Asthma

RISK FACTORS

Distinct Immune Phenotypes in Infants Developing Asthma During Childhood

PURPOSE OF THE STUDY: To address whether a deregulated immune response to generic microbial exposures in infancy is associated with later development of asthma.

STUDY POPULATION: In this population-based birth cohort, children at 18 months of age had blood samples were analyzed by flow cytometry (n = 552) and ex vivo stimulation (n = 567), resulting in a total of 541 infants with combined data.

METHODS: Flow cytometry was used to detect relative frequencies of 18 cell subtypes. Whole blood was stimulated for 24 hours with 7 microbial-derived ligands, and 21 cytokines were measured. Using hierarchical clustering techniques, infants were grouped according to similar cytokine responses to identify relationships between innate immune response phenotypes and development of childhood asthma.

RESULTS: In 18-month-old infants, 5–7 different immune response phenotypes were identified. The overall prevalence of asthma was 23% (127 of 541). At age 6 years, 16% had outgrown their asthma diagnosis, which was termed transient asthma, whereas asthma persisted in 7% of children at age 6 years. Infants who developed transient asthma had antiviral responses associated with type 17 cytokine enhancement without concomitant type 1 immune activation. Infants who developed persistent asthma at 6 years of age showed enhanced Th2 responses (IL-5 and IL-13).

CONCLUSIONS: This study of 18-month-old infants demonstrated distinct antiviral, antibacterial, and T cell response phenotypes that were linked to transient or persistent asthma during the first 6 years of life. Inadequate immune response to single-stranded RNA viruses may be a risk factor for the development of transient asthma whereas enhanced Th2 responses may increase risk for development of persistent childhood asthma.

REVIEWER COMMENTS: With the development of targeted biological therapies, personalized medicine is achievable. This, however, requires a sophisticated understanding of asthma characteristics. Traditional asthma phenotyping, which is a description of observable characteristics, does not provide insight regarding underlying mechanisms of disease and is thus of limited utility in predicting response to therapy. In contrast, asthma endotyping characterizes groups based on functional or pathophysiological mechanisms. Defining innate immune responses in at-risk infants, as shown in this study, could therefore help to identify asthma endotypes and to guide personalized strategies for asthma treatment and prevention.

Effects of Age, Sex, Race/Ethnicity, and Allergy Status in Obesity-Related Pediatric Asthma

PURPOSE OF THE STUDY: To determine the relationship between obesity and asthma incidence and assess the impact of age, gender, race/ethnicity and allergic status.

STUDY POPULATION: The study included 507,496 children ages 2–17 years. Children without a history of asthma prior to the pre-defined study start date were included and overweight or obese children were 1:1 matched with healthy weight children.

METHODS: This was a large retrospective cohort study from 8 Pediatric institutions in the United States that were a part of PEDSNet (National Pediatric Clinical Network for Research), utilizing data through the Observational Health Data Sciences and Informatics (OHDSI) common data model from January 2009 to December 2015. Children were stratified 2–6 years, 7–11 years, and 12–17 years. Children with a BMI ≥95th percentile were categorized as obese. Asthma incidence was defined as ≥2 asthma encounters and ≥1 asthma prescription, and a subset included spirometry. Adjusted incident asthma rates and risk ratios were estimated by multivariate Poisson regression (adjusted for race, ethnicity and gender).

RESULTS: The risk of incident asthma was higher among obese children in all the age-groups as compared with children with healthy weights [age 2–7 years: RR 1.24 (95% CI 1.14–1.36); age 7–11 years: RR 1.45 (95% CI 1.29–1.64); and 12–17 years: RR 1.35 (95% CI 1.16–1.56)]. Children with no underlying allergic rhinitis had an increased risk of asthma across all age-groups [age 2–7 years: RR 1.25 (95% CI 1.15–1.37); age 7–11 years: RR 1.50 (95% CI 1.33–1.69); and 12–17 years: RR 1.40 (95% CI 1.21–1.63)], but this effect was not seen among children with an underlying allergic rhinitis diagnosis. Additionally, among younger children <12 years, obese females had a higher risk of asthma whereas among older children, the higher risk was seen among obese males.

CONCLUSIONS: Obesity is a preventable risk factor for asthma, especially among non-allergic children, and interventions to reduce obesity in the pediatric population need to be addressed as a public health priority.

REVIEWER COMMENTS: This is the largest study to date looking at the impact of pediatric onset obesity on the development
of asthma, despite limitations of a retrospective observational design. With the rising prevalence of obesity and the substantial impact of asthma on emergency department visits, hospitalizations and quality of life in children, there is a need to identify potentially modifiable factors for the development of asthma. This study identifies obesity as a risk factor across all age groups for the development of asthma but more importantly, highlights the differential effect among allergic and nonallergic children as well as the risk differences by sex and age. This points to the heterogeneity of asthma phenotypes in children that are likely a result of these different endophenotypes in children with underlying obesity and atopy, potentially raising questions about optimal treatment strategies in these different groups. Identification of a potentially modifiable risk factor provides opportunities to impact the lives of children, and further studies are needed to determine if early life interventions may prevent the subsequent development of asthma.

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**Early Pubertal Maturation and Risk of Childhood Asthma: A Mendelian Randomization and Longitudinal Study**


**PURPOSE OF THE STUDY:** To explore the correlation, if any, between precocious puberty on the incidence of asthma and any combined effect of early puberty and being overweight.

**STUDY POPULATION:** The data were obtained using the Taiwan Children Health Study of children 11–17 years old (2991 children).

**METHODS:** Parents, or patients themselves if they were 17 years old, completed a questionnaire to classify the child’s asthma. Staging of puberty was performed in 112 patients; 12-year-old children were assessed using a questionnaire and definitions were derived using the Tanner composite stage (TDCS). If a child met a certain pubertal stage earlier than the median age for that developmental stage, they were classified as having early pubertal maturation. To calculate the incidence of asthma, children with history of asthma prior to the age of 12 were excluded. Children were classified as overweight if their calculated BMI was ≥ 85th percentile. Using findings from a prior meta-analysis of genome wide association studies, 6 single nucleotide polymorphisms (SNPs) associated with early pubertal maturation were used for Mendelian randomization (MR) analysis. Longitudinal follow up survey was conducted at 17 years of age to assess for new onset asthma and the temporal relation to onset of puberty.

**RESULTS:** When evaluating both genders together, early pubertal maturation was associated with increased risk of asthma history, current wheeze, and active asthma. A statistically significant increased risk of active asthma in male adolescents was seen in those with early pubertal maturation (OR=1.38, 95% CI: 1.01–1.90). Furthermore, there was a statistically significant increased risk of new-onset physician diagnosed asthma (HR 1.57, 95% CI: 1.08–2.28) and incident current wheeze in the past 12 months (HR 2.15, 95% CI: 1.21–3.84) in children with early pubertal maturation. There was an increased risk of incident current wheeze in male adolescents with early puberty (HR 2.63, 95% CI: 1.27–5.34) and incident risk physician-diagnosed asthma in female adolescents with early puberty (HR 2.05, 95% CI: 1.10–3.82). Children who were defined as overweight and having early pubertal maturation had a statistically significant increased risk of physician-diagnosed asthma (OR 1.08, 95% CI: 1.04–1.11) and current wheeze (OR 1.04, 95% CI: 1.02–1.07).

**CONCLUSIONS:** There is a synergistic effect of early puberty and obesity on the development of asthma in both genders.

**REVIEWER COMMENTS:** This study concluded that early pubertal maturation increases risk of asthma in male and female children with weight playing a synergistic role. This study highlights 3 commonly encountered conditions in the general pediatric practice: asthma, overweightness or obesity, and precocious puberty. Clinicians should consider screening for each condition when one of these is present.

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**Lung Computational Models and the Role of the Small Airways in Asthma**


**PURPOSE OF THE STUDY:** Asthma is an inflammatory disease that affects the entire airway. Although there is increasing recognition of the role that small airways play in asthma, measuring small airway inflammation has been challenging. Forced oscillation technique–derived resistance (FOT) at 5 Hz (R5) to 20 Hz (R20) has been shown to correlate with small airway inflammation. The purpose of this study is to further validate the use of forced oscillation R5–R20 as a measurement of small airway narrowing and investigate the impact of small airway narrowing on asthma control and quality of life.