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Abstract

Background: The aim of this study was to explore the association between maternal allergies with preterm birth by different total immunoglobulin E (IgE) levels.

Methods: Data of 81,791 pregnant women from the Japan Environment and Children's Study, a prospective birth cohort, were used. Maternal allergic diseases, including history of bronchial asthma (BA), atopic dermatitis (AD), and allergic rhinitis (AR) were obtained by self-administered questionnaires, serum total IgE level was measured at the first trimester, and obstetrical outcomes from medical records transcripts were analyzed. The association between maternal allergic disease and obstetric outcome, including threatened abortion, preterm labor, early preterm birth (22–33 weeks), and late preterm birth (34–36 weeks), were examined by logistic regression. Subgroup analyses were performed by IgE level.

Results: Maternal BA and AR were associated with an increased risk of threatened abortion and preterm labor, but high total IgE level was associated with a decreased risk of preterm labor. There was little difference in associations between allergic disease and threatened abortion and preterm labor by total IgE levels. Although there was no significant association between allergic disease and preterm birth, if total IgE was high, AR was significantly associated with a decreased risk of early preterm birth (aOR, 0.60; 95%CI, 0.43–0.86). There was significant evidence for differences associated with total IgE levels (p-values for the interaction of the effects of AD and AR on early preterm birth were 0.039 and 0.015, respectively).

Conclusions: The effect of allergy on preterm birth might differ depending on the total IgE level.

Key words: allergic diseases, immunoglobulin E, preterm birth, threatened abortion, preterm labor

1 Introduction

Preterm babies have a high risk of mortality, heart failure and disabilities, and are more susceptible to respiratory disorders, hypothermia, hypoglycemia, and infection than full-term neonates ^{1,2}. Allergic diseases, including bronchial asthma (BA), atopic dermatitis (AD), and allergic rhinitis (AR) are the most common chronic disorders among pregnant women ³. It was suggested that allergic diseases might influence obstetric outcomes ^{4,5}. Previous studies showed that maternal BA was associated with increased risk of adverse obstetric outcomes, including preterm birth (PTB) ⁴. However, associations between other maternal allergic diseases including AD and AR and adverse obstetric outcomes have rarely been reported ^{5,6}. Saito et al. reported the associations between maternal allergic features, including BA, AD and AR, and small for gestational age ⁷ and preterm pregnancy outcomes ⁶. They found maternal history of allergic diseases (BA, AR, allergic conjunctivitis, food allergy, drug allergy, and contact dermatitis) increased the risk of preterm labor (PTL) ⁶. In addition, they found maternal history of allergic conjunctivitis and AD decreased the risk of early PTB and late PTB, respectively ⁶.

During pregnancy, immunological deviation, a shift from T-helper (Th) cell type 1-dominated to Th2-dominated immune responses prevented fetal rejection ⁸⁻¹⁰. Allergic disease is also Th2-biased, and IgE is an alternative marker for Th2-biased immune responses ¹¹. Furthermore, Th2-dominated immunological deviation among allergic mothers favored the continuation of pregnancy compared with non-allergic mothers ⁵. Moreover, Th2-cytokine levels were reported to be lower and Th1-cytokine levels higher among mothers with recurrent abortions ¹². Thus, atopy was hypothesized to be protective against PTB. The Norwegian National Cohort study showed maternal BA was associated with an increased risk of PTB, but AD and AR were associated with a decreased risk of PTB ⁵. Although the authors suggested that immunological deviation to Th2 helped prevent adverse obstetric outcomes, they did not assess immunological deviation including maternal blood total IgE level. To date, no study has reported an association between maternal allergic features with PTB considering the maternal total IgE level. We hypothesized that the effects of allergic diseases on PTB differ by the level of IgE.

The aim of this study was to explore associations of maternal allergic disease with threatened abortion, PTL, and PTB considering the total IgE level in a large Japanese birth cohort from the Japan Environment and Children's Study (JECS).

2 Methods

2.1 Population and ethics

The subjects of this study were pregnant women participating in the JECS, a nationwide birth cohort study to evaluate the impact of environmental factors during the fetal period and early childhood on child health, with follow-up until age 13 years^{13,14}. The protocol and baseline data of JECS were described elsewhere^{13,14}. Overall, 100,000 pregnant women who lived in one of 15 JECS study Areas covering a wide geographical area of Japan, were recruited during early pregnancy from January 2011 to March 2014.

The JECS protocol was approved by the Ministry of the Environment's Institutional Review Board on Epidemiological Studies (no. 100910001) and by the Ethics Committees of all participating institutions. Written informed consent was obtained from all participants. The JECS was conducted in accordance with the Helsinki Declaration and Japanese national regulations.

2.2 Sample selection

The present study is based on the dataset of jecs-an-20180131, which was released in March 2018. The data set included 104,065 fetal records. Of these women, 5,689 women participated two or three times in the JECS; however, only their first record was included in this analysis (i.e. when the same mother registered multiple children). Pregnant women with a singleton pregnancy, and who had a live birth were included, and cases of multiple pregnancies were excluded ($n = 1,910$). Of 96,466 women, we excluded those for whom data for serum IgE level, allergic history, or pregnancy complication history were missing. The final study population was 81,791 pregnant women.

2.3 Variables

2.3.1 Outcomes

The outcomes of the present study were threatened abortion, PTL and PTB. Because of the definitions used, each outcome might have overlapped. Trained research Co-ordinators performed data transcription from medical records regarding the medical histories of past and present pregnancies, participants' and their offspring's physical status, and obstetrical complications. Threatened abortion was a condition in which there were signs of abortion, but it had not yet occurred. Preterm labor (PTL) was defined as a condition in which regular uterine contractions and/or premature cervical maturation occurred prior to 37 weeks gestation, and the risk of PTB was high. Preterm birth (PTB) was defined as birth before 37 weeks gestation and divided into two categories: early (22–33 weeks) and late PTB (34–36 weeks). Obstetrical complications, including threatened abortion and PTL, were diagnosed by a clinician based on the Guidelines for Obstetrical Practice in Japan 2014¹⁵.

2.3.2 Exposures

The exposures of present study, maternal allergic diseases, including the history of BA, AD and AR, were confirmed by self-administered questionnaires. Participants were asked to report their lifetime history of allergic

diseases as diagnosed by clinicians ³. Maternal blood samples were collected during the first trimester and the serum total IgE level was assayed using an ImmunoCAP system (Thermo Fisher Scientific, Sweden). High levels of serum total IgE level were defined as >170 IU/mL ⁷, and sensitization to specific IgE, including *Dermaphagoides pteronyssinus* (Der p 1) or Japanese cedar, was defined as ≥ 0.7 UA/mL.

2.3.3 Covariates

Information on parity was classified into four categories: 0, 1, 2, and more. We calculated the pre-pregnancy body mass index (BMI) from information regarding pre-pregnancy height and weight, which was then categorized into three groups: underweight (<18.5 kg/m²), normal (18.5–24.9 kg/m²) and overweight (≥ 25 kg/m²).

Information on lifestyle (maternal and partner smoking and maternal drinking habits) and other background information (maternal education, household income and maternal employment at the first trimester) was collected using self-administered questionnaires. Maternal or partner smokers were classified as nonsmokers, ex-smokers, or current smokers. Drinking habits were defined as non-drinker, ex-drinker, and current drinker. The length of maternal education was categorized as ≤ 12 years and >12 years. Household income was categorized as ≥ 6 million yen, and < 6 million yen. Maternal age at the time of delivery was categorized as <20 years, 20–24 years, 25–29 years, 30–34 years, 35–39 years, and ≥ 40 years. Those who answered that they were housewives, students, or unemployed at the first trimester were defined as non-employed, and others were defined as employed. We selected the above covariates for models based on prior studies of obstetric risks associated with PTB ^{2,16,17}.

2.4 Statistical analyses

Summary measures of demographic and social variables, and obstetrical outcomes were calculated according to maternal allergic diseases (BA, AD, AR, and high level of IgE) or none of these diseases. Women with a record of more than one of the three diseases were included in the analysis of each.

In the main analyses, we evaluated how maternal allergic diseases were related to obstetric outcomes, including threatened abortion, PTL, and PTB. A logistic regression model was used to examine the association of maternal allergic diseases with PTB-related obstetric outcomes. The total IgE was analyzed as a binary variable (low IgE [≤ 170 IU/mL] as reference group). Potential confounders, including maternal age, parity, BMI at early pregnancy, smoking and alcohol use during pregnancy, maternal education, maternal employment, and annual family income were used to estimate the adjusted odds ratio (aOR), and 95% confidence interval (CI) in the multivariable analysis. For PTL and PTB, in addition to the above covariates, we adjusted for threatened abortion, and threatened abortion and PTL, respectively. Moreover, to examine modification of effect of allergic history obstetric outcomes by IgE level, subgroup analyses were performed for each allergic history by total IgE level. We also tested whether the association between allergic disease and obstetric outcome changed by the level of total IgE using the Wald test. Analyses considering specific IgE sensitization (Der p 1 or Japanese

cedar) were also conducted. All analyses were conducted using SAS.9.4 (SAS Institute Inc., Cary, NC, USA). A p-value <0.05 was considered significant for every statistical analysis.

3 Results

Table 1, 2 and Supporting information Table 1 present the characteristics of participants. Overall, 8,897 (10.9%) mothers had BA, 12,951 (15.8%) had AD, 29,512 (36.1%) had AR, and 18,991 (23.2%) had a high total IgE level. The overall rates were: threatened abortion = 12.5%; PTL = 19.6%; early PTB = 1.0%; and late PTB = 3.7%. Of 820 early PTB, 18.1%, 52.2% and 27.9% had threatened abortion, PTL and premature rupture of membranes, respectively. And of 3006 late PTB, 14.8%, 46.0% and 24.1% had threatened abortion, PTL and premature rupture of membranes, respectively.

Tables 3 and 4 present the OR of threatened abortion, PTL, and PTB adjusted for confounders with allergic disease and total IgE level. Maternal history of BA and AR were associated with an increased risk of threatened abortion and PTL (BA for threatened abortion: aOR, 1.06; 95%CI, 0.98–1.14; AR for threatened abortion: aOR, 1.11; 95%CI, 1.06–1.17; BA for PTL: aOR, 1.11; 95%CI, 1.04–1.18; AR for PTL: aOR, 1.09; 95%CI, 1.05–1.14, respectively, Table 3). However, women with a high IgE level were associated with a decreased risk of PTL (aOR, 0.92; 95%CI, 0.87–0.96, Table 3). Interactions between allergic disease and total IgE level on threatened abortion and PTL were not significant. Subgroup analysis showed that BA with a low total IgE level was significantly associated with an increased risk of PTL (aOR, 1.13; 95%CI, 1.05–1.23, Table 5) and that AR with a low total IgE level was significantly associated with an increased risk of threatened abortion and PTL (aOR, 1.12; 95%CI, 1.06–1.18; aOR, 1.11; 95%CI, 1.06–1.16, respectively, Table 5).

There was no significant association between allergic disease and PTB (Table 4). The effects of allergic disease on early PTB vary but not on late PTB by the level of total IgE: p-values for the interaction of the effects of BA, AD, and AR on early PTB were 0.24, 0.039, and 0.015 respectively, and p-values for the interaction of the effects of BA, AD, and AR on late PTB were 0.49, 0.32, and 0.32 respectively. Moreover, AR with a high total IgE level were significantly associated with a decreased risk of early PTB (aOR, 0.60; 95%CI, 0.43–0.86, Table 6). Subgroup analyses stratified by the level of specific IgE sensitization (Der p 1 or Japanese cedar) revealed that the stratum specific effect estimates were similar to that of the subgroup analysis stratified by total IgE level (Supporting information Tables 2–5).

4 Discussion

The findings of this study suggested that maternal BA and AR were associated with an increased risk of threatened abortion and PTL, and that a high total IgE level was associated with a decreased risk of PTL. There was little difference in associations between allergic disease and threatened abortion and PTL by total IgE levels. There was no significant association between allergic disease and PTB. However, if total IgE was high, AR was significantly associated with decreased risk of early PTB. There was significant differences in the effects of AD and AR on early PTB by total IgE levels.

Previous studies suggested that BA, especially when poorly controlled, was a risk for PTL and PTB^{4,18}. BA was described as having a disease-specific adverse mechanism, and because this outweighed the protective effects of Th2 immune responses, BA increased the risk of PTL and PTB⁴. However, AR and AD were reported to reduce the risk of PTB,⁵ though AR but not AD were reported to increase risk of PTL¹⁹. The results of the current study mostly agree with these previous results^{4,5,19}, except there was no significant association between allergic disease and PTB (Table 4). Our results showing that high levels of IgE were protective against PTL (Table 3) and the modification effects of total IgE in AR and AD on early PTB (Table 6) were in line with a previous hypothesis: “atopy was protective against PTB”⁵.

In terms of BA, the results of this study were in line with those of previous studies. A systematic review reported that BA increased the risk of PTB⁴. Three mechanisms by which BA might increase the risk of PTB have been proposed: maternal chronic hypoxia, smooth muscle hyperactivity, and asthma medication^{4,18}. With regard to the use of asthma medications during pregnancy, there were several reports of a risk of PTB²⁰⁻²². However, many studies support the fact that inadequate asthma treatment or management, rather than the potential risks of drugs, affects pregnancy outcomes, including PTB^{4,20}. Furthermore, the greater the severity of BA, the greater the risk of PTB⁴. In the current study, the effects of BA on PTB did not vary significantly by total IgE level; however, when stratified by IgE level, BA tended to increase the risk of PTB when IgE was not high (Table 6), suggesting the balance between the preventive effect of Th2 immunity and BA itself affected the risk of PTB. According to Saito et al., non-allergic BA (BA with a low total IgE level) increased the risk of small for gestational age, which was explained by the higher severity of asthma in non-allergic BA cases⁷. However, in the current study, we did not investigate whether the BA with high total IgE group had severe asthma; therefore, we could not conclude that a BA-specific mechanism overshadowed the preventive effect of Th2 immunity in the BA with low total IgE group. Further studies including the current severity of BA are needed to clarify the preventive effects of total IgE.

There have been few reports of an association between AD and PTB^{5,23}. The Norwegian National Cohort study reported maternal BA was associated with an increased risk of PTB, but that AD and AR were associated with a decreased risk of PTB⁵. The authors explained the mechanism was related to a Th2 immune deviation by AD and AR. In our study, we found that AD with a high total IgE tended to have a preventive effect for PTL (Table 5), and significant modification of the effects of total IgE and AD on early PTB using interaction terms (Table 6). In contrast to BA, hypoxemia in AD is unlikely, and therefore Th2-biased immunity might be

linked to preventive effects to PTB, but more research is needed.

Regarding AR, consistent preventative effects of AR have been reported in PTB^{5,23,24}, but AR was reported to increase the risk PTL in the previous study¹⁹, which were in line with our study results. It was unclear why AR had opposite effects on PTB and PTL. In our study, we found that AR with a high total IgE had a significant preventive effect on early PTB (Table 6), and a significant modification of the effects of total IgE and AR on early PTB using interaction terms (Table 6). These results suggest that there is a need for stratified analysis by IgE levels, when studying the association between AR and PTB. Th2-biased immunity may be linked to preventive effects of AR, but more research is needed.

The strengths of this study were examining the association between maternal allergy and PTB, threatened abortion and PTL, using a large representative sample of the Japanese general population¹⁴, and to adjust for numerous confounding factors. We demonstrated an association between allergy and PTB in terms of total IgE level at the first trimester. However, this study had some limitations. Allergies in the present study have been asked about their lifetime prevalence, and the severity of any current allergic diseases were unknown^{3,7}. Therefore, it was not possible to evaluate the severity of current allergic diseases or the relationship between therapeutic drugs and PTB. In addition, the results of the current study might have a misclassification bias, but this would be underestimated because this bias is considered a non-differential misclassification. We examined total IgE level as an alternative marker for Th2-biased immune responses, but did not assess T-cell subset or Th1 and Th2 cytokine profiles. Thus further study is needed for immunological deviation during pregnancy.

In conclusion, we found that maternal BA and AR were associated with an increased risk of threatened abortion and PTL. The current study did not find significant evidence regarding a difference in the effects of allergic disease on threatened abortion and PTL by the level of IgE. Although there was no significant association between allergic disease and PTB, the results of sub-group analyses indicated that AR might have protective effects on early PTB when the level of total IgE is high. And there was significant differences in the effects of AD and AR on early PTB by total IgE levels. Further studies are needed to confirm the potential influence of total IgE on the association between allergic diseases and obstetric outcomes.

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Disclosure

The authors declare no conflict of interest.

Author contribution

R.K. contributed to the conception and design of this study, performed the statistical analysis, and drafted the manuscript. H.Y., Y.A., T.O., K.M. and S.H. critically reviewed the manuscript. R.S. and Z.Y. critically reviewed the manuscript and supervised the whole study process. All authors read and approved the final manuscript.

Data availability:

Data are unsuitable for public deposition due to ethical restrictions and legal framework of Japan. It is prohibited by the Act on the Protection of Personal Information (Act No. 57 of 30 May 2003, amendment on 9 September 2015) to publicly deposit the data containing personal information. Ethical Guidelines for Medical and Health Research Involving Human Subjects enforced by the Japan Ministry of Education, Culture, Sports, Science and Technology and the Ministry of Health, Labour and Welfare also restricts the open sharing of the epidemiologic data. All inquiries about access to data should be sent to: jecs-en@nies.go.jp. The person responsible for handling enquiries sent to this e-mail address is Dr Shoji F. Nakayama, JECS Programme Office, National Institute for Environmental Studies.

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Table 1 Characteristics of participants (n = 81761)

Maternal age at birth		
mean ± SD	30.8	± 5.0
Pre-pregnancy Body Mass Index (kg/m ²)		
mean ± SD	21.2	± 3.3
Education (%)		
<=12 years	28812	(35.7)
>12 years	51808	(64.3)
Household income (%)		
<6 million yen	55120	(73.1)
>=6 million yen	20320	(26.9)
Maternal smoking (%)		
Non-	47636	(58.7)
Ex-	29821	(36.7)
Current	3758	(4.6)
Partner's smoking (%)		
Non-	21943	(27.4)
Ex-	20841	(26.0)
Current	37314	(46.6)
Drinking (%)		
Non-	28212	(34.6)
Ex-	45168	(55.5)
Current	8063	(9.9)
Maternal job (%)		

yes	53601	(67.5)
Total IgE		
mean ± SD	161.5	± 401.8
Parity (%)		
0	33535	(42.0)
1	30230	(37.9)
≥2	16009	(20.1)
Mode of delivery (%)		
Vaginal delivery	66176	(81.1)
Caesarean section	15394	(18.9)

Table 2 Perinatal characteristics of women with or without allergic disease

	Total		Mother with asthma		Mother with atopic dermatitis		Mother with allergic rhinitis		Mother with high IgE (>170 IU/mL)		Mother with no atopic disease	
	(n = 81791)		(n = 8897)		(n = 12951)		(n = 29512)		(n = 18991)		(n = 36877)	
Gestational age (%)												
22–33weeks (early preterm birth)	820	(1.0)	91	(1.0)	121	(0.9)	281	(1.0)	191	(1.0)	360	(1.0)
34–36weeks (late preterm birth)	3006	(3.7)	327	(3.7)	421	(3.3)	1053	(3.6)	644	(3.4)	1418	(3.9)
37–41weeks	77765	(95.1)	8449	(95.0)	12375	(95.6)	28120	(95.3)	18109	(95.4)	35006	(94.9)
42–45weeks	200	(0.2)	30	(0.3)	34	(0.3)	58	(0.2)	47	(0.3)	93	(0.3)
Pregnancy complications (%)												
Threatened aborthion	10143	(12.4)	1162	(13.1)	1674	(12.9)	3891	(13.2)	2349	(12.4)	4428	(12.0)
Preterm labor	16004	(19.6)	1882	(21.2)	2537	(19.6)	6054	(20.5)	3581	(18.9)	7033	(19.1)
Birthweight (g)												
mean ± SD	3022.8	±420.2	3019.8	±425.4	3020.5	±416.6	3028.9	±419.0	3022.2	±421.4	3021.1	±418.7

Mothers with more than one disease was included in each category.

Table 3. Association between threatened abortion, preterm labor, and allergic disease and total IgE level.

	Threatened abortion						Preterm labor					
	crude OR	95%CI		aOR [†]	95%CI		crude OR	95%CI		aOR [†]	95%CI	
IgE	1.00	0.95	−1.05	0.97	0.91	−1.02	0.94	0.90	−0.98	0.92	0.87	−0.96
BA	1.07	1.00	−1.14	1.06	0.98	−1.14	1.12	1.06	−1.18	1.11	1.04	−1.18
AD	1.06	1.00	−1.12	1.03	0.97	−1.10	1.00	0.96	−1.05	0.98	0.93	−1.03
AR	1.12	1.07	−1.17	1.11	1.06	−1.17	1.10	1.06	−1.14	1.09	1.05	−1.14

OR, odds ratio; aOR, adjusted odds ratio; BA, bronchial asthma; AD, atopic dermatitis; AR, allergic rhinitis.

[†]Fully adjusted model includes maternal age, maternal smoker, partner smoker, maternal drinking, BMI, maternal education, maternal job, household income and threatened abortion (for preterm labor).

Table 4. Association between preterm birth and allergic disease and total IgE level.

	Early preterm birth (22–33 weeks)						Late preterm birth (34–36 weeks)					
	crude OR	95%CI		aOR [†]	95%CI		crude OR	95%CI		aOR [†]	95%CI	
IgE [‡]	1.00	0.85	–1.18	1.04	0.86	–1.27	0.90	0.82	–0.98	0.97	0.87	–1.07
BA	1.02	0.82	–1.27	0.96	0.74	–1.25	1.00	0.89	–1.12	1.00	0.88	–1.15
AD	0.92	0.78	–1.12	1.01	0.80	–1.27	0.86	0.78	–0.96	0.89	0.79	–1.01
AR	0.92	0.80	–1.07	0.85	0.71	–1.01	0.95	0.88	–1.03	0.94	0.87	–1.03

OR, odds ratio; aOR, adjusted odds ratio; BA, bronchial asthma; AD, atopic dermatitis; AR, allergic rhinitis.

[†]Fully adjusted model includes maternal age, maternal smoker, partner smoker, maternal drinking, BMI, maternal education, maternal job, household income, threatened abortion and preterm labor.

[‡]Reference group was low IgE (<= 170 IU/mL).

Table 5. Association between threatened abortion, preterm labor, and allergic disease in the total IgE status subgroup.

	Threatened abortion						Preterm labor					
	low IgE (<= 170 IU/mL)			high IgE (>170 IU/mL)			low IgE (<= 170 IU/mL)			high IgE (>170 IU/mL)		
	aOR [†]	95%CI		aOR [†]	95%CI		aOR [†]	95%CI		aOR [†]	95%CI	
BA	1.03	0.94	−1.13	1.10	0.98	−1.25	1.13	1.05	−1.23	1.06	0.96	−1.17
AD	1.04	0.97	−1.13	1.01	0.91	−1.12	0.96	0.90	−1.03	1.01	0.92	−1.10
AR	1.12	1.06	−1.18	1.10	1.00	−1.21	1.11	1.06	−1.16	1.04	0.96	−1.13

OR, odds ratio; aOR, adjusted odds ratio; BA, bronchial asthma; AD, atopic dermatitis; AR, allergic rhinitis.

[†]Fully adjusted model includes maternal age, maternal smoker, partner smoker, maternal drinking, BMI, maternal education, maternal job, household income and threatened abortion (for preterm labor).

P–value for interaction on threatened abortion; BA and total IgE = 0.41; AD and total IgE = 0.72; AR and total IgE = 0.75.

P–value for interaction on preterm labor; BA and total IgE = 0.27; AD and total IgE = 0.65; AR and total IgE = 0.15

Table 6. Association between preterm birth and allergic disease in the total IgE status subgroup.

	Early preterm birth (22–33 weeks)						Late preterm birth (34–36 weeks)					
	low IgE (<= 170 IU/mL)			high IgE (>170 IU/mL)			low IgE (<= 170 IU/mL)			high IgE (>170 IU/mL)		
	aOR [†]	95%CI		aOR [†]	95%CI		aOR [†]	95%CI		aOR [†]	95%CI	
BA	1.03	0.74	–1.42	0.88	0.56	–1.39	1.04	0.88	–1.23	0.95	0.76	–1.19
AD	1.17	0.89	–1.53	0.74	0.49	–1.13	0.93	0.84	–1.07	0.84	0.68	–1.03
AR	0.94	0.77	–1.15	0.60	0.43	–0.86	0.94	0.85	–1.04	0.94	0.79	–1.13

OR, odds ratio; aOR, adjusted odds ratio; BA, bronchial asthma; AD, atopic dermatitis; AR, allergic rhinitis.

[†]Fully adjusted model includes maternal age, maternal smoker, partner smoker, maternal drinking, BMI, maternal education, maternal job, household income, threatened abortion and preterm labor.

P–value for interaction on early preterm birth; BA and total IgE = 0.24; AD and total IgE = 0.039; AR and total IgE = 0.015.

P–value for interaction on late preterm birth; BA and total IgE = 0.49; AD and total IgE = 0.32; AR and total IgE = 0.91.

Table S1. Characteristics of women with or without allergic disease

	Total (n = 81791)		Mother with asthma (n = 8897)		Mother with atopic dermatitis (n = 12951)		Mother with allergic rhinitis (n = 29512)		Mother with high IgE (>170 IU/mL) (n = 18991)		Mother with no allergic disease (n = 36877)	
Maternal age at birth												
mean ± SD	30.8	±5.0	30.5	±5.0	30.4	±4.7	31.0	±4.9	30.2	±5.1	30.8	±5.1
Pre-pregnancy BMI (kg/m ²)												
mean ± SD	21.2	±3.3	21.7	±3.7	21.2	±3.2	21.2	±3.2	21.4	±3.4	21.2	±3.2
Education (%)												
<=12	28812	(35.7)	3388	(38.8)	4063	(31.8)	9239	(31.8)	7087	(37.9)	13627	(37.5)
>12	51808	(64.3)	5342	(61.2)	8706	(68.2)	19860	(68.2)	11602	(62.1)	22734	(62.5)
Household income (%)												
<6 million yen	55120	(73.1)	6160	(75.1)	8747	(72.6)	19691	(71.8)	13203	(75.7)	24837	(73.2)
>=6 million yen	20320	(26.9)	2041	(24.9)	3295	(27.4)	7738	(28.2)	4249	(24.3)	9077	(26.8)
Maternal smoking (%)												
Non-	47636	(58.7)	4623	(52.3)	7558	(58.8)	17422	(59.4)	10439	(55.4)	21696	(59.3)
Ex-	29821	(36.7)	3638	(41.1)	4737	(36.8)	10762	(36.7)	7311	(38.8)	13234	(36.1)
Current	3758	(4.6)	581	(6.6)	565	(4.4)	1138	(3.9)	1090	(5.8)	1687	(4.6)
Partner's smoking (%)												
Non-	21943	(27.4)	2246	(25.8)	3551	(27.8)	8238	(28.4)	4880	(26.3)	9810	(27.2)
Ex-	20841	(26.0)	2239	(25.7)	3424	(26.8)	7931	(27.4)	4572	(24.6)	9185	(25.5)
Current	37314	(46.6)	4216	(48.5)	5782	(45.3)	12831	(44.2)	9105	(49.1)	17051	(47.3)
Drinking (%)												
Non-	28212	(34.6)	2965	(33.5)	4429	(34.3)	10008	(34.0)	6570	(34.7)	12864	(35.0)
Ex-	45168	(55.5)	5059	(57.1)	7221	(56.0)	1636	(55.6)	10581	(55.9)	20250	(55.2)
Current	8063	(9.9)	834	(9.4)	1248	(9.7)	3036	(10.3)	1760	(9.3)	3596	(9.8)
Maternal job (%)												
yes	53601	(67.5)	5849	(67.7)	8455	(67.1)	19212	(66.7)	12261	(66.4)	24333	(68.1)
Total IgE												
mean ± SD	161.5	±401.8	324.6	±679.4	354.7	±819.4	221.5	±479.1	525.3	±719.0	43.1	±40.6
Parity (%)												
0	33535	(42.0)	3614	(41.7)	5688	(45.2)	11763	(40.9)	7873	(42.5)	15183	(42.2)
1	30230	(37.9)	3246	(37.4)	4739	(37.7)	11123	(38.7)	6886	(37.2)	13562	(37.7)
>=2	16009	(20.1)	1814	(20.9)	2156	(17.1)	5878	(20.4)	3751	(20.3)	7265	(20.2)
Mode of delivery (%)												
Vaginal delivery	66176	(81.1)	7061	(79.6)	10599	(82.1)	23862	(81.1)	15323	(80.9)	29885	(81.3)
Caesarean section	15394	(18.9)	1809	(20.4)	2312	(17.9)	5564	(18.9)	3609	(19.1)	6898	(18.8)

Mothers with more than one disease were included in each category.

Table S2. Association between threatened abortion, preterm labor, and allergic disease in the Derp1 IgE status subgroup.

	Threatened abortion						Preterm labor					
	Derp1 IgE (<0.7UA/mL)			Derp1 IgE (0.7UA/mL ≤)			Derp1 IgE (<0.7UA/mL)			Derp1 IgE (0.7UA/mL ≤)		
	aOR [†]	95%CI		aOR [†]	95%CI		aOR [†]	95%CI		aOR [†]	95%CI	
BA	1.06	0.93	-1.22	1.07	0.98	-1.17	1.12	1.00	-1.25	1.12	1.04	-1.21
AD	1.01	0.92	-1.11	1.06	0.97	-1.15	1.01	0.93	-1.09	0.95	0.88	-1.02
AR	1.10	1.03	-1.18	1.14	1.06	-1.23	1.09	1.03	-1.15	1.10	1.04	-1.17

OR, odds ratio; aOR, adjusted odds ratio; BA, bronchial asthma; AD, atopic dermatitis; AR, allergic rhinitis.
†Fully adjusted model includes maternal age, maternal smoker, partner smoker, maternal drinking, BMI, maternal education, maternal job, household income and threatened abortion (for Preterm labor).
P-value for interaction on threatened abortion; BA and Derp1 IgE = 0.82; AD and Derp IgE = 0.42; AR and Derp1 IgE = 0.42
P-value for interaction on Preterm labor; BA and Derp1 IgE = 0.98; AD and Derp1IgE = 0.30; AR and Derp1 IgE = 0.87

Table S3. Association between preterm birth and allergic disease in the Derp1 IgE status subgroup.

	Early preterm birth (23–31 weeks)						Late preterm birth (32–36 weeks)					
	Derp1 IgE (<0.7UA/mL)			Derp1 IgE (0.7UA/mL ≤)			Derp1 IgE (<0.7UA/mL)			Derp1 IgE (0.7UA/mL ≤)		
	aOR [†]	95%CI		aOR [†]	95%CI		aOR [†]	95%CI		aOR [†]	95%CI	
BA	1.35	0.90	–2.02	0.83	0.59	–1.18	1.02	0.81	–1.30	0.99	0.84	–1.16
AD	1.11	0.81	–1.52	0.96	0.69	–1.32	0.79	0.66	–0.95	0.97	0.83	–1.14
AR	0.85	0.67	–1.07	0.89	0.68	–1.15	0.92	0.81	–1.03	0.97	0.86	–1.11

OR, odds ratio; aOR, adjusted odds ratio; BA, bronchial asthma; AD, atopic dermatitis; AR, allergic rhinitis.

[†]Fully adjusted model includes maternal age, maternal smoker, partner smoker, maternal drinking, BMI, maternal education, maternal job, household income, threatened abortion and Preterm labor.

* p for interaction <0.05

P–value for interaction on early preterm birth; BA and Derp1 IgE = 0.053; AD and Derp1IgE = 0.43; AR and Derp1 IgE = 0.98

P–value for interaction on late preterm birth; BA and Derp1 IgE = 0.89; AD and Derp1IgE = 0.079; AR and Derp1 IgE = 0.35

Table S4. Association between threatened abortion, preterm labor, and allergic disease in the Cedar IgE status subgroup.

	Threatened abortion						Preterm labor					
	Cedar IgE (<0.7UA/mL)			Cedar IgE (0.7UA/mL ≤)			Cedar IgE (<0.7UA/mL)			Cedar IgE (0.7UA/mL ≤)		
	aOR [†]	95%CI		aOR [†]	95%CI		aOR [†]	95%CI		aOR [†]	95%CI	
BA	1.04	0.93	-1.17	0.83	0.57	-1.20	1.16	1.05	-1.28	1.05	0.97	-1.14
AD	1.07	0.97	-1.18	0.83	0.60	-1.13	0.99	0.91	-1.07	0.95	0.89	-1.02
AR	1.13	1.04	-1.22	0.86	0.69	-1.08	1.03	0.96	-1.11	1.12	1.06	-1.18

OR, odds ratio; aOR, adjusted odds ratio; BA, bronchial asthma; AD, atopic dermatitis; AR, allergic rhinitis.

[†]Fully adjusted model includes maternal age, maternal smoker, partner smoker, maternal drinking, BMI, maternal education, maternal job, household income and threatened abortion (for Preterm labor).

P-value for interaction on threatened abortion; BA and Cedar IgE = 0.94; AD and Cedar IgE = 0.22; AR and Cedar IgE = 0.45

P-value for interaction on Preterm labor; BA and Cedar IgE = 0.15; AD and Cedar IgE = 0.49; AR and Cedar IgE = 0.17

Table S5. Association between preterm birth and allergic disease in the Cedar IgE status subgroup.

	Early preterm birth (23–31 weeks)							Late preterm birth (32–36 weeks)						
	Cedar IgE (<0.7UA/mL)			Cedar IgE (0.7UA/mL ≤)				Cedar IgE (<0.7UA/mL)			Cedar IgE (0.7UA/mL ≤)			
	aOR [†]	95%CI		aOR [†]	95%CI			aOR [†]	95%CI		aOR [†]	95%CI		
BA	1.18	0.81	–1.72		0.83	0.57	–1.20	1.06	0.87	–1.30	0.94	0.79	–1.13	
AD	1.30	0.94	–1.80	*	0.83	0.60	–1.13	0.88	0.73	–1.06	0.89	0.76	–1.03	
AR	0.76	0.55	–1.03		0.86	0.69	–1.08	1.02	0.88	–1.18	0.87	0.78	–0.98	

OR, odds ratio; aOR, adjusted odds ratio; BA, bronchial asthma; AD, atopic dermatitis; AR, allergic rhinitis.

[†]Fully adjusted model includes maternal age, maternal smoker, partner smoker, maternal drinking, BMI, maternal education, maternal job, household income, threatened abortion and Preterm labor.

* p-value for interaction <0.05

P-value for interaction on early preterm birth; BA and Cedar IgE = 0.11; AD and Cedar IgE = 0.042; AR and Cedar IgE = 0.80

P-value for interaction on late preterm birth; BA and Cedar IgE = 0.24; AD and Cedar IgE = 0.82; AR and Cedar IgE = 0.089