measurements, all potential parts of a meaningful composite endpoint.

In an age of social distancing and virtual visits, are platforms such as this the future for clinical follow-up? Perhaps. But the results of Moor and colleagues may not be generalizable to other clinical or research programs without paying heed to the key considerations outlined above. To date, there have been successes and less-than-successful applications of home monitoring in IPF, and it recently proved challenging for implementation in a large clinical trial (11). An invested coordination team is critical to provide training and troubleshoot technical issues so that data acquisition is optimized and patients are supported. Future work should evaluate the cost effectiveness of such platforms considering both the clinic and patient perspectives. Such tools should also be viewed through a lens of accessibility with a goal of reducing disparate access to ILD specialist care. For successful implementation of such home-monitoring platforms, clinicians and trialists should emulate Moor and colleagues' patient-centered approach. ■

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Occupational Exposures and Lung Cancer

Despite decreases in the incidence of certain cancers and associated mortality, cancer remains highly lethal and very common. About 41% of Americans will develop some form of cancer (including nonmelanoma skin cancer) in their lifetimes. One-fifth of Americans will die of cancer. Notwithstanding important progress made in the reduction of lung cancer in the United States with antismoking campaigns, it still tops the list for the most common cause of cancer death in the United States, as well as the world. Lung cancer is a global public health problem. There were an estimated 2.1 million lung cancer cases and 1.8 million deaths in 2018 worldwide. Incidence and mortality rates vary 20-fold between regions, mainly because of variation in carcinogen exposure such as tobacco smoking. However, if tobacco smoking were removed altogether, lung cancer would still be in the top 10 cancers worldwide (1). There are a number of well-known lung carcinogens to which exposure occurs mainly in the workplace. But studies of lung cancer in occupational populations are often hampered by small sample size and inability to control for, or assess interactions with, tobacco smoking. It is critical to understand the risks posed by exposures to occupational lung carcinogens to develop effective control programs for this deadly disease.

In this issue of the *Journal*, two papers by Ge and colleagues (pp. 402–411 and pp. 412–421) address major issues related to occupational lung cancer (2, 3). One critical feature in this published

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work is the large sample sizes garnered by pooling multiple case–control studies in their respective assessments of occupational diesel exhaust and crystalline silica exposure while adjusting for and examining interactions with tobacco smoking. Both papers leverage a large pooled sample of 14 case–control studies in Europe and Canada, numbering a total of 37,866 cases (16,901 lung cancer and 20,965 controls).

The first paper showed that diesel exhaust exposure caused increased lung cancer risk even in the lowest category of cumulative exposure using a job-exposure matrix. Moreover, lung cancer risk was increased in nonsmoking workers and there were superadditive joint effects of diesel and smoking in males for all four lung cancer subtypes. Finally, there was evidence for cell subtype differential risk, with the highest frequency of squamous cell and small cell and lowest of adenocarcinoma. Although diesel was classified by the International Agency for Research on Cancer as a class 1 human carcinogen based on prior studies, including a large cohort study performed by the U.S. National Cancer Institute and National Institute for Occupational Safety and Health (4), the added power of the current study aids our understanding of exposure–response at relatively low levels of cumulative exposure, smoking interactions, and cell type distribution. The public health consequences of the results are significant, as there are an estimated 1 million U.S. workers, 3.6 million European workers, and millions more in Asia who are exposed to diesel exhaust.

The second paper examined the risk of occupational exposure to crystalline silica and lung cancer using the same large pooled data. Although silica is also classified as a class 1 human carcinogen by the International Agency for Research on Cancer, the results addressed key knowledge gaps. There was an increased risk of lung cancer with cumulative occupational exposure in workers both with and without silicosis as well as in current, former, and never-smokers. Moreover, there was increased risk for all major histologic subtypes of lung cancer. Finally, there was a supermultiplicative risk with smoking and silica exposure for overall lung cancer risk. This paper has great significance at the current time because in addition to the nearly 2 million silica-exposed workers in the United States, 11.5 million in India, and millions in China, Turkey, Australia, and elsewhere, there has been an uptick in the number of workers exposed to crystalline silica while manufacturing and installing stone countertop materials for household use and sandblasting of denim for fashionwear (5).

For decades, research has been focused on the mechanisms of carcinogenesis, the genetics of cancer initiation and progression, and the epidemiology of cancer as a complex chronic disease. Researchers have aimed to identify avoidable causes of cancer, increase early detection, and develop treatments to improve outcomes in patients with cancer. The relative contributions of genetic and nongenetic (i.e., "environmental," broadly speaking) factors to the development of common cancers have been studied and debated for decades. Relative contributions are expressed in terms of the "population attributable fraction"—the proportion of disease incidence that would be eliminated if a given risk factor, such as smoking or asbestos exposure, was removed. Toxic exposures in the environment, including workplace exposures, are responsible for a substantial percentage of all cancers (6). Precise apportionment is not possible because of gaps in the exposure data, interactions between environmental and lifestyle carcinogens, and differences from country to country in exposure patterns (7) However, credible estimates from the World Health Organization and the International Agency for Research on Cancer (8–10) suggest that the fraction of global cancer currently attributable to toxic environmental exposures is between 7% and 19%.

Efforts at reducing mortality from lung cancer have included early detection and precision therapies. Although more effective therapies and better early detection and screening methods are indispensable, the most valuable approaches to reducing cancer morbidity and mortality lie in primary prevention—avoiding introducing carcinogenic agents into the environment and eliminating existing exposures to carcinogenic agents. The first approach would be most effective if carcinogenic substances were identified before they could be introduced, although it is impossible to quantify the success of this approach. The value of the second approach has been demonstrated by the disappearance or reduced incidence of particular types of cancers following the elimination of specific occupational exposures. For example, occupational-related small cell lung cancer was eliminated after exposure to Bis-chloromethyl ether (used in producing bulletproof glass) was banned in most countries, and mesothelioma incidence was decreased after restrictions or bans were placed on asbestos use. Furthermore, risk has been reduced through greater regulatory control over compounds that remain in use—for instance, the U.S. Occupational Safety and Health Administration restrictions on exposure to asbestos fibers, coke oven emissions, crystalline silica, and other carcinogens.

A sobering realization about occupational lung cancer is that despite significant advances in reducing occupational carcinogen exposures in North America and Western Europe, the number of workers exposed globally to agents such as crystalline silica and diesel continues to rise. It is time for all stakeholders to work together to reduce the burden of occupational lung cancer by developing effective prevention measures to identify, control, and eliminate exposures to carcinogenic agents. ■

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Premature Aging and Increased Risk of Adult Cardiorespiratory Disease after Extreme Preterm Birth

Getting to the Heart (and Lungs) of the Matter

Preterm birth is increasingly recognized as a risk factor for cardiopulmonary disease in adults. The sequelae of underdeveloped heart and lungs at birth, among other impairments, are now being considered as significant contributors to impaired exercise tolerance (1, 2) and pulmonary (3) and systemic hypertension (4) in early adulthood. How these cardiopulmonary developmental challenges are linked to and impact long-term outcomes for this ever-increasing population remain active areas of investigation. In this issue of the *Journal*, Hurst and colleagues (pp. 422–432) provide the 19-year follow-up data from the EPICure cohort examining respiratory and cardiovascular health and function in individuals born extremely preterm (EP) (gestational age ⩽25 wk) with and without bronchopulmonary dysplasia (BPD) (5). These longitudinal data provide unique evidence for the idea that cardiovascular function, respiratory function, and exercise capacity are impaired in individuals born EP at 11 and 19 years. Although those with BPD demonstrated the worst respiratory outcomes, adults born EP with and without BPD demonstrated worse cardiovascular outcomes compared with term-born peers. Several additional interesting aspects of this article warrant further consideration, including the absence of lung catch-up growth, the presence of airflow obstruction consistent with chronic obstructive pulmonary disease (COPD), the close association of lung health with cardiovascular health in EP individuals, and that EP-born individuals may represent a model of "premature aging."

An important finding from this cohort is that there appears to be no catch-up in lung function after adolescence (11 yr) and through puberty (19 yr), consistent with other smaller studies in adults born EP (6). Given the parallel growth trajectory between term- and EP-born individuals, obtaining pulmonary function testing at a single time point during adolescence may be sufficient to clinically identify the majority of EP-born individuals with significant airflow obstruction. Early identification of these individuals could help improve long-term health by promoting healthy lifestyle habits and avoidance of secondary insults, such as occupational, environmental, and smoking-related exposures, which are likely increasingly relevant as these individuals transition into adulthood.

The authors note EP-born adults were more likely to have reversible airflow obstruction (defined as greater than 12% change in FEV_1; 26.5% of EP-born adults vs. 6.5% of term-born adults). Importantly, despite the increased degree of reversible airflow obstruction, the phenotype is not one of typical allergic asthma because the EP-born subjects also had lower fractional exhaled nitric oxide concentrations. Furthermore, 19% of the EP-born cohort had irreversible airflow obstruction (defined as FEV_1/FVC <lower limit of normal), suggesting that they already meet the airflow obstruction criteria for COPD (5, 7). Although the authors claim that "this poses a risk of misdiagnosis and potential overtreatment for a second chronic respiratory condition," we disagree, at least with respect to the concept of misdiagnosis. COPD is characterized by persistent respiratory symptoms and airflow limitation but notably serves as an umbrella diagnosis that includes several underlying phenotypes. There is growing recognition that host factors, including genetic abnormalities, abnormal lung development, and accelerated aging, all contribute to the pathogenesis of COPD, as included in the 2020 Global Initiative for Chronic Obstructive Lung Disease Report (8). To strictly avoid this terminology among adults born preterm, including those with a history of BPD, misses an opportunity for a shared language between pediatric and adult providers. Hurst and colleagues (5) acknowledge poor consideration of early-life factors among many adult physicians, and there is a compelling and urgent need to increase awareness of neonatal factors among adult providers. Whether EP-born individuals with diagnosed COPD, or asthma-like airflow reversibility, for that matter, will be overtreated remains to be seen because there is very limited pharmacologic phenotyping in this population, and additional research will be required.

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