



Editorial

Nature and nurture

Lifelong consequences of environmental exposures



Environmental nonallergenic exposures, such as microbes and air pollutants, are thought to influence the clinical manifestations of allergic and atopic disease. However, as patterns of urbanization, climate change, and socioeconomic health disparities persist, the health effects of the envirome are increasingly relevant to practitioners and policymakers. In this issue of *Annals*, Peden¹ outlines the influence of pollutant, infectious, and psychosocial conditions on the incidence and severity of allergic disease.

The effects of air pollution, including ambient ozone, oxides of nitrogen, and particulate matter (PM) 2.5 and 10 (both related to tobacco and biomass fuel use) are arguably the best characterized amongst envirome exposure. Air quality inversely correlates with asthma symptoms, as observed during air pollution reduction efforts in California and Japan. However, recent data suggest that early exposure to air pollution also increases the incidence of allergic disease: infants exposed to high levels of oxides of nitrogen, PM_{2.5}, and traffic-related particulate matter were more likely to develop asthma in European and American cohorts.^{2,3} Children in Germany, France, and China were also more likely to be diagnosed with eczema if exposed to oxides of nitrogen, PM_{2.5}, and PM₁₀.^{4,5}

Although the pathophysiology remains unclear, gene $\times$ environment interactions play a role mediating the development of allergic disease. For example, when individuals with “pro- $\ast$ allergic” alleles of inflammatory response mediators are exposed to tobacco or traffic-related particulate matter, the incidence of allergic disease increases. Similarly, a comparison of children with asthma living in high- and low-pollution settings found that high pollution was associated with decreased FoxP3 expression, lower T-cell activity, and worse lung function.⁶ At the cellular level, some data suggest that polyaromatic hydrocarbons in diesel exhaust may increase IgE expression and promote development of new IgE responses.⁷

Compared with pollutants, the data are more mixed with respect to the effect of microbial exposure on allergic disease. The composition of the airway microbiome seems to affect IgE expression and symptom burden in people with asthma, although data regarding endotoxin are still conflicting. Children exposed to endotoxin early in life, particularly those with exposure to farm environments or pets, have a lower incidence of asthma, whereas those with asthma exposed to indoor endotoxin have increased asthma symptoms.^{8,9} It has been theorized that there may be more than one type of endotoxin (not differentiated by current

technology) or that endotoxin affects distinct inflammatory pathways in the lung, either of which could explain the heterogeneity in the literature. The role of viral infections remains similarly unclear: they cause asthma morbidity, epithelial injury, and remodeling, but do not consistently affect the incidence of allergic disease. There is less ambiguity with respect to antibiotics, however, with early childhood exposure increasing the incidence of asthma in a dose-dependent fashion across multiple studies.¹⁰

Finally, Peden¹ reviews an emerging body of literature documenting the effect of psychosocial stressors on the incidence of asthma. Stressors, including neighborhood violence, physical or sexual abuse, maternal depression, intimate partner violence, and poor or insecure housing, have all been implicated in increased incidence of asthma. In particular, Sternthal et al¹¹ reported that children in Chicago neighborhoods with “medium to high violence” had higher asthma incidence than those in safer neighborhoods, even when controlled for race/ethnicity, socioeconomic status, and maternal asthma. The study did not, however, report on neighborhood pollution, so it is plausible that the effect of neighborhood violence is confounded by ambient exposures.

To that point, Peden¹ also reviews several studies that report that high parental stress or low household income augment the effect of air pollutants on asthma incidence, suggesting that stress amplifies the response to environmental exposures, especially in developing immune systems. One study¹² found that monocytes in cord blood from low-income new mothers expressed a larger interleukin 13 response to allergens than those from higher-income homes. At the molecular level, proposed mechanisms for this effect include methylation of the steroid receptor and upregulated corticosteroid response. The implications of these data are profound as we seek solutions to well-documented socioeconomic disparities in asthma outcomes; what may have previously been attributed to inequities in access to care or disparate allergen exposures is called into question as we find that early-life stressors modulate epigenetics and the inflammatory response years after exposure.

As a whole, these data shed light on the profound and complex effects of environment on human biology. Namely, the envirome can modulate biologic characteristics to the molecular level in a way that persists through adulthood. As practitioners, it may be prudent to take a more holistic approach toward evaluating our patients' environment with respect to allergenic and nonallergenic exposure, paying closer attention to the social history. More broadly, Peden's review¹ reinforces the importance of clinician advocacy to curtail pollution and ameliorate socioeconomic disparities as we find increasing evidence of their durable negative effect on health.

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Carmela Socolovsky, MD*
Wanda Phipatanakul, MD, MS†

*Brigham and Women's Hospital
Harvard Medical School
Boston, Massachusetts

†Boston Children's Hospital
Harvard Medical School
Boston, Massachusetts

Wanda.Phipatanakul@childrens.harvard.edu

References

1. Peden DB. The "envirome" and what the practitioner needs to know about it. *Ann Allergy Asthma Immunology*. 2019;126:542–549.
2. Bowatte G, Lodge C, Lowe AJ, et al. The influence of childhood traffic-related air pollution exposure on asthma, allergy and sensitization: a systematic review and a meta-analysis of birth cohort studies. *Allergy*. 2015;70(3):245–256.
3. Gehring U, Wijga AH, Hoek G, et al. Exposure to air pollution and development of asthma and rhinoconjunctivitis throughout childhood and adolescence: a population-based birth cohort study. *Lancet Respir Med*. 2015;3(12):933–942.
4. Jedrychowski W, Perera F, Mauger U, et al. Effects of prenatal and perinatal exposure to fine air pollutants and maternal fish consumption on the occurrence of infantile eczema. *Int Arch Allergy Immunol*. 2011;155(3):275–281.
5. Deng S, Huang D, Wang W, Yan H, Li S, Xiang H. Associations of gestational and the first year of life exposure to ambient air pollution with childhood eczema in Hubei, China. *Environ Sci Pollut Res Int*. 2019;26(23):23842–23849.
6. Nadeau K, McDonald-Hyman C, Noth EM, et al. Ambient air pollution impairs regulatory T-cell function in asthma. *J Allergy Clin Immunol*. 2010;126(4):845–852.e10.
7. Diaz-Sanchez D, Dotson AR, Takenaka H, Saxon A. Diesel exhaust particles induce local IgE production in vivo and alter the pattern of IgE messenger RNA isoforms. *J Clin Invest*. 1994;94(4):1417–1425.
8. Stein MM, Hrusch CL, Gozdz J, et al. Innate immunity and asthma risk in Amish and Hutterite Farm children. *N Engl J Med*. 2016;375(5):411–421.
9. Mendy A, Wilkerson J, Salo PM, et al. Endotoxin predictors and associated respiratory outcomes differ with climate regions in the U.S. *Environ Int*. 2018;112:218–226.
10. Donovan BM, Abreo A, Ding T, et al. Dose, timing, and type of infant antibiotic use and the risk of childhood asthma [published online May 31, 2019]. *Clin Infect Dis*. <https://doi.org/10.1093/cid/ciz448>.
11. Sternthal MJ, Jun HJ, Earls F, Wright RJ. Community violence and urban childhood asthma: a multilevel analysis. *Eur Respir J*. 2010;36(6):1400–1409.
12. Wright RJ, Visness CM, Calatroni A, et al. Prenatal maternal stress and cord blood innate and adaptive cytokine responses in an inner-city cohort. *Am J Respir Crit Care Med*. 2010;182(1):25–33.