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Obesity and asthma: the egg, the chicken, or both?

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The simultaneous rise in the epidemics of childhood asthma and obesity leading to a combined phenotype[1,2] has driven research trying to answer which comes first: obesity or asthma. Asthma is a chronic inflammatory disease of the airways that is characterized by episodes of wheezing, shortness of breath, and chest tightness, whereas obesity, also an inflammatory disease, is characterized by excess body fat. In part due to the complexity of these conditions, accurately predicting which comes first, or if the two conditions co-develop remains challenging. Ideally, to help defining the egg or the chicken, detailed assessments of obesity (e.g., measures that reflect growth, or fat composition and distribution) and asthma phenotypes (including longitudinal data from birth cohort studies) are posited to be useful.

Thus far, several studies have tried to solve the puzzle.[3-5] However, much of this work has been observational and cross-sectional in design. In addition, the definition of obesity and asthma is not consistent between studies, making it difficult to compare results and derive strong conclusions. In the existing literature, BMI, skin fold thickness, weight-for-age, and body fat percentage are often used as obesity markers. Yet, these markers, despite being similar on the surface, may represent different underlying physiological and metabolic processes. For example, weight-for-age may reflect a growth metric (e.g., birth weight may be used as a marker of intrauterine growth). Conversely, body fat percentage may be a measure of obesity or could represent an inflammatory trigger marker. Furthermore, it is recognized that differences in regional adiposity (e.g., visceral adiposity or skeletal mass) may have more relevance for asthma when compared to total body adiposity measures.[6] Similar issues exist for the definition of asthma. Although it is clear that there are different asthma endotypes, asthma is defined inconsistently throughout studies. The majority of studies define asthma based on the presence of wheezing in the last 12 months, and some require the presence of atopy or the support of lung function tests, or use a physician-diagnosis. The above heterogeneity makes it difficult to generate a clear understanding of the relationship between asthma and obesity.

To add to the complexity of the definitions, study designs, populations, and data analyses are also factors that often contribute to the inconsistent findings. While we know that there are sex[7-9] and ethnic[10] differences in asthma and obesity prevalence during different stages of development (e.g., puberty), sex- and age-stratified analyses are often neglected. Despite the heterogeneity in designs, populations, and analysis strategies, the data do suggest an association between asthma and obesity, two leading causes of chronic disease.

In this issue of the *Brazilian Journal of Pulmonology,* Weisshahn et al.[11] presented data from the longitudinal 1993 birth cohort in the city of Pelotas, Brazil. The authors explored obesity (defined by BMI cut-offs) and asthma (defined as wheezing in the last 12 months). They used bidirectional analyses with exposures collected at ages 11, 15, and 18 years, and outcomes measured at the age of 22 years. Overall, a bidirectional association was seen between obesity and asthma, with greater odds in the asthma-to-obesity direction, especially in females. The authors accounted for several covariates in their analyses (including parental history of asthma, birth weight, gestational age at birth, smoking, physical activity, use of corticosteroids, etc.) and speculate potential mechanisms to explain their findings. The authors also discussed similar analyses published before from their cohort at a younger age and revealed that obese adolescents have higher odds of wheezing. While the results from Weisshahn et al.[11] are very intriguing and add to the existing body of literature, future work will refine these observations.

Specifically, studies examining the obesity-asthma association would benefit from: a) longitudinal data collected from birth onwards; b) detailed phenotypes; c) an examination early in life for combined syndromes; d) samples defining inflammatory profiles/signatures; e) the use of artificial intelligence and machine learning approaches to define trajectories that lead to both asthma/wheezing and obesity. The future looks promising as longitudinal birth cohort studies offer datasets that will advance the understanding of early life trajectories and the evolution of asthma and obesity.[12,13]

While there are speculated and unanswered mechanisms about how obesity and asthma are linked, our CHILD Cohort Study[14] data suggest that traits of wheezing may be reflected by smaller lungs in part as a consequence of extra weight on airways,[15] which in addition might be triggered by or a trigger for inflammation. This last piece is supposition and needs a deeper look into acute or accumulated inflammatory markers (e.g., CRP and GlycA). It will be of interest to understand if acute inflammation can trigger asthma and obesity simultaneously, or if accumulation of inflammation triggers one of them first. Employing a life course approach to identify critical risk factors and pathways that alter an individual's physiology

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to increase the risks of asthma and obesity will ultimately translate into the development of early life interventions to promote lifelong health. So, which comes first, obesity or asthma? For now, we can say both.

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