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# When the Fetus Is Exposed to Smoke, the Developing Lung Is Burned

Some have questioned why the *Journal* has published so many papers on the health effects of household air pollution (HAP) from domestic cooking in recent years. There are compelling reasons to do so. Approximately 3 billion people, or 40% of the world's population, still cook using open fires or simple stoves fueled by kerosene, biomass (wood, animal dung, and crop waste), or coal that generate considerable HAP (1). The Global Burden of Disease project attributes multiple noncommunicable diseases, including chronic obstructive pulmonary disease (COPD) and lung cancer, to HAP (2). In low- and middle-income countries (LMICs) where most women do not smoke tobacco, HAP may be the major cause of COPD and lung cancer in women. The World Health Organization estimates that HAP causes close to 3 million deaths per year, including 500,000 deaths of young children due to pneumonia or nearly half of all deaths due to pneumonia in children under 5 (1). Simply put, HAP has a huge public health impact that is theoretically preventable.

A major criticism of the evidence base used to estimate the health impacts of HAP is the relative paucity of both measured exposure data and objectively measured outcome data, evidence gaps that are understandable given the difficulty of obtaining such data in the low-resource environments of countries where cooking with dirty fuels is common (3). The paper by Lee and colleagues (pp. 738–746) published in this edition of the *Journal* provides data that help fill both of these gaps (4). These investigators used 48-hour personal monitoring of carbon monoxide (CO) exposures four times over the course of pregnancy to assess prenatal exposure to HAP among rural participants in a cluster-randomized intervention trial of cleaner-burning cookstoves (GRAPHS [Ghana Randomized Air Pollution and Health Study]), an impressive exposure assessment effort. They then measured lung function parameters (i.e., the ratio of the time to peak tidal expiratory flow to expiratory time, tidal volume, respiratory rate, and minute ventilation with flow–volume loops, as well as passive respiratory system compliance with the single-occlusion technique) on the infant offspring of the monitored mothers at 1 month of age. This again is an impressive effort, and the first to obtain high-quality infant lung function measurements in such a low-resource setting.

The primary finding of this elegant study is that maternal CO exposure during gestation was associated with lower infant lung function. This effect of HAP exposure was greater in girls than in boys. Moreover, infant lung function measured at 1 month of age was associated with an increased risk of pneumonia before age 1 as assessed by active weekly surveillance by fieldworkers, followed by physician evaluation of suspected cases using the World Health Organization's Integrated Management of Childhood Illness guidelines. Physician-assessed severe pneumonia was also associated with infant lung function.

Although the authors acknowledge some limitations of their study, including the relatively small sample size, lack of dietary data, and inability to confirm a diagnosis of pneumonia with chest imaging, the implications of their findings are profound. The fetal programming hypothesis, which proposes that prenatal environmental conditions are important determinants of disease in adulthood, is supported by both epidemiological and animal experimental data (5). Advances in epigenetic research also provide a plausible mechanism for such programming. Considerable evidence exists to suggest that maternal exposure to ambient air pollution and environmental tobacco smoke during gestation can lead to reduced lung function in offspring, which in turn can lead to a low lung function trajectory in adulthood associated with an increased risk of COPD (6–8). In addition to the lower infant lung function associated with maternal prenatal CO exposure, Lee and colleagues found that lower infant lung function increased the risk of early-childhood pneumonia. These findings now add exposure to HAP as another prenatal environmental risk factor for poor respiratory health later in life. The greater effect of prenatal exposure to HAP on girls in the current study is notable given that the greatest burden of HAP-related respiratory disease in LMICs is for adult women.

What can be done to prevent the harmful effects of *in utero* exposure to HAP on respiratory health during the subsequent life course? The published results from randomized control trials of "cleaner" biomass cookstoves are mixed with regard to the efficacy of such interventions for the prevention of early-childhood pneumonia (9, 10), and the results of a multicountry trial of liquefied-petroleum gas stoves are not likely to be published for several years. Moreover, widespread distribution of liquefied-petroleum gas stoves may not be available in many low-income countries for a number of years. That said, reduction of prenatal and infant exposures to HAP through behavioral changes, such as not burning rubbish near the home and keeping young children away from open biomass fires, may be of some



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benefit. The results of one study conducted in rural Guatemala suggest that reduced exposure to HAP through the use of a chimney stove intervention could improve lung function as measured by spirometry later in childhood (11).

Poverty is inextricably intertwined with exposure to HAP as drivers of early-childhood respiratory illnesses that put children on a lower lung function growth trajectory and at increased risk of developing an adult respiratory illness (12). As the economies of LMICs develop, increased emissions from traffic and power generation will contribute to the cumulative exposure to air pollution. A great challenge for public health officials in these countries will be to prevent increased exposures of children to air pollution while the necessary economic development is being pursued. Distributed energy generation from solar-power microgrids is one potential solution, but the search for low-cost, feasible, clean cooking solutions must continue so that this public health problem can be addressed sooner rather than later. ■

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# Mediastinal Lymphadenopathy in Interstitial Lung Disease
## Time to Be Counted

The history of digital biomarker research based on computed tomography (CT) in interstitial lung disease (ILD) is long, spanning more than 20 years. Early studies involved radiologists visually quantifying the extent of parenchymal disease and investigating its prognostic effect, mainly in the setting of fibrotic lung disease. This research has mostly provided consistent results: that with increasing fibrosis, honeycombing or severity of traction bronchiectasis comes with an increased risk for mortality (1, 2). Attempts have also been made to construct multidimensional staging systems for different ILDs designed to provide an objective score that maps to an evidence-based management strategy, much in the same way that lung cancer is staged (3, 4).

Despite these efforts, CT-based biomarkers and staging tools have largely failed to translate from research to routine clinical practice for a number of reasons. First, visual quantification of



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