

Correspondence

A novel strategy to identify asthma-associated microbial clusters

To the Editor:

Increasing evidence indicates that the development of asthma is associated with microbial communities in indoor environments.^{1,2} However, because of high temporal and spatial variations and the multidimensionality of microbiome data set, it is challenging to identify an accurate set of protective and risk microbes for asthma. The current standard is performing association analysis between asthma and microbial community composition or quantity of cellular components (eg, endotoxins or microbial volatile organic compounds). However, studies with this approach produced weak and inconsistent associations for asthma³⁻⁵ compared with traditional nonmicrobiological assessments, such as tobacco smoking, moisture, dampness, and mold.⁵ Thus, optimal measurements for microbial exposure are still to be explored by scientists.

In the November issue of the *Journal of Allergy and Clinical Immunology*, Karvonen et al⁶ proposed a novel strategy to identify asthma-associated microbes in the article titled “Indoor bacterial microbiota and development of asthma by 10.5 years of age.” Unlike previous health association studies using stringent cutoff ($P < .01$ or false-discovery rate $q < 0.05$), the new strategy used a relaxed cutoff to screen potential microbial clusters first (correlation $r > 0.4$ or $P < .1$). Twelve genera, mainly from Actinomycetales, were borderline negatively associated with asthma and added up as a new variable. The combined variable showed a much stronger association with the development of asthma than any single genus, and the variable explained the majority of association between microbial diversity and asthma. Although it still needs to be verified in other studies, the new concept could be used as an improved microbiological assessment with better statistical power to reduce heterogeneous results produced by previous association studies.

However, there still exist a few limitations of the study. First, the study only screened 139 high abundant bacterial genera (top 20%) with relative abundance greater than 0.1%, among the total 658 detected bacteria. In contrast, previous association studies identified that many asthma-associated microbes were present in low frequency in the indoor environment, such that the protective yeast *Kondoa* was present in only 13 of 196 homes in a cohort study in the northeastern United States.^{3,4} We recently performed the first association study in schools in Malaysia and found that all

7 asthma-associated bacteria were present in low frequency (range, 0.01%-0.2%).⁷ A study with an anchor-based approach found that many low-frequency microbes (abundance, $<0.05\%$) contributed to the protective effect in the farm environment, and these microbes were included in the training model to predict the health outcomes indoor.⁸ Thus, various lines of evidence suggest that low-frequency microbes play an important role in asthma development. We suggest that Karvonen et al include these microbes in the model to test whether they can further improve the model, or provide a rational explanation for not including them. Another small issue is that the 12 microbes selected in the combined variable should have been listed in the article for future reference and comparison.

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REFERENCES

1. Ege MJ, Mayer M, Normand AC, Genuneit J, Cookson WO, Braun-Fahrlander C, et al. Exposure to environmental microorganisms and childhood asthma. *N Engl J Med* 2011;364:701-9.
2. Bello MGD, Knight R, Gilbert JA, Blaser MJ. Preserving microbial diversity. *Science* 2018;362:33-4.
3. Dannemiller KC, Gent JF, Leaderer BP, Peccia J. Indoor microbial communities: influence on asthma severity in atopic and nonatopic children. *J Allergy Clin Immunol* 2016;138:76-83.e1.
4. O'Connor GT, Lynch SV, Bloomberg GR, Kattan M, Wood RA, Gergen PJ, et al. Early-life home environment and risk of asthma among inner-city children. *J Allergy Clin Immunol* 2018;141:1468-75.
5. Mendell MJ, Adams RI. The challenge for microbial measurements in buildings. *Indoor Air* 2019;29:523-6.
6. Karvonen AM, Kirjavainen PV, Täubel M, Jayaprakash B, Adams RI, Sordillo JE. Indoor bacterial microbiota and development of asthma by 10.5 years of age. *J Allergy Clin Immunol* 2019;144:1402-10.
7. Fu X, Norback D, Yuan Q, Li Y, Zhu X, Deng Y, et al. Indoor microbiome, environmental characteristics and asthma among junior high school students in Johor Bahru, Malaysia: arXiv; 2019. 1911.06946.
8. Kirjavainen PV, Karvonen AM, Adams RI, Täubel M, Roponen M, Tuoresmäki P, et al. Farm-like indoor microbiota in non-farm homes protects children from asthma development. *Nat Med* 2019;25:1089-95.

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