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Influence of antibiotic use in early childhood on asthma and allergic diseases at age 5

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ABSTRACT

Background: In the past few decades, the prevalence of allergic diseases has increased rapidly worldwide. At the same time, the overuse of antibiotics has been observed, especially in Japan.
Objective: To elucidate the association of early childhood antibiotic use with allergic diseases in later childhood at 5 years of age.
Methods: Relevant data were extracted from the hospital-based birth cohort study, the Tokyo Children's Health, Illness and Development Study. To identify signs of asthma and allergic diseases in children, the International Study of Asthma and Allergies in Childhood questionnaire was used. Logistic regression models were applied to estimate the effect of antibiotic use on outcomes in later life.
Results: Antibiotic exposure in children within the first 2 years of life was associated with current asthma (adjusted odds ratio [aOR] 1.72, 95% confidence interval [CI] 1.10–2.70), current atopic dermatitis (aOR 1.40, 95% CI 1.01–1.94), and current allergic rhinitis (aOR 1.65, 95% CI 1. 05–2.58) at 5 years of age. Analysis of the associations by type of antibiotics showed that cephem was associated with current asthma (aOR 1.97, 95% CI 1.23–3.16) and current rhinitis (aOR 1.82, 95% CI 1.12–2.93), and macrolide was associated with current atopic dermatitis (aOR 1.58, 95% CI 1.07–2.33).
Conclusion: Our findings suggest that antibiotic use within the first 2 years of life was a risk factor for current asthma, current atopic dermatitis, and current allergic rhinitis in 5-year-old children.

Introduction

Allergic diseases such as asthma, atopic dermatitis, and allergic rhinitis are common chronic diseases around the world and have led to a greater economic burden in health care costs.[1] The prevalence of asthma and rhinoconjunctivitis in Japanese children is high in the Asia-Pacific region.[2] In 2015, the Japanese Ministry of Health, Labour and Welfare reported that 3 of the most common diseases in outpatients younger than 15 years were allergic rhinitis, asthma, and atopic dermatitis.[3] In addition, a government report from 2013 documented a marked increase in food allergies in school children in Japan.[4]

The developmental origins of health and disease theory has proposed that fetal adaptations to intrauterine and maternal conditions during development shape the structure and function of organs.[5] Based on this theory, many studies have examined the associations of prenatal exposures with allergic diseases. However, children also are exposed to and influenced by various environmental factors, such as medications. From 2000 until 2010, total global antibiotic consumption increased, although a decrease in antibiotic consumption was observed in Japan during this period.[6] Despite this decrease, antibiotic prescriptions were still made on a large scale in Japan, with 60% of patients prescribed antibiotics for upper respiratory infections in 2009.[7] The associations of postnatal exposures to antibiotics in the first year of life with later development of allergic diseases in children have been reported in some studies from several non-Asian countries.[8,9] However, no studies have evaluated the associations of postnatal exposures to antibiotics in the first 2 years of life in children in Asia. The aim of this study was to elucidate the relation between postnatal antibiotic exposures within the first 2 years of life and allergic diseases in children at 5 years of age in Japan.

Methods

The Tokyo Children's Health, Illness and Development Study (T-CHILD) was a hospital-based prospective birth cohort study.[10,11]

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A flowchart of the participants in the present study is presented in Figure 1. A total of 1,701 pregnant women were recruited at the first antenatal visit at the National Center for Child Health and Development in Tokyo, Japan from 2003 through 2005. This resulted in a total of 1,550 newborns registered in this cohort from March 2004 to August 2006. Baseline data were collected from questionnaires answered by mothers during pregnancy and medical charts. Subsequently, parents were sent questionnaires assessing their child's exposures and health outcomes when children turned 2 and 5 years of age. Of 1,701 pregnant women who participated in the T-CHILD, 1,323 participants completed and returned the questionnaire when children were 2 years old (77.8%) and 1,196 participants did so when children were 5 years old (70.3%). The definitions of outcomes and exposures are presented in Table 1.

For the statistical analysis, we analyzed data without multiple births and missing variables. The differences in patient characteristics between the antibiotic and nonantibiotic groups were tested using the χ^2 test and Mann-Whitney test for continuous variables. Potential confounders were maternal history of allergy, maternal age at pregnancy, maternal smoking during pregnancy, mode of delivery, gestational age at delivery, daycare attendance, number of previous live births, bronchitis, and sex of the child. Univariate and multivariate logistic regression analyses were used to analyze the association between antibiotic use within the first 2 years of life and wheeze and allergic diseases in children. These potential confounders were included in multivariate models to obtain the adjusted odds ratios (aORs). Then, we performed a power analysis. All associations based on these models were presented with ORs and 95% confidence intervals (CIs). Statistical analyses were conducted using SAS 9.4 (SAS Institute, Cary, North Carolina), with a P value less than .05 defined as statistically significant. The study was approved by the institutional review board of the National Center for Child Health and Development. Written informed consent was obtained from all participants.

Table 1
Definitions of Outcomes and Exposures

Outcomes of children at 5 y old	
Wheeze current	A positive answer from the caregiver to the question (child at 5 y old), "Has your child ever had wheezing or whistling in the past 12 months?"
Asthma current	A positive answer from the caregiver to the question (child at 5 y old), "Has your child ever been diagnosed by a doctor as having asthma in the past 12 months?"
Rhinitis current	A positive answer from the caregiver to the question (child at 5 y old), "In the past 12 months, has your child had a problem with sneezing, or a runny, or blocked nose when he/she *did not* have a cold or the flu?"
Eczema current	A positive answer from the caregiver to the questions (child at 5 y old), "Has your child had an itchy rash at any time in the past 12 months?" and "Has this itchy rash at any time affected any of the following places: the folds of the elbows, behind the knees, in front of the ankles, under the buttocks, or around the neck, ears or eyes?"
Exposure to antibiotics	
History of antibiotic use	A positive answer from caregivers to the question (child at 2 y old), "Has your child ever taken antibiotics?"
Types of antibiotics use	A positive answer from caregivers to the question (child at 2 y old), "What types of antibiotics has your child taken?," which was classified into 4 groups (penicillin, cephem, macrolide, and others).

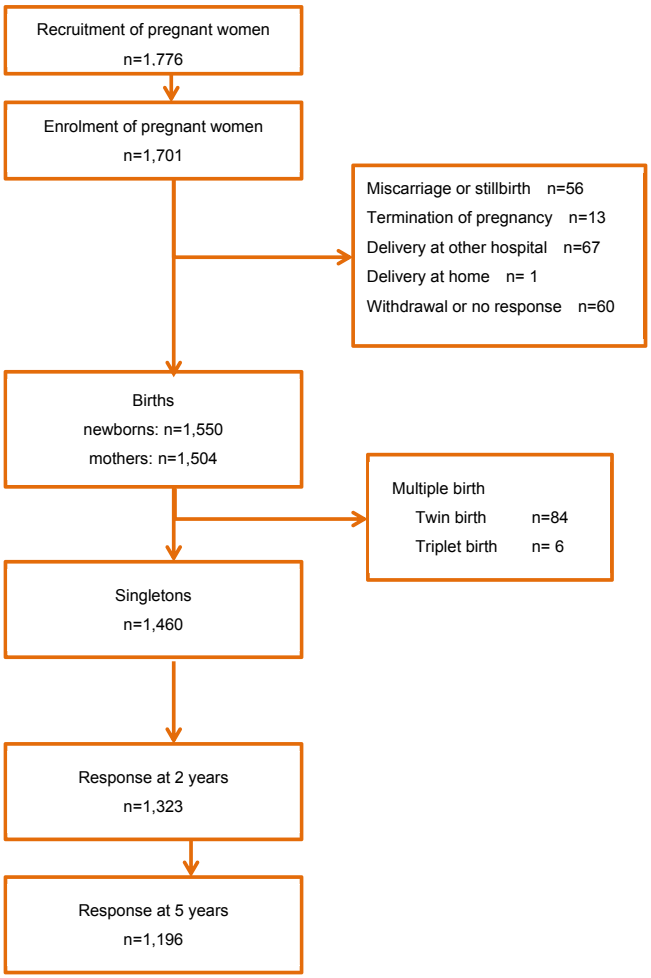

Figure 1. Flowchart of the study population in the Tokyo Children's Health, Illness and Development Study.

Results

A comparison of participants analyzed in our study with those lost to follow-up showed a difference in the number of previous live births ($P < .001$) and use of antibiotics within the first 2 years of life ($P = .003$; Table 2). Antibiotic use within the first 2 years of life was reported for 48.3% of children. The most common antibiotic was cephem (21.5%) and the second most common was macrolide (19.2%). Table 3 presents participant characteristics according to antibiotic use. Comparisons between the antibiotic-use group and nonantibiotic-use group showed statistically significant differences for daycare attendance (24.8% vs 16.3%; $P = .002$) and bronchitis (ever) at 2 years old (22.9% vs 10.1%; $P < .001$) and for current asthma (18.6% vs 14.4%; $P = .009$), current atopic dermatitis (24.5% vs 18.7%; $P = .032$), and current allergic rhinitis (13.5% vs 7.9%; $P = .006$) in child outcomes at 5 years old. Table 4 presents the results of the logistic and power analyses. Antibiotic exposure in children within the first 2 years of life was associated with current asthma (aOR 1.72, 95% CI 1.10–2.70), current atopic dermatitis (aOR 1.40, 95% CI 1.01–1.94), and current rhinitis (aOR 1.65, 95% CI 1.05–2.58) at 5 years of age. For associations by type of antibiotics, cephem was associated with current asthma (aOR 1.97, 95% CI 1.23–3.16) and current rhinitis (aOR 1.82, 95% CI 1.12–2.93). Macrolide also was associated with current atopic dermatitis (aOR 1.58, 95% CI 1.07–2.33).