting level of airway neutrophilic inflammation and oxidative stress (Leukotriene B4 and 8-isoprostane) beyond the first year of life has been observed in adolescent pre-term survivors, which may be related to future lung disease(95). (vi) Stem cell exhaustion - in COPD, endogenous stem cell exhaustion, due to response to persistent injuries, leading to a deficient repair of the epithelium has been reported(95). Altered repair has also been suggested as a key factor for neonatal lung diseases, and in animal models of bronchopulmonary dysplasia, treatment with mesenchymal stromal/stem cells (MSCs) have the capability to prevent disease progression, suggesting similar approaches could be adopted in the future to prevent chronic lung diseases(96). (vii and viii) Extracellular matrix remodelling, including the alteration in collagen composition a prominent feature of severe COPD, has also been reported in pre-term children(97). Finally, mitochondrial dysfunction, a hallmark of lung fibrosis and COPD, has also been observed in adult survivors of pre-term birth in the systemic domain(98).

**What follows from understanding the origins of COPD?**

The evidence presented so far suggests a range of areas in which there are research questions to answer (Table 1). In terms of prevention, these may include developing the evidence base as to what will be effective interventions (for example, how to reduce exposure to biomass smoke or optimise nutrition), and implementation science research as to how interventions that are known to be effective (smoking cessation support, vaccination) can best be implemented in ways that are as efficient and comprehensive as possible. Advocacy for the introduction and enforcement of smokefree generation policies(99) that will end youth uptake of smoking, should highlight the importance of ensuring a smoke free pregnancy. Strengthened strategies for prevention of LRTI early in life are important including wider global and equitable access to new vaccines for all children.

Approaches to improve maternal health, pre-conception through to delivery, will of course have benefits for children over and above healthy lung development. However, given the impact of prematurity and low birth weight on respiratory function, understanding how to reduce their occurrence is a key area specifically for COPD prevention. Strategies around ventilatory support, supplemental oxygen and other aspects of perinatal care need to be optimised.

It is clear that lung function trajectories can track from infancy through to adult life, but also that some individuals gain and some fall behind over time. Mechanisms include patterns of lung development, infections and the lung microbiome, oxidative stress, immune responses and as well as accelerated lung aging. Very recently, the first paper published by the BEACON (British Early COpd Network), characterised COPD related pathology radiologically among young smokers, showing the emergence of emphysema during the fourth and fifth decade of life(100). Such novel data will hopefully reveal new ways to characterise and identify COPD development at an earlier stage(101).

Unravelling the biology that underpins the early life origins of COPD may open the door to strategies that can enhance recovery or protect against deterioration. These will require appropriate tools to assess lung function systematically at an early age, as well as identifying biomarkers of risk and recovery. Based on such tools, clinical trials of potential interventions can be developed. There is clearly a relationship between early life wheezing illness, infections, asthma, and atopy and adult lung health. However accurate phenotyping will be needed as

the effects of these different processes are not identical and are likely to have different impacts in different individuals.

This also raises the need to establish the role of routine lung function testing as a screening tool, either in the general population or in those identified as being at higher risk based on past or current exposures or events. People with COPD typically present late and with extensive irreversible lung damage. Identifying early disease is an essential component of any strategy to prevent progression. At present, although smoking cessation and preventing inhaled or infectious exposures, as well as treatment where appropriate to reduce exacerbation risk are all important, we have limited treatment interventions to reverse susceptibilities and damage that have arisen from early life exposures.

**Conclusion**

COPD has historically had a low status compared to other health conditions with a similar or lesser impact, being framed as a self-inflicted condition, typically affecting individuals with low social status(3, 11). However, most people with COPD are not the authors of their own misfortune, rather they are victims of adversity from even before they were conceived. COPD should be reframed as a disease with its roots in childhood or even earlier, where failures to alleviate social deprivation and poverty are combined with systematic failures to promote child health. This can hopefully guide research to open up new approaches to prevention and treatment, as well as encouraging a more positive and less stigmatising(102) attitude towards people living with the condition.

**Table 1 Research needs to address COPD across the life course.**

| Factors predisposing to COPD | Research Questions |
|---|---|
| **Adverse social structures** | Social sciences approaches to reduce or mitigate poverty / inequality / commercial determinants of health.<br>How to advance health in all policies. |
| **Lung growth and development** | |
| Preconception | How to optimise maternal health.<br>What is the extent/mechanism of transgenerational susceptibility.<br>How do prepubertal adverse exposures impact the health of future children. |
| Nutrition | Macro (too many/few calories. Food types).<br>Specific micronutrients (vitamins etc) that might influence lung growth.<br>Microbiome factors. |
| Smoking cessation | How to support preconception and during pregnancy.<br>How to prevent youth uptake of smoking and vaping. |
| Neonatal care | Reduce risk of prematurity / low birth weight.<br>Optimize care for prematurity (oxygen, nutrition, ventilatory support). |
| Lung trajectories | How to track early lung function trajectories from birth through preschool years.<br>How do trajectories in LMICs compare to those in HICs.<br>What underpins the “catch up” phenomenon and can it be encouraged. |
| Atopy | Can inherited susceptibility be modified.<br>Early effective identification and treatment. |
| Infections | Prevention (maximise vaccine coverage, reduce transmission).<br>Early treatment to minimise damage.<br>Optimizing repair/recovery. |
| Physical inactivity | What mechanisms underpin link with lung function decline. |
| Lung function testing | How to test (what parameters at what age, how often, which specific groups). |
| Impact beyond the lungs | What is significance of lung function impairment for cardiovascular screening/risk calculation/treatment.<br>What is significance of lung function impairment on all-cause premature mortality.<br>Modifying spillover systemic processes (inflammation, immune activation). |
| **Priming mechanisms that increase vulnerability** | |
| | What are underpinning mechanisms. |
| | Are their biomarkers that identify risk. |
| | Role of early life microbiome. |
| | Role of early life medication exposures (e.g. antibiotics). |
| **Lifetime exposures** | |
| Smoking | How to achieve tobacco endgame. |
| Occupation | How to reduce occupational exposures/ensure occupational protection.<br>How to identify vulnerable individuals.<br>How to identify harm promptly (screening etc). |
| Stressors | How to mitigate effects of increased allostatic load – hypothalamic, pituitary, adrenal pathways, autonomic nervous system, cellular stress, oxidative stress. |
| **Environmental pollution** | |
| | Interactions of inhaled particulates, allergens, gases.<br>Effects of global heating. |

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**Figure 1 Processes acting on lung health across the life course.**