racial/ethnic group and the loss of protective lifestyle factors in another group. In a high-risk sample of families, Kimbro and colleagues found that Mexican immigrant women had threefold increased odds of initiating breastfeeding, whereas Mexican American women had 40% decreased odds of initiating breastfeeding, compared with white women (16). Mexican immigrant status was also associated with lower maternal educational attainment (16). The findings of Thakur and colleagues of potential complex relationships between SES and asthma are intriguing and if confirmed will be important for generating hypotheses to better understand the associations. Larger longitudinal studies, with socioeconomic and racial/ethnic diversity or larger samples of defined racial/ethnic groups, measurement of potential mediators or confounders, and inclusion of cumulative SES exposures and measures of social support, will help to further delineate the association between factors such as SES, acculturation, and child asthma and atopy outcomes.

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The Yin and Yang of Indoor Airborne Exposures to Endotoxin

A number of indoor factors have been identified that affect and potentiate asthma in children living in urban environments. The evidence supports the role of cockroach, dust mite, and mouse antigens and indoor air pollutants like second-hand smoke, volatile organic hydrocarbons, and nitrogen oxides (1, 2). Studies on endotoxin exposure have noted a more complicated relationship with development of asthma or atopic symptoms. Early-life exposure to endotoxin in rural populations, where it is often noted (3, 4), can reduce asthma incidence; however, endotoxin exposure, with its presumed proinflammatory effects, can increase asthma symptoms in other settings (5). A recent review on the topic noted 71 studies looking at the role of indoor endotoxin in asthma, with some of the studies noting a protective effect (6). Understanding how these different exposures interact may help

unravel some of the key mechanistic steps leading to the increasing incidence and prevalence of asthma seen in the developed world, and also improve our understanding of the role of endotoxin in asthma morbidity in urban populations.

In this issue of the *Journal*, Matsui and colleagues (pp. 1210–1215) conducted a well-designed prospective cohort study involving 146 children and adolescents with persistent asthma from inner-city Baltimore to assess whether indoor air pollution modifies the effect of endotoxin exposure on asthma outcomes (7). Very little is known about the role of endotoxin exposure on asthma outcomes in urban homes. The authors evaluated the participants by conducting repeated clinical assessments across 12 months to assess spirometry, IgE levels, fractional exhaled nitric oxide level, skin prick testing, healthcare use, asthma medications, and questionnaires for parents or guardians. They performed careful home assessments of indoor air pollutants using airborne particulate matter monitoring to determine particulate matter $\leq 10 \mu\text{m}$ (PM_{10}) and $\leq 2.5 \mu\text{m}$ ($\text{PM}_{2.5}$) in the child's bedroom, using integrated sampling methods for a 5- to 7-day period within 2 weeks of each study visit. The primary focus of the study was to test the hypothesis that endotoxin exposure

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would be associated with worse asthma, but its effects would be modified by coexposure to indoor pollutants. Thus, the authors believed that interactions between exposures in the home could explain disparate results seen in prior population-based studies and could also provide additional opportunities to intercede and improve asthma outcomes in urban inner-city children.

The authors did not find evidence to suggest that endotoxin exposure is associated with worse asthma; rather, they found intriguing and likely clinically relevant interactions suggesting that nitrogen dioxide (NO₂) and nicotine exposure modify the impact of endotoxin on clinical outcomes in asthma. The authors generally conclude that endotoxin was protective in homes without ambient airborne nicotine but harmful in the setting of homes with airborne nicotine. Similarly, they suggest that endotoxin may be harmful in the setting of low NO₂ levels but protective in the setting of high NO₂ levels in the home. These complex interactions between ambient exposures may clarify different pathways of airway inflammation in asthma and improve our understandings regarding achieving better environmental control to prevent worsening symptomatology in asthmatic children. These results are biologically plausible based on a body of cell culture and *in vivo* animal models (8–10).

Although the findings presented in this paper are innovative, one of the major challenges of this type of analysis is that it relies on the statistical testing and interpretation of interaction terms between endotoxin and each of the effect modifiers of interest. A significant interaction can be present in the absence of a primary effect, but concerns have been raised about the face validity of such effects (11). As in the current study, no overall effect was reported for the association between endotoxin and the asthma outcomes assessed, and therefore, we presume that there was no significant association between the two. Despite this, there is a clear suggestion of effect modification. One must interpret these findings with caution, however, as one might be led to believe that the effect of endotoxin has opposite effects among those exposed to low and high levels of nicotine or NO₂, but in reality the data suggest that endotoxin has an impact in one subgroup but no evidence for an effect in the other. Endotoxin exposure was found to be associated with significantly higher odds of need for oral corticosteroids among those with low NO₂ (odds ratio, 2.09; 95% confidence interval, 1.12–3.92), but no apparent effect among those with high NO₂ (odds ratio, 1.05; 95% confidence interval, 0.70–1.57). Thus, one must be careful to differentiate between an interaction meaning that the exposure has opposite effects on the subgroups of interest and it meaning that the exposure simply has an effect in one group but not the other.

Another challenge related to assessing interactions in statistical modeling is that they are often assessed in a multiplicative fashion when in reality, in the biologic setting, they are more likely to be additive or synergistic (12). Rarely do authors specifically report that the interaction is additive versus multiplicative. More importantly, reporting of interactions is often inadequate in the medical literature; ideally, authors should report the individual effects of both exposures and also their joint effect (13). Another choice that investigators face is whether to categorize variables or model them as continuous variables. By categorizing the variables, one is essentially collapsing the data and losing the diversity of responses. Such categorization, if used, should be based on biologic mechanism or on clearly demonstrated cut points for categories noted in prior literature. One of the greatest challenges to assessing interactions relates to the power to detect these differences. In a simulation study assessing various interactions for subgroups in clinical trial data, interaction assessments are often underpowered (14). Matsui and colleagues have appropriately assessed only key interactions of interest to decrease the chances of false inference due to multiple comparisons/multiple testing (7); however, they did

choose a nonconservative α for the test of interaction ($P \leq 0.10$) to determine a significant interaction, increasing their chance of making a type 1 error. Despite their clear hypothesis-driven analysis, Matsui and colleagues have presented 22 different adjusted models with 3 with significant findings (defined by a $P < 0.05$) plus 5 significant interactions using a $P < 0.10$ definition (7).

One approach to convincing oneself of the veracity of the findings is to look to see whether the effects of the interaction were similar in the setting of different outcomes that measure asthma morbidity. The interaction between NO₂ and endotoxin presented by Matsui and colleagues is much more convincing because multiple outcomes were noted to have a significant interaction term, even if it was at the <0.10 level (7). However, the associations also could have been due to an unmeasured confounder that is associated with the various exposures.

Despite some of these limitations, the approach the authors have taken is laudable—they have comprehensively evaluated specific interactions identified in an *a priori* fashion based on biological processes and the scientific literature. At the end of the day, the goal of cohort studies is to be able to inform future studies by suggesting potential causal associations between a predictor and an outcome variable. We do believe that Matsui and colleagues have taken us closer to the goal of unraveling the interactions between varying indoor environmental exposures, which will permit appropriate interventions to mitigate the negative effects of these exposures.

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Endobronchial Ultrasound-guided Transbronchial Needle Aspiration for Lymphoma: The Final Frontier

In 2002, endobronchial ultrasound (EBUS) was developed by integrating a convex transducer with a frequency of 7.5 MHz into the tip of a flexible fiber-optic bronchoscope (XBF-UC40P, Olympus, Tokyo, Japan). For the first time, the linear curved array transducer allowed real-time sampling of lymph nodes adjacent to the airway by scanning in parallel to the insertion direction of the bronchoscope. The immediate application for the new technology in lung cancer staging was clear, and EBUS-guided transbronchial needle aspiration (EBUS-TBNA) is now performed by trained interventional pulmonologists and thoracic surgeons in selected centers around the world for a range of indications.

However, the technique has faced many hurdles along the way, and uptake of the procedure was surprisingly slow initially. This was due not just to capital costs but also to problems with appropriate reimbursement and the fact that many pulmonologists preferred conventional TBNA. However, we believe that most pulmonologists across the world now agree that EBUS-TBNA is superior to blind or conventional TBNA. In 2008, Wallace and colleagues showed in a prospective study where patients underwent conventional TBNA and EBUS-TBNA (as well as endoscopic ultrasound-guided fine needle aspiration) that EBUS-TBNA had a significantly better sensitivity than conventional TBNA for diagnosing lymph node metastases in patients with lung cancer (1). EBUS-TBNA allows sampling of smaller lymph nodes and in lymph node locations that are challenging for conventional TBNA. It has long been the argument that EBUS-TBNA is not required when lymph nodes are bulky. However, in patients with sarcoidosis, a condition often characterized by bulky intrathoracic lymphadenopathy, a randomized controlled trial of EBUS-guided versus conventional TBNA demonstrated a statistically higher diagnostic yield for the EBUS group (83% vs. 54%, $P < 0.05$) (2).

Thoracic surgeons were understandably anxious and skeptical about the rise of EBUS-TBNA and the potential fall of mediastinoscopy. In a crossover trial in patients with lung cancer, mediastinoscopy had a sensitivity of 78% for detecting lymph node metastases, whereas EBUS-TBNA had a sensitivity of 90%, primarily due to the ability of EBUS-TBNA to sample posterior subcarinal lymph nodes (3). However, many thoracic surgeons have embraced the new technology, taken it into the operating theater, and also helped

to advance the field. A recent trial led by pioneering thoracic surgeons demonstrated a similar sensitivity for mediastinoscopy and EBUS-TBNA and led them to conclude that EBUS-TBNA could replace mediastinoscopy in patients with lung cancer (4). Although EBUS-TBNA may be a barrier to training in mediastinoscopy, many thoracic surgeons value the presence of EBUS-TBNA as it frees operating room time for more therapeutic rather than diagnostic surgical procedures.

While pulmonologists and surgeons were being persuaded that EBUS-TBNA was superior to conventional TBNA and a suitable alternative to mediastinoscopy in patients with lung cancer, the landscape of lung cancer management was changing. Oncologists became increasingly interested in tissue acquisition to allow suitable samples for the personalized management of patients with advanced lung cancer. EBUS-TBNA has risen to this challenge as well. In a study of 774 patients undergoing EBUS-TBNA, 90% of samples submitted were suitable for epidermal growth factor receptor mutation status testing (5). Samples obtained in routine practice were also suitable for immunohistochemistry to aid subtyping of lung cancer. Many oncologists understand the merits of EBUS-TBNA, as it offers a technique that allows sampling of multiple tumor metastatic sites, which may be important as we increasingly recognize tumor heterogeneity (6). Because EBUS-TBNA is easily repeated, it can also be performed after disease progression to recharacterize tumor phenotype and genotype. This may be of particular significance if the patient is on a first-line TKI, given the occasional transformation of epidermal growth factor receptor-positive adenocarcinomas to small cell carcinoma (7). EBUS-TBNA has a role in the restaging of the mediastinum after chemotherapy (8) and can also biopsy parenchymal lesions adjacent to the airway (9). Radiation oncologists may use EBUS-TBNA for mapping disease in the mediastinum to guide radiotherapy fields in conjunction with integrated positron emission tomography-computed tomography and also for minimally invasive mediastinal staging prior to stereotactic radiotherapy. In patients with extrathoracic malignancy and enlarged mediastinal lymphadenopathy, oncologists often turn to EBUS-TBNA to confirm metastases and exclude other processes in the mediastinum (10).

EBUS-TBNA has further been found to be of importance in patients with isolated mediastinal lymphadenopathy (IML), where the differential diagnosis often lies between sarcoidosis, tuberculosis, and lymphoma (11). In patients with sarcoidosis, EBUS-TBNA has recently been confirmed to be superior to conventional

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