Growing large and fast: is infant growth relevant for the early origins of childhood asthma?

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Early growth seems to be important for the risk of respiratory diseases in childhood and adulthood. A recent meta-analysis reported that low birth weight is associated with impaired lung function and asthma in childhood, and that these associations are partly explained by gestational age at birth.[1] Low birth weight seems also associated with impaired lung function and increased risks of asthma and chronic obstructive airway disease in adulthood.[2] Although birth weight is an important early growth measure and may reflect early development, it has important limitations. Birth weight is the end point of fetal growth and the beginning of infant growth.

Different prospective cohort studies have recently been set up to disentangle the association of early growth with respiratory diseases at later ages. A prospective birth cohort study showed that a higher fetal crown–rump length in first trimester was associated with a lower risk of wheezing, asthma and higher lung volumes.[3 4] Also, a greater abdominal circumference during second half of pregnancy was associated with lower risk of atopic wheezing,[5] whereas a higher femur length in second trimester was associated with lower risk of asthma.[3] However, when individual fetal growth characteristics were combined into estimated fetal weight, associations of fetal weight growth with childhood wheezing or asthma were not consistent.[4 6 7] Restricted fetal weight growth was associated with higher respiratory resistance[6] and lower FEV_1 in childhood.[4] Thus, these findings are in line with the findings using birth weight as early growth measure. Increased fetal growth from early pregnancy onwards seems to lead to lower risks of respiratory diseases at later ages.

Studies that examined the combined effects of growth in both fetal life and infancy are scarce, but suggest that increased infant growth is associated with an increased risk of asthma symptoms in preschool children.[5 7] Most studies used weight measures for infant growth. To better understand how infant growth affects childhood asthma, knowledge is needed on more detailed and specific individual longitudinal infant weight and length growth measures. In *Thorax*, Popovic *et al*[8] examined the associations of three biologically interpretable weight growth measures, including size, weight gain velocity and age at peak weight velocity, with wheezing among 4492 children up to age 18 months participating in the NINFEA study, an internet-based birth cohort. Results showed that size and weight gain velocity, but not age at peak weight velocity, were both independently associated with an approximately 1.3-fold risk of wheezing between 6 and 12 months, and stronger when a more specific wheezing phenotype combined with asthma medication use as the outcome was used. Since wheezing in early life is not specific for asthma and could also be present in preterm or small for gestational age born infants with small airways, or in infants with respiratory tract infections, the authors performed sensitivity analyses excluding children born small for gestational age, or adjusted for respiratory tract infections. The results were not explained by these specific groups. Thus, their results suggest that growing large and fast in infancy could affect the risk of wheezing in early life.

In line with the study from Popovic *et al*, previous birth cohort studies showed that early persistent obesity[9] or rapid weight growth in the first 2 years[10] were associated with an up to twofold increased risk of asthma at school age. More specifically, rapid weight growth between 0 and 3 months seemed most consistently associated with increased risk of asthma, bronchial responsiveness and reversibility, and lower FEV_1/FVC and FEF_{75}/FVC ratios.[11] Peak weight velocity was associated with an up to 1.3-fold increased risk of wheezing or asthma up to age 10 years, and with lower lung function at 15 years, while peak height velocity seemed not associated with these outcomes.[12–15] The additional value of the current study is that size and velocity of infant weight growth, measured by a complex but carefully applied method, and their associations with wheezing were independently examined. This is important when studying underlying mechanisms for these associations, which might be different. Altogether, results of these studies strongly suggest that early infancy is a critical age window in which increased infant weight and weight gain velocity, possibly independent of fetal growth, could lead to the development of respiratory diseases at later ages.

The mechanisms by which infant growth affects respiratory outcomes at later ages are not well known. It has been suggested that adaptations related to infant growth and specifically alveolar growth, which partly appear in the first years after birth, affect the risk respiratory diseases. It could be hypothesised that the influence of increased infant weight on wheezing or asthma might be due to direct mechanical effects of intrathoracic and abdominal fat deposition leading to reduced pulmonary capacity or increased production of systemic proinflammatory mediators by fat tissue.[16] Increased infant weight gain velocity could lead to dysanapsis, a dissociation between somatic and pulmonary growth, which subsequently might lead to wheezing.

An important limitation of the study by Popovic *et al* is that causality cannot be directly inferred because of the observational design. Also, size and weight gain velocity could affect wheezing but reversed causation may be present. A cross-lagged modelling approach, taking potential directions of associations into account, and further longitudinal follow-up studies with respiratory outcomes at older ages might address this issue. It also remains of interest whether it is infant growth that affects the risk of wheezing or whether endocrine or inflammatory factors related to infant growth are more relevant for the development of wheezing. Infant growth could affect body composition such as fat mass index, android to gynoid fat ratio and abdominal fat.[17] Also, infant growth is mainly affected by child's diet. Detailed

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measurements of neonatal and infant body composition and diet might be better predictors for the development of wheezing. Infant growth is related to neonatal and fetal growth. The role of narrow or small airways in the neonatal period reflected by lower neonatal lung function[18] and detailed fetal weight trajectories, including fetal weight velocity and gestational age at peak fetal weight velocity, and their relation with infant growth and wheezing need to be elucidated.

The NINFEA study has made a welcome addition to the literature and supports the concept of using more detailed infant growth measures to better understand the origins of respiratory diseases focused on growth. Further long-term follow-up studies are needed to support the reported findings. Furthermore, identification of the mechanisms underlying the associations of early growth with respiratory health and disease throughout the life course is urgently needed to develop preventive strategies focused on pregnant women and their young children.

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