Early growth characteristics and the risk of reduced lung function and asthma: A meta-analysis of 25,000 children

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Background: Children born preterm or with a small size for gestational age are at increased risk for childhood asthma.
Objective: We sought to assess the hypothesis that these associations are explained by reduced airway patency.

Methods: We used individual participant data of 24,938 children from 24 birth cohorts to examine and meta-analyze the associations of gestational age, size for gestational age, and infant weight gain with childhood lung function and asthma

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(age range, 3.9-19.1 years). Second, we explored whether these lung function outcomes mediated the associations of early growth characteristics with childhood asthma.
Results: Children born with a younger gestational age had a lower FEV_1, FEV_1/forced vital capacity (FVC) ratio, and forced expiratory volume after exhaling 75% of vital capacity (FEF_{75}), whereas those born with a smaller size for gestational age at birth had a lower FEV_1 but higher FEV_1/FVC ratio ($P < .05$). Greater infant weight gain was associated with higher FEV_1 but lower FEV_1/FVC ratio and FEF_{75} in childhood ($P < .05$). All associations were present across the full range and independent of other early-life growth characteristics. Preterm birth, low birth weight, and greater infant weight gain were associated with an increased risk of childhood asthma (pooled odds ratio, 1.34 [95% CI, 1.15-1.57], 1.32 [95% CI, 1.07-1.62], and 1.27 [95% CI, 1.21-1.34], respectively). Mediation analyses suggested that FEV_1, FEV_1/FVC ratio, and FEF_{75} might explain 7% (95% CI, 2% to 10%) to 45% (95% CI, 15% to 81%) of the associations between early growth characteristics and asthma.
Conclusions: Younger gestational age, smaller size for gestational age, and greater infant weight gain were across the full ranges associated with childhood lung function. These associations explain the risk of childhood asthma to a substantial extent. (J Allergy Clin Immunol 2015;■■■:■■■-■■■.)

Key words: *Preterm birth, low birth weight, infant growth, asthma, lung function, children, meta-analysis*

Children born extremely preterm or with a low birth weight have high rates of neonatal respiratory diseases, such as infant respiratory distress syndrome and bronchopulmonary dysplasia.[1] An accumulating body of evidence suggests that these children also have an increased risk of chronic obstructive respiratory diseases in adulthood.[2] Moreover, recent prospective studies in children suggest that preterm birth and small size for gestational age at birth increase the risk of childhood asthma.[3] Recent results of a meta-analysis of individual participant data of 147,000 children taking part in prospective birth cohort studies showed consistent associations of younger gestational age at birth and greater infant weight gain with childhood asthma.[4] The associations of lower birth weight with childhood asthma seemed to be largely explained by gestational age at birth.[4] The mechanisms underlying the associations of early growth characteristics with childhood asthma are not yet known.

Airway caliber is a key determinant of total airway resistance. A reduced airway caliber could result in airway obstruction that predisposes to asthma and chronic obstructive pulmonary diseases.[5-7] Therefore we hypothesized that the associations of early growth characteristics with childhood asthma might be explained by developmental adaptations of the lungs and airways, leading to relatively small airways and hence a reduction in expiratory flows reflected by lower lung function values.[8] Thus far, previous studies focused on the associations of birth weight and infant weight gain with childhood lung function have reported inconsistent results.[9-16] These inconsistent results might be due to the different ages at which spirometry was performed and not taking other early growth characteristics or potential confounders into account.

To test the hypothesis that the associations of early-life growth characteristics with childhood asthma are explained by reduced airway patency, we performed an individual participant data meta-analysis of 24,938 children from 24 birth cohort studies. We examined the strength, consistency, and independence of the associations of gestational age at birth, birth weight, and infant weight gain with lung function outcomes in childhood and whether these lung function outcomes explain the previously reported associations of early growth characteristics with the risk of childhood asthma.

Abbreviations used
ATS: American Thoracic Society
ERS: European Respiratory Society
FEF_{25-75}: Forced midexpiratory flow
FEF_{75}: Forced expiratory flow after exhaling 75% of the vital capacity
FVC: Forced vital capacity
GLI: Global Lung Initiative
SDS: SD score

METHODS

Data sources

European population–based birth and mother-child cohorts participated if they included children born between 1989 and 2011, had information available on at least gestational age and weight at birth and lung function measurements in childhood (until age 18 years), and were willing and able to exchange original data.[4] We identified 50 European cohorts selected from existing collaborations on childhood health or asthma-related outcomes (www.chicosproject.eu, www.birthcohortsenrieco.net, www.ga2len.org, and www.birthcohorts.net; accessed until May 29, 2012). In total, 24 cohorts comprising data on 24,938 children fulfilled the criteria (see supplemental information on Methods and Fig E1 in this article's Online Repository at www.jacionline.org).

Information about gestational age and weight at birth and weight in the first year of life was obtained by means of measurements, medical registries, or parental questionnaires (see Table E1 in this article's Online Repository at www.jacionline.org). We created gestational age–adjusted birth weight SD scores (SDSs) based on European reference values.[17] Infant weight gain in the first year was defined as the difference between weight at age 1 year (range, 6-18 months) and weight at birth divided by the number of months between these 2 measurements. SDSs for age-specific infant weight gain were derived by using intracohort means and SDs.[18] Cohort-specific growth characteristics are provided in Table E2 in this article's Online Repository at www.jacionline.org.

All cohorts obtained lung function measurements by using spirometry, of which 22 were according to the recent guidelines of the American Thoracic Society (ATS)/European Respiratory Society (ERS)[19-21] and 2 were according to earlier guidelines of the ATS[22] or ERS and European Coal and Steel Community[23] (see Table E1). If cohorts had collected lung function data at multiple time points (n = 6 cohorts), we used the measurement closest to the mean age of children (8.5 years) in the full meta-analysis. Variables for analyses were forced vital capacity (FVC), FEV_1, forced midexpiratory flow (FEF_{25-75}), and forced expiratory flow after exhaling 75% of vital capacity (FEF_{75}). We mainly focused on FEV_1, FEV_1/FVC ratio, and FEF_{75}, which reflect reduced airway patency in patients with obstructive lung diseases, such as asthma or bronchopulmonary dysplasia, associated with preterm birth or low birth weight.[24,25] All lung function variables were converted into sex-, height-, age-, and ethnicity (white vs nonwhite)–adjusted z scores based on Global Lung Initiative (GLI) reference values.[26] Asthma (yes/no) was defined as ever having physician-diagnosed asthma and was obtained by medical registries (2 cohorts) or parental questionnaires adapted from the International Study on Asthma and Allergy in Childhood (22 cohorts)[27] at the age of spirometry (see Table E1). Cohort-specific