Moving Beyond the Confines of Body Mass Index in the Quest to Understand Obese Asthma

Childhood asthma and obesity constitute significant public health challenges that affect millions of children around the world. In the United States, approximately 9% of children have asthma and ~30% are overweight or obese. Although we must always review our concepts and inferences as new data arise, a considerable body of epidemiological evidence suggests that obesity is a risk factor for childhood asthma and increased asthma morbidity. Some studies have reported that asthma can precede childhood obesity, but their findings may have been driven by children who were already overweight at baseline and thus much more likely to become obese (1, 2). Bidirectional Mendelian randomization studies in children and adults have shown associations between obesity genetic risk scores and subsequent development of asthma but not between asthma genes and subsequent obesity (3, 4). Mendelian randomization studies allow us, to a certain degree, to examine directionality while eliminating various potential confounders. Moreover, weight loss can lead to significant improvements in asthma symptoms, quality of life, and lung function, further supporting the directionality of the association (5). In all likelihood, "obese asthma" is a complex group of phenotypes comprised of individuals in whom obesity contributes to asthma risk and morbidity, others in whom obesity complicates symptoms from existing asthma, and still others in whom poorly controlled asthma may be a risk factor for weight gain (6).

For the field to move forward, however, we must shift our focus from evaluating *whether* there is a relationship between obesity and asthma to untangling the underlying pathways. Some of these pathways are likely shared by all obese individuals with asthma, whereas others may be specific to certain subphenotypes. Relying solely on the body mass index (BMI) will be vastly insufficient for this task. Though convenient in its simplicity, the BMI has inherent limitations, including the inability to discern body composition, adipose tissue distribution, or metabolic dysregulation. It serves as a readily available proxy for obesity, but it was never meant to provide insight into the mechanisms of disease. As a consequence, over time, physicians and researchers have had to coin terms such as "healthy obese" and "obesity paradox" to explain why outcomes do not match what one might expect from looking at a high BMI (7).

In this issue of the *Journal*, Mensink-Bout and colleagues (pp. 348–355) go beyond the confines of BMI by assessing body composition and fat distribution by magnetic resonance imaging in 5,421 children at 10 years of age and evaluating their association with asthma risk and lung function (8). They report that total fat mass is associated with higher FEV_1 and FVC but lower FEV_1/FVC ratios. Moreover, only visceral fat was associated with these changes when conditioned on total fat mass; in other words, the amount of visceral fat deposition was associated with lung function independently of total body adiposity. Furthermore, in a longitudinal analysis, they showed that the fat mass index at 6 years of age (measured by dual-energy X-ray absorptiometry and ultrasound at that earlier time point in the cohort) was associated with increased asthma risk and higher FEV_1 and FVC by age 10. These findings are consistent with prior studies, and the authors extend our knowledge by using magnetic resonance imaging to directly quantify fat mass, by evaluating specific adiposity patterns associated with lung function, and by performing cross-sectional and longitudinal analyses. Other strengths of the study include the large sample size and the population-based design of the well-characterized Generation R Study cohort. Among the weaknesses that the authors transparently acknowledge are the questionnaire-based ascertainment of asthma and the possibility of residual confounding by diet or other factors. In addition, as has been the case with many other longstanding birth cohorts, there was significant loss to follow-up through 10 years of age.

Rather than being a quiescent energy storage organ, adipose tissue actively participates in several processes and can promote an inflammatory state that contributes to the development of disease. Mechanisms include the production of adipokines such as leptin and adiponectin, immune cell signaling, and metabolic dysregulation (9). Visceral adipose tissue in particular has been linked to cardiovascular disease and other complications of obesity. It could well be that it is also more actively involved in obese asthma. Visceral fat in obese women with asthma shows higher leptin gene expression and lower adiponectin expression than that in obese women without asthma, and leptin expression correlates with airway hyperreactivity (10). Alternatively, visceral adiposity and asthma could be downstream consequences of common inflammatory pathways. Chitinase 3-like-1, for example, contributes to both allergic inflammatory responses and visceral fat accumulation (11). With this in mind, and in light of the findings reported by Mensink-Bout and colleagues, it will be crucial for future studies to confirm whether visceral or other specific adipose tissue depots are associated with asthma and other respiratory outcomes, and then focus on elucidating the underlying pathways and corresponding biomarkers. This will not only further our understanding of the disease, but in a "virtuous cycle" it will also improve our ability to discern different subphenotypes and endotypes of obese asthma, making it easier for us to study them and to manage our patients.

Another plausible explanation for the reported findings is that certain distributions of adiposity might be associated with anatomical, developmental, or mechanical changes in the lungs. We previously reported that childhood obesity is associated with airway dysanapsis (with a stronger effect in boys than in girls) and that dysanapsis in turn is associated with more frequent asthma symptoms and exacerbations (12). In the current study, Mensink-Bout and colleagues report that visceral fat was associated with airway dysanapsis independently of the total fat mass. They also report stronger effect estimates for pericardial fat on FEV_1 and FVC in boys than in girls. Lungs from adults with and without asthma show accumulation of adipose tissue in the outer wall of medium and large

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airways with higher BMI, and the amount of airway fat correlates with wall thickness and the number of inflammatory cells (13). Airway adipose tissue accumulation by itself may therefore partly explain some of the changes seen in asthma, including airway narrowing and remodeling. Future studies should examine whether excess visceral and/or pericardial fat in children denotes a phenotype of obesity that tends to accumulate adipose tissue in certain organs, including the airways. We must also learn whether certain adiposity distribution profiles have a more immediate proinflammatory effect on the lungs.

The BMI will certainly continue to play an important role in epidemiological studies of obesity (and consequently of obese asthma). But in the era of big data, detailed phenotyping, multiomics, gene editing, and machine-learning, we owe it to our patients to shift our focus to a more nuanced approach—one that better characterizes "obesity" and studies the specific profiles and characteristics of adipose tissue that lead to obese asthma. ■

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Use of Modeling to Inform Tuberculosis Elimination Strategies

Although the United States reported its lowest number of tuberculosis (TB) diagnoses in 2018 (2.8 cases per 100,000 persons), the decline in TB incidence has slowed in recent years (1) and the current pace of this decline is too slow to reach the national goal of TB elimination (defined as an annual incidence of less than one case per 1 million population [2]) within this century.

In a study presented in this issue of the *Journal*, Menzies and colleagues (pp. 356–365) compared three epidemiologic models to analyze the potential impact of different interventions in California, where 82.6% of individuals with TB in 2018 were born outside of the United States (3). Although the authors credit the successful implementation of TB control principles (e.g., early detection of active TB disease and prompt initiation and completion of appropriate therapy) for reducing TB incidence to historic lows in the United States, all three models show that in the absence of additional interventions, these activities alone will not be enough to significantly reduce TB incidence in the United States in the coming decades.

The authors provide a thoughtful and nuanced discussion about the role and utility of modeling, and their use of multiple modeling methodologies in this study helps to strengthen the impact of results that are concordant across the models. However, the authors also note the inherent limitations of these models in the absence of more robust data. Such an approach can also help individuals involved in TB control programs and policy makers better understand the implications and potential applications of these findings within their own local context.

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