receptor, a host receptor co-opted by pneumococci to adhere to cells.[9]

Benowitz and colleagues[8] go on to consider the effects of nicotine—and other constituents of tobacco products—per se on COVID-19. For smokers, the role of nicotine in cigarette smoke is a moot point, since they must inhale a complex mix of toxic chemicals, particles, and gases. But humans can also be exposed to nicotine as inhaled nicotine salts, and as emissions from heated tobacco products and e-cigarettes (novel electronic nicotine-delivery systems or ENDS). ENDS products are not only causing a new wave of nicotine addiction, but also, as recently reported by the American Heart Association, altering immune responses that are relevant to increased susceptibility to viral and bacterial infections.[10] Thus, the possibility raised by Benowitz and colleagues[8]—on the basis of cellular and animal studies—that nicotine might reduce the risk of COVID-19 by either competing with the virus for surface binding or attenuating inflammation must, at the very least, be treated with great caution. Indeed, the limited published evidence to date on the effect of nicotine on airway cells in vitro suggests that it can induce rapid and long-lasting increases in gene and protein expression of ACE2, which in turn increases the capacity of SARS-CoV-2 to replicate in cells and cause a cytopathic effect.[11] Clearly, more cellular, animal, and epidemiological studies are urgently needed. Because a COVID-19 diagnosis was five times more likely among ever-users of e-cigarettes in the only study identified by Benowitz and colleagues[8] that included young people, and because there is a high likelihood that the COVID-19 nicotinic hypothesis[12] will be misused by those with vested interests in the sale of tobacco products, further speculation about the beneficial effects of nicotine on COVID-19 in humans would be unhelpful in the absence of conclusive evidence. Importantly, individuals must not consider using ENDS to reduce COVID-19 risk and, in line with the policy of the European Respiratory Society, should not use ENDS for smoking cessation.[13] And, certainly, young people should be discouraged from initiating ENDS, whatever the effects of ENDS use on vulnerability to airway infection turn out to be.

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The low flyers: persistent airflow limitation in young adults

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On May 18, 2022, at an American Thoracic Society research symposium held in San Francisco, CA, USA, delegates discussed how to best define and treat a new subgroup of patients who are increasingly been recognised: the so-called low flyers.

Since the landmark paper on the existence of multiple lung function pathways to chronic obstructive pulmonary disease (COPD) was published,[1] investigation into lung function trajectories across the lifespan has increased. Although at the population level there is an infinite number of lung function trajectories, studies across both lung growth and decline phases are likely to identify more nuanced lung function trajectories. Multiple early-life risk factors have been identified for

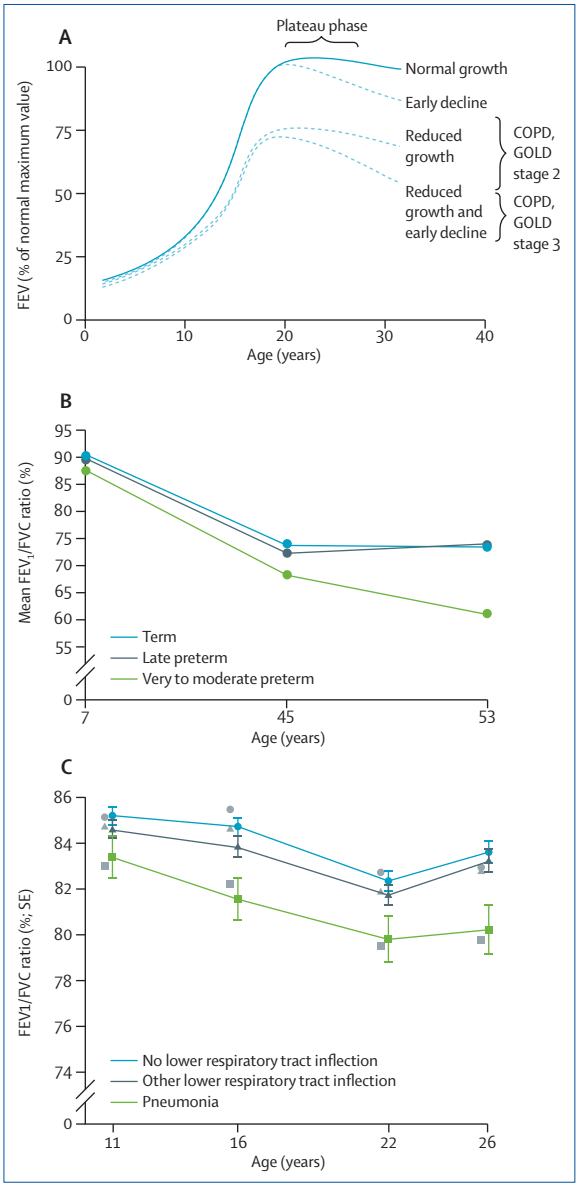

Figure: **Lung function trajectories in longitudinal cohorts**
(A) Possible lung function trajectories during the first three decades of life; the lung function plotted for each age is the percentage of the maximum FEV_1 in a person without lung disease; the maximum value is usually attained at age 18–30 years. A normal pattern of lung function growth and decline is characterised by a steep increase during adolescence, a plateau in early adulthood, and a gradual decline into old age. Abnormal trajectories include reduced growth, normal growth and an early decline, and reduced growth and an early decline. The brackets indicate FEV_1 criteria according to GOLD stage 2 (FEV_1 of ≥50% and <80%) and stage 3 (FEV_1 of ≥30% and <50%) of COPD, when accompanied by a FEV_1 to FVC ratio of <0·70. Reproduced from McGeachie et al,[4] by permission of Massachusetts Medical Society. (B) Mean FEV1/FVC ratio (%) over time among preterm birth (<37 weeks), term birth (≥37 weeks), and very (28–32 weeks) to moderate (32–37 weeks) preterm birth groups among current smokers. Reproduced from Bui et al, with permission of Elsevier.[5] (C) Predicted (grey datapoints) and estimated (colours datapoints) mean values for FEV1/FVC ratio in non-Hispanic white males at ages 11, 16, 22, and 26 years by lower respiratory tract infections. Reproduced from Chan et al, with permission of the American Academy of Pediatrics.[6] COPD=chronic obstructive pulmonary disease. FVC=forced vital capacity. GOLD=Global Initiative for Chronic Obstructive Lung Disease.

the low flyers, defined as those with a low maximally attained FEV_1 trajectory starting from childhood.[2] This early life disadvantage in lung function might continue into adult life, placing these individuals at higher risk for developing COPD.[3] The most consistent evidence exists for preterm birth, childhood asthma, and childhood infection (figure A).[4]

Improvements in medical care have resulted in an increase in premature and very premature livebirths, with more than 15 million babies estimated to be born preterm each year.[7] Bronchopulmonary dysplasia (BPD), also known as chronic lung disease of prematurity, is a common lung disease related to preterm birth, with more than 10 000–15 000 new cases in the USA annually.[7] BPD is increasing in incidence as neonatal survival improves. Infants, children, and adolescents born prematurely with and without BPD have reduced lung function and early onset decline in lung function compared with term infants. The decreased lung function and decline in lung function associated with prematurity predisposes these individuals to life-long structural and functional lung abnormalities that can evolve into premature chronic lung function limitation (figure B).[5,8]

Patterns of lung growth have been characterised in a large cohort of children with mild-to-moderate asthma (enrolled at age 5–12 years and followed up closely until early adulthood).[4] Throughout the 4–6 year treatment and observational periods, 75% of these children had abnormal trajectories of lung growth with 49% having reduced growth and 26% having normal growth and early decline.[4] Individuals with reduced lung growth patterns were more likely to meet the criteria for COPD than those with normal lung growth patterns. 6% of the cohort had severe asthma in late adolescence and early adulthood, and they had reduced lung growth over time, with 40% of them also having an early decline.[9] Similarly, early-life lower respiratory tract infections (RTIs), including bronchitis, bronchiolitis, and pneumonia, were associated with low lung function in childhood and increased risk of chronic airflow limitation (figure C).[6] Interestingly, the effect sizes for the associations of lower RTIs with asthma are much larger than those observed for upper RTIs with asthma.[10] This observation suggests that the small airways, thought to be the greatest contributor to bronchoconstriction and fixed airflow obstruction,[11] might be the link between childhood asthma and early

COPD, because small airway remodelling in asthma might lead to irreversible airflow obstruction.

Randomised phase 2 and 3 pharmacological trials for COPD over the past 30 years have had little success in altering lung function trajectories, which is probably related to late diagnosis of lung function deficits. Emerging data are indicating that smokers diagnosed with mild COPD have irreversibly lost more than 40% of terminal bronchioles, patients with moderate or severe COPD have irreversibly lost 47–78% of their terminal bronchioles, and that small airways are reduced in number before microscopic emphysematous tissue destruction.[12] These data highlight that spirometry is not sensitive enough to detect these early changes in small airway structure.

While lifetime lung function trajectories are based on spirometry, longitudinal imaging data are likely to provide an in-depth view of structural lung abnormalities over time. However, our understanding of disease progression is mainly informed by cross-sectional imaging snapshots or by imaging over short periods of time that are then extrapolated. Several imaging biomarkers using CT have been described as being helpful in predicting changes in lung function. These biomarkers include parameters to quantify airway disease and measures to quantify parenchymal disease[13] and the mismatch between the two (dysnapsis). These measures can be used to identify associations with lung function decline in those at risk for or with mild airflow obstruction, and hence could be useful in predicting and targeting disease trajectories. One major limitation in understanding the pathobiological changes underlying the onset and progression of fixed airflow limitation is the current absence of non-invasive ways to sensitively measure or image changes in patients who are at risk for airflow limitation or who have not yet developed more substantial clinical symptoms of disease. There is a need for imaging techniques that are safe for longitudinally tracking patients with pulmonary childhood diseases who might transition into fixed airflow limitation.

In primary care, the most frequent cause of chronic airflow limitation in young adulthood is asthma, implicating the need for maintenance treatment with inhaled corticosteroids (ICSs) and long-acting beta-2-agonists (LABAs).[14] If the post-bronchodilator airflow limitation persists despite optimal inhaler technique and good adherence to ICSs and LABAs, adding a long-acting muscarinic antagonist has been found to significantly improve lung function and moderately reduce exacerbation rates. In patients with uncontrolled severe asthma despite triple inhaled therapy (ICS plus LABA plus LAMA), add-on treatment with monoclonal antibodies should be tailored to the clinical phenotype (eg, allergic, eosinophilic, or type 2 severe asthma).[15] For young patients with early-onset COPD, there is an urgent need for randomised controlled trials to investigate the efficacy and safety of existing and novel treatments to fill this major evidence gap.

In summary, the definition of chronic airflow limitation encompasses a number of clinical and pathological features that are too diverse to be clustered under the same diagnostic label of asthma or COPD. Due to these challenges, evolving airflow limitation in childhood and young adulthood should not be managed as a treatable trait in isolation. Although it should be tracked and characterised even early on, there is still a need for optimal preventive and treatment strategies.

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Smoking and e-cigarette use: key variables in testing IgA-oriented intranasal vaccines

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Vaccines are an essential component in the fight against highly virulent respiratory pathogens such as influenza virus, *Bordetella pertussis,* and SARS-CoV-2. Although most existing vaccines for respiratory pathogens are injectable, development of efficacious intranasal vaccine formulations is a clear goal for the immunological community, especially as a result of the SARS-CoV-2 pandemic.[1] Beyond the logistical benefits of needle-free vaccination,[2] intranasal vaccines aim to induce mucosal immune responses in addition to systemic immunity, providing an additional layer of protection at the vulnerable respiratory interface.[1]

One important component of mucosal immunity is the induction of secretory IgA antibodies, which can help to neutralise inhaled microbes to preclude pathogen acquisition and dissemination, particularly in the upper airways. Induction of secretory IgA is a major impetus in the development of mucosal immunisation strategies.[1,2] Ultimately, although injectable vaccines are able to reduce the burden of respiratory disease, intranasal vaccines have the potential advantage of limiting disease transmission by better defending the airway mucosa, a frequent site of initial infection. Vaccines that protect against acquisition and transmission, as well as severe disease following infection, have the potential to further reduce the health-care burden associated with respiratory pathogens.

Given that intranasal vaccines target the upper airways, it is of interest whether inhaled irritants such as cigarette smoke and e-cigarette aerosols (which both affect numerous immune functions[3,4]) impair mucosal aspects of intranasal vaccine efficacy. Some studies have shown decreased total salivary IgA levels in smokers,[5] whereas others have shown that smoking increases oral IgA.[6] Although little is known about the impact of smoking on antigen-specific IgA induction following respiratory infection in humans, the nasal secretions of smokers have been shown to contain lower levels of lipopolysaccharide-specific IgA than those of non-smokers,[7] indicating that some local deficit might exist. By comparison, serum haemagglutination-inhibiting antibody titres did not differ between smokers and non-smokers following intranasal live-attenuated influenza virus vaccine immunisation,[8] suggesting that systemic adaptive responses to mucosal vaccination are not broadly impaired. However, this study did not assess IgA induction in the upper airways.

Recently, our research groups[9,10] showed that cigarette smoke and e-cigarette exposure can interfere with the induction of antigen-specific IgA immunity in the upper airways. In humans, Rebuli and colleagues[9] showed that the induction of influenza-specific IgA was diminished by about 40% in the nasal lavage fluid of smokers and e-cigarette users at day 8 following live-attenuated influenza virus immunisation relative to never-smokers. In mice, McGrath and colleagues[10] showed that intranasal immunisation with lipopolysaccharide and ovalbumin during concurrent cigarette smoke exposure resulted in