Influence of childhood growth on asthma and lung function in adolescence

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Background: Low birth weight and rapid infant growth in early infancy are associated with increased risk of childhood asthma, but little is known about the role of postinfancy growth in asthmatic children.

Objectives: We sought to examine the associations of children's growth patterns with asthma, bronchial responsiveness, and lung function until adolescence.

Methods: Individual growth trajectories from birth until 10 years of age were estimated by using linear spline multilevel models for 9723 children participating in a population-based prospective cohort study. Current asthma at 8, 14, and 17 years of age was based on questionnaires. Lung function and bronchial responsiveness or reversibility were measured during clinic visits at 8 and 15 years of age.

Results: Rapid weight growth between 0 and 3 months of age was most consistently associated with increased risks of current asthma at the ages of 8 and 17 years, bronchial responsiveness at age 8 years, and bronchial reversibility at age 15 years. Rapid weight growth was associated with lung function values, with the strongest associations for weight gain between 3 and 7 years of age and higher forced vital capacity (FVC) and FEV_1 values at age 15 years (0.12 [95% CI, 0.08 to 0.17] and 0.11 [95% CI, 0.07 to 0.15], *z* score per SD, respectively) and weight growth between 0 and 3 months of age and lower FEV_1/FVC ratios at age 8 and 15 years (−0.13 [95% CI, −0.16 to −0.10] and −0.04 [95% CI, −0.07 to −0.01], *z* score per SD, respectively). Rapid length growth was associated with lower FVC and FVC_1 values at age 15 years.

Conclusion: Faster weight growth in early childhood is associated with asthma and bronchial hyperresponsiveness, and faster weight growth across childhood is associated with higher FVC and FEV_1 values. (J Allergy Clin Immunol 2015;135:1435-43.)

Key words: *ALSPAC, asthma, cohort study, growth, lung function*

Asthma is the most prevalent chronic respiratory disease in children worldwide.[1,2] Many factors have been associated with increased risk of asthma or lower lung function, such as gestational age, tobacco smoke exposure, breast-feeding habits, and a family history of asthma or allergy.[3-7] Respiratory morbidity might also be the result of abnormal growth. Fetal growth[8-10] and low birth weight[10-16] have been associated with asthma. Several studies have explored the associations of infant or childhood growth with the risk of asthma or lung function in later life.[10,17-26] They reported an increased risk of asthma symptoms in preschool children with accelerated growth in early infancy,[10,23] an increased incidence of asthma at 6 years after a rapid increase in body mass index in early childhood,[22] a lower $FEV_{0.4}$ value in the first months of life in children with greater postnatal weight gain,[21] and a negative association of growth with lung function during the first year of life.[27] However, other studies observed no evidence for increased risk of asthma caused by rapid growth[24] or observed that weight gain during the first year was positively associated with lung function.[19] These inconsistencies could be explained in part by methodological issues, including differences in the definitions of growth or asthma outcomes and adjustment for potential confounders.

It was suggested in a published study that growth in early infancy, especially from birth to 3 months,[10] might be an

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Abbreviations used
ALSPAC: Avon Longitudinal Study of Parents and Children
FEF_{25-75}: Forced expiratory flow between 25% and 75%
FVC: Forced vital capacity
OR: Odds ratio

important influence on asthma risk. However, it is unknown whether this association persists until adolescence or influences lung function, although tracking of lung function suggests that its trajectory is established by midchildhood.[20,28] It is also not known whether the first 3 months after birth is the only important time period or whether any specific period after the first year of age might play a role as well.

The underlying mechanism of the associations between growth and respiratory morbidity might include abnormal growth and development of the lungs or immunologic or inflammatory effects, such as adiposity-related systemic and tissue-specific inflammation.[29-33] To test our hypothesis that rapid early growth is negatively associated with respiratory health, we examined the association of children's growth trajectories from birth until age 10 years with current asthma, bronchial responsiveness or reversibility, and lung function in adolescence in a population-based prospective birth cohort study among 9723 children.

METHODS

Design and setting

Subjects were participants in the Avon Longitudinal Study of Parents and Children (ALSPAC) in the United Kingdom, which has been described previously[34] and on the study's Web site (www.bristol.ac.uk/alspac). In brief, 15,247 pregnant women residing in one of 3 Bristol-based health districts with an expected delivery date of between April 1, 1991, and December 31, 1992, were recruited and gave birth to 14,316 singleton children who were alive at the age of 1 year. Children with no information on either growth trajectories (n = 701) or any asthma outcome (n = 3,892) were excluded, leaving a total of 9,723 children included in the current analyses (see Fig E1 in this article's Online Repository at www.jacionline.org). Ethical approval for the study was obtained from the ALSPAC Law and Ethics Committee and local research ethics committees. Witten informed consent was obtained from all participants and their parents or guardians.

Growth trajectories

Height and weight measurements were available from birth up to age 10 years from a variety of sources (see the Methods section and Table E1 in this article's Online Repository at www.jacionline.org for full details). Linear spline multilevel models were used to estimate trajectories of height and weight. The models estimate mean and person-specific birth weight or length and mean and person-specific rates of weight or height growth between 0 and 3 months, 3 months and 1 year, 1 and 3 years, 3 and 7 years, and 7 and 10 years of age and are described in full elsewhere.[35] Early growth was defined as growth between birth and the age of 1 year, midchildhood growth as growth between the ages of 1 and 7 years, and late childhood growth as growth between 7 and 10 years of age. We generated SD scores (*z* scores) for birth weight and length and rate of weight/height growth in each period of childhood by subtracting the mean from the person-specific value and dividing by the SD. These SD scores for birth weight/length and rates of growth are used as exposures in our analyses.

Asthma and lung function

Current asthma status was obtained at the ages of 8, 14, and 17 years. Current asthma was defined as a reported doctor's diagnosis of asthma ever and reported wheezing, asthma, or use of asthma medication in the previous 12 months. Skin prick test reactivity was determined at the age of 7 years. A child was deemed to react to an allergen (grass, house dust, or cat) if their wheal and/or flare responses were 2 mm or greater and they had no reaction to the negative control. Bronchial hyperresponsiveness, unselected for asthma or wheezing, was measured at the ages of 8 and 15 years.[36] At age 8 years, we tested the provoking dose of methacholine causing a decrease in FEV_1 from baseline. The dose-response slope was calculated by fitting a linear function to the plot of percentage decrease from baseline. We dichotomized bronchial responsiveness using the highest tertile as responders and the rest as nonresponders. At age 15 years, we defined bronchial reversibility as a change of equal to or greater than 12% between FEV_1 before and after inhalation of a standard dose (400 μg) of salbutamol.[37] Spirometry (Vitalograph 2120; Vitalograph, Maids Moreton, United Kingdom) was performed at 8 and 15 years of age according to American Thoracic Society standards.[38] Lung function measurements (FEV_1, forced vital capacity [FVC], forced expiratory flow between 25% and 75% [FEF_{25-75}], FEV_1/FVC ratio, and FEF_{25-75}/FVC ratio) were converted into sex-, age-, and height-adjusted *z* scores (see Table E1 for time points of outcomes).[39]

Covariates

Maternal age, highest qualification, body mass index, parity, and a history of asthma or atopy were reported in questionnaires at 12 weeks of gestation, and smoking during pregnancy was assessed at 18 weeks of gestation by using self-completion questionnaires sent to the mothers. Maternal anxiety during pregnancy was measured at 32 weeks of pregnancy and was defined as the highest quartile of the Crown-Crisp Experiential Index.[40] Children's gestational age and sex were obtained from birth records. Breast-feeding status at age 8 months was obtained from maternal self-completion questionnaires.

Statistical analysis

We used logistic regression models to assess associations between growth trajectories and current asthma, atopy, and bronchial responsiveness or reversibility. Linear regression models were used to assess associations of growth trajectories with lung function measurements. Analyses were adjusted for potential confounders, including maternal age, body mass index, anxiety, education, history of asthma or atopy, smoking habits, parity, and the child's sex, gestational age at birth, and breast-feeding status. Models of weight gain were additionally adjusted for birth weight, and preceding rates of height-adjusted weight growth trajectories and models of height gain were additionally adjusted for preceding rates of height growth trajectories and birth weight. Models for current asthma or lung function were additionally adjusted for previous current asthma or lung function measurements. In addition, body mass index at the age of outcome assessment was added as an interaction to explore potential effect modification on the associations of childhood growth with asthma and lung function.

Missing data in confounders were imputed by using multiple imputations. Percentages of missing values within the population for analysis were lower than or near 10%, except for maternal body mass index (13.1%), anxiety (13.6%), and child's breast-feeding duration (11.5%). Ten new data sets were created by means of imputation based on all covariates, determinants, and outcomes in the model.[41] All data sets were analyzed separately, after which results were combined. No differences in results were observed between analyses with imputed missing data or complete cases only. Therefore we present only results based on imputed data sets. Statistical analyses were performed with the Statistical Package of Social Sciences version 19.0 for Windows (SPSS, Chicago, Ill).

RESULTS

Characteristics of mothers and their children are presented in Table I. Children were born at a median gestational age of 40 weeks (95% range, 35-42 weeks), with an average birth weight of 3436 grams (SD, 524 grams). Current asthma was reported in 13.9%, 13.2%, and 15.3% of the children at the age of 8, 14, and 17 years. All covariates differed between those included