The Exposome Applied: A Step toward Defining the Totality of Environmental Exposures in Asthma

Asthma is a common noncommunicable disease and a major global public health problem (1, 2). Despite the existence of highly effective controller medications, we have made little progress in reducing asthma morbidity (3), especially among high-risk populations such as children and minority groups living in high-poverty, urban neighborhoods (4). It is thus critical to identify preventable risk factors to reduce the asthma global health burden and inequalities.

As genetic factors contribute to only 40–60% of overall asthma risk (5), it is increasingly clear that the other half is due to mostly unknown environmental contributors (6). Most previous studies have relied on classical exposure science, focusing on the association of asthma with a single or few exposures. In this issue of the *Journal*, Guillien and colleagues (pp. 1208–1219) have adopted a more holistic approach by querying the association between the exposome and asthma (7). The exposome is the totality of human environmental (i.e., nongenetic) exposures, both internal and external, from conception to death, that interplay with underlying genetic susceptibility factors (6, 8).

Ideally, exposome studies should capture *1*) the internal exposome (including the metabolome, epigenome, microbiome, etc.); *2*) indoor and outdoor external chemical, physical, and biological contaminants, including occupation and lifestyle factors; and *3*) psychosocial, economic, and ecological factors (6, 9). To date, however, a complete description of the exposome is impossible. We can, however, cast a wider net by foregoing some rigor in assessment and compensating with the statistical power of rich datasets (10). Guillien and colleagues have approached this by investigating the association between asthma phenotypes with a substantial number ($n = 87$) of combined factors spanning four exposome domains (socioeconomic, external environment, early-life environment, and lifestyle–anthropometric), collected through self-reported questionnaires and geographic information system–based computations, in a large study population of 20,833 adults from the French NutriNet-Santé cohort.

What sets this study apart from previous asthma exposome studies is that Guillien and colleagues accounted for the complexity and clinical heterogeneity of asthma by assessing both the continuous asthma symptoms score and asthma control. This allows the discovery of exposome associations across the spectrum of disease and is essential for translation to eventual asthma management purposes. In addition, most previous multifactorial asthma studies did not control for coexposures. In this study, associations of the exposome with the asthma symptom score and asthma control were assessed by using a relatively novel exposome approach (11) considering all exposures simultaneously within each of the indicated exposome domains through unsupervised clustering analysis.

Using this approach, Guillien and colleagues identified two socioeconomic profiles ("deprived area–high income–high education" and "married–retired–low education") associated with a lower risk for higher asthma symptom score (but not uncontrolled asthma). However, single-exposure studies suggest that lower socioeconomic position (12) and neighborhood deprivation (13) are associated with increased asthma risk. These profiles thus indicate that interactions among the different factors clearly influence the overall asthma risk.

The association between the lifestyle–anthropometric profile ("unhealthy diet–high smoking–overweight") and increased asthma symptoms (highest score) and asthma control confirms the well-established independent associations for these factors commonly addressed in asthma control guidelines. Three early-life exposure profiles ("high passive smoking–own dogs," "poor birth parameters–daycare attendance–city center," and "⩾2 siblings–breastfed" compared with "farm–pet owner–molds–low passive smoking") were associated with increased asthma symptoms and uncontrolled asthma, supporting the concept of the developmental origins of health and disease. At the single level, this study confirms the negative effect of passive smoking and the protective effects of growing-up in traditional farms, "owning pets," and "daycare attendance" (14). However, once interactions with "poor birth parameters" and "born in the city center" are considered, the protective effect of "daycare attendance" is lost. The increased risk for asthma symptoms with the profile "⩾2 siblings–breastfed" is controversial, because most previous studies have demonstrated that a larger number of siblings is protective against asthma (15), whereas previous associations of breastfeeding with asthma are inconsistent (14). These different outcomes once interactions are considered thus highlight the importance of analyzing exposure-related health risks using a more holistic exposome approach.

The external environment profile ("high built-up land–low greenness–low water areas") was associated with an increased risk for uncontrolled asthma but not asthma symptom score. This interaction profile likely represents individuals living in urban areas, thus confirming previous associations of urban areas with uncontrolled asthma (16). The difference in associations with asthma symptom score versus asthma control stresses the point that multiple disease endpoints need to be considered in exposome studies to ensure a complete disease risk assessment.

It is well known that there are clear sex differences in susceptibility to asthma (17). Therefore, it is surprising that this

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study did not reveal major sex differences for any of the identified asthma risk profiles. The reported small number of men in the cohort and statistical power may be limiting factors. However, it is more likely that interactions with other factors, such as from the "internal exposome" (6, 9), need to be explored to capture such differences.

From an all-inclusive exposome perspective, the present study has a few limitations. For example, there is a chance that recall bias can occur when using self-assessed questionnaires, particularly for past or early-life exposures. The study design did not allow the validation of any of the self-reported individual exposures with actual (either targeted or untargeted) exposure measurements. Moreover, certain known asthma risk factors, such as pesticides, pollens, dampness, and facilities density, were not captured. Even though the field still relies on reductionist approaches to facilitate exposome studies, certain domains such as the internal exposome are arguably omissible (6, 9, 10). Failure to include the internal exposome would miss potential disease associations driven by interactions with essential features of the internal chemical environment caused by, for example, sex and gender, stress, and endogenous processes, as well as their signature on the biological state of the individual (6, 10). Importantly, the study design did not include data on ethnicity or race (4). The findings may thus not necessarily be generalizable to the whole population. Finally, the results remain to be validated in other (geographically different) populations. Nevertheless, this study still allows a thorough assessment of the associations of exposure-related interaction profiles with asthma and provides a useful starting point for future asthma exposome studies that are more inclusive of biological omics data.

By using a reductionist exposome approach, Guillien and colleagues have demonstrated that for effective asthma risk assessment and identification of control and prevention targets, there is a need to consider the interactions between early-life and current environmental risk factors with individual risk factors such as socioeconomic and lifestyle–anthropometric factors. Ultimately, this study highlights the importance of exposomics as the future of exposure epidemiology. ■

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Fenna C. M. Sillé, Ph.D., M.S.
Department of Environmental Health and Engineering
Johns Hopkins University
Baltimore, Maryland

Meredith McCormack, M.D.
Department of Environmental Health and Engineering
Johns Hopkins University
Baltimore, Maryland

and

School of Medicine
Johns Hopkins University
Baltimore, Maryland

Thomas Hartung, M.D., Ph.D.
Department of Environmental Health and Engineering
Johns Hopkins University
Baltimore, Maryland

and

Department of Biology
University of Konstanz
Konstanz, Germany

ORCID IDs: 0000-0003-4305-2049 (F.C.M.S.); 0000-0003-1702-3201 (M.M.); 0000-0003-1359-7689 (T.H.).

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