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No association between prenatal antibiotics exposure and atopic dermatitis among Japanese infants

To the editor,

Prenatal antibiotics exposure has been suggested to be a risk factor for childhood allergic disease, possibly by affecting the development of a healthy and diverse microbiome, which is important for immune maturation (1-3). Atopic dermatitis (AD) is often the first manifestation of the so-called 'atopic march' and has a prevalence of over 10% among children in many developed countries (4). We aimed to investigate the association between prenatal antibiotics exposure and AD at age 1 in the Japan Environment and Children's Study (JECS).

JECS is a nationwide government-funded birth cohort study that aimed to evaluate the effects of environmental factors on children's health and development. The study method is described in detail elsewhere (5). Briefly, women in early pregnancy were recruited at 15 regional centres in Japan between 2011 and 2014 and followed up by self-administered questionnaires, interviews and obstetric medical records. The JECS protocol was approved by the Institutional Review Board on Epidemiological Studies of the Ministry of the Environment and by the Ethics Committees of all participating institutions. A written informed consent was obtained from all participants.

The present study was based on the dataset of jecs-an-20180131, released in March 2018. Prenatal antibiotics exposure was defined as systemic antibiotics use (orally or by injection) reported 1) by the mother

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at the first interview (at recruitment) or second interview (during second/third trimester) or 2) in medical records transcribed after delivery. Use of local antibiotics, such as in the form of ointments, gels or drops, were not included as prenatal antibiotic exposure. Data on demographic factors, medical history and environmental exposures were collected using self-administered questionnaires conducted at the time of the interviews. AD at age one-year-old was defined as having a doctor's diagnosis or an itchy skin rash, which was coming and going for at least 2 months on specific locations, as indicated in a questionnaire completed by the mother when the child was 12 months old (supplementary table 1).

All children with data on prenatal antibiotics use, data on AD status at age 1 and born through vaginal delivery were included in the analysis (supplementary figure, n=70,408). We excluded children born through Caesarean section because they were most likely to be exposed to antibiotics at delivery (n=20,099). Multiple logistic regression models were used to analyse the association between antibiotics use and AD at age 1 year by including the following potential confounders based on the results of previous studies: maternal education, maternal smoking during pregnancy, maternal history of asthma, AD and allergic rhinitis and child's sex (6). The following additional potential confounders were considered but not included in the model because they did not change the magnitude between the exposure and outcome by more than 10%: household income, maternal age at pregnancy, season of birth, gestational age, birth weight, having older siblings and duration of exclusive breastfeeding. We also stratified the analysis to assess whether the effect was modified by maternal allergic disease. All statistical analyses were performed using Stata version 15.1 (StataCorp, College Station, TX, USA).

Characteristics of the study population by prenatal antibiotics use are described in Supplementary Table 2. Among the 70,408 children included in the analysis, 20,869 (29.6%) reported prenatal antibiotics use. Table 1 describes the association of demographic and clinical characteristics to AD at age 1. The prevalence of AD among those who did not have any prenatal antibiotics use and those who did were 18.0% and 18.1%, respectively. In the multiple logistic regression analysis, the adjusted odds ratio (aOR) for the association

between prenatal antibiotics use and AD at age 1 year was 1.01 (95% confidence interval [CI]: 0.97–1.06), showing no evidence for the association (Table 2). The association was not modified by the history of maternal allergic disease.

The JECS study not only has a large sample size but is shown to be representative of the Japanese population (7), which is the major strength of our study. Furthermore, the study design has allowed us to collect information on a wide range of demographic and environmental factors before the development of AD.

Our result is in line with those of studies conducted in the US and those of the high-risk cohort study conducted in Denmark (8, 9), showing no association between prenatal antibiotics exposure defined by questionnaire or medical chart reviews and AD at age 2–3 years. On the contrary, a European cohort study of 1080 children showed that parent-reported prenatal antibiotics use was associated with an increased risk of diagnosed or observed AD at age 1-year old (aOR: 1.66, 95% CI: 1.11–2.48) (3). Additionally, a Danish birth cohort study of 62,650 mother-child pairs reported that prenatal antibiotics exposure increased the odds of developing AD at 18 months of age, which was consistent across different definitions of AD; however, this finding was only observed among children born from atopic mothers who used antibiotics in the first, second, and third trimesters (aOR: 1.45, 95% CI: 1.19–1.76), which only accounts for less than 2% of the entire cohort (2). A major limitation of our study is that we did not have sufficient data to assess the difference in the effect by the timing or dose of antibiotics used, as previously suggested (2, 10). Furthermore, data was not available in our study to investigate the difference in the effect according to the type of systemic antibiotics used. Thus, it remains uncertain whether the effect of prenatal antibiotics on AD was diluted in our study results. Additionally, our study population may be more ethnically and genetically homogenous than that of previous studies in Europe or Northern America, and therefore the results may not be directly comparable.

To account for the potential limitation of defining AD at age 1 without any objective measures, we conducted a sensitivity analysis using only diagnosed AD and obtained similar results (aOR: 1.02, 95% CI: 0.95–1.11). Furthermore, antibiotic use reported by the mother may have caused some misclassification of the

exposure, also leading to the underestimation of the effect. However, sensitivity analysis using only the data from medical records showed similar results (aOR: 0.98, 95% CI: 0.94–1.03).

In conclusion, in this cohort of approximately 70,000 Japanese children born by vaginal delivery, no association was found between prenatal antibiotics exposure and AD at age 1 year. Although several studies have examined the effect of prenatal exposures on the development of human microbiome and allergic diseases, further investigation is required to determine whether prenatal antibiotics exposure is a potential risk factor for childhood AD.

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Conflict of interest

All authors declare that they have no relevant conflicts of interest.

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Table 1. The association of demographic, clinical characteristics with atopic dermatitis at age one

	n	/N*	% atopic dermatitis
Prenatal antibiotics use			
No	8922	/49539	(18.0)
Yes	3780	/20869	(18.1)
<i>Maternal and family characteristics</i>			
Mother's age at pregnancy (years)			
<25	1369	/7780	(17.6)
25-29	3923	/21638	(18.1)
30-34	4520	/24985	(18.1)
≥35	2863	/15825	(18.1)
Household annual income (yen)			
<4million	4735	/25910	(18.3)
4-5	3999	/22021	(18.2)
6-7	1847	/10480	(17.6)
≥8	1299	/7083	(18.3)
Maternal education (years)			
<10	512	/2941	(17.4)
10-12	3717	/21437	(17.3)
≥13	8391	/45527	(18.4)
Maternal history of asthma			
No	10926	/62778	(17.4)
Yes	1751	/7460	(23.5)

Maternal history of allergic rhinitis

No	7322	/44782	(16.4)
Yes	5355	/25456	(21.0)

Maternal history of atopic dermatitis

No	9647	/58996	(16.4)
Yes	3030	/11242	(26.9)

Maternal smoking during pregnancy

No	10630	/58296	(18.2)
Yes	1967	/11475	(17.1)

Older siblings

No	5783	/31774	(18.2)
Yes	6894	/38464	(17.9)

Child characteristics

Child's sex

Male	7395	/36091	(20.5)
Female	5306	/34299	(15.5)

Season of birth

spring-summer	6055	/35173	(17.2)
autumn-winter	6647	/35235	(18.9)

Gestational age (weeks)

≥37	12330	/68144	(18.1)
<37	370	/2249	(16.5)

Birth weight (g)

≥2500	12033	/66060	(18.2)
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<2500 665 /4336 (15.3)

Exclusive breast feeding for 4 months or more

No 6603 /38624 (17.1)

Yes 6099 /31784 (19.2)

* Numbers do not add up to the total (n=70,408) for the following variables due to missing data. The numbers of missing data; mother's age at pregnancy: n=180, household annual income: n=4914, maternal education: n=503, maternal history of asthma, allergic rhinitis and atopic dermatitis: n=170, maternal smoking during pregnancy: n=637, older siblings: n=170, child's sex: n=18, gestational age: n=15 and birth weight: n=12.

Table 2. Multiple logistic regression for the association between prenatal antibiotics use and atopic dermatitis at age one, stratified by maternal allergic disease*

	Odds ratio for atopic dermatitis at age one, 95%CI	P value
Total population		
Crude OR	1.01, 0.97-1.05	0.746
Adjusted OR**	1.01, 0.97-1.06	0.589
Stratification by maternal allergic disease		
No maternal allergic disease		
Crude OR	1.00, 0.93-1.07	0.981
Adjusted OR [†]	1.00, 0.94-1.07	0.994
Any maternal allergic disease		
Crude OR	1.00, 0.95-1.06	0.967
Adjusted OR [†]	1.00, 0.95-1.06	0.907

* N=69,324 with complete data were included in the final model, maternal allergic disease is defined as having either maternal history of asthma, atopic dermatitis or allergic rhinitis.

** Adjusted for child's sex, maternal education, maternal smoking during pregnancy, maternal history of asthma, atopic dermatitis and allergic rhinitis.

[†] Adjusted for child's sex, maternal education, maternal smoking during pregnancy.

1 Supplementary table 1. Definition of prenatal antibiotics use and atopic dermatitis at age one

	Definitions
Prenatal antibiotics use	Systemic use of antibacterial agents reported either, 1) by the mother at the first interview (at recruitment) or second interview (during second/third trimester) or 2) in medical records transcribed after delivery*
Atopic dermatitis at age one	Having either 1) a doctor diagnosis of atopic dermatitis, or 2) an itchy skin rash, which was coming and going for at least 2 months on one or more of the following locations; behind the knees; thigh; outside of the lower leg; in front of the ankles; under the buttocks; around the neck, ears, or eyes; cheek, scalp or forehead, in the questionnaire completed when the child was 12 months old.

2 * The timing of antibiotics use during pregnancy was only recorded in 1), thus it was not assessed for
3 this analysis.

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5 Supplementary table 2. Demographic and clinic characteristics of the study population by prenatal
6 antibiotics use

	No antibiotics (n=49,539)		Antibiotics used (n=20,869)		Total (n=70,408)	
	No	(%)	No	(%)	No	(%)
<i>Maternal and family characteristics</i>						
Maternal age at pregnancy (years)						
<25	5276	(10.7)	2504	(12.0)	7780	(11.0)
25-29	15243	(30.8)	6395	(30.6)	21638	(30.7)
30-34	17737	(35.8)	7248	(34.7)	24985	(35.5)
≥35	11195	(22.6)	4630	(22.2)	15825	(22.5)
missing	88	(0.2)	92	(0.4)	180	(0.3)
Household annual income (yen)						
<4million	18099	(36.5)	7811	(37.4)	25910	(36.8)
4-5	15632	(31.6)	6389	(30.6)	22021	(31.3)
6-7	7465	(15.1)	3015	(14.4)	10480	(14.9)
≥8	4975	(10.0)	2108	(10.1)	7083	(10.1)
missing	3368	(6.8)	1546	(7.4)	4914	(7.0)
Maternal education (years)						
<10	1973	(4.0)	968	(4.6)	2941	(4.2)
10-12	14961	(30.2)	6476	(31.0)	21437	(30.4)
≥13	32305	(65.2)	13222	(63.4)	45527	(64.7)
missing	300	(0.6)	203	(1.0)	503	(0.7)
Maternal history of asthma						
no	44439	(89.7)	18339	(87.9)	62778	(89.2)
yes	5020	(10.1)	2440	(11.7)	7460	(10.6)
missing	80	(0.2)	90	(0.4)	170	(0.2)
Maternal history of allergic rhinitis						
no	31881	(64.4)	12901	(61.8)	44782	(63.6)
yes	17578	(35.5)	7878	(37.7)	25456	(36.2)
missing	80	(0.2)	90	(0.4)	170	(0.2)
Maternal history of atopic dermatitis						
no	41637	(84.0)	17359	(83.2)	58996	(83.8)
yes	7822	(15.8)	3420	(16.4)	11242	(16.0)
missing	80	(0.2)	90	(0.4)	170	(0.2)
Maternal smoking during pregnancy						
no	41315	(83.4)	16981	(81.4)	58296	(82.8)
yes	7814	(15.8)	3661	(17.6)	11475	(16.3)
missing	410	(0.8)	227	(1.1)	637	(0.9)
Older sibling						
no	22443	(45.3)	9331	(44.7)	31774	(45.1)
yes	27016	(54.5)	11448	(54.9)	38464	(54.6)
missing	80	(0.2)	90	(0.4)	170	(0.2)
<i>Child characteristics</i>						
Child's gender						
male	25361	(51.2)	10730	(51.4)	36091	(51.3)
female	24164	(48.8)	10135	(48.6)	34299	(48.7)
missing	14	(<0.1)	4	(<0.1)	18	(<0.1)
Season of birth						
spring-summer	24659	(49.8)	10514	(50.4)	35173	(50.0)

autumn-winter	24880	(50.2)	10355	(49.6)	35235	(50.0)
Gestational age (weeks)						
≥37	48215	(97.3)	19929	(95.5)	68144	(96.8)
<37	1315	(2.7)	934	(4.5)	2249	(3.2)
missing	9	(<0.1)	6	(<0.1)	15	(<0.1)
Birth weight (g)						
≥2500	46673	(94.2)	19387	(92.9)	66060	(93.8)
<2500	2855	(5.8)	1481	(7.1)	4336	(6.2)
missing	11	(<0.1)	1	(<0.1)	12	(<0.1)
Exclusive breastfeeding for 4 months or more						
no	26979	(54.5)	11645	(55.8)	38624	(54.9)
yes	22560	(45.5)	9224	(44.2)	31784	(45.1)

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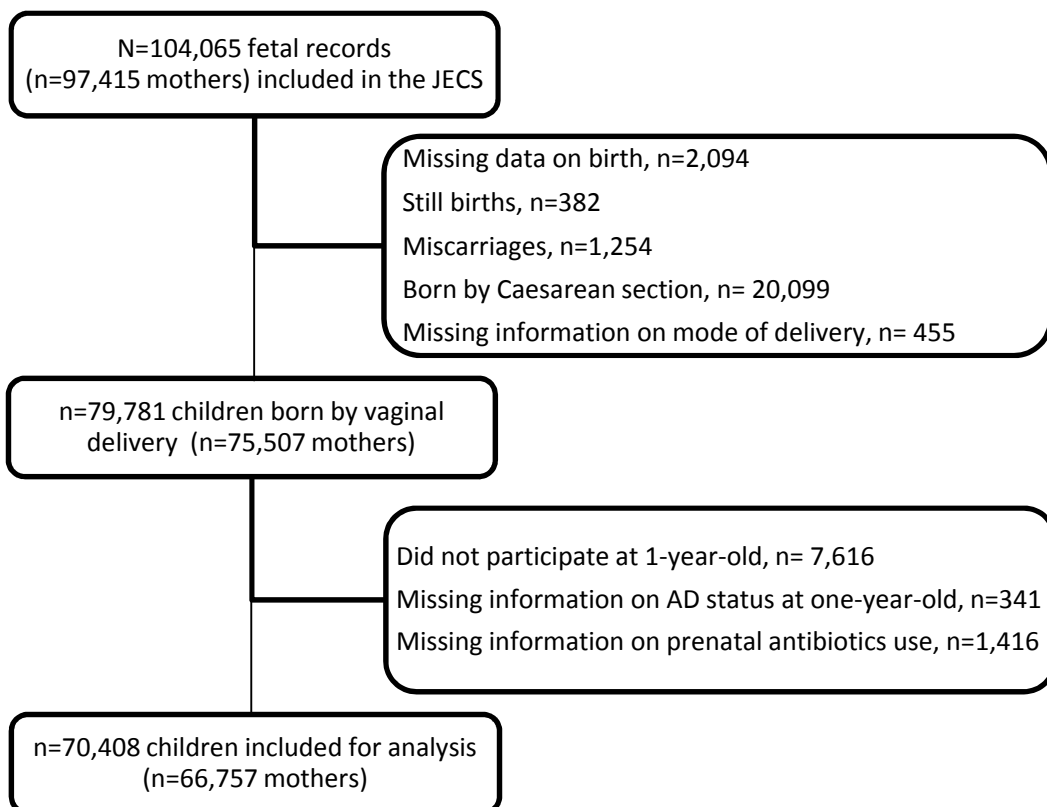
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17 Supplementary figure 1. Flow chart of the study population

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