

# Will This Toddler Wheeze Again?



Elsa R. Treffeisen, MD<sup>a</sup>, and Ann Chen Wu, MD, MPH<sup>b</sup> *Boston, Mass*

This winter's triple epidemic overwhelmed U.S. pediatric hospitals.<sup>1</sup> Children largely avoided the brunt of the coronavirus disease 2019 (COVID-19) pandemic to be hit by respiratory syncytial virus, influenza, and COVID-19 this season. Pediatricians were overwhelmed with children presenting to their offices with upper respiratory infections, some with the first or most severe respiratory episodes of their lives. "Will this toddler wheeze again? Will this toddler develop an asthma-like picture?" pediatricians asked themselves. With few data points to make an assessment and plan, pediatricians managed these first-time wheezers as best they could.

Knowledge of which risk factors are most likely to contribute to asthma-like symptom burden could help pediatricians. In the study entitled, Risk factors and age-related patterns of asthma-like symptoms in early childhood, Kyvsgaard and colleagues<sup>2</sup> decipher risk factors for asthma-like episodes, a term previously validated by this group and defined as cough, wheeze and/or shortness of breath, in children ages 0 to 3 years.<sup>2-5</sup> The population in this study was from the Danish prospective COP-SAC<sub>2010</sub> cohort. Seven hundred mother-child dyads were followed between 2008 and 2011.<sup>2</sup> Binary asthma-like symptoms were monitored by daily diary cards that were validated by physicians at regular visits and at acute care visits.<sup>2</sup>

The authors assessed risk factors for the cumulative number of asthma-like episodes, termed episode burden, and episode duration. In a multivariable analysis, male sex, maternal asthma, low birth weight, maternal antibiotic use, and 2 previously published scores—the high asthma polygenic risk score and the high airway immune score—were associated with higher episode burden.<sup>6,7</sup> The impact of certain risk factors depended on the child's age, with the following risk factors having more of an impact as the child aged: lower birth weight, maternal asthma, preterm birth, and caesarean section. Conversely, having a sibling at birth had the largest effect during the first year of life and its effect diminished with time. A combined score composed of

information readily available to physicians included male sex, low birth weight, and maternal asthma. In this score, there was a 34% increase in asthma-like episodes for each of these 3 factors present (male sex, low birth weight, and maternal asthma) and an 18% increase in asthma-like episodes for each of the 6 factors present in the multivariable analysis (male sex, maternal asthma, low birth weight, maternal antibiotic use, the high asthma polygenic risk score, and the high airway immune score).

This study is the first, to our knowledge, to demonstrate that asthma-like episodes in early childhood have age-related symptom patterns.<sup>2</sup> Importantly, this study suggests that prediction of asthma-like symptoms in early childhood may be possible.<sup>2</sup> Another strength of this study is that it includes genetic information as a factor in addition to clinical factors. Personalized treatment based on risks for asthma-like symptoms has the potential to prevent morbidity from asthma including hospitalizations.<sup>2</sup> Nevertheless, additional studies are needed before prediction of asthma-like episodes could be used in clinical practice.

There are several ways to expand this study's implications in future work. The first step would be to validate these findings in a second population to evaluate generalizability. As an additional step, the authors may create a scale for pediatricians to use in their practice, mirroring the Pediatric Asthma Risk Score (PARS) or Asthma Predictive Index (API), but in this case, predicting asthma-like episodes at a younger age, more directly leveraging immediate patient management.<sup>8,9</sup> As alluded to by the authors, researchers could study the use of different treatment regimens, such as supportive care, short-acting beta-agonists or inhaled corticosteroids, depending on an infant or toddler's risk of asthma-like episodes. Children could be grouped into a low, medium, or high risk of asthma-like episodes in years 0 to based on the 3 risk factors of male sex, maternal asthma, and low birth weight.

It would be helpful to see how generalizable these findings are, especially given the participants from this study were all Danish. Do these risk factors predict asthma-like episodes among different populations, for example, children living in a developing country or children from underserved and minoritized populations in the United States? Social determinants of health such as income, race, ethnicity, and access to health care may be important factors in predicting the burden of asthma-like episodes, especially in regions of the world most affected by health care disparities. This study started to assess this important issue. The investigators included a risk factor termed social circumstances using a primary component analysis score that included household income, maternal age, and maternal educational level when that child was 2 years of age. This risk factor did not significantly predict the number of asthma-like symptoms during the first 3 years ( $P = .365$ ). Nevertheless, future studies could include diverse populations and examine the role of additional social determinants of health measures such as race,

<sup>a</sup>Division of Immunology, Department of Pediatrics, Boston Children's Hospital, Harvard Medical School, Boston, Mass

<sup>b</sup>Department of Population Medicine, Harvard Medical School; Department of Population Medicine, Harvard Pilgrim Health Care Institute; Division of General Pediatrics, Department of Pediatrics, Boston Children's Hospital, Boston, Mass  
Conflicts of interest: E. R. Treffeisen is supported by the National Institute of Health (grant number 5T32AI007512-35); and is funded in part from the Boston Children's Hospital Pediatric Health Equity Fellowship. The other author declares that she has no relevant conflicts of interest.

Received for publication April 5, 2023; accepted for publication April 6, 2023.

Corresponding author: Ann Chen Wu, MD, MPH, Department of Population Medicine, Harvard Medical School and Harvard Pilgrim Health Care Institute, 401 Park Drive, Suite 401, Boston, MA 02215. E-mail: [ann.wu@childrens.harvard.edu](mailto:ann.wu@childrens.harvard.edu).

J Allergy Clin Immunol Pract 2023;11:1785-6.  
2213-2198

© 2023 American Academy of Allergy, Asthma & Immunology  
<https://doi.org/10.1016/j.jaip.2023.04.021>

ethnicity, access to adequate nutrition, housing, transportation, or health care, and other factors that are associated with asthma-like symptoms.<sup>10</sup>

In summary, this study by Kyvsgaard and colleagues<sup>2</sup> characterizes risk factors for wheezing, cough, and shortness of breath among children ages 0 to 3 years, providing pediatricians with some insight into the management of these infants and toddlers. Future studies could assess these risk factors with the addition of social determinants of health within different populations to better understand the generalizability of these findings. In addition, researchers could create a scale for clinical use and explore differing treatment therapies based on risk of asthma-like episodes in early childhood. In the future, with these additional data, pediatricians may more confidently answer the question, Will this toddler wheeze again?

## REFERENCES

1. Furlow B. Triple-demic overwhelms paediatric units in US hospitals. *Lancet Child Adolesc Health* 2023;7:86.
2. Kyvsgaard JN, Krogsgaard Chawes BL, George Horner DL, Hesselberg LM, Melgaard ME, Jensen SK, et al. Risk factors and age-related patterns of asthma-like symptoms in early childhood. *J Allergy Clin Immunol Pract* 2023; 11:1773-84.
3. Bisgaard H, Pipper CB, Bønnelykke K. Endotyping early childhood asthma by quantitative symptom assessment. *J Allergy Clin Immunol* 2011;127: 1155-1164.e2.
4. Skytt N, Bønnelykke K, Bisgaard H. "To wheeze or not to wheeze": that is not the question. *J Allergy Clin Immunol* 2012;130:403-407.e5.
5. Bisgaard H, Swern AS, Knorr B. "To wheeze or not to wheeze": that is not the question—the sequel. *J Allergy Clin Immunol* 2012;130:531-2.
6. Ahluwalia TS, Eliassen AU, Sevelsted A, Pedersen CET, Stokholm J, Chawes B, et al. FUT2—ABO epistasis increases the risk of early childhood asthma and *Streptococcus pneumoniae* respiratory illnesses. *Nat Commun* 2020;11:6398.
7. Thorsen J, Rasmussen MA, Waage J, Mortensen M, Breginrod A, Bønnelykke K, et al. Infant airway microbiota and topical immune perturbations in the origins of childhood asthma. *Nat Commun* 2019;10:5001.
8. Castro-Rodríguez JA, Holberg CJ, Wright AL, Martinez FD. A clinical index to define risk of asthma in young children with recurrent wheezing. *Am J Respir Crit Care Med* 2000;162:1403-6.
9. Biagini Myers JM, Schaubberger E, He H, Martin LJ, Kroner J, Hill GM, et al. A Pediatric Asthma Risk Score to better predict asthma development in young children. *J Allergy Clin Immunol* 2019;143:1803-18010.e2.
10. Trivedi M, Pappalardo AA, Udoko M, Garg A, Phipatanakul W, Szefer SJ, et al. Social determinants of health in asthma through the life course. *J Allergy Clin Immunol Pract* 2022;10:953-61.