

# 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.

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## 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.<sup>1</sup> The prevalence of asthma and rhinoconjunctivitis in Japanese children is high in the Asia-Pacific region.<sup>2</sup> 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.<sup>3</sup> In addition, a government report from 2013 documented a marked increase in food allergies in school children in Japan.<sup>4</sup>

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.<sup>5</sup> 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.<sup>6</sup> 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.<sup>7</sup> 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.<sup>8,9</sup> 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.<sup>10,11</sup>

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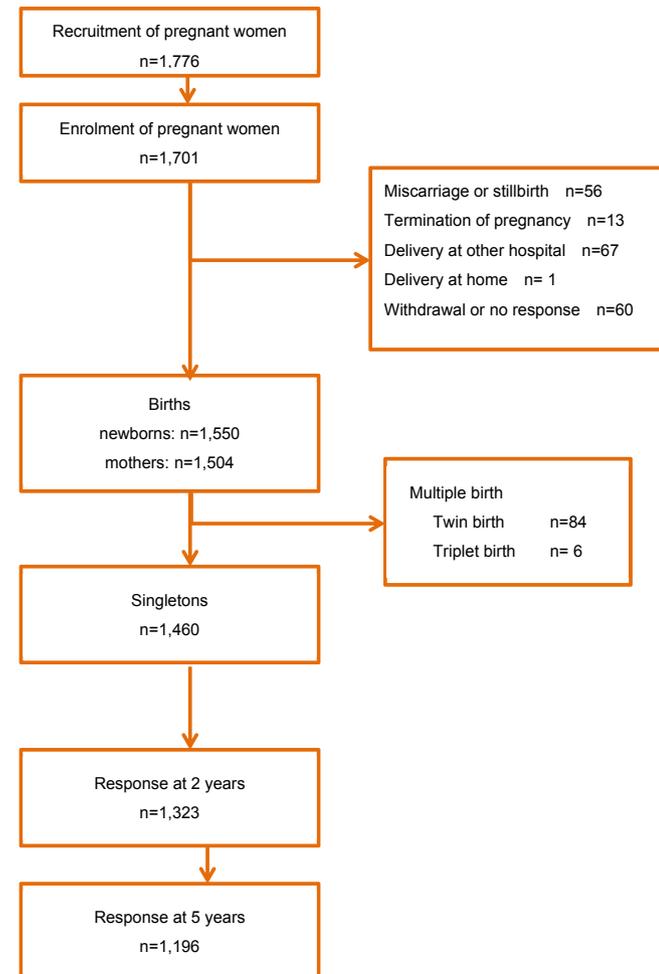
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A flowchart of the participants in the present study is presented in Figure 1. A total of 1,701 pregnant women were recruited at the first antenatal visit at the National Center for Child Health and Development in Tokyo, Japan from 2003 through 2005. 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  $\chi^2$  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

**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 <i>did not</i> 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.

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.

## 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).

**Table 2**  
Comparison Between Participants' Characteristics Included in the Analysis and Lost to Follow-up

|   | Data used for analysis, n (%) | Data not used for analysis, n (%) | P value |
|---|-------------------------------|-----------------------------------|---------|
| <b>Maternal characteristics</b>               |                               |                                   |         |
| Maternal history of allergy                   |                               |                                   |         |
| Yes   | 493 (54.7)                    | 281 (56.8)                        | .448    |
| No  | 409 (45.3)                    | 214 (43.2)                        |         |
| Smoking during pregnancy                      |                               |                                   |         |
| Yes   | 18 (2.0)                      | 20 (3.6)                          | .061    |
| No  | 884 (98.0)                    | 534 (96.4)                        |         |
| Maternal age at pregnancy (y)                 |                               |                                   |         |
| <35   | 521 (57.8)                    | 343 (61.6)                        | .149    |
| ≥35   | 381 (42.2)                    | 214 (38.4)                        |         |
| Previous live births                          |                               |                                   |         |
| 0   | 530 (58.8)                    | 247 (44.3)                        | <.001   |
| ≥1  | 372 (41.2)                    | 310 (55.7)                        |         |
| Type of delivery                              |                               |                                   |         |
| Caesarean                                     | 208 (23.1)                    | 112 (20.3)                        | .21     |
| Vaginal                                       | 694 (76.9)                    | 441 (79.7)                        |         |
| Weeks of gestation, median (IQR) <sup>a</sup> |                               |                                   |         |
|   | 39 (38–40)                    | 39 (38–40)                        | .056    |
| <b>Child's characteristics</b>                |                               |                                   |         |
| Sex   |                               |                                   |         |
| Male  | 460 (51.0)                    | 301 (53.9)                        | .274    |
| Female  | 442 (49.0)                    | 257 (46.1)                        |         |
| Attends daycare                               |                               |                                   |         |
| Yes   | 184 (20.4)                    | 84 (21.2)                         | .755    |
| No  | 718 (79.6)                    | 313 (78.8)                        |         |
| Bronchitis (ever) at 2 y old                  |                               |                                   |         |
| Yes   | 147 (16.3)                    | 33 (12.9)                         | .184    |
| No  | 755 (83.7)                    | 223 (87.1)                        |         |
| Antibiotic use before 2 y of age              |                               |                                   |         |
| Yes   | 436 (48.3)                    | 137 (46.8)                        | .638    |
| No  | 466 (51.7)                    | 156 (53.2)                        |         |
| Penicillin                                    |                               |                                   |         |
| Yes   | 73 (8.1)                      | 23 (7.8)                          | .894    |
| No  | 829 (91.9)                    | 270 (92.2)                        |         |
| Cephem  |                               |                                   |         |
| Yes   | 194 (21.5)                    | 57 (19.5)                         | .453    |
| No  | 708 (78.5)                    | 236 (80.5)                        |         |
| Macrolide                                     |                               |                                   |         |
| Yes   | 173 (19.2)                    | 60 (20.5)                         | .626    |
| No  | 729 (80.8)                    | 233 (79.5)                        |         |
| Others  |                               |                                   |         |
| Yes   | 140 (15.5)                    | 25 (8.5)                          | .003    |
| No  | 762 (84.5)                    | 268 (91.5)                        |         |

Abbreviation: IQR, interquartile range (25th to 75th).

<sup>a</sup>By Mann-Whitney test.

## Discussion

To the best of our knowledge, this study is the first to report that exposure to antibiotics in the first 2 years of life increases the risk of later development of current asthma, atopic dermatitis, and allergic rhinitis in Japanese children at 5 years of age. In addition, we found that cephem antibiotics were associated with current asthma and allergic rhinitis, and macrolide antibiotics were associated with current atopic dermatitis. The key strength of our study was its prospective birth cohort study design, which consisted of the general population and measured potential confounders included in the analysis.

Our findings demonstrated that any antibiotic and cephem use within the first 2 years of life was associated with current asthma at 5 years. However, penicillin and macrolide were not associated with current asthma at 5 years. Pender et al<sup>12</sup> found a weak association of antibiotic use within the first year of life with wheeze and asthma in children in a systematic review and meta-analysis (pooled OR 1.27, 95% CI 1.12–1.43) of wheeze of asthma. In an Italian birth cohort study, Pitter et al<sup>8</sup> examined the associations of classes of antibiotics with the development of allergic disorders and found that the use of any antibiotics (incident rate ratio [IRR] 1.35, 95% CI 1.30–1.41), penicillin (IRR 1.29, 95% CI 1.24–1.35),

**Table 3**  
Participants' Characteristics According to Antibiotic Use

|   | No antibiotic use, n (%) | Antibiotic use, n (%) | P value |
|---|--------------------------|-----------------------|---------|
| <b>Maternal characteristics</b>               |                          |                       |         |
| Maternal history of allergy                   |                          |                       |         |
| Yes   | 242 (51.9)               | 251 (57.6)            | .089    |
| No  | 224 (48.1)               | 185 (42.4)            |         |
| Smoking during pregnancy                      |                          |                       |         |
| Yes   | 10 (2.1)                 | 8 (1.8)               | .739    |
| No  | 456 (97.9)               | 428 (98.2)            |         |
| Maternal age at pregnancy (y)                 |                          |                       |         |
| <35   | 275 (59.0)               | 246 (56.4)            | .431    |
| ≥35   | 191 (41.0)               | 190 (43.6)            |         |
| Previous live births                          |                          |                       |         |
| 0   | 273 (58.6)               | 257 (58.9)            | .912    |
| ≥1  | 193 (41.4)               | 179 (41.1)            |         |
| Type of delivery                              |                          |                       |         |
| Caesarean                                     | 101 (21.7)               | 107 (24.5)            | .307    |
| Vaginal                                       | 365 (78.3)               | 329 (75.5)            |         |
| Weeks of gestation, median (IQR) <sup>a</sup> |                          |                       |         |
|   | 39 (38–40)               | 39 (38–40)            | .438    |
| <b>Child's characteristics</b>                |                          |                       |         |
| Sex   |                          |                       |         |
| Male  | 238 (51.1)               | 222 (50.9)            | .963    |
| Female  | 228 (48.9)               | 214 (49.1)            |         |
| Attends daycare                               |                          |                       |         |
| Yes   | 76 (16.3)                | 108 (24.8)            | .002    |
| No  | 390 (83.7)               | 328 (75.2)            |         |
| Bronchitis (ever) at 2 y old                  |                          |                       |         |
| Yes   | 47 (10.1)                | 100 (22.9)            | <.001   |
| No  | 419 (89.9)               | 336 (77.1)            |         |
| Allergy outcomes at 5 y old                   |                          |                       |         |
| Current wheeze                                |                          |                       |         |
| Yes   | 67 (14.4)                | 81 (18.6)             | .089    |
| No  | 399 (85.6)               | 355 (81.4)            |         |
| Current asthma                                |                          |                       |         |
| Yes   | 37 (7.9)                 | 58 (13.3)             | .009    |
| No  | 429 (92.1)               | 378 (86.7)            |         |
| Current atopic dermatitis                     |                          |                       |         |
| Yes   | 87 (18.7)                | 107 (24.5)            | .032    |
| No  | 379 (81.3)               | 329 (75.5)            |         |
| Current allergic rhinitis                     |                          |                       |         |
| Yes   | 37 (7.9)                 | 59 (13.5)             | .006    |
| No  | 429 (92.1)               | 377 (86.5)            |         |

Abbreviation: IQR, interquartile range (25th to 75th).

<sup>a</sup>By Mann-Whitney test.

cephalosporin (IRR 1.27, 95% CI 1.20–1.33), and macrolide (IRR 1.38, 95% CI 1.30–1.47) in the first year of life increased the risk of current asthma at 6 years. In a Canadian birth cohort study, Marra et al<sup>9</sup> also reported that any antibiotic use and various types of antibiotics (amoxicillin, penicillin, cephalosporin, and macrolide) had positive associations with the risk of developing asthma in children 2 to 9 years old. However, Sun et al<sup>13</sup> found an association of macrolide in the first year of life only with wheeze in European children 3 years old. Metsala et al<sup>14</sup> reported that a child's exposure to cephalosporins (OR 1.79, 95% CI 1.59–2.01), sulfonamides and trimethoprim (OR 1.65, 95% CI 1.34–2.02), macrolides (OR 1.61, 95% CI 1.46–1.78), and amoxicillin (OR 1.46, 95% CI 1.35–1.58) during the first year of life was associated with an increased risk of asthma at 3 years of age and older in Finnish populations.

In our study, cephem was the most common antibiotic and macrolide was the second most common in our populations. In contrast, cephem was not a commonly used antibiotic in populations of past studies. Our finding on the association of cephem and cephalosporin with asthma was similar to previous reports.<sup>8,9,14</sup> Nevertheless, our study did not show an association of penicillin and macrolide with asthma, which differed from results of previous studies. The differences in results could be due to differences in exposures to antibiotics, populations, and target sample size.

For atopic dermatitis, a systematic review reported that a pooled analysis of 10 longitudinal studies showed that postnatal antibiotic

**Table 4**  
Associations of Antibiotic Use in Children Younger Than 3 Years With Wheeze and Allergy Outcomes in Children at 5 Years Old

|                              | Crude OR | 95% CI |       | P value | Adjusted OR <sup>a</sup> | 95% CI |       | P value | Power <sup>b</sup> |
|------------------------------|----------|--------|-------|---------|--------------------------|--------|-------|---------|--------------------|
|                              |          | Lower  | Upper |         |                          | Lower  | Upper |         |                    |
| <b>Current wheeze</b>        |          |        |       |         |                          |        |       |         |                    |
| All antibiotics              | 1.36     | 0.95   | 1.94  | .089    | 1.24                     | 0.86   | 1.78  | .255    |                    |
| Penicillin                   | 1.11     | 0.60   | 2.09  | .736    | 1.16                     | 0.61   | 2.18  | .653    |                    |
| Cephem                       | 1.44     | 0.96   | 2.16  | .075    | 1.39                     | 0.92   | 2.09  | .122    |                    |
| Macrolide                    | 1.20     | 0.78   | 1.85  | .410    | 1.04                     | 0.66   | 1.64  | .856    |                    |
| <b>Current asthma</b>        |          |        |       |         |                          |        |       |         |                    |
| All antibiotics              | 1.78     | 1.15   | 2.75  | .009    | 1.72                     | 1.10   | 2.70  | .017    | 0.75               |
| Penicillin                   | 1.88     | 0.58   | 2.53  | .602    | 1.21                     | 0.58   | 2.56  | .612    |                    |
| Cephem                       | 2.02     | 1.28   | 3.20  | .003    | 1.97                     | 1.23   | 3.16  | .005    | 0.84               |
| Macrolide                    | 2.59     | 0.97   | 2.60  | .064    | 1.46                     | 0.88   | 2.44  | .145    |                    |
| <b>Current atopic eczema</b> |          |        |       |         |                          |        |       |         |                    |
| All antibiotics              | 1.42     | 1.03   | 1.95  | .032    | 1.40                     | 1.01   | 1.94  | .044    | 0.55               |
| Penicillin                   | 1.42     | 0.83   | 2.44  | .203    | 1.41                     | 0.82   | 2.43  | .219    |                    |
| Cephem                       | 1.41     | 0.98   | 2.04  | .068    | 1.37                     | 0.94   | 1.99  | .103    |                    |
| Macrolide                    | 1.59     | 1.09   | 2.32  | .016    | 1.58                     | 1.07   | 2.33  | .022    | 0.64               |
| <b>Current rhinitis</b>      |          |        |       |         |                          |        |       |         |                    |
| All antibiotics              | 1.82     | 1.18   | 2.80  | .007    | 1.65                     | 1.05   | 2.58  | .030    | 0.68               |
| Penicillin                   | 1.29     | 0.23   | 1.52  | .278    | 0.58                     | 0.22   | 1.51  | .264    |                    |
| Cephem                       | 1.88     | 1.19   | 2.98  | .007    | 1.82                     | 1.12   | 2.93  | .015    | 0.73               |
| Macrolide                    | 1.77     | 1.10   | 1.52  | .020    | 1.50                     | 0.90   | 2.49  | .121    |                    |

Abbreviations: CI, confidence interval; OR, odds ratio.

<sup>a</sup>Adjusted for maternal history of allergy (asthma, atopic dermatitis, or allergic rhinitis), maternal education level, maternal age at pregnancy, maternal body mass index, maternal smoking during pregnancy, mode of delivery, gestational age at delivery, previous live births, daycare, bronchitis, and sex of the child.

<sup>b</sup>Post hoc power ( $\alpha = .05$ ,  $N = 902$ ).

exposure in the first year of life increased the risk of eczema (pooled OR 1.40, 95% CI 1.19–1.64).<sup>15</sup> Our finding of a positive association of antibiotic use with atopic dermatitis supports the result of that review. Our study found that macrolide antibiotics were associated with atopic dermatitis. In fact, tacrolimus ointment is often prescribed to patients with atopic dermatitis. The structure of tacrolimus contains a 23-membered macrolide lactone, which could have an influence on the development of asthma. A case series noted the development of asthma in liver transplant recipients receiving systemic tacrolimus treatment.<sup>16</sup> In a liver transplantation cohort, eczema developed in 56% and asthma developed in 44% of patients.<sup>17</sup> One study reported on the development of food allergies in children taking tacrolimus after heart and liver transplantation, suggesting an association between tacrolimus and the development of food allergies.<sup>18</sup> The phenomenon of transplant-acquired food allergy has been well documented.<sup>19</sup> Considered together, tacrolimus in addition to antibiotics might be a risk factor for the development of allergic diseases. Further investigation on the association of tacrolimus with allergic diseases is needed in future studies.

For allergic rhinitis, a birth cohort study in Sweden showed that antibiotic use in the first week of life increased the risk of current allergic rhinitis at 8 years of age (aOR 1.75, 95% CI 1.03–2.97). Although the timing of antibiotic exposure in the study was different from that in our study, our finding on the positive association between antibiotic use and allergic rhinitis at 5 years of age was supported by the results of the Swedish cohort study.<sup>20</sup>

In consideration of past reports, the influence of antibiotics on allergic diseases such as asthma, atopic dermatitis, and allergic rhinitis in Japan seems to be similar to that in western countries.

Because our study design was not based on basic science research, we could not show how exposures to antibiotics played a role in the later development of allergic diseases compared with other studies. A birth cohort study in Finland found that taking antibiotics altered and led to less diversity in the gut microbiota.<sup>21,22</sup> In addition, the study found it took a long time for microbiota to recover from exposure to antibiotics.<sup>21</sup> In mice, the gut microbiota regulates the immune system of several types of T cells.<sup>23,24</sup> Cahenzli et al<sup>25</sup> indicated that appropriate gut microbiota

was important for protecting against immunoglobulin E induction. Microbiota altered by antibiotic exposure can compromise the immune system, leading to the development of allergic diseases. In a mouse model, mice treated with kanamycin during infancy showed a decrease in the production of interleukin (IL)-12, which regulates the maturation of T-helper type (T<sub>H</sub>) T<sub>H</sub>1 cells, and led to T<sub>H</sub>2-polarized immune deviation.<sup>26</sup> Similarly, adding moxifloxacin to human monocytes decreased IL-8, IL-1 $\beta$ , and tumor necrosis factor- $\alpha$  secretion,<sup>27</sup> suggesting that suppressing the T<sub>H</sub>1 response could polarize the immune system toward a T<sub>H</sub>2 response.

A Danish cohort study showed that antibiotic use increased the risk of inflammatory bowel diseases.<sup>28</sup> Exposure to antibiotics in the first 6 months of life has been shown to raise the risk of increasing late-life body mass or obesity.<sup>29,30</sup> Antibiotic exposure also can influence other health conditions, such as inflammatory bowel diseases and obesity.<sup>28–30</sup> Because the microbial community could play an important role in health and various diseases,<sup>31</sup> further studies are needed to investigate how various health outcomes regarding gut microbiota are affected by antibiotic exposure.

This study has several limitations. First, exposure and outcome measurements were assessed by questionnaire and we did not confirm the diagnosis of allergic diseases directly with physicians or obtain information about the number of times antibiotics were used. We used validated questionnaires to evaluate outcomes in the same way as other cohort studies. In addition, we could not evaluate the dose-response analysis because we did not obtain details of antibiotic doses or courses. Hoskin-Parr et al<sup>32</sup> observed a dose-dependent relation between antibiotic exposure and asthma development before 7.5 years of age. Ong et al<sup>33</sup> also found a dose-dependent influence of antibiotic exposure on the onset of asthma before 3 years of age. A dose-dependent association between exposure to antibiotics and the development of allergic disorders such as asthma are apparent in the results of these past studies. Most past studies evaluated the association of postnatal exposure to antibiotics within the first year of life. Although we did not confirm the exact timing and course of antibiotics in our study, we found that any antibiotic exposure in children younger than 3 years was associated with allergic diseases. We hypothesize that the wide range of timing of antibiotic exposure in infants is

associated with the development of allergic diseases. Further studies are expected to examine the relation of the frequency and timing of exposure to antibiotic use and allergic diseases. Second, we could not fully take into account other possible confounders such as prebiotics and probiotics because of a lack of information, although potential confounders including 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 were included in the multivariate regression analysis to obtain the aORs. Chawes<sup>34</sup> observed that high levels of C-reactive protein, a sensitive marker of systemic low-grade inflammation in early life, was related to a lower forced expiratory volume in 1 second and a higher prevalence of bronchial hyperresponsiveness. Low-grade infections might be another important confounder, although in the present study history of bronchitis was included as a confounder. Wang et al<sup>35</sup> demonstrated an association of exposure to antibiotics and/or acetaminophen to allergy development and found acetaminophen exposure in particular to be an important factor. In addition, we did not collect stool samples to evaluate microbiota or DNA samples of the mother and child. A previous study showed the additive effects of unfavorable IL-13 or CD14 genotypes, prenatal antibiotic exposure, and delivery mode on the development of atopic dermatitis in infancy.<sup>36</sup> Further studies are needed to examine how these confounders and antibiotics play a role in the development of allergic diseases. Third, our study was a single-center and small birth cohort study, and we lost some participants during follow-up. A comparison of participants analyzed in our study with those lost to follow-up showed a difference in the number of previous live births ( $P < .001$ ). Background differences constituted another limitation. Lack of statistical significance for the ORs in the models used might be due to the small sample with insufficient power to demonstrate the statistical significance of the effects. Our study was not an intervention study but an observational study. However, although the evidence level in our study was lower than that of an intervention study, we could demonstrate the association between antibiotic use and allergic outcomes. In future, we would like to confirm these findings using data from a large nationwide birth cohort study in Japan.<sup>37</sup>

In conclusion, our birth cohort study in Japan suggested that exposure to antibiotics at younger than 3 years increased the risk of developing allergic diseases at 5 years. Although the use of antibiotics is unavoidable when treating bacterial infections, appropriate antibiotic use for young children is encouraged as an approach to prevent the development of allergic diseases.

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