Before the First Breath: Prenatal Ultrafine Particulate Exposure and Incident Asthma

Air pollution policy has long focused on protecting the most vulnerable (1), and who could be more vulnerable than a developing fetus who has yet to take a breath? Although they have yet to breathe contaminated air, the impact of prenatal exposure to multiple air pollutants on subsequent respiratory health in children has been well documented (2). Although we regulate fine particulate matter at the 2.5-μm cutoff (particulate matter ⩽2.5 μm in aerodynamic diameter [$PM_{2.5}$]), the effects of prenatal exposure to $PM_{2.5}$ on subsequent respiratory health are inconsistent. Wright and colleagues found a potential critical window of susceptibility of prenatal exposure to $PM_{2.5}$ among boys coexposed to high levels of maternal stress and also found that oxidative stress is likely the primary mechanism (3). However, ultrafine particles (UFPs; <0.1 μm) are more likely to be associated with systemic inflammation and oxidative stress and are more likely to cross the lung barrier and be in systemic circulation (4). Black carbon particles, which are typically ultrafine, can even accumulate on the fetal side of placenta (5).

Despite the potential impacts of UFPs on sensitive populations, only the European Union regulates UFPs, albeit only filterable UFPs >23 nm from vehicles (6), and there are no policies in occupational settings (7). Although there is growing evidence from animal studies on the effects of *in utero* UFP exposure on development and subsequent disease (8), there have been relatively few studies in humans (9). In this issue of the *Journal*, Wright and colleagues (pp. 788–796) add to this weight of evidence with the first analysis of prenatal UFP exposure and incident asthma in a prospective birth cohort in the United States (10). They determined that for females there is a critical window of susceptibility during the third trimester when UFPs more strongly impact incident asthma (odds ratio [OR], 2.71; 95% confidence interval [CI], 0.47–15.7), whereas for males, increased UFP exposure at any time during gestation was associated with similarly lower risk (third trimester OR, 1.29; 95% CI, 0.23–7.36). More generally, they found that UFP exposure across pregnancy greatly increased the risk of asthma for both males (OR, 3.37; 95% CI, 1.55–7.06) and females (OR, 2.56; 95% CI, 1.15–5.11).

One of the strengths of this study is the well-validated daily estimates of UFP, nitrogen dioxide, $PM_{2.5}$, and temperature exposure for the entire gestation period at such a low resolution (20 m). In the only previous birth cohort analysis of UFPs, which was conducted in Canada (11), estimates were at the city block resolution, likely introducing exposure misclassification for such highly localized pollutants. Of particular interest is Wright and colleagues' finding that UFPs and $PM_{2.5}$ are not associated with each other, and that UFPs are better correlated with local sources, including vehicular traffic. This provides additional evidentiary support that $PM_{2.5}$ legislation offers reduced protection to this vulnerable population from traffic-related air pollution (12) and that policy must directly address reducing UFPs or at least not inadvertently increasing them (e.g., increased fuel efficiency may create more UFPs [13]).

Another strength of this study is the use of Bayesian distributed lag interaction models, which provide an elegant tool for identifying critical windows of susceptibility for *in utero* UFP exposure, and if these varied by sex. For example, UFP exposures between Weeks 28 and 35 were associated with significantly more incidents of asthma among females. Although UFP exposures within the first year of life were not associated with incidence of asthma in these cohorts, it will also be important for future studies to perform analyses to determine if there are other critical windows of susceptibility during periods of postnatal development for exposure to UFPs, such as the alveolarization process or puberty, when interactions with hormones may be important.

Although the findings in this report are compelling, the average age of asthma diagnosis was 3.6 years. Many children who have wheezing episodes before age 3 years do not continue to wheeze (14), and it will be important to assess if these *in utero* exposures are associated with the development of persistent asthma in these cohorts as they age.

This analysis uses data from two cohorts—ACCESS (Asthma Coalition on Community, Environment and Social Stress) and PRISM (Programming of Intergenerational Stress Mechanisms)—yet only 376 of 1,379 total dyads (27%) were included, with limited explanation of exclusion criteria. This subsample had younger mothers who were more likely to self-identify as Black than in the overall cohorts. Both of these characteristics are associated with increased susceptibility of air pollution exposures in other cohorts (15). However, both these cohorts only included infants that were >37 weeks gestation, and the PRISM cohort excluded mothers who drank ⩾7 alcoholic drinks per week before pregnancy. Thus, these may be relatively healthy cohorts and this bias may result in underestimating the effects of *in utero* UFP exposure in the general population. For example, children with the highest UFP prenatal exposures may have been more likely to be born before 37 weeks (9). Although the study adjusts for tobacco smoke exposure, future studies should account for e-cigarette exposures, which contain more nanosized particles and may confound the relationship with ambient UFPs (16).

The coronavirus disease (COVID-19) pandemic has underscored the systemic health inequities in the United States. Many of the regions most impacted by the pandemic are regions that already have markedly more traffic-related air pollution. Although more research is needed to better characterize inequities of UFP

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exposures in our cities, the findings from Wright and colleagues highlight how important it is to understand disproportionate impacts on lifelong health outcomes from exposures even before the first breath. We need policies aimed at the most important exposures impacting lifelong health, including UFPs, and to promote transportation and environmental justice so that everyone has the same opportunity for a long and healthy life, regardless of where they are born. ■

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Shear Wave Elastography of the Diaphragm: Good Vibrations?

Diaphragm ultrasound is rapidly gaining popularity in the ICU, as it allows a bedside, safe, repeatable, and noninvasive assessment of respiratory muscle function. Current main applications include the measurement of thickness and inspiratory thickening fraction (TFdi) (1). Both decreases and increases in diaphragm thickness were reported early in the course of mechanical ventilation, which seemed modulated by contractile activity (i.e., TFdi) (2) and with atrophy strongly associated with prolonged ventilation and ICU duration (3); however, how such findings relate to functional alterations in the muscle are yet uncertain. The application of shear wave elastography is an emerging novel technique to provide biomechanical information of large tissue structures by quantifying the shear wave speed and converting that to the Shear Modulus (SM). Briefly, this technique relies on the creation of a vibration source by the acoustic radiation force from a focused ultrasound beam, resulting in the generation of a shear wave. Tracking the propagating shear waves orthogonal to this ultrasound beam allows for the quantification of shear wave speed (v) and the directly related SM (i.e., $SM = \rho \times v^2$, with ρ the density of the tissue). SM reflects elastic tissue properties, and a higher diaphragmatic SM indicates a stiffer muscle. In the context of other ultrasound applications or indices, such as strain imaging, TFdi, and tissue Doppler imaging, shear wave elastography might be the most promising modality for qualitative assessment of diaphragm muscle properties. The assessment of changes in SM during the breathing cycle may reflect diaphragm contractile activity

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