

Correspondence

Reply

To the Editor:

The correspondence from Amaral¹ raises important methodological issues associated with metabolomic studies of asthma. Although such studies might identify novel pathways for drug discovery, a primary challenge that remains in the field is the curation of the metabolome because most of the chemicals detected by using high-resolution metabolomics are presently uncharacterized. To this point, we believe there is a critical need for a reference database of high-resolution metabolomic data for healthy subjects. However, there is no consensus on how a healthy control subject should be defined. Given the degree of variability present within a nonasthmatic population, we believe that “not having asthma” would not be sufficient for such a purpose because issues of confounding related to multimorbidity, the exposome, the genome, and the proteome would ultimately remain.

For these reasons and others, our metabolomic study of severe asthma² did not seek to identify biomarkers of asthma susceptibility but rather to identify biomarkers of asthma severity. Although the former approach implies a case versus control design, the latter approach instead was selected and was therefore limited to an asthma-only population. We believe this approach minimizes some confounding by medication exposure, allergic sensitization, and other factors relevant to the asthma medical history (including genetics). However, despite our best attempts, there are remaining sources of confounding, as recognized by Amaral,¹ that cannot be fully addressed with an observational study design. Therefore we can only hope that our preliminary findings will lay critical groundwork for future studies. Studies incorporating a variety of “-omics” (ie, systems biology approaches) are of greatest need if we intend to truly advance the understanding and treatment of asthma. However, such studies will remain challenging and perhaps be nonreproducible unless the issue associated with the identification and characterization of healthy control populations is solved.

How might investigators in the metabolomics community identify and characterize healthy control subjects? We believe the solution to this challenge might rest with children. The literature on multimorbidity³ demonstrates that most children are

in a predisease state and, furthermore, that they are in a state of premultimorbidity. Sampling of blood, urine, breath, and other noninvasive biospecimens from a very large number (ie, thousands) of children might help to unravel the metabolome in a state of health, which could then be compared with states of disease and, eventually, multimorbidity. Implicit in this notion is the need for integrated, phenotypic-intensive biospecimen repositories with publicly accessible databases, perhaps similar to what is currently present for genomic research. As pediatric researchers who routinely struggle with methodological research issues and knowledge gaps in childhood asthma,⁴ a collaborative pediatric approach would be of great interest. Given that most studies of asthma are conducted in adults and the findings are then extrapolated to children,⁴ a large pediatric research initiative, such as this one, would be a refreshing change of pace as we seek to enhance understanding of the asthma spectrum across the age span.

Anne M. Fitzpatrick, PhD^a

Youngja Park, PhD^{b,c}

Lou Ann Brown, PhD^a

Dean P. Jones, PhD^b

From the Departments of ^aPediatrics and ^bMedicine, Emory University School of Medicine, Atlanta, Ga, and ^cthe College of Pharmacy, Korea University, Seong City, Korea. E-mail: anne.fitzpatrick@emory.edu.

The original article associated with this correspondence was funded by grant RO1 NR012021 and the National Center for Advancing Translational Sciences UL1 TR000454.

Disclosure of potential conflict of interest: A. M. Fitzpatrick has consultant arrangements with MedImmune, Merck, GlaxoSmithKline, Boehringer-Ingelheim, and Genentech. The rest of the authors declare that they have no relevant conflicts of interest.

REFERENCES

1. Amaral AFS. Metabolomics of asthma. *J Allergy Clin Immunol* 2014 ■■■:■■■.
2. Fitzpatrick AM, Park Y, Brown LAS, Jones DP. Children with severe asthma have unique oxidative stress-associated metabolomic profiles. *J Allergy Clin Immunol* 2014;133:258-61.e8.
3. Barnett K, Mercer SW, Norbury M, Watt G, Wyke S, Guthrie B. Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study. *Lancet* 2012;380:37-43.
4. Szeffler SJ, Chmiel JF, Fitzpatrick AM, Giacoia G, Green TP, Jackson DJ, et al. Asthma across the ages: knowledge gaps in childhood asthma. *J Allergy Clin Immunol* 2014;133:3-13.

<http://dx.doi.org/10.1016/j.jaci.2014.02.012>