

## Early-life weight gain, prematurity, and asthma development

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Early childhood asthma is a clinical syndrome, the development and clinical manifestations of which result from a complex interplay among airway anatomy, physiology, and inflammation. Although multiple phenotypes of early childhood wheezing and asthma have been described, the mechanisms that promote and differentiate these phenotypes remain poorly understood.

Over the past decade, substantial understanding has emerged as to the early-life factors that influence childhood asthma development. One area of great interest has been the relationships between patterns of fetal and infant growth, subsequent wheezing, and asthma. Although several studies strongly suggest that intrauterine growth patterns do not influence the risk of childhood wheezing or asthma,<sup>1,2</sup> Pike et al<sup>3</sup> noted an inverse association between fetal growth and risk of atopic wheeze by age 3 years. The relationship between birth weight and subsequent asthma is inconsistent, with studies finding absent,<sup>4</sup> inverse,<sup>5</sup> or positive<sup>6,7</sup> associations between birth weight and asthma. Postnatal weight gain in early life has consistently been identified as an important contributor to asthma risk,<sup>8</sup> with several large studies showing greater weight gain in infancy being associated with an increased risk for incident asthma. This was recently illustrated in a study of 12,050 subjects from 8 European birth cohorts, which reported that rapid growth in body mass index (BMI) during the first 2 years of life increased the risk of asthma up to 6 years of age,<sup>9</sup> with no additional effect of rapid BMI gains between 2 and 6 years of age.

In this issue of the *Journal*, Sonnenschein-van der Voort et al<sup>10</sup> advance our understanding of these associations through an analysis of more than 147,000 children participating in 31 European birth cohort studies. The occurrence of preschool (first 4 years of life) wheezing and asthma (between 5 and 10 years of age) was identified by using questionnaires adapted from the International Study on Asthma and Allergy in Childhood. The authors used random-effects meta-analysis on individual

participants' data and controlled for relevant factors, such as smoking during pregnancy, maternal asthma, day care attendance, and presence of siblings, as well as intermediates, such as breast-feeding and lower respiratory tract infections. Younger gestational age and greater weight gain during the first year of life were independent risk factors for any episodes of preschool wheeze and asthma at 5 to 10 years of age, and both demonstrated dose-response associations. Although birth weight was also inversely associated with asthma risk, this was explained by gestational age at birth. Children born preterm with high infant weight gain ( $\geq 700$  g/mo) had the highest risk of preschool wheezing (odds ratio, 3.27) and school-age asthma (odds ratio, 4.47) compared with children born at term ( $\geq 37$  weeks) with normal rates of weight gain (500-600 g/mo) during the first year of life. Although the authors adjusted for several important covariates in their analyses, residual confounding might persist because other factors that can influence asthma risk were not included, such as maternal BMI, type of delivery (vaginal vs surgical), birth length, neonatal course and complications, mechanical ventilation, antibiotic exposures, vitamin D status, and infections, such as chorioamnionitis. The populations studied were of European origin and comprised predominantly white children, limiting the generalizability of these findings to other ethnic groups. Asthma status was determined by using a variety of questionnaires, raising the possibility of misclassification of the asthma outcome, although sensitivity analyses, including studies that used the original International Study on Asthma and Allergy in Childhood questionnaire, were supportive of the overall findings. Furthermore, although the study focused on early-life weight gain, current weight status at school age was not considered.

The findings of Sonnenschein-van der Voort et al<sup>10</sup> strongly support an augmented risk of childhood wheeze and asthma among infants born prematurely.<sup>11</sup> There are several potential mechanisms that might underlie the link between premature birth and heightened asthma risk. Prematurity is a well-described risk factor for respiratory tract disease throughout childhood, with interruption of the normal process of lung development being a certain contributor. This disruption of lung development might lead to smaller and/or dysfunctional airways, lungs, or both, predisposing to subsequent lower respiratory tract disease. In addition, infants born prematurely experience multiple medical interventions, including endotracheal intubation, surfactant replacement, multiple infections and courses of antibiotics, and extended hospital courses, all of which might contribute to the heightened risk of subsequent airway disease. Chorioamnionitis is a major factor leading to preterm birth, and its occurrence has been associated with an increased risk of early childhood wheezing and asthma, especially among children with birth before 33 weeks' gestation.<sup>12</sup> Exposure to triggers of inflammation, such as significant perinatal infection, might lead to skewing

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of the infant's immune system toward a  $T_H2$ -dominant process, increasing the risk of subsequent allergic disease.

Accelerated infant weight gain is a risk factor for multiple diseases in later life, including asthma, cardiovascular disease, and type 2 diabetes mellitus.<sup>13</sup> Premature infants typically experience catch-up growth over the first year of life, potentially placing this population at even greater risk for these long-term health consequences. The mechanisms by which accelerated infant weight gain promote development of asthma phenotypes are likely multiple and might include factors related to the development of adiposity and its associated proinflammatory state.<sup>14</sup> Infant feeding practices appear to provide lifelong influence on the development of obesity and cardiometabolic disease through a variety of interconnected pathways.<sup>15</sup> Infants who consume human milk, which contains lower levels of energy and protein and higher fat content than formula, might experience slower rates of weight gain and appear to have lower risks of becoming overweight,<sup>16</sup> although the effects of exclusive breast-feeding on subsequent asthma risk are inconsistent.<sup>17</sup>

Recent findings related to the establishment and role of the human gut microbiota on the development of atopic diseases and asthma might also help explain the association of infant growth and asthma. The enteral microbiota becomes established during the first several years of life. Enteral microbiome composition differs between preterm and term infants, with infants born prematurely having lower enteral microbiome diversity than term infants after the first week of life.<sup>18</sup> Reduced diversity of the intestinal microbiota during infancy has been associated with an increased risk for allergic sensitization<sup>19</sup> and asthma at 7 years of age.<sup>20</sup> Environmental exposures, including infant feeding practices, substantially influence microbiota composition, as evidenced by formula and breast-fed infants differing in fecal microbiota structure.<sup>21</sup> Other perinatal factors can influence microbiota structure, including antibiotics. Administration of antibiotics to mice early in life induces changes in the microbiota, along with the development of adiposity.<sup>22</sup> The enteral microbiota differs between obese and lean adults, and transfer of fecal microbiota from human adult twins discordant for obesity into germ-free mice resulted in the microbiota from the obese donor leading to the mice becoming obese, whereas microbiota from the lean adult twin did not result in obesity.<sup>23</sup> In addition to the critical role of the enteral microbiota in the shaping of the immune system, it also appears capable of creating of a state of heightened adiposity and might serve as a potentially modifiable factor bridging early-life weight gain and asthma risk.

Accelerated infant weight gain is an antecedent to multiple long-term health consequences, including asthma. Although parents and health care providers of infants often focus on robust weight gain as a marker of health, there are negative aspects of the "chubby baby." Much attention has been paid to the role of obesity in later childhood and adulthood as a factor for asthma inception and morbidity. Recent work, highlighted by the findings of Sonnenschein-van der Voort and colleagues,<sup>10</sup> should serve as a reminder that obesity and asthma have their origins in early infancy. Close attention to and modification of infant feeding practices, particularly among children born prematurely, might help reduce the prevalence of asthma in childhood.

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