Biodiversity: The new kid on the block?

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Children living in inner cities in the United States are at particularly high risk of recurrent wheeze and asthma.[1] Not all wheezers in the preschool years progress to chronic asthma, but a majority lose their symptoms around age 3 to 4 years, a phenotype that has been termed transient wheeze.[2] However, no valid biomarker distinguishing transient wheeze from asthma exists. Only the developmental trajectory until age 4 to 7 years allows a correct *a posteriori* categorization.

Any risk or protective exposure must occur before disease onset, and this temporal relation is one of several Bradford Hill criteria in favor of a causal association in epidemiologic studies. Therefore much attention has been paid to early-life exposures in a number of prospective birth cohort studies following children from pregnancy to school age and beyond. In this issue of the *Journal of Allergy and Clinical Immunology*, O'Connor et al[3] present findings from the Urban Environment and Childhood Asthma (URECA) birth cohort following 442 infants with a parental history of asthma and allergies in inner-city Baltimore, Boston, New York City, and St Louis up to age 7 years.

The URECA study is a meticulously followed cohort with frequent and careful assessment of child health through parental questionnaires every 3 months through age 7 years and annual visits starting at 1 year of age. Objective measurements were included to complement and substantiate parental reports. Asthma at age 7 years was defined through an algorithm of symptom history, medication use, and baseline and postbronchodilator lung function. Allergic sensitization was assessed repeatedly by means of skin prick tests and measurements of specific IgE antibodies to a wide array of allergens.

A very comprehensive and detailed assessment of infant exposures occurred. Maternal stress was ascertained with the Perceived Stress Scale and the Edinburgh Postpartum Depression Scale and included additional questions assessing stress related to neighborhood factors, violence, and economic hardship. Indoor exposures were carefully measured: passive smoking through cord blood cotinine levels and airborne nicotine concentrations and indoor NO_2 concentrations over a 14-day period. Over the first 3 years of life, house dust samples from beds and floors were collected repeatedly for measurements of house dust mite, cockroach, mouse, cat, and dog allergen levels. These indoor dust samples were also assayed for endotoxin and ergosterol, cell-wall components of gram-negative bacteria and fungi, respectively. Furthermore, dust specimens collected at 3 months of age underwent culture-independent microbiome profiling by using 16S rRNA sequencing.

This very thorough characterization of young children and their indoor exposures in inner-city environments confirmed a number of known asthma risk factors, such as passive smoke exposure, frequent colds up to age 3 years, and maternal stress. Surprisingly, levels of cockroach, cat, and mouse allergens in the first 3 years of life were inversely related to asthma development. Although these allergens correlated significantly with bacterial exposures, their protective effect was only marginally attributable to the microbes (Fig 1). In turn, the abundance of a large number of individual bacterial taxa in indoor dust was significantly associated with asthma development independent of allergen levels. Some taxa were associated with asthma risk, such as *Staphylococcus*, *Haemophilus*, and *Corynebacterium* species and several members of the *Sphingomonas* genus. In contrast, dust from the homes of children without asthma was enriched in *Kocuria*, *Alloiococcus*, *Bifidobacterium*, and *Acinetobacter* species. Interestingly, the microbial signal was only detected when analyzing single taxa but not when assessing bacterial richness and diversity or measuring endotoxin and ergosterol levels.

These findings are intriguing because allergen exposures, particularly to house dust mites, cat, mouse, and cockroach, had been related to an increased risk of atopy and asthma, in particular within inner-city environments.[4] These epidemiologic findings have prompted 2 trials in high-risk populations randomizing to strict house mite allergen avoidance and control groups.[5,6] Both trials achieved very significant reductions (61% and 97.6%) in dust mite allergen exposures very early in life[5,6] but did not prevent asthma. On the contrary, allergen avoidance measures were associated with an increased risk of atopic dermatitis ($P = .06$) in Australia[5] and allergic sensitization ($P = .04$) in Manchester.[7] Thus environmental allergen reduction at young age might not only lack beneficial effects but also pose some risks.

The mechanisms through which allergen exposure relates to protection in the URECA cohort are unknown. In addition to being the source of allergenic peptides, cockroach, mice, and cats are animals that carry compounds from outdoor environments into the home. Nonetheless, the protective cockroach exposure

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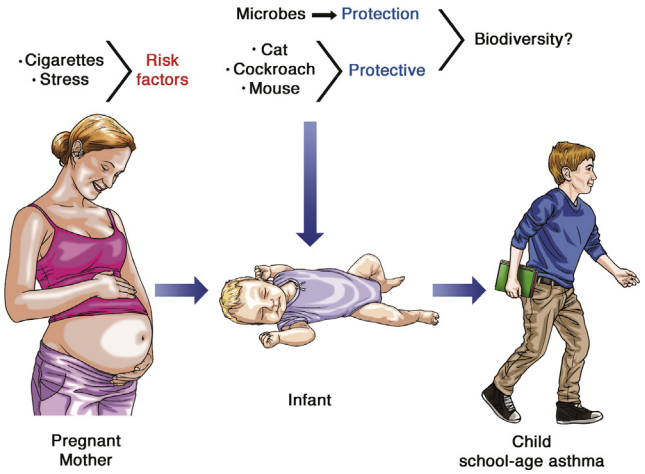

FIG 1. Findings from the comprehensive URECA birth cohort in US inner cities suggest that perinatal risk factors, such as maternal stress and maternal smoking, increase the risk up to school age. In turn, environmental exposure to certain bacteria and allergens, such as mouse, cat, and cockroach, early in life might confer protection from asthma. Therefore the diversity of such biological exposures from animals and microbes might matter, as has also been suggested from the findings of farm studies.

was explained only to a small extent by *Bifidobacterium* and *Brevundimonas* species.

For food allergies, the route of allergen exposure matters in terms of sensitization risk. In young children oral ingestion of food allergens can induce tolerance, whereas allergen penetration through damaged skin, such as in patients with eczema, might initiate the process of allergic sensitization, as so elegantly demonstrated in the Learning Early About Peanut study.[8]

For environmental allergen exposures, neither the route nor magnitude of exposure might matter but rather the extent of biodiversity. The biodiversity hypothesis is based on epidemiologic observations linking the diversity of animal exposures, such as those found on traditional dairy farms; the diversity of plant exposures, as seen in rural areas of Finland[9]; and the diversity of human exposures (higher number of siblings and crowding) to a reduced risk of atopy. Decreasing biodiversity in the environment might translate into a decreased diversity of the human microbiome, which in turn might contribute to allergic and autoimmune diseases. Interestingly, the biodiversity effect in rural Finland and the farm effect in rural alpine areas on atopy was not associated with bacterial richness but with exposure to *Acinetobacter lwoffii*.[9,10] In the URECA cohort *Acinetobacter* species were also found among the protective bacterial exposures, although its characterization down to the species level was not reported. However, it is a remarkable replication of findings from different independent environmental microbiome studies, although the authors of the URECA study did not report findings for asthma and atopy separately.

Reproducibility of findings from microbiome studies has otherwise been rather limited, which might be attributable to a lack of understanding of the underlying mechanisms. Thus not only might exposures to certain species and strains *per se* convey risk or benefit but also cocktails of microbial exposures with the right ingredients, such as specific metabolites or immune stimulatory compounds, might matter.

In the URECA cohort reproducibility of microbiome findings is also limited. Although the inverse association of cockroach, mouse, and cat allergen exposure with allergic sensitization and recurrent wheeze was already apparent at age 3 years, the microbiome signals differed. Relative bacterial richness was inversely related to atopy at age 3 years, which is no longer seen in the current report at age 7 years. Protective environmental bacterial exposures for atopic wheeze were found for the Prevotellaceae, Lachnospiraceae, and Ruminococcaceae families at age 3 years but not for asthma at age 7 years. This discrepancy might be attributable to the lack of stratification into asthma and atopy, the limited concordance of recurrent wheeze at age 3 years and asthma at age 7 years, and differences in technology to assess the environmental microbiome (phylogenetic microarray versus 16S rRNA sequencing).

Although the biodiversity hypothesis is an interesting concept, the underlying mechanisms are completely unclear. A link to the diversity of the environmental and human microbiome is just one potential explanation. Stimulation of innate immunity by other thus far unknown biologic structures is another conceivable scenario. Certainly the new kid on the block deserves attention and more scrutiny.

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