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New Developments in Our Understanding of the Origins and Treatment of Asthma

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Asthma is the most common chronic disease of childhood. While asthma is a highly heritable condition, the dramatic increased prevalence of disease over the past half-century strongly suggests that the environment plays an important role in disease expression. Asthma disproportionately affects children in urban communities in the United States and imposes a great personal and health care burden. Despite treatment advances, a significant proportion of patients do not achieve control of their disease and continue to experience high levels of morbidity. Unfortunately, tremendous health care disparities exist in asthma, with Black and Hispanic children in the United States bearing the greatest disease burdens. While children raised on farms have reduced risk of developing asthma, rural children who develop asthma often experience worse disease outcomes. Thus, the factors underlying differential burdens of disease across urban, suburban, and rural environments are an important area of study.

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What has been learned about asthma from birth cohort studies led by UW-Madison investigators?

University of Wisconsin-Madison has a long-standing track record of internationally recognized contributions to asthma research. One area in which we have led the way is with birth cohort studies performed in diverse environments. The Childhood Origins of Asthma (COAST) birth cohort study, initiated in 1998 and comprising predominantly suburban Madison children/families, has identified the critical synergistic contributions of early-life respiratory allergies and wheezing with the common cold virus, rhinovirus, to the inception of asthma. The Urban Environment and Childhood Asthma (URECA) birth cohort study, initiated in 2004 at four urban centers in the United States, seeks to identify the specific components of urban environments that impact the development of asthma. URECA has identified both environmental exposures and distinct patterns of gene expression in the airways that are linked to clinical phenotypes of disease during later childhood. The Wisconsin Infant Study Cohort (WISC) began in 2013 as a partnership between UW-Madison and Marshfield Clinic researchers to understand the components of rural farm environments, such as early-life microbial exposures, that can reduce the risk for allergic disease and asthma, with a long-term goal of identifying preventive strategies for the broader population. To address the importance of studying diverse populations and the difficulty in extrapolating findings from one study population to another, UW-Madison investigators are leading the Children's Respiratory and Environment Workgroup (CREW), a consortium of researchers from 12 birth cohort studies, in the Environmental Influences on Child Health Outcomes (ECHO) program.

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Why do children in urban environments have increased asthma morbidity, and how can we reduce disparities?

The National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health (NIH), has been funding research to address asthma disparities in urban communities for more than 30 years. The UW School of Medicine and Public Health has led the NIAID-funded Inner City Asthma Consortium (ICAC) since 2002. These studies have implicated exposures common to urban environments—

such as pollution, cockroach and mouse allergens, stress, and violence—to variable phenotypes and severity of asthma. ICAC has demonstrated that guideline-based asthma care can significantly improve outcomes, although many children continue to have uncontrolled disease despite these evidence-based approaches. Recently, ICAC has leveraged airway transcriptomics, an assessment of gene expression, to identify how different triggers such as viruses and pollution provoke asthma attacks. We have identified both common and distinct pathways according to the trigger(s) of an episode, and we have further identified the incomplete impact of systemic corticosteroids, the current standard therapy for these episodes, which carry significant short- and long-term adverse effects. Recent studies have shown that even a single course of systemic corticosteroids can increase the risk of fracture, sepsis, GI bleeding, and other consequences. We can do better!

In 2021, we received new NIAID funding to lead the next iteration of this program called the Childhood Asthma in Urban Settings (CAUSE) Network, a group of multiple clinical sites and scientific centers that work collaboratively to better understand disease mechanisms and improve asthma outcomes. The overall goal of our CAUSE Leadership Center at UW-Madison is to address high-priority, unmet needs for childhood asthma in disadvantaged children in urban communities, including: (a) developing strategies to prevent asthma; (b) improving treatment and inhibiting disease progression; (c) reducing severe asthma attacks; and d) defining endotypes of respiratory health and disease. In this program, we link cutting-edge, mechanistic investigations to clinical trials and observational studies, with an aim of developing novel and targeted therapies for the prevention and treatment of asthma in urban communities and beyond.

What is new in the treatment of asthma?

The Global Initiative for Asthma (GINA) recently put forth paradigm-changing recommendations for the treatment of asthma. GINA has strongly encouraged the use of inhaled corticosteroids (ICS) in combination with a reliever therapy (beta agonist) for the treatment of asthma symptoms, even in patients with mild asthma. Multiple recent studies have shown that an ICS in combination with either albuterol or formoterol is superior to albuterol alone as a reliever therapy. Implementation of these recommendations has been challenging in clinical practice and is an example of where we can do better as a health care system to improve patient outcomes. Furthermore, the vast majority of these studies have been performed in adult patients, and more evidence is needed to clearly determine the effectiveness of these approaches in children.

Targeted biologic therapies have dramatically improved the treatment of severe asthma patients with a "Type 2" phenotype (elevated biomarkers such as peripheral blood eosinophils and/or fractional exhaled nitric oxide). However, studies of these therapies in children and Black and Hispanic populations have been more limited to date and represent an unmet need. Further, treatments are still tremendously lacking for asthma patients who do not have evidence of Type 2 inflammation. UW-Madison investigators are addressing these gaps within ongoing collaborative research programs such as the NIH National Heart, Lung, and Blood Institute's Precision Interventions for Severe and Exacerbation-Prone Asthma (PrecISE) Network and the NIAID's CAUSE Network.

CONCLUSION

Much has been learned about the origins and treatment of asthma over the past several decades. UW-Madison investigators are at the forefront of an exciting time in asthma research, leveraging environmental, genomic, epigenetic, metabolomic, and other "big data" to reduce asthma disparities with tangible goals of asthma precision treatment and disease prevention.

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