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Too Little, Too Late: Adult Lung Disease Cannot Be Prevented by Interventions in Adult Life

Ask a layperson what images heart disease conjures up, and they will probably talk about a relatively young adult suddenly clutching their chest and being rushed off to hospital, defibrillators, intensive care units, and interventions and maybe surgery. The sentiment will be "there but for the Grace of God go I". Ask the same layperson about lung disease, and it will be an old person coughing and maybe on oxygen, the author of their own misfortunes because of current or previous smoking. This is a totally unfair caricature, but without doubt, the perception exists and accounts in part for the disparities in charity funding for heart and lung disease.

However, it is becoming increasingly clear that many adults with lung disease are actually the victims of early life adverse events, long before they had any control over their own fate. The prime example is chronic obstructive pulmonary disease (COPD). Failure to reach a normal plateau of spirometry at age 20–25 years carries a 26% risk of COPD (1), and peak attained spirometry is largely determined by antenatal and early preschool exposures (reviewed in [2]). If early lung growth is normal, the risk of COPD reduces to 6%, which relates to an accelerated decline in spirometry (1). There are likely many reasons for an accelerated decline in lung function, and no consistent single cause is reported from the big COPD cohorts recruited in adult life, but early adverse exposures such as maternal smoking in pregnancy and severe respiratory infections are implicated in three large studies (3–5). Adult smoking is a factor, but not one that is consistently reported (6). Asthma in the third and fourth decades of life can be traced back to antenatal adverse exposures (7). Women with so-called late onset asthma in fact had airway disease by six years of age, which they had forgotten (8), reminding us how inaccurate retrospective recall of childhood respiratory disease actually is (9). Early adverse life events also increase the risk of occupational asthma (10); in a study of 13,499 occupational cleaners who were administered the Respiratory Health in Europe (RHINE) III questionnaire, the risk of self-reported wheeze, adult-onset asthma and COPD were greatest in those with early life disadvantage, including maternal smoking and severe respiratory tract infection before five years of age.

In this issue of the *Journal*, He and colleagues (pp. 173–182) add to these concerning studies by relating lung cancer risk to early adverse life events (11). They included nearly 400,000 participants from the UK Biobank study in their analysis, in whom nearly 2,000 lung cancers were recorded. These volunteers were recruited to the Biobank at age

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between 40 and 69 years in 2006–2010. Childhood events were thus retrospectively recalled, a weakness of the study. As expected, a personal history of smoking greatly increased the risk of both lung cancer and death from lung cancer. After appropriate adjustment for a number of covariates, frighteningly, *in utero* smoke exposure dramatically increased the risks of both lung cancer incidence and mortality in adult life. The earlier active smoking was initiated the bigger the risk (hazard ratio a staggering 17.41 (13.89–21.82) for childhood initiation of smoking in those exposed to tobacco *in utero*!). What the study could not determine is any contribution of post-natal passive smoke exposure to this increased risk or smoking by adults co-habiting with the pregnant mother. There is likely at least some effect, hypothetically both by a direct effect and because children are more likely to smoke if their parents smoke. Among other conclusions, He and colleagues (11) suggest that around 14.5% of lung cancer cases and 16.1% of deaths would be prevented by if women did not smoke in pregnancy. There would have been substantially less risk of lung cancer and death if smoking initiation had been delayed to adult life. The authors also report an important gene-environment interaction. They constructed a polygenic risk score (PRS) comprising 18 variants for their cohort from the International Lung Cancer Consortium. Those who were exposed to smoke in pregnancy and initiated their smoking in childhood and who also had higher PRSs had an enhanced risk of lung cancer.

Among the many strengths of this study are the prospective design and especially the large numbers reported, giving confidence in their findings. There are inevitably weaknesses. As stated, the authors could not score the effects of passive smoking while the mother was pregnant, or during childhood. There are also likely other risk factors which they could not measure, for example pollution, known to have adverse effects on the fetus (12) and also increase adult lung cancer risk (13). They also relied on retrospective recall childhood events and death certificate data, neither of which are always accurate. As the authors discuss, replication in non-European cohorts would be desirable. Nonetheless, the huge numbers and internal consistency of the study findings give confidence in the conclusions.

The data reported by He and colleagues (11) add to the mounting evidence that prevention of adult lung disease will not be achieved by intervening in adult life. Of course, we must not take the pressure off smoking cessation and other later life exposures. Clean air legislation clearly delivers better lung growth (14). But we must devote renewed energy and focus to protecting the unborn baby and the preschool and school-age child. Urgent political action is needed across the globe to tackle childhood poverty, exposures to tobacco and pollutants, and reduction of respiratory tract infection by immunization, including in high-income countries. The increased vulnerability of young people to the effects of tobacco also underscores the need to protect them from the as yet unquantifiable risks of e-cigarette use, in which context, the recent actions of the Federal Drug Administration banning a popular brand for marketing to children are particularly welcome (15) and the judgment of the U.S. Court of Appeals for the District of Columbia Circuit particularly damaging (16). The potentially big reduction in lung cancers and deaths reported by He and colleagues (11) should be a fillip to preventive medicine to pro-actively take steps to protect the vulnerable young to improve lung health outcomes across the life course. Also, importantly, we need to get the public to see adult respiratory disease through this developmental lens. ■

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How Much Does the United States Spend on Respiratory Diseases?

Respiratory conditions are associated with significant morbidity and mortality costs in the United States and around the world. Allergic rhinitis, asthma, chronic obstructive pulmonary disease (COPD), lower respiratory tract infections, interstitial lung disease, tuberculosis, and other respiratory diseases cause substantial health, quality of life, and economic burdens to patients, payers, and society (1–8).

But what if a disease magically disappeared? How might we put to the best use all the resources formerly devoted to it? Imagine that we could drastically reduce hospitalizations and emergency department visits caused by chronic bronchitis; where, instead, might we most efficiently invest the savings? And what is the value of increased productivity at work or school from getting a good night's sleep, uninterrupted by nighttime asthma symptoms? These questions can be answered by analyzing all direct and indirect costs of the illness (2), also called the "opportunity cost" (9).

Healthcare expenditure in the United States is greater than in any other country in the world, reaching 17.7% of the gross domestic product in 2018, a large increase from 5% in 1960 (10). Respiratory diseases are among the leading contributors to overall healthcare costs (11). The amount paid for all medical and pharmaceutical services associated with an illness, called expenditure, is one of the largest parts of the healthcare cost. Payments are made by public and private insurances and by the patient or the patient's caregiver as out-of-pocket payments. Studies quantifying the cost of respiratory illnesses may inform prioritization of programs, policy development, and efficient management of resources.

Evaluation of disease expenditure reveals how much each payer spends on healthcare services associated with the disease or, as it also could be said, the amount that could be saved if the disease were eliminated. It identifies the different components of the cost and the contribution of each component to the overall expenditure. Such information can help identify funding priorities by highlighting inefficiencies and potential savings (12).

In this issue of the *Journal*, Duan and colleagues (p. 183–192) provide a comprehensive analysis of medical and pharmaceutical expenditures for respiratory diseases (13). On the basis of data from the Disease Expenditure Project (DEX), the authors derived expenditures by payer, type of care, and demographics. The study also analyzed trends in spending changes from 1996 to 2016 and associations between these changes and five factors: population growth, population aging, disease prevalence, healthcare utilization, and service price and intensity.

On the basis of their analysis, the total expenditure for all respiratory diseases was $170.8 billion, with asthma being the most expensive among all respiratory conditions, followed by COPD. The largest contribution to the total spending for asthma was prescribed pharmaceuticals (48.0%); for COPD, it was inpatient services (28.8%) and prescription medications (28.5%). For interstitial lung disease, hospitalization costs were the largest part, constituting almost 62.8% of total spending. Ambulatory (58.1%) and emergency department (21.7%) services were the largest costs for upper respiratory tract infections. Although almost all spending for COPD occurred for persons age 45 and older, asthma expenditures were spread evenly over all age groups. Slightly more than half of asthma spending came from private payers (51.5%), whereas almost 70% of spending for COPD was paid by public insurers.

The paper also focuses on the rate of change in spending from 1996 to 2016. On the basis of the analysis, pharmaceutical spending not only was the most expensive type of service for asthma and COPD but also had the highest annual growth rate of 2.7% and the largest absolute increase in spending among all respiratory conditions, adjusted for inflation. The rate of growth in pharmaceutical spending for asthma and COPD remained constant throughout the study period. Spending increase in prescription medications was strongly associated with the price of inhalers, which, according to the authors, "became more expensive over time with minimal clinical innovation, driven by extended patent protections on new delivery devices, new combination inhalers, and the 2008 change from chlorofluorocarbon to hydrofluoroalkane propellants" (p. 189–190). It appears also that the rate of increase in spending from 1996 through 2016 was the highest for public insurance compared with private payers and out-of-pocket payments.

Using decomposition analysis, the authors of the study investigated the drivers of spending growth for respiratory conditions. They determined that the effect of service price and intensity on the rate of growth in spending is larger than the effect of an aging population, contrary to a common perception in the popular media (14).

The paper has some limitations. The authors focus on the aggregate spending and, unlike in the original DEX study (11), per-person spending was not included in the paper's scope. Analyzing per-person spending brings important insights regarding the spending change over time and the factors associated with per-person expenditure, including sex, age, race and ethnicity, geographic

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