suggests that obesity is not causative for asthma per se but likely an important inflammatory modifier. Previous studies suggest that leptin, an adipocyte-derived hormone, may upregulate inflammatory immune responses in general and thus could amplify asthma, a chronic inflammatory airway disease. This study also documented an increased risk of sensitization to inhalant allergens among children with a high BMI at 7 years; this association was not seen for food allergens. Although not proved in this study, it is also plausible leptin could play an important role in this pathway through hormone-specific receptors on a variety of cells, including eosinophils.


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Obesity-Associated Asthma in Children: A Distinct Entity

PURPOSE OF THE STUDY. To evaluate the underlying mechanisms in obesity-associated asthma in children.

STUDY POPULATION. One hundred twenty children 7 to 11 years of age were enrolled and assigned to 4 different groups: (1) obese asthmatic children, (2) atopic nonobese asthmatic children, (3) obese nonasthmatic children, and (4) nonobese, nonasthmatic children.

METHODS. All children performed pulmonary function testing, and anthropometric data were obtained. Asthma severity was classified based on daytime and nighttime symptoms, exercise limitation, and albuterol use (parental report). Blood was obtained for serum cytokines, T-cell responses to mitogen and allergen, and phenotyping.

RESULTS. Serum interleukin (IL)-4 and IL-13 levels were higher among nonobese asthmatic children, consistent with a T-helper (Th)2 phenotype of atopic asthma. In contrast, obese asthmatic children had lower levels of IL-13 and higher levels of tumor necrosis factor-α and IL-6, consistent with a Th1 phenotype. Obese asthmatic children had higher Th1 response to phorbol 12-myristate 13-acetate and tetanus and lower Th2 responses to phorbol 12-myristate 13-acetate and dust mite allergen compared to nonobese asthmatic children. The Th pattern did not differ between obese asthmatic children and obese nonasthmatic children. Spirometric data were within the normal range in all 4 study groups. However, the forced expiratory volume in 1 second/forced vital capacity ratio was lower in obese asthmatic children compared with the other asthmatic children.

CONCLUSIONS. Obese asthmatic children exhibited a Th1 polarization in contrast to the Th2 polarization seen in atopic childhood asthma. The Th1 response did not differ between obese asthmatic children and obese nonasthmatic children. This suggests that obese asthmatic children exhibit a systemic Th1 polarization that may be modulated more by obesity and less by their asthma.

REVIEWER COMMENTS. Obesity-associated asthma has been proposed as a distinct entity, and this is one of the first studies to try to characterize the underlying mechanism and compare them to atopic asthma in children. Given the obesity epidemic facing our children, understanding these differences can be helpful in treating this population. Given the fact that the inflammation seems to be influenced more by the obesity itself, addressing the obesity may be a major therapeutic intervention to treat obese asthmatic patients.

Prevalence of Asthma and Its Association With Glycemic Control Among Youth With Diabetes

PURPOSE OF THE STUDY. To estimate the prevalence of asthma among children with types 1 and 2 diabetes and examine associations between asthma and glycemic control.

STUDY POPULATION. Children diagnosed with type 1 (N = 1683) and type 2 (N = 311) diabetes from 2002 to 2005 as part of the SEARCH for Diabetes in Youth study.

METHODS. Asthma status and medications were determined from medical records and self-administered questionnaires, and glycemic control was assessed from hemoglobin A1c measured during study visits.

RESULTS. The prevalence of asthma in all children with diabetes was 10.9% (95% confidence interval [CI], 9.6%–12.3%). The prevalence was 10% (95% CI, 8.6%–11.4%) among children with type 1 and 16.1% (95% CI, 12.0%–20.2%) among children with type 2 diabetes and differed by race/ethnicity. Among children with type 1 diabetes, higher mean A1c levels were observed in asthmatics versus nonasthmatics after adjustment for age, gender, race/ethnicity, and BMI (7.77% vs 7.49%, P = .034). Youth with asthma were more likely to have poor glycemic control, particularly those with type 1 diabetes whose asthma was not treated with routine pharmacotherapy.

CONCLUSIONS. The prevalence of asthma may be elevated in children with diabetes relative to the general US population. In children with type 1 diabetes, asthma is associated with poor glycemic control, especially if asthma is not treated with antiinflammatory medications.

REVIEWER COMMENTS. This study further explores the complex relationships between systemic inflammatory diseases...
including obesity and both asthma and diabetes. The association between type 2 diabetes and asthma is not surprising as a high proportion of youth were overweight or obese (90.6%) and the linkage between asthma and increased BMI is well described in many studies. It is interesting to note that children whose asthma was treated with leukotriene modifiers, alone or in combination with inhaled corticosteroids or rescue inhalers, had the lowest prevalence of poor glycemic control; in fact, 72% had good glycemic control. The authors speculate that this could be because leukotriene synthesis or receptor blockers may help reduce the systemic inflammation present in both obesity and diabetes as well as the direct effect on ameliorating airway inflammation.

DNA Hypomethylation at ALOX12 Is Associated With Persistent Wheezing in Childhood

PURPOSE OF THE STUDY. To determine if epigenetic changes play a role in asthma phenotypes.

STUDY POPULATION. There were 2 groups studied, both involved children enrolled from pregnancy cohorts. The first group (Menorca cohort) was 122 children with data available through age 6 years. The second group (Sabadell cohort) was 236 children with available DNA extracted from whole cord blood.

METHODS. Children were assigned wheezing phenotypes at age 4 to 6 years based on validated questionnaires (never, transient, late-onset, or persistent wheezing). Prenatal exposure data were collected through questionnaire and by measuring for presence of a specific pollutant, dichlorodiphenyldichloroethane, in cord blood.

RESULTS. DNA hypomethylation was associated with increased risk for persistent wheezing in both studies, although only 1 of the 2 was statistically significant (Menorca: odds ratio 1.13, 95% confidence interval 0.99–1.29, \( P = .077 \); Sabadell: odds ratio 1.16, 95% confidence interval 1.03–1.37, \( P = .017 \)). Higher levels of dichlorodiphenyldichloroethane were associated with hypomethylation of ALOX12 in the Menorca study (\( P = .033 \), but not the Sabadell study (\( P = .377 \)). Level of methylation at ALOX12 was strongly influenced by polymorphisms in the gene.

CONCLUSIONS. DNA hypomethylation at ALOX12 was associated with a higher risk of persistent wheezing. This may be an epigenetic biomarker that predicts increased likelihood of persistent wheezing in childhood.

Identification of IL6R and Chromosome 11q13.5 as Risk Loci for Asthma

PURPOSE OF THE STUDY. To identify novel genetic variations imputing asthma risk.

STUDY POPULATION. Pediatric and adult Australians of European descent consisting of 2669 asthmatic subjects (28% diagnosed by clinical examination, 54% childhood onset, 59% atopic) and 4528 controls (40% with unknown asthma status) produced candidate asthma genetic variations. Meta-analysis of 12 475 physician-diagnosed asthmatic subjects and 19 967 controls provided a prioritization cohort. Four additional individual cohorts totaling 3322 asthmatic subjects and 22 036 controls provided replication.

METHODS. Microarray-derived genotypes of Australian asthmatic subjects and controls underwent a genome-wide association study to produce asthma candidate loci. Meta-analysis using unique adult Australian and previously published GABRIEL genotypes prioritized candidate novel genetic loci. The prioritized, novel genetic loci endured replication analysis via 4 individual cohorts and a combined meta-analysis. A genomic phenotype prediction model for asthma was produced and subsequently tested. Secondary analysis considered asthma and other immune disease associations.

RESULTS. Two novel loci were significantly associated with asthma risk. The interleukin-6 receptor (IL6R) loci on chromosome 1q21.3 associated more significantly (odds ratio [OR] = 1.09, \( P = .0033 \)) than the indeterminate loci (rs7130588) at chromosome 11q13.5 (OR = 1.07, \( P = .328 \)) in the replication cohorts. However, when considering all available data, 1q21.3 and 11q13.5 both demonstrated very significant asthma association (\( OR = 1.09, P = 2.3 \times 10^{-8} \) and OR = 1.09, \( P = 1.8 \times 10^{-8} \), respectively). Secondary analyses of 11q13.5 revealed an association with atopy and no asthma risk association.
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