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Perinatal factors and the development of childhood asthma

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ABSTRACT

Background: Perinatal factors are suspected to have a significant impact on the development of asthma; however, sufficiently powered studies have not been performed to investigate this issue.
Objective: To evaluate whether perinatal factors and other risk factors have an independent or combined effect on the development of asthma.
Methods: This study involved 3,770 children (mean age 9.1 years, range 5.68–12.16 years; 51.9% boys) who were enrolled in the Elementary School Student Cohort (2009–2014) in Ulsan University Hospital (Ulsan, Korea). Subjects were divided into an asthma group (n = 514) and a non-asthma group (n = 3,256).
Results: Multivariate analyses showed that early life (within first week) oxygen therapy (adjusted odds ratio [aOR] 1.864, 95% confidence interval [CI] 1.156–3.004) and breastfeeding (aOR 0.763, 95% CI 0.606–0.960) were 2 significant perinatal factors influencing the development of asthma. Environmental tobacco smoke (aOR 1.634, 95% CI 1.298–2.058) and parental allergic disease (aOR 1.882, 95% CI 1.521–2.328) also were identified as risk factors. Using subgroup analyses, combined effects on asthma development were observed between perinatal factors (early life oxygen therapy and breastfeeding) and other risk factors (vicinity to major roadway [traffic-related air pollution], environmental tobacco smoke, parental allergic disease, and atopy).
Conclusion: Early life oxygen therapy and breastfeeding were identified as 2 important perinatal factors influencing the development of asthma. Furthermore, these factors showed combined effects with other risk factors (environmental tobacco smoke, traffic-related air pollution, parental allergic disease, and atopy) on the development of asthma.

Introduction

Asthma is a serious health problem worldwide. There are approximately 334 million patients with asthma globally, and its prevalence ranges from 1% to 16%.[1] Further, asthma is the most common chronic disease in children, and the prevalence of childhood asthma has increased during the past 30 years.[1,2]

Asthma is caused by a combination of genetic predisposition and environmental factors. Although there is clear evidence that genetic predisposition contributes to the development of asthma, the rapid increase in its prevalence during the past 30 years suggests that environmental factors play a more crucial role.[2,3] Previously known environmental risk factors for asthma development include environmental tobacco smoke (ETS), air pollution, Westernized living conditions, dietary habits, allergen exposure, obesity, pet breeding, and the use of antibiotics in the first year of life.[2,4]

To date, however, most studies evaluating risk factors for the development of asthma have been limited to life events occurring long after birth. In fact, from the moment of conception, humans are affected by various environmental factors. Fortunately, active research is investigating various environmental risk factors for asthma development that are present in utero or during the perinatal period.[5–7]

The role of perinatal risk factors in the development of asthma is not firmly established. Although preterm birth,[8–10] low birth weight,[11,12] cesarean section,[11,12] general anesthesia,[13] respiratory distress syndrome (RDS),[14,15] transient tachypnea of the newborn (TTN),[15,16] and meconium aspiration syndrome (MAS)[17] have been associated with the development of asthma, the number of studies is small and in some factors the results are inconsistent; therefore, further researches are needed. Recently, interesting studies investigating synergistic mechanisms of perinatal factors in the development of asthma have been published.[8–10] According to these

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studies, perinatal factors alone have little to no impact on the development of asthma or confer only a slight increase in risk. However, in the presence of associated risk factors, such as prematurity plus chorioamnionitis, prematurity plus atopy, or prematurity plus maternal smoking during pregnancy, the risk for asthma dramatically increases.[8–10] In other words, perinatal factors alone (eg, prematurity) are not significant risk factors for asthma development. However, simultaneous exposure to other risk factors (eg, atopy) could affect asthma development.

With these considerations, we hypothesized that perinatal factors would be associated with the development of asthma; however, this association would depend on exposure to other risk factors. The objective of the present study was to evaluate whether perinatal factors and other risk factors have an independent or combined effect on the development of asthma.

Methods

Study Participants

Subjects included 3,770 children (mean age 9.1 years, range 5.68–12.16 years; 51.9% boys) who were enrolled in the Elementary School Students Cohort (2009–2014) for Identifying Environmental Factors of Allergic Disease in the Atopy Environmental Health Center of Ulsan University Hospital (Ulsan, Korea).[18,19] The study participants were recruited from 3 elementary schools in Ulsan. Parental consent was obtained before enrollment. This study was approved by the institutional ethics review committee of Ulsan University Hospital (approval number 2009-09-061-011). At the time of enrollment, the subjects were examined by a detailed questionnaire and laboratory tests.

The questionnaires used in this study included International Society of Asthma and Allergy of Children (ISAAC) survey items.[20] Various asthma-related outcomes were gathered using the following questions: previously diagnosed with asthma (ie, asthma ever diagnosis): "Has your child ever been diagnosed with asthma by a physician?"; ever experienced wheeze (ie, ever wheezing): "Has your child ever experienced wheezing or whistling in chest?"; and current (<1 year) wheezing: "Has your child experienced wheezing or whistling in chest in the past 12 months?" In the present study, asthma was defined as physician-diagnosed asthma (ie, ever diagnosis) or wheeze in the prior year (ie, current wheezing).[21–24] Accordingly, subjects were divided into an asthma group (n = 514) and a non-asthma group (n = 3,256). Demographic information, including sex, age, height, and weight, were collected. Parental socioeconomic data, including monthly household income, parental education, birth order, and parental asthma and allergic diseases, also were gathered. Perinatal factors, including birth weight (low birth weight [< 2.5 kg] or ≥2.5 kg), delivery method (cesarean section or vaginal delivery), gestational age (preterm [< 37 weeks] or term), oxygen therapy in the first week after birth, breastfeeding (any or not at all), and a history of general anesthesia before 1 year of age, were collected. These data were collected using the following questions: "Was your child born with a low birth weight?"; "What was the delivery method of your child?"; "Was your child premature?"; "Did your child undergo oxygen therapy in first week after birth?"; "Did your child consume breast milk (including colostrum)?"; "Has your child ever undergone general anesthesia before 1 year of age?" Any current exposure to ETS, vicinity to a major roadway, and exposure to traffic exhaust were obtained as environmental factors. Any current exposure to ETS was identified using the following question: "Is there any chance that your child is exposed to someone else's cigarette smoke?" Vicinity to a major roadway and exposure to traffic exhaust were identified as parameters of traffic-related air pollution. These items were examined using the following questions: "How far is the nearest major roadway for the city bus from the house in which you live?"; "How much traffic do you have on the adjacent roads described above?"

Blood levels of eosinophils and immunoglobulin E (IgE) were examined. Forced expiratory volume in 1 second and forced vital capacity data were collected using forced spirometry[25] and percentage of predicted values were calculated.[26] The presence of atopy was confirmed using the skin allergy reaction test. The allergens examined included *Dermatophagoides pteronyssinus, Dermatophagoides farinae,* tree pollen mixtures, grass pollen mixtures, ragweed, mugwort, cat fur, dog fur, cockroach, *Aspergillus* species, *Alternaria* species, and other fungus mixtures (Allergopharma, Darmstadt, Germany). If any positive response was found for the skin test, then the subject was defined as having atopy.[27]

Statistical Analysis

SPSS 21 (IBM Corporation, Armonk, New York) was used for statistical analyses. The independent t test and χ^2 test were used to analyze baseline differences. Univariate and multivariate analyses were performed to determine possible relations between the variables and asthma development. Multivariate logistic regression analyses were performed using variables found to be significant (ie, $P < .05$) in the univariate analysis and those reported to be associated with asthma development in previous studies. Age, sex, body mass index, ETS, air pollution factor (vicinity to a major roadway), monthly household income, parental education level, birth order, presence of parental allergic disease, delivery method, low birth weight, prematurity, oxygen therapy in first week after birth, breastfeeding, eosinophil and IgE levels, forced expiratory volume in 1 second, and atopy were adopted for adjustment.[2,4] In addition, significant perinatal factors identified as independent risk factors in multivariate analyses were further investigated by subgroup analyses to identify the presence of a combined effect with other risk factors on various asthma-related outcomes (such as overall asthma development, ever diagnosis of asthma, ever wheezing, ever diagnosis and current wheezing, and current wheezing). In the subgroup analyses, adjustments were made to the same variables in the multivariate analysis except variables needed to differentiate subgroups. A P value less than .05 was considered statistically significant in all analyses.

Results

Characteristics of Study Participants

Table 1 presents the characteristics of study participants. Demographically, in the asthma group the mean age was younger, male sex was more common, and body mass index was higher. Among perinatal factors, there were no significant differences between the 2 groups for cesarean section, low birth weight, prematurity, breastfeeding, and general anesthesia before 1 year of age. However, oxygen therapy in the first week after birth was significantly higher in the asthma group. For environmental factors, the asthma group had significantly higher exposure to ETS. There were no differences in the vicinity to major roadways and exposure to traffic exhaust between the asthma and non-asthma groups. For the socioeconomic and parental factors, parental asthma and parental allergic disease were significantly associated with asthma. In addition, there was a higher prevalence of asthma in first-born children. Monthly household income and parental education did not differ between the 2 groups. Laboratory findings showed that the asthma group had higher IgE and eosinophil levels. In addition, the asthma group had a higher prevalence of atopy and poorer lung function compared with the non-asthma group.