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Prenatal and early-life antibiotic use and risk of childhood asthma: A retrospective cohort study

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Abstract

Background: Although associations between antibiotic exposure in infants and asthma development are reported, few studies have examined the effects of prenatal exposure to antibiotics. We evaluated this association considering the antibiotic types using a large-scale claim database in Japan.

Methods: This retrospective study using health insurance administrative claim data in Japan included children born between January 2005 and September 2014. We constructed 2 cohorts: initial cohort, with information on children's mothers, and sibling cohort, with at least one sibling. Cox proportional hazard regression and sibling-matched cohort analyses were performed to determine the association between exposure to antibiotics in utero or the first year of life and asthma development until age 6.

Results: In the initial cohort, antibiotic exposure during the foetal period was associated with early asthma development (until age 3; HR: 1.18, 95% CI: 1.08-1.30). However, this association disappeared after 3 years. The association between antibiotic exposure in the first year of life and asthma was stronger in early (HR: 2.43, 95% CI: 2.20-2.69) than later (HR: 1.23, 95% CI: 1.11-1.36) life. In the sibling cohort, we observed positive associations between foetal exposure and asthma by adjusting for familial factors (HR: 1.34, 95% CI: 1.05-1.72), which remained during the first year of life (HR: 1.62, 95% CI: 1.27-2.07).

Conclusions: Exposure to antibiotics during the first year of life was associated with childhood asthma even after adjusting for familial factors. However, a weak association was observed between prenatal antibiotic exposure and asthma development.

KEYWORDS

antibiotics, asthma, children, claim data, early-life exposure

1 | INTRODUCTION

To date, several studies have evaluated associations between antibiotic exposure in the early years of childhood and the development of asthma. Most studies reported positive associations between antibiotic exposure in the early years of life and an increased risk of childhood asthma.¹⁻⁴ In contrast, reports on antibiotic exposure in utero and asthma development have been less extensive, and only a limited number of studies have examined the

effects of antibiotic exposure during pregnancy.⁵⁻⁹ Although some studies have reported a positive association between exposure to antibiotics in utero and the risk of asthma,⁵⁻⁸ recent reports revealed that this association may no longer be present after adjusting for sibling factors or respiratory infection.^{9,10} While reports on early-life exposure to antibiotics and asthma development remain controversial, some studies have demonstrated that the use of broad-spectrum antibiotics in early life increased asthma incidence.^{1,4,6,7}

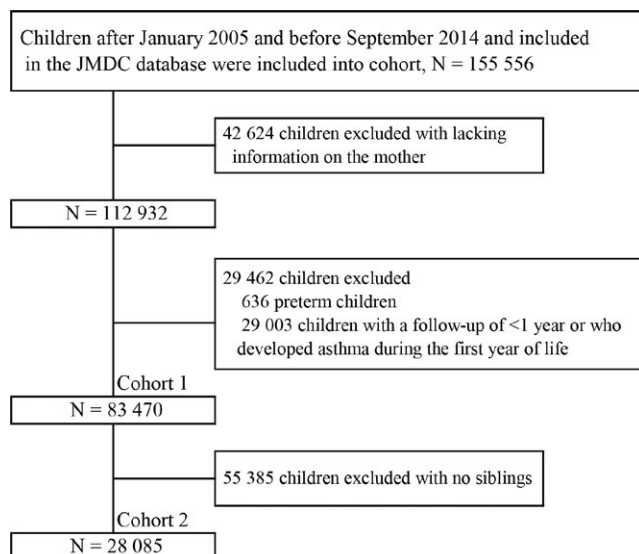


FIGURE 1 Flow chart showing selection of cohort subjects

In the absence of clinical trial data, claim data are promising resources in evaluating the effects of exposure to medications during pregnancy or infancy.¹¹ However, these data do not include familial history and environmental factors, which may influence disease incidence. D'Onofrio et al¹² indicated that family-based quasi-experimental designs provide effective solutions for causal inferences using a claim database study. Ortqvist et al⁹ used sibling information to adjust for familial factors and investigated the association between antibiotic exposure in early life and asthma development in childhood. To further investigate this, we evaluated the association between antibiotic exposure in early life and asthma development in childhood considering the types of antibiotics using a large-scale claim database in Japan.

2 | METHODS

2.1 | Study setting and design

We conducted a retrospective cohort study, using claim data for mothers and children born between January 2005 and September 2014. Data were obtained from an administrative claim database maintained by the Japan Medical Data Center Co., Ltd.^{13,14} As of 2016, the database consists of medical and pharmacy claims and insurance eligibility data from a total of 4 800 000 beneficiaries (corporate employees and their dependent family members). The database represents approximately 4% of the total population in Japan. We extracted information on pairs of mothers and children from 2005 January to 2014 September (total: 250 971: mothers: 95 415; children: 155 556). We linked information on mothers and children using family identifiers and determined when the child was in utero. Database includes information on sex, year and month of birth, medical services provided or drugs prescribed, day of diagnoses, inpatient or outpatient status, size and speciality of medical facilities used, and types of claims.

We defined the follow-up period from the twelfth month after birth to avoid overlap between exposure and outcome. The birth month of the sixth year (72 months) was considered as the end of the follow-up period. We excluded children lacking information on mothers and preterm children who were born before 37 weeks of gestation, because of the risk of misclassification of the pregnancy period. In addition to the initial cohort, where children met the above criteria, we created a sibling cohort, which included children with at least one sibling. Our study protocol was approved by the Kyoto University Graduate School and Faculty of Medicine, Ethics Committee (Approval Number R0202).

2.2 | Exposure

To evaluate exposure, information on prescription of antibiotics (ATC J01) to the mother during pregnancy or the child during the first year of birth was collected according to the Anatomical Therapeutic Chemical (ATC) classification. The pregnancy period was considered as 9 months before the birth month of the child. If the mother was prescribed antibiotics during this period, the child was included in the group that was exposed during the foetal period. Infant exposure was defined as antibiotics prescribed during the first year after birth (up to 12 months from birth). Antibiotics examined were penicillin, cephalosporin, macrolides, among others. The frequency of antibiotic prescription within target periods was classified as 0, 1-2, 3-4 and >5 times.

2.3 | Outcome

The incidence of asthma was determined from the first diagnosis of asthma with prescription of inhaled corticosteroids (ICS) and 1 or more control therapies during the follow-up period. Diagnoses were coded by the International Classification of Diseases, 10th Revision (ICD-10). Children were considered asthmatic if they were diagnosed with asthma (ICD J45) and administered ICS and other controllers as asthma medication, such as leukotriene-receptor antagonists, long-acting beta 2 agonists, short-acting beta 2 agonists, theophylline and disodium cromoglycate. At each analysis, the age of asthma development was classified as 12-35 months and 36-72 months.

2.4 | Statistical analysis

We evaluated associations between antibiotic exposure during the foetal period and the first year of life, and the incidences of asthma up to age 6. We performed statistical analysis for the initial cohort (Cohort 1; $n = 83\,470$), where children had mothers' information, and the follow-up period was ≥ 1 year. Cox proportional hazard regression analysis was used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for associations between exposure to antibiotics in utero or the first year of life and development of asthma. Furthermore, we performed matched cohort analysis for the sibling cohort (Cohort 2; $n = 28\,085$; for children with siblings) to adjust for shared factors within families, using the "stcox" with "strata"

command.¹⁵ In the sibling analysis, we estimated HRs and 95% CIs for associations between exposure to antibiotics in utero or the first year of life and development of asthma. All statistical analyses were performed using Stata ver. 13.0 (Stata Corp LP, College Station, TX, USA).

3 | RESULTS

Of the total of 155 556 children in the database, 83 470 were included in Cohort 1 after excluding those who did not meet the recruitment criteria (Figure 1). From Cohort 1, 55 385 were excluded

because they had no siblings; the remaining 28 085 children were included in Cohort 2. Overall, 3633 children in Cohort 1 developed asthma (4.4%), while 1582 (5.6%) developed asthma in Cohort 2. The mean observation periods were 34.4 months in Cohort 1 and 43.7 months in Cohort 2. In Cohort 1, from 3625 children diagnosed with asthma by the age of 6 years, 57.7% were male (Table 1). Data were similar in Cohort 2, where 57.4% of children with asthma were male. In Cohort 1, exposure to antibiotics during the foetal or infant period was greater in those who subsequently developed asthma, with cephalosporin being the most prescribed drug. In contrast, in Cohort 2, development of asthma was not associated with exposure during infancy and not the foetal period.

TABLE 1 Cohort characteristics for children exposed to antibiotics during the foetal period or infancy

Characteristics	Cohort 1 (Initial cohort)		Cohort 2 (Sibling cohort)	
	No asthma (N = 79 837)	With asthma (N = 3633)	No asthma (N = 26 503)	With asthma (N = 1582)
Infant sex				
Male	40 879 (51.2)	2097 (57.7)	13 665 (51.6)	908 (57.4)
No. of siblings (in the database)				
0	53 334 (66.8)	2051 (56.5)	—	—
1	12 707 (15.9)	742 (20.4)	12 707 (48.0)	742 (46.9)
2	12 741 (16.0)	759 (20.9)	12 741 (48.1)	759 (48.0)
3	1003 (1.3)	78 (2.2)	1003 (3.8)	78 (4.9)
Over 4	52 (0.1)	3 (0.1)	52 (0.2)	3 (0.2)
Antibiotic exposure during the foetal period				
Exposure to any antibiotic	19 632 (24.6)	998 (27.5)	6972 (26.3)	422 (26.7)
Exposure by type of antibiotic				
Penicillin	4115 (5.2)	211 (5.8)	1482 (5.6)	98 (6.2)
Cephalosporin	11 557 (14.5)	606 (16.7)	4029 (15.2)	235 (14.9)
Macrolide	5721 (7.2)	275 (7.6)	1947 (7.4)	113 (7.1)
Other type of antibiotics	3731 (4.7)	203 (5.6)	1518 (5.7)	97 (6.1)
No. of antibiotic prescriptions				
1-2	15 155 (19.0)	753 (20.7)	5341 (20.2)	320 (20.2)
3-4	2688 (3.4)	152 (4.2)	1005 (3.8)	62 (3.9)
Over 5	1789 (2.2)	93 (2.6)	626 (2.4)	40 (2.5)
Antibiotic exposure during infancy				
Exposure to any antibiotic	44 045 (55.2)	2517 (69.3)	14 854 (56.1)	1066 (67.4)
Exposure by type of antibiotic				
Penicillin	16 053 (20.1)	939 (25.9)	5298 (20.0)	368 (23.3)
Cephalosporin	29 523 (37.0)	1791 (49.3)	9958 (37.6)	743 (47.0)
Macrolide	19 501 (24.4)	1380 (38.0)	6566 (24.8)	566 (35.8)
Other type of antibiotics	9275 (11.6)	570 (15.7)	3033 (11.4)	214 (13.5)
No. of antibiotic prescriptions				
1-2	28 950 (36.3)	1371 (37.8)	9865 (37.2)	623 (39.4)
3-4	10 170 (12.7)	679 (18.7)	3410 (12.9)	273 (17.3)
Over 5	4925 (6.2)	466 (12.8)	1579 (6.0)	170 (10.8)

Table 2 shows HRs for associations between antibiotic exposure and asthma in Cohort 1. Exposure during the foetal period was associated with the development of asthma in early life, up to 3 years of age (HR: 1.18, 95% CI: 1.08-1.30). This association disappeared in children diagnosed with asthma after 3 years of age. The association between antibiotic exposure during the first year of life and asthma development was stronger in early (HR: 2.43, 95% CI: 2.20-2.69) than in later life (HR: 1.23, 95% CI: 1.11-1.36). Furthermore, the risk of asthma was influenced by the type of antibiotics prescribed. Macrolide exposure during the first year of life was more strongly associated with asthma diagnosis up to age 3 (HR: 2.00, 95% CI: 1.83-2.20) compared with other types of antibiotics (HR: 1.55, 95% CI: 1.41-1.70). There was also a dose-response relationship between the number of courses of antibiotics in the first year of life and subsequent development of asthma regardless of age of asthma incidence.

Table 3 shows the results of a matched cohort analysis for the association between antibiotic exposure and asthma in Cohort 2. An association between exposure to any antibiotic during the foetal period and development of asthma remained significant after adjusting for siblings (HR: 1.34, 95% CI: 1.05-1.72). In addition, the association between antibiotic exposure during the first year of life and asthma remained significant after adjustment (HR: 1.62, 95% CI: 1.27-2.07). In this matched cohort analysis, cephalosporin (HR: 1.35, 95% CI: 1.07-1.71) and macrolide exposure (HR: 1.48, 95% CI: 1.17-1.87) were associated with asthma development in children. Furthermore, dose-response relationships with asthma development were still present after adjustment for siblings (HR: 1.40, 95% CI: 1.08-1.83, HR: 1.94, 95% CI: 1.41-2.67, HR: 2.75, 95% CI: 1.80-4.20).

4 | DISCUSSION

We confirmed that exposure to antibiotics during the first year of life increased the risk of asthma in early childhood. This association remained notable after adjusting for familial factors, with a sibling cohort design. The effects of antibiotics during the first year were strong for early asthma development, and a dose-related association was observed between increasing numbers of antibiotic prescriptions and risk of asthma. The use of macrolide antibiotics also resulted in a stronger association with childhood asthma than that with other antibiotics. In contrast, exposure to antibiotics during the prenatal period was only slightly associated with increased risk of childhood asthma, although the association remained after adjusting for familial factors.

Recent studies suggested that antibiotic exposure during early life was associated with an increased risk of asthma. The relative risks reported were based on the type of study and the age of onset of asthma, and were approximately 1.12- to 1.65-fold after adjusting for covariates.^{1,3,4} A systematic review reported that the pooled odds ratio was approximately 1.52.¹⁶ Our study confirmed positive associations between antibiotic exposure during the first year of life and onset of childhood asthma, in a dose-dependent manner.^{1,7} Furthermore, in accordance with some reports,^{1,4} we revealed that macrolide use was more associated with childhood asthma compared with other antibiotics, that is asthma development may be enhanced by the use of broad-spectrum antibiotics, such as macrolides. Meanwhile, a few studies have investigated the use of antibiotics during pregnancy and their effects on the foetus, but these have yielded controversial results. It has been suggested that exposure in utero is positively associated

TABLE 2 Hazard ratios for developing asthma following antibiotic exposure during the foetal period or infancy; Cohort 1 (N = 83 470)

Variables	Antibiotic exposure during the foetal period		Antibiotic exposure during the first year of life	
	Age at diagnosis	Age at diagnosis	Age at diagnosis	Age at diagnosis
	12-35 mo	36-72 mo	12-35 mo	36-72 mo
	N = 41 662	N = 41 808	N = 41 662	N = 41 808
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Male infant	1.37 (1.26-1.50)	1.21 (1.09-1.33)	1.33 (1.21-1.45)	1.19 (1.09-1.32)
Any antibiotic exposure*	1.18 (1.08-1.30)	1.09 (0.97-1.22)	2.43 (2.20-2.69)	1.23 (1.11-1.36)
Exposure by type of antibiotics*				
Penicillin	1.15 (0.96-1.38)	1.01 (0.81-1.25)	1.39 (1.26-1.53)	0.87 (0.76-0.98)
Cephalosporin	1.18 (1.05-1.33)	1.10 (0.95-1.26)	1.55 (1.41-1.70)	1.20 (1.08-1.33)
Macrolide	1.09 (0.93-1.27)	0.86 (0.69-1.07)	2.00 (1.83-2.20)	1.17 (1.05-1.31)
Other type of antibiotics	1.04 (0.86-1.26)	1.28 (1.03-1.60)	1.07 (0.95-1.20)	1.17 (1.00-1.36)
No. of antibiotic prescriptions*				
0 (Reference)	1.00	1.00	1.00	1.00
1-2	1.14 (1.02-1.26)	1.08 (0.95-1.22)	1.89 (1.69-2.11)	1.15 (1.03-1.29)
3-4	1.41 (1.16-1.73)	1.02 (0.76-1.35)	2.93 (2.58-3.33)	1.28 (1.11-1.48)
Over 5	1.20 (0.92-1.57)	1.31 (0.94-1.82)	4.66 (4.04-5.36)	1.53 (1.28-1.83)

CI, confidence interval; HR, hazard ratios. Bold values indicate the statistical significance.

*Adjusted for sex.

TABLE 3 Sibling-matched cohort analysis for developing asthma following antibiotic exposure; Cohort 2 (N = 28 085)

Variables	Antibiotic exposure during the foetal period	Antibiotic exposure during the first year of life
	HR (95% CI)	HR (95% CI)
Male infant	1.43 (1.17-1.75)	1.41 (1.15-1.72)
Any antibiotic exposure*	1.34 (1.05-1.72)	1.62 (1.27-2.07)
Exposure by type of antibiotic*		
Penicillin	1.21 (0.77-1.91)	1.28 (0.97-1.69)
Cephalosporin	1.18 (0.87-1.61)	1.35 (1.07-1.71)
Macrolide	1.20 (0.81-1.78)	1.48 (1.17-1.87)
Other type of antibiotics	1.25 (0.83-1.88)	0.84 (0.61-1.15)
No. of antibiotic prescriptions*		
0 (Reference)	1.00	1.00
1-2	1.36 (1.04-1.79)	1.40 (1.08-1.83)
3-4	1.44 (0.87-2.39)	1.94 (1.41-2.67)
Over 5	1.03 (0.50-2.12)	2.75 (1.80-4.20)

CI, confidence interval; HR, hazard ratios. Bold values indicate the statistical significance.

*Adjusted for sex and siblings.

with an increased risk of asthma (relative risk 1.3-3.1, depending on the study).^{5,7,8} Our findings partly support their finding. Although antibiotic exposure during the foetal period slightly increased the risk of childhood asthma, this association disappeared after age 3 in our study. On the other hand, from the sibling-matched cohort analysis, we observed a significant association between antibiotic exposure in utero and asthma development. Environmental and hereditary factors are shared by siblings,¹² and we were able to adjust these potential confounders to investigate the development of asthma. Thus, antibiotic exposure in utero may influence the development of childhood asthma after considering familial factors.

One biologically plausible mechanism to explain the effects of antibiotic exposure in early life on the risk of asthma is that these drugs change the composition of the human gut microbiota.¹⁷ Gastrointestinal flora is important for the development of a healthy immune system, and overuse of antibiotics decreases the microbes in the bowel of infants.¹⁸ Furthermore, timing of antibiotic exposure may play a crucial role,¹⁹ because the effects of antibiotics are stronger during the first year of life than that after the first year. Antibiotic use during pregnancy was reported to be associated with an increased risk of asthma in the foetus, which indicates that the association of antibiotic exposure with asthma development is mediated through the modification of the bacterial ecology of the mother and foetus. However, our data did not provide enough evidence that antibiotic exposure in utero increased the risk of asthma development in the child. We conclude that direct influence by the use of antibiotics during pregnancy is weak compared to the remarkable impact of antibiotic use during the child's first year.

Our study used siblings as a comparison group in a matched cohort study. Instead of explicitly matching using a set of measured variables, the use of siblings as controls will automatically match on several unmeasured factors such as parental characteristics and genetic factors.²⁰ However, the estimate may be biased by confounders if siblings

are less similar with regard to confounders than to the exposure under study.²¹ In addition, our data restricted the children only to those who had siblings. With less numbers of subjects, a more limited statistical analysis may lead to bias. Our results demonstrated that the incidence of asthma was different between Cohort 1 and Cohort 2. This could be a result of restricting the subjects and may affect the association between antibiotics exposure and asthma development. On the other hand, an advantage in our study is that we used a large-scale database representing the general population. Furthermore, to the best of our knowledge, ours is the first study to consider the effects of antibiotic exposure during pregnancy and subsequent development of childhood asthma considering the type of antibiotics and counts of prescription using sibling information for adjustment of familial factors.

This study has several limitations. First, our cohort was drawn from an administrative claim database that did not include information on socio-economic status or environmental factors, which have also been suggested to influence the risk of asthma.^{22,23} In addition, we did not consider information on congenital heart disease or other diseases in our analysis, which could affect our results. Asthma has a variety of differential diagnosis, and congenital heart defects and primary immunodeficiency are among them. Second, from this database, we were unable to assess adherence to antibiotic medication by the children. If the children did not take antibiotics as prescribed, it may result in misclassification of exposure and results of any associations found may be weaker. Third, we have information on the birth year and month of the children but not the date because of the privacy protection policy of the data provider. Although we excluded preterm children and estimated the gestation period of the mothers' pregnancies, there may have been some degree of misclassification of the gestation period, resulting in misclassification of antibiotic exposure during the foetal period. Fourth, our definition of asthma may underestimate its incidence. We identified asthma development by

the prescription of ICS and other controllers, which may represent moderate or severe asthma cases but fail to identify milder cases. However, clinicians may find it difficult to differentiate between mild asthma and transient wheezing.²⁴ Wheezing is common symptom among preschool children, and Tenero et al²⁵ reported that approximately 50% of children experience wheezing up to 6 years of age. Therefore, to confirm robust asthma in children, we define asthma children as users of ICS and other controllers. Finally, our analysis did not identifying the situation for which antibiotics had been prescribed. Antibiotics are often prescribed for children with respiratory infections that lead to asthma.²⁶ Children who are at a risk of asthma may likely be prescribed antibiotics, resulting in an indication bias between antibiotic use and asthma development;²⁷ thus, further studies addressing indication bias of antibiotics are needed.

In conclusion, our study showed that exposure to antibiotics during the first year of life was associated with the development of childhood asthma even after adjusting for familial factors. A dose-response relationship between antibiotic exposure and asthma development and with the use of macrolide antibiotics was robustly observed. In contrast, we did not find enough evidence for an association between prenatal exposure and asthma development because of the weak relationship observed. Taken together, excessive concerns may not be associated with the use of prenatal antibiotics, and macrolide prescription in the early years after birth should be used with discretion.

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