



Early weight gain and the development of asthma and atopy in children

Gustavo F. Wandalsen^a, Herberto J. Chong-Neto^b, Fabíola S. de Souza^{a,c}, Dirceu Solé^a, and Leonard B. Bacharier^{d,e}

Purpose of review

To provide perspective to the most recent evidence regarding the association between early weight gain in infancy and the development of asthma and atopy during childhood, and highlight the potential mechanisms involved.

Recent findings

Recently, several birth cohort studies involving more than 25 000 children have found a consistent association between early weight gain in the first 2 years of life and incident asthma during school age. Methodology differs substantially between the studies and complicates the establishment of definite conclusions. Specific mechanisms for this association have been proposed, including impairment in lung development and elevated levels of growth factors and cytokines associated with airway inflammation and remodeling. A limited number of studies indicate that early weight gain in infancy is also associated with recurrent wheezing during preschool age but not with the development of atopy.

Summary

A consistent association between early weight gain in infancy and incident asthma during school age has been observed in several cohort studies. The identification of this modifiable risk factor for the development of asthma opens the possibility of preventive intervention. Additional studies are necessary to clarify the involved mechanisms and some pending questions, such as the influence of early weight gain in asthma phenotypes and severity.

Keywords

asthma, children, obesity, weight gain, wheezing

INTRODUCTION

Both developed and nonaffluent countries clearly face epidemics of an overweight and obese populace. The WHO estimates that 35% of adults aged 20 or more have weight above expected [1]. Overweight status and obesity frequently starts early in life and it is estimated that more than 40 million children under the age of 5 years are overweight [2].

The parallel increases in the prevalence of both asthma and obesity observed during the last decades suggest a potential causal link and some shared environmental or genetic factor(s). At least two cross-sectional studies [3,4] in children and adolescents show a positive relationship between these two conditions. Obesity specifically has been associated with higher risk for the development of asthma [5], severe asthma [6], greater lung function impairment [7], and impaired response to asthma treatment [8].

Research on the relationship between somatic growth and asthma has focused largely on the associations with fetal growth and birth weight [9,10]. Recently, early-life events, particularly early nutrition and lifestyle factors, have been connected with later susceptibility to several chronic diseases [11–13]. Rapid weight gain at an early age has been consistently associated with subsequent risk of obesity in later life [14,15] and has also been related

^aFederal University of São Paulo, São Paulo, Brazil, ^bFederal University of Paraná, Curitiba, Brazil, ^cABC Medical School, Santo André, Brazil, ^dWashington University School of Medicine and ^eSt. Louis Children's Hospital, St. Louis, Missouri, USA

Correspondence to Gustavo F. Wandalsen, MD, PhD, Rua dos Otonis 725, São Paulo, SP 04025 002, Brazil. E-mail: gfwandalsen@unifesp.br; gfwandalsen@uol.com.br

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KEY POINTS

- A consistent association between early weight gain in infancy and incident asthma has been observed in several cohort studies involving more than 25 000 children. Early weight gain appears to have a modest effect on asthma incidence, increasing the asthma risk at school age up to 1.5 times.
- A limited number of studies have observed a positive association between early weight gain in infancy and recurrent wheezing during preschool age. One study has found that being overweight during infancy was associated with recurrent postbronchiolitis wheezing.
- There is no evidence to support an association between early weight gain in infancy and the development of atopy during childhood.
- Specific mechanisms involved in the relationship between early weight gain and asthma have been proposed, including impairment in lung development with reduction in lung function and elevated levels of growth factors and cytokines associated with airway inflammation and remodeling. These mechanisms still need to be better defined.

to hypertension, coronary heart disease, and type 2 diabetes mellitus [11,16].

The relationship between early weight gain and the development of asthma and atopy has received more attention in the last few years with an increasing number of prospective studies. The objective of this article is to provide perspective to the most recent evidence regarding these associations.

RELATIONSHIP BETWEEN EARLY WEIGHT GAIN AND ASTHMA OR WHEEZING: EPIDEMIOLOGICAL ASSOCIATIONS

Data from published studies generally indicate a positive association between early weight gain and the presence of asthma or wheezing during childhood. Methodological issues including the differences in duration of weight/growth follow-up and asthma-related outcomes might be responsible for difficulties in establishing a definitive conclusion regarding the association between early weight gain and asthma. Quantification of early weight gain in infants has no standard definition, and thus has been reported as either change in weight or in BMI. Studies [17[•],18,19,20[•],21^{••}] have evaluated early weight gain over several different periods of time during infancy, varying from the first 3 months to the first 2 years of life. Whereas rapid weight gain is commonly defined as change in weight z-score of more than 0.67 [17[•],18,19], several studies have analyzed weight gain or growth

differently, studying peak height and peak weight velocities [20[•]], BMI profile subgroups [21^{••}], or rates of weight and length/height gain [22]. In addition to the variability in the metrics for weight gain, assessment of respiratory outcomes also varies across the studies with the potential for misclassification. Parent report of medical diagnosis of asthma at school age has been the most frequently employed outcome [17[•],20[•],21^{••},22], but respiratory symptoms [19], lung function [17[•],18], and asthma exacerbations [18] have also been studied.

Recently, several cross-sectional and cohort studies, mainly from Europe, have examined the potential association between early weight gain and asthma or wheezing.

Sonnenschein-van der Voort *et al.* [19] followed a cohort of 5125 Dutch newborns up to the age of 4 years while monitoring fetal and infant growth during the first year of life. An International Study of Allergy and Asthma in Childhood (ISAAC)-adapted questionnaire was applied annually to parents asking about asthma symptoms. Rapid weight gain (z-score >0.67) in the first 3 months of life was significantly associated with higher risk of respiratory symptoms in the first 4 years of life such as wheezing {odds ratio [OR] [95% confidence interval (CI)]: 1.44 [1.2–1.7]}, dry cough [OR (95% CI): 1.16 (1.0–1.6)], and persistent phlegm [OR (95% CI): 1.30 (1.1–1.6)]. No association with respiratory symptoms was found for different patterns of fetal growth [19].

In another European study [20[•]], 9806 German children who participated in two birth cohorts (GINIplus and LISAPlus) were followed up until the age of 10 years. Weight gain during the first 2 years of life was studied by peak height and peak weight velocities. The risk of medical diagnosis of asthma increased significantly with each interquartile range increase in peak weight velocity [adjusted hazard ratio: 1.22 (1.0–1.5)] [20[•]]. No significant association was found between peak weight and height velocities and wheezing.

In a study by Rzehak *et al.* [21^{••}], data from eight European birth cohorts were combined, with 12 050 children followed up until 6 years of age. Three subpopulations of children were identified based on their BMI profile in the first 6 years of life. Children with early rapid growth (rapid BMI gain in the first 2 years but not after) had a significantly higher risk for incident asthma up to the age of 6 than those with a normal BMI gain [hazard ratio: 1.3 (1.1–1.5)] [21^{••}]. Interestingly, despite the higher prevalence of obesity or overweight, children with persistent rapid growth had a similar risk for incident asthma to those with early rapid growth. This might suggest that early rapid weight gain in infancy has a role in asthma development that is

independent from current obesity at the age of 6 years [21[■]].

In addition to evaluating the respiratory symptoms, Van der Gooten *et al.* [17[■]] also evaluated lung function (spirometry) at the end of 5 years' follow-up in 1431 children from a Dutch birth cohort. Wheezing in the first year of life was significantly more prevalent among those with rapid weight gain in the first 3 months of life (change in z-score >0.67) than those with normal or slow weight gain (39% vs. 34% and 24%, respectively) [17[■]]. At school age, every one-point z-score increase in early weight gain resulted in a 37% increase in days with wheeze and a 16% increase in medical visits because of wheezing. Each one-point z-score increase in early weight gain was also associated with significant decreases in forced expiratory volume in the first second (FEV₁) (−2.7%) and forced expiratory flow between 25% and 75% of forced vital capacity (FEF_{25–75%}) (−5.4%) [17[■]].

The PROBIT Study [22], an interventional trial conducted in the Republic of Belarus to promote and study breastfeeding effects on childhood health, reported data from 12 171 infants followed up until the age of 6 years. Asthma symptoms were investigated using ISAAC translated questionnaires. Although early weight gain was positively associated with ever having wheezed, no significant association was found between early weight gain and medical diagnosis of asthma or wheezing in the last year. However, current height and weight were more strongly associated with the development of atopic phenotypes [22]. The observed prevalence of asthma (1.2%) and asthma symptoms (3.1% of wheeze in the last year) were both quite low, and may have limited the statistical power and the generalizability of the findings [22].

A limited number of studies have evaluated the relationship between early weight gain and respiratory outcomes during infancy or preschool age. Two birth cohorts have followed up infants until the age of 3 years. A North American cohort with 932 children found that infants with higher weight-for-length z-scores (third and fourth quartiles) at 6 months of age had greater risks of recurrent wheezing by the age of 3 years [23]. In this study [23], each one-unit increment in weight-for-length z-score was associated with 1.46 greater odds of recurrent wheezing and 1.23 greater odds for any wheezing. In a Korean cohort with 422 children, those in the highest BMI tertile were at increased risk for respiratory symptoms [adjusted odds ratio (aOR): 3.68 (1.2–10.9)] when compared with those children in the middle tertile [24].

In a clinical trial involving 197 toddlers with high risk for asthma, early-life weight gain was not

associated with daily asthma symptoms or lung function after 3 years of follow-up [18]. Those children with a decelerated weight gain pattern had fewer prednisone courses and fewer urgent physician visits because of wheezing than those with an average or rapid weight gain. In a Brazilian cross-sectional study [25] involving 9159 infants, rapid weight gain in the first year of life was associated with significantly higher prevalence of recurrent wheezing, hospitalization for wheezing disorders, and medical diagnosis of asthma in first year of life.

EARLY WEIGHT GAIN AND THE DEVELOPMENT OF ATOPY

In contrast to the association between early weight gain and wheezing, the relationship between obesity and atopy in children remains uncertain [3,4]. Few studies have evaluated the association between weight gain in infancy or growth and the development of atopy.

In the United Kingdom, 1548 full-term infants were followed from birth to 3 years. Atopy at the age of 3 years was defined as skin prick test (SPT) reactivity to any allergen (cat, dog, house dust mite, milk, grass pollens, and egg) [26]. Atopic status was known for 1184 children (76%), and 199 children (17%) were atopic. Atopy risk was associated with greater crown-heel length at birth [relative risk (RR): 1.17], but not with prenatal head circumference growth, birth weight, or measures of postnatal growth velocity. Results were similar when sensitization to food allergens was excluded from the definition of atopy, and the authors concluded that postnatal growth and adiposity gain did not influence the RR of atopy [26].

Similar negative findings were reported in the PIAMA Dutch birth cohort [27]. At the end of 8 years' follow-up, sensitization to any inhalant allergen was not associated with change in BMI status between 1 and 2 years of life. In the PROBIT trial, the relationship between early weight gain and atopy was studied in 9772 children who had atopic evaluation at 6.5 years [22]. No evidence of consistent associations of infant to mid-childhood weight and length/height gain with atopy phenotypes was found, although there was weak evidence for an association of weight and length gain rate between 0 and 3 months with ever having allergic rhinitis [22].

EARLY WEIGHT GAIN AND POSTBRONCHIOLITIS WHEEZING

In a prospective study, 127 healthy full-term infants hospitalized in Finland for bronchiolitis at 0–6 months of age were followed for 12 months

after hospitalization. The aim was to evaluate birth weight, weight gain from birth to hospitalization, and weight at the end of follow-up assessed by weight for length (WFL) as risk factors for post-bronchiolitis wheezing by 1.5 years of age [28[¶]]. Increased WFL was uncommon in this cohort [$>110\%$ (overweight) in 11 of 127 children, $>120\%$ (obesity) in only 3 of 127 children]. Both occurrence and recurrence of postbronchiolitis wheezing were associated with birth weight greater than 4000 g vs. birth weight less than 4000 g. The recurrence of postbronchiolitis wheezing was also associated with WFL greater than 110% at the end of follow-up [28[¶]]. There was no association between weight gain and postbronchiolitis wheezing, but there was a significant association between weight gain before bronchiolitis and wheezing after bronchiolitis if the birth weight was greater than 4000 g. These findings provide evidence that birth weight greater than 4000 g may be associated with post-bronchiolitis wheezing at 0.5–1.5 years and that being overweight at 1.5 years was associated with recurrent postbronchiolitis wheezing by the age of 1.5 years [28[¶]].

POTENTIAL MECHANISMS

The mechanisms involved in the interconnections between asthma and obesity are complex and not fully understood. Genetic, hormonal, immunological, and mechanical factors might be involved [8]. Obesity is a state of chronic low-grade systemic inflammation, and inflammation has been described as an important mechanism in association with the two diseases [8,29]. All of these mechanisms may also be involved in the association between early-life weight gain and the development of asthma and respiratory symptoms, but other specific mechanisms have been suggested. Furthermore, in early life, several factors related to rapid weight gain can also act in the development of asthma, such as gene–environmental interactions, prenatal diet and nutrition, breastfeeding, maternal smoking during pregnancy, acquisition of adipose tissue, and changes in gut microbial flora [18,30].

Two independent studies [31,32] have found that higher rates of early infancy weight gain are associated with impaired lung development in normal infants. In a prospective Australian cohort, lung function of normal infants was evaluated at 1 and 12 months of age, and an inverse association between change in $V'_{\max FRC}$ and change in weight ($r: -0.18$; $P < 0.001$) was observed during the first year of life [31]. In this study [31], exclusive breast feeding until 6 months of life was associated with reductions in both weight gain and asthma

symptoms at 3 years of age. In a similar way, $FEV_{0.4}$ (adjusted for FVC) was found to be significantly related to infant weight gain during the first trimester of life in a cross-sectional European study [32], falling by 3.2% for each standard deviation increase in weight gain.

Accelerated postnatal weight gain can occur secondarily to high intake of growth-enhancing nutrients such as protein in the infant diet [12]. Higher protein intake in infancy is related to higher tissue and plasma levels of insulin and insulin-like growth factor (IGF)-I, important mediators in growth and adipogenesis in early life [33]. IGF-I is known to play a role in airway inflammation and remodeling [34,35]. In a murine asthma model, ovalbumin inhalation induced IGF-I expression at the airways, and the administration of IGF-I neutralizing antibody inhibited the elevation of airway resistance, airway inflammation, and airway wall thickening [36]. Early weight gain in infancy could also affect the lung development by elevated levels of adipokines. Leptin receptors are found in human lung tissue, and leptin may have stimulatory effects on lung growth [37].

CONCLUSION

A consistent association between early weight gain in infancy and incident asthma has been observed in several cohort studies involving more than 25 000 children. Early weight gain seems to have a modest effect on asthma incidence, increasing the asthma risk at school age by less than 1.5 times. This association seems to be independent of birth weight and has also been observed for recurrent wheezing during preschool age. Early weight gain in infancy does not appear to be associated with the development of atopy during childhood. Currently, there is no evidence that the increase in asthma incidence related to the early weight gain in infancy might be connected to atopy.

The identification of a modifiable risk factor (early rapid weight gain) for the development of a high prevalent chronic disease like asthma represents an exciting opportunity of interventional strategies and programs leading to asthma prevention.

Additional studies are necessary to clarify the pending questions regarding the association between early weight gain in infancy and the development of asthma. Mechanisms involved in this relationship should be better defined, and it is not yet clear whether there is a specific and critical period during infancy, such as the first 3 months of life, when rapid weight gain may confer the highest risk for future asthma. Early weight gain

in infancy may also affect asthma or wheezing severity, but outcomes of severity have been evaluated only in a very limited number of studies and no firm conclusion can be made at this time. The contribution of weight gain to specific asthma phenotypes, the role of sex differences, and the relationship with atopy also need to be investigated further.

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Conflicts of interest

G.F.W. has served as an advisor for Ache Pharmaceutical. H.J.C.-N. and F.S. de S. have no conflicts of interest to declare. D.S. a member of the board of Sanofi-Aventis. L.B.B. is a member of the Data Safety Monitoring Board for DBV, has received honoraria from Merck, Glaxo-SmithKline, and Teva, has served as an advisor for AstraZeneca, Merck, GlaxoSmithKline, BoehringerIngelheim, and Teva.

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- of special interest
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