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Leptin as a Predictor of Incident Asthma in Offspring of Obese Mothers

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Children with asthma around the world continue to suffer from diminished quality of life and frequent hospitalizations (1). Despite extensive research, the exact environmental and genetic mechanisms that give rise to childhood asthma remain poorly described. The majority of pediatric asthma cases present roughly in the first 5 years of life, suggesting that, in addition to genetics, *in utero* environmental factors likely contribute (2). For example, accumulating evidence suggests that maternal obesity during pregnancy, excessive gestational weight gain (3), and early childhood obesity are all closely linked and associate with development of childhood asthma (4–6). An estimated 25% of new asthma cases in obese children appear to be attributable to obesity (6). However, there is a lack of a clear understanding of the obesity-mediated mechanism(s) that underlie the association of maternal obesity and incident childhood asthma.

In this issue of *AnnalsATS*, Castro-Rodriguez and colleagues (pp. 1583–1589) address this gap in knowledge through an elegant study involving participants in the Maternal Obesity and Asthma birth cohort (7). This registered study (NCT02903134)

Supported by U.S. National Institutes of Health grant #HL141849.

DOI: 10.1513/AnnalsATS.202008-1000ED

was approved by the School of Medicine Ethics Committee of Pontificia Universidad Catolica de Chile and analyzed clinical and environmental factors and leptin levels at birth and age 30 months in more than 300 mothers and infants from the Hospital Sotero del Rio in Santiago, Chile. The researchers compared the risk of asthma predictive index positivity (definition of asthma risk) at 30 months of age according to maternal obesity status using logistic regression models. They found a nonsignificantly increased prevalence of asthma risk in infants born to obese mothers (16.8%) compared with those born to normal-weight (12.2%) and overweight mothers (14.7%) ($P = 0.18$). Offspring of obese mothers had higher cord blood leptin compared with infants of nonobese mothers, but this difference did not retain statistical significance at 30 months of age. Following adjusted analysis, infants born to obese mothers with elevated cord blood leptin were found to have a 30% increased asthma risk (adjusted odds ratio, 1.30; 95% confidence interval, 1.1–1.55; $P = 0.003$). Children of obese mothers also had a higher prevalence of bronchiolitis at 30 months, although they did not have more frequent neonatal complications or occurrence of atopic diseases by 30 months of age.

There are several analytic strengths of this prospective cohort study. The researchers used comprehensive longitudinal maternal and infant phenotyping, including gestational medications, smoking, and environmental exposures, and blood collection at birth (cord) and during infancy (30 mo), with detailed quantification of circulating immune and metabolic measures and adipokines. Clinical phenotyping was done on all offspring longitudinally in a concurrent manner every 6 months during infancy to age 30 months, allowing clarity around the temporal sequence of leptin and asthma diagnosis. Their design using concurrent (prospective) enrollment and comprehensive phenotyping also avoids selection bias at enrollment and the examination of multiple effects of the exposure of maternal obesity and cord leptin. Limitations of note include the fact that 30 months of age is a difficult time to reliably establish the diagnosis of persistent childhood asthma. Because childhood asthma cases also present after 30 months and reliable lung function testing is not yet feasible, significant false-positive and -negative predictions may result. It is intriguing that the 30% risk is very similar to the 25% risk found in a prior study that quantified the contribution of childhood obesity to incident asthma (6). The limitation of anthropometric data being available only for a small subset of infants limited the ability to assess the role of childhood obesity in mediating asthma risk, as a potential mechanism distinct from maternal obesity. Furthermore, the current study used a surrogate for asthma that is skewed toward identification of atopic asthma, although maternal obesity has been most closely associated with nonatopic asthma in offspring (3). Although the study is prospective in nature, observational studies of this kind without experimental manipulation are not able to establish causality. Therefore, one may speculate that leptin may exist within the mechanistic link connecting maternal obesity and asthma in offspring or it may simply be associated with other obesity-related causal mechanisms.

Leptin is known to be elevated in obese pregnant women and increases with gestational weight gain (8). Being a proinflammatory adipokine (9), leptin has been proposed to underlie several maternal obesity–mediated complications in the offspring, including immediate neonatal complications, such as sepsis and respiratory distress, and long-term effects such as incident obesity, diabetes, and cardiovascular disease (10). The findings by Castro-Rodriguez and colleagues (7) suggest a potential role of leptin in incident asthma in the offspring of obese women. However, few studies, primarily in murine models, have mechanistically linked leptin with neonatal or long-term complications in children of obese mothers (10).

From the perspective of pulmonary disease, leptin has many effects that may underlie the observations reported by Castro-Rodriguez and colleagues (11). Although the proinflammatory effect of leptin is one of the most commonly proposed mechanisms linking maternal obesity with neonatal and early childhood diseases (9, 11) Castro-Rodriguez and colleagues did not find substantive differences in immune markers among children born to obese as compared with normal-weight women at birth or at the 30-month follow-up time point. This negative finding highlights the need to investigate additional mechanisms that are mediated by leptin. For instance, leptin has neural effects and was found to influence airway caliber via cholinergic responses in murine models of obesity (12). Through its effect on pulmonary development (11), leptin may contribute to incident asthma by promoting lung dysanapsis (i.e., delayed airway caliber development relative to lung growth), proposed to be one of the explanations for pulmonary function deficits in obese children with asthma (13). Alternatively, leptin may be a surrogate measure for a pathway distinct from its direct effects. For example, leptin and insulin levels frequently correlate because leptin modulates satiety (14). Insulin resistance has been associated with pulmonary function deficits in both children and adults and mediates the association of nonallergic immune responses with pulmonary function deficits (15). These myriad direct and indirect effects of leptin highlight a need for mechanistic studies that investigate the specific and distinct mechanism(s) that directly link leptin with incident asthma in children.

Addressing the need for biomarkers to facilitate early identification of children at risk to develop asthma, the study by Castro-Rodriguez and colleagues, in conjunction with the prior literature, supports consideration of leptin as a biomarker of respiratory issues in offspring of obese mothers. Prior cross-sectional studies have linked leptin with asthma and pulmonary function deficits in children (16). The longitudinal finding from this study is suggestive of a causal link, although replicate work is needed (7). However, for convincing consideration of leptin as a biomarker, future studies that validate the links between maternal/cord blood leptin and incident asthma in childhood will benefit from investigation of the independent contribution of the child's body weight and inclusion of a mechanistic component investigating the mechanisms and pathways by which leptin may cause airway disease in children of obese mothers. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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On Baseball, Counterfactuals, and Measuring Care Delivery Performance at the Emergency Department—Intensive Care Unit Interface

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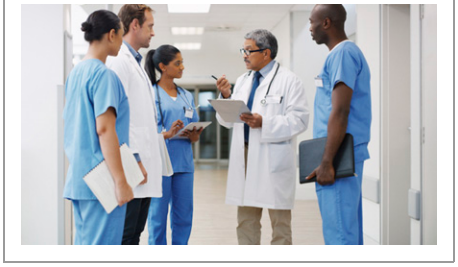
In professional baseball, despite use of videography and analytics to evaluate professional baseball players, it is difficult to measure fielders' performance accurately. Multiple factors underlie this challenge. First, most batted balls are either surefire "outs" (e.g., routine pop-ups) or surefire hits (e.g., home runs) (1). The remaining opportunities are spread among nine fielders, leaving each fielder few chances to move the needle of performance. Additionally, the dichotomous "out" lacks important counterfactual information. What differentiates "routine" from extraordinary outs or identifies the error of omission when a ball would have been caught, had the fielder been appropriately positioned?

An analogous challenge exists in measuring care delivery performance in and around the intensive care unit (ICU). Among the heterogeneous population of critically ill patients, many have syndromes that they are extremely likely (e.g., uncomplicated diabetic ketoacidosis) or extremely unlikely (e.g., advanced malignancy with multisystem organ failure) to survive. For remaining patients—whose trajectories and outcomes would be most strongly affected by different care delivery approaches—outcomes like mortality are necessary but insufficient to evaluate the performance of the ICU treating them (2). With few randomized trials of care delivery practices, sophisticated observational methodologies are needed to draw inferences regarding the utility of many care delivery interventions.

Together, these factors make it hard to interpret much observational and quality improvement data from the ICU. One approach to this challenge that has become increasingly popular in health services research is the quasiexperimental interrupted time series (ITS) design. ITS controls for temporal trends by comparing outcomes observed after an intervention



DOI: 10.1513/AnnalsATS.202008-951ED