partly to the airway eosinophilia, were inadequately attenuated by anti–IL-5 treatment. Although eosinophil progenitor cells were not measured in the study by Kelly and coworkers, others have shown that in those with severe asthma treatment with low doses of mepolizumab does not suppress sputum eosinophilia in approximately 50% of patients, and these patients have more modest exacerbation reduction and prednisone sparing, compared with patients whose sputum eosinophilia is suppressed (14). The results from the study by Kelly and coworkers help to explain why a reduction in circulating eosinophils does not necessarily prevent activation of eosinophils within the airways. However, whether or not activated eosinophils within the airways are the cause of asthma exacerbations remains to be confirmed. ■

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Sensitive Windows for *In Utero* Exposures and Asthma Development
Layers of Complexity

There is strong scientific support for a relationship between *in utero* exposures such as environmental pollution or maternal smoking during pregnancy and lung growth and development (1, 2) as well as subsequent pulmonary function (3, 4). Until recently, most studies have examined *in utero* exposures globally (i.e., cumulative or trimester exposure during pregnancy) (5, 6). However, evidence increasingly points to a more complex interplay among the toxic exposure, timing of exposure, and individual characteristics such as sex and genetic predisposition that culminate in altered lung structure and function (7).

In this issue of the *Journal*, Bose and colleagues (pp. 1396–1403) report that they employed novel Bayesian distributed lag interaction models to identify sensitive prenatal windows for the influence of nitrate (NO_3^-) exposure on childhood asthma, accounting for effect modification by fetal sex and maternal psychological stress (8). In this primarily data-driven analysis, the relationship between prospectively collected cumulative daily prenatal NO_3^- exposure and the overall incidence of asthma by

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6 years of age was not significant (odds ratio [OR], 1.20; 95% confidence interval [CI], 0.93–1.70; per interquartile range increase in ln NO_3^-) among the total sample of 752 mother–child dyads born later than 37 weeks of gestation, and no sensitive gestational window for exposure was identified.

However, more detailed slicing of the data revealed a significant interaction with offspring sex and maternal psychological stress (high vs. low) as measured by the Crisis in Family Systems–Revised survey (9). Two distinct sensitive windows, at 7–19 weeks and 33–40 weeks of gestation, were identified in males exposed to high prenatal maternal stress. In addition, for male offspring of mothers who reported high stress, the odds of being diagnosed with asthma by 6 years of age was significantly increased (OR, 2.64; 95% CI, 1.27–5.39; per interquartile range increase in ln NO_3^-). No significant relationship was found between NO_3^- exposure and asthma diagnosis among males whose mothers reported low prenatal stress or among females with low or high maternal prenatal stress exposure. Sensitive windows were not significant for any female offspring or for males of mothers who did not report high prenatal stress.

This article boasts a number of strengths. It uniquely examines the potential three-way interactions of prenatal maternal stress and fetal sex and their modifying effects on the relationship between prenatal NO_3^- pollution exposure and the development of childhood asthma. Other strengths include its prospective, longitudinal design and ethnically diverse population, with 54% being Hispanic and 29% being black. The authors adjusted for a large number of potential confounders, measured daily prenatal NO_3^- exposures using a hybrid chemical transport land-use regression model (10), and applied novel Bayesian distribution lag interaction models that adopt sliding windows of NO_3^- exposures throughout the pregnancy (11). This model identifies sensitive windows that are defined by where the estimated pointwise 95% CI does not include an OR of 1.

Bose and colleagues conclude that increased prenatal NO_3^- exposure during distinct sensitive windows was associated with incident asthma in boys concurrently exposed to high prenatal stress. Of note, the 95% CIs for this group are quite wide, and there were only 169 boys with high prenatal stress. This raises some concerns regarding study power of the subset analysis. In addition, a relatively large portion of subjects, 176 infants (about 24%), were born after 37 weeks but prior to the last week of gestation. For these patients, postnatal NO_3^- estimates corresponding to time were used. When the authors performed a sensitivity analysis using the imputed NO_3^- values at Weeks 37–39 for those infants, the missing data points and their imputed values greatly influenced the identification of the sensitive windows. That is, their Figure E2 suggests that there was no longer a sensitive window for boys with high prenatal maternal stress when imputed data were used. The authors adopted a polynomial spline regression imputation for missing values. This model-based imputation method might have helped to reduce bias or increase precision if missingness mechanisms (e.g., missing at random) had been examined (12).

Although the study is novel and well designed, the usual limitations of observational studies apply, and caution should be taken in interpreting the results. There is potential for misclassification of the exposure and the outcome (maternal report of physician diagnosis of asthma), unmeasured confounding, and the inability to infer causation. For instance, multiple risk factors for asthma have been identified, which are difficult to disentangle in such a homogeneous population of low socioeconomic status, given that people with limited resources have historically been forced to live in areas with more exposure to pollution. For infants born between 37 and 40 weeks, the authors used postnatal NO_3^- estimates, which may have different biological effects than a known intrauterine exposure.

This paper also raises interesting questions of interpretation. Does the fact that female offspring, or male offspring of low stress mothers, are less sensitive mean that there is less concern for NO_3^- exposure in these pregnancies, or rather does the identification of specific sensitivities reinforce the toxicity of NO_3^- exposures in general and begin to point to mechanisms of injury? The biologic underpinning for the effect modification by fetal sex suggested by the authors is focused on NO_3^- and stress exposures in relation to slower lung maturation among male fetuses. This raises some questions. Primarily, regardless of more rapid lung maturation, how do the authors explain the apparent lack of effect of NO_3^- and high stress exposure during the first critical window on the outcome of asthma in girls? In addition, it is not clear that sensitive windows can be clearly tied to stages of lung development at the sensitive time, because the window of sensitivity may be affecting subsequent patterns of gene expression in later periods of lung development.

In summary, this article reinforces the dangers of *in utero* exposure to air pollution and stresses the importance of first considering and identifying critical windows for exposure and not using a one-size-fits-all model of the dangers of toxic exposures. In addition, it is highly likely that different components of air pollution will have different critical windows, requiring further analysis of the specific temporal and subgroup toxicities of pollutants. ■

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Through the Looking Glass and What Was Found There: Imaging Biomarkers of Chronic Obstructive Pulmonary Disease

Through the Looking-Glass and What Alice Found There (1) describes adventures in a new and alternative world that Alice discovered after stepping through to the other side of a mirror. Importantly, one of this enduring novel's underlying themes is the presence of inverse reflections and the notion that in the looking-glass world, one's basic assumptions can be reversed. In a similar manner, in this issue of the *Journal*, Bodduluri and colleagues (pp. 1404–1410) present a new "through the looking-glass" way of evaluating normal lung regions that, surprisingly, reveals gas trapping not detected using the typical X-ray computed tomography (CT) density thresholds (2). Like the looking-glass adventures, this approach is intuitive and stimulating, and these findings are both clinically relevant and revelatory. Notably, their findings add to the substantial body of work that stems from the Genetic Epidemiology of COPD (COPDGene) study (3), which has improved our understanding of chronic obstructive pulmonary disease (COPD) and provided novel biomarkers of COPD using high-resolution CT. Although COPDGene was designed to identify genetic factors associated with COPD, reports of CT imaging biomarkers as objective measures of disease have dominated, in that nearly half of all COPDGene publications describe CT findings (using PubMed "COPDGene" and "COPDGene and CT").

Smokers and ex-smokers often present with symptoms and exercise limitation consistent with COPD, but with apparently normal airflow measured using spirometry (4) and CT data that do not provide obvious evidence of small airways disease or emphysema. The notion, in such symptomatic patients, is that small airways disease (5) precedes the onset of emphysema, but in these patients it is neither hinted at by spirometry (6, 7) nor revealed by CT. Moreover, because of dose and other inherent limitations, CT cannot be used to visualize the fine details of the small airways in patients (8), although the macroscopic effects of small airways disease can manifest as hypolucencies in expiratory CT, representing trapped gas, and in some cases very mild emphysematous tissue destruction. Alternative CT image analysis approaches incorporate coregistration of paired inspiratory-expiratory CT images alongside established CT lung density thresholds for gas trapping and emphysema, such as parametric response mapping (PRM) (9). However, PRM estimates of functional small airways disease require fixed CT thresholds that may limit the detection of mild disease in what may appear as normal lung on CT images. Moreover, COPDGene has also provided a large patient group in which more complex biomarkers have been discovered, including biomechanical measurements generated using deformation fields from coregistered inspiration-expiration images (10). Although clearly important, such complex CT imaging biomarkers are less straightforward to use and to understand.

Here, Bodduluri and colleagues ingeniously crafted a new but very intuitive and straightforward way to evaluate normal lung regions and reveal the presence of mild gas trapping (2). In Figure 1, we show how this can be performed for an ex-smoker from another COPD cohort study (11) who had very mild disease. After segmenting the lung regions in both inspiration and expiration CT, lung density histograms may be generated to determine the pulmonary distribution of CT Hounsfield units (HU). CT lung density thresholds for gas trapping on expiratory CT (−856 HU, shown in *green* in Figure 1) and mild emphysema on inspiratory CT (−910 HU, shown in *yellow* in Figure 1) can be used to classify the histogram distributions into "diseased" and "normal" density. Finally, the mean of the normal lung density region can be independently calculated at

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