

Association of Maternal History of Allergic Features with Preterm Pregnancy Outcomes in the Japan Environment and Children's Study

Mayko Saito-Abe^{a, b} Kiwako Yamamoto-Hanada^a Kyongsun Pak^c Miori Sato^{a, b}
Makoto Irahara^a Hidetoshi Mezawa^a Hatoko Sasaki^a Minaho Nishizato^a
Kazue Ishitsuka^a Mizuho Konishi^a Limin Yang^a Yukihiro Ohya^a Kohta Suzuki^b
the Japan Environment and Children's Study (JECS) Group

^aMedical Support Center for the Japan Environment and Children's Study, National Center for Child Health and Development, Tokyo, Japan; ^bDepartment of Health and Psychosocial Medicine, Aichi Medical University School of Medicine, Nagakute, Japan; ^cDivision of Biostatistics, Department of Data Management, Center for Clinical Research, National Center for Child Health and Development, Tokyo, Japan

Keywords

Cohort study · Japan Environment and Children's Study · Maternal allergy · Preterm birth · Threatened preterm labor

Abstract

Introduction: Previous studies have reported that maternal asthma increases the risk of preterm birth. We hypothesized that inflammatory reactions caused by allergic diseases might affect the uterine environment and, subsequently, perinatal outcomes. The objective of this study was to examine the associations between allergic features among mothers and preterm pregnancy outcomes in a nationwide birth cohort. **Methods:** We analyzed data from pregnant women obtained from the Japanese Environment and Children's Study (JECS), a nationwide general birth cohort study. We used binomial and multinomial logistic regression models to examine the associations between maternal allergic features and preterm birth, threatened preterm labor (TPL), and preterm premature rupture of the membrane (PPROM). **Results:** A total of 97,683 pregnant women were included. Prevalence of preterm birth, TPL, and PPRM was 4.7, 19.6, and 1.2%, respectively. Maternal history of allergic diseases (asthma, allergic rhinitis, allergic conjunctivitis, food allergy, drug

allergy, and contact dermatitis) increased the risk of TPL (adjusted odds ratio [aOR] = 1.11 [95% CI: 1.06–1.17], aOR = 1.12 [1.08–1.16], aOR = 1.10 [1.04–1.16], aOR = 1.17 [1.09–1.26], aOR = 1.35 [1.23–1.48], and aOR = 1.34 [1.20–1.49], respectively). Although some maternal allergic features showed a negative association with preterm birth, the variables affecting preterm birth differed according to the gestational age of the fetus (22–33 weeks vs. 34–36 weeks). There were no significant associations between maternal allergic features and PPRM. **Conclusion:** Maternal allergic disease, except atopic dermatitis, may increase the risk of TPL. Comorbidity of maternal allergic disorders and perinatal adverse outcomes require further investigation.

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Introduction

Atopic diseases are the most common chronic disorders among pregnant women, and the prevalence of allergy has increased over the last half century. Approxi-

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mately 70% of pregnant women in Japan had IgE sensitization to common allergens, and nearly half of them had a past history of allergic diseases [1]. Previous studies demonstrated that maternal asthma can affect adverse pregnancy outcomes such as preterm birth [2–9]. Our group also found that IgE production and a history of atopic dermatitis were positively associated with small-for-gestational-age (SGA) births in a nationwide birth cohort study (Japan Environment and Children's Study: JECS) [10]. Based on these results, we hypothesized that immunological inflammations related to allergic diseases may affect the uterine environment and perinatal outcomes.

Preterm birth is defined as a birth that occurs before 37 weeks of gestation. This phenomenon is relatively common, occurring in 5–18% of births worldwide [11–13], and it is a major cause of perinatal mortality and morbidity [14, 15]. The rate of preterm birth is increasing in most countries with reliable trend data [16]. Threatened preterm labor (TPL) and preterm premature rupture of the membranes (PPROM) are major prodromes of preterm birth. TPL, which occurs in approximately 9% of all pregnancies, is the leading cause of hospital admission during pregnancy (excluding labor at term) [17, 18]. Although inpatient bed rest has been widely prescribed to prevent preterm birth in women with TPL in Japan, it can induce a number of maternal and infantile problems [19–23]. PPROM occurs in approximately 3–4% of pregnancies and directly precedes 40–50% of all preterm births [24, 25]. Once PPROM is diagnosed, and if there is no immediate indication for delivery, interventions will then be implemented (e.g., antibiotic therapy to prevent infections of the fetus) [26]. It is suggested that antibiotic treatment during pregnancy may have undesired effects regarding the maternal and fetoplacental microbiomes [27].

Although TPL and PPROM do not always precede preterm birth, their prevalence is not low, and they have significant effects on the course of a pregnancy. Unfortunately, treatments for these conditions often carry side effects. To the best of our knowledge, although previous studies have thoroughly examined adverse pregnancy outcomes of preterm birth related to maternal allergic diseases, only a few studies have analyzed the association between maternal allergy and TPL or PPROM [3, 5, 7, 28].

Considering the increasing prevalence of atopic diseases and preterm birth all over the world, we aimed to examine the associations between maternal allergic profiles and perinatal outcomes regarding preterm events in our study population. We also assessed the associations

of preterm pregnancy outcomes (preterm birth, TPL, and PPROM) with allergic features among pregnant women in the JECS birth cohort.

Materials and Methods

Study Design, Setting, and Participants

Our study design was a cross-sectional analysis within a general prospective birth cohort study, the Japan Environment and Children's Study (JECS). As previously described, JECS is a nationwide, multicenter, prospective general birth cohort study [29–31]. JECS was funded by Japan's Ministry of the Environment. It covers a wide geographical area within Japan and comprises 15 regional centers (Hokkaido, Miyagi, Fukushima, Chiba, Kanagawa, Koshin, Toyama, Aichi, Kyoto, Osaka, Hyogo, Tottori, Kochi, Fukuoka, and South Kyushu/Okinawa). Participants including pregnant women and their partners were recruited during the first trimester of pregnancy from hospitals or from local government offices in which the Maternal and Child Health Handbook was distributed. Recruitment was conducted between January 2011 and March 2014.

The eligibility criteria for participants (expecting mothers) were as follows: patients residing in the study areas at the time of recruitment and expecting to retain Japan residency for the foreseeable future; expected delivery date between August 1, 2011, and mid-2014; and the ability to participate in the study without difficulty, including the ability to comprehend the Japanese language and complete the self-administered questionnaire. Our study population was composed of 97,454 mothers and 49,679 fathers.

The JECS was conducted based on the Ethical Guidelines for Medical and Health Research Involving Human Subjects in Japan. The Ministry of the Environment's Institutional Review Board on Epidemiological studies and the Ethics Committees of all participating institutions approved the JECS protocol. Written informed consent was obtained from all participants. The present study was based on the fixed data set "jecs-ag-20160424," released in June 2016.

Assessment of Preterm Complications and Allergic Features

We administered a paper-based questionnaire to pregnant women during their second and third trimesters. Their medical records were transcribed by physicians, nurses/midwives, and/or research staff at 3 separate points in time: upon registration, just after delivery, and at 1 month after delivery. Blood samples were also obtained during the first trimester of pregnancy [1].

All preterm complications were identified based on the obstetrician's diagnosis in the medical record transcription. Preterm birth was defined as a spontaneous or induced delivery before 37 weeks of gestation and was divided into 2 categories: early preterm birth (22–33 weeks of gestation) and late preterm birth (34–36 weeks of gestation) based on the difference in risk of infant morbidity and mortality [32, 33]. TPL is defined as the onset of labor before the end of the 37th week of pregnancy and is characterized by regular uterine contractions and/or premature maturation of the uterine cervix. PPROM refers to a rupture of the fetal membrane with leakage of amniotic fluid at fewer than 37 weeks of gestation [26, 34]. TPL and PPROM were identified if the obstetrician diagnosed them even once during the entire pregnancy. In this

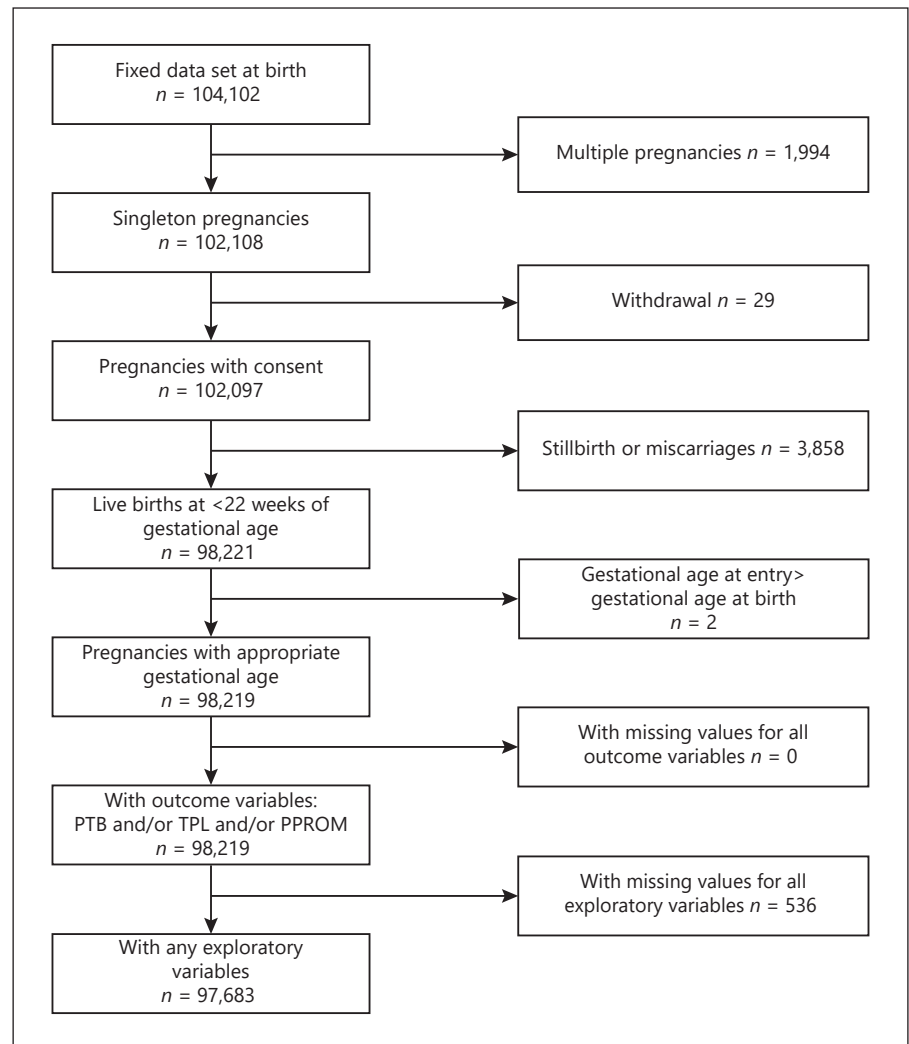


Fig. 1. Flowchart of participant selection in this study. TPL, threatened preterm labor; PPRM, preterm premature rupture of the membranes.

study, preterm birth, TPL, and PPRM were attributed as independent outcomes and were not mutually exclusive.

Allergic disease diagnosis was assessed using a questionnaire. Maternal allergic features included a history of bronchial asthma (BA), allergic rhinitis (AR), atopic dermatitis (AD), allergic conjunctivitis, food allergy (FA), drug allergy, or contact dermatitis. The terms “any allergic disease” (defined as any one of the allergic diseases listed above) and “the number of allergic disease” (defined as the number of allergic diseases listed above) were used as explanatory variables (the latter being added during the post hoc analysis). Total serum and allergen-specific IgE titers were assayed using ImmunoCAP (Thermo Fisher Scientific, Inc., Uppsala, Sweden) and analyzed by an independent clinical laboratory during pregnancy. We used 3 categories of explanatory variables according to the production of maternal IgE log-transformed nonspecific IgE levels, high levels of nonspecific IgE (≥ 170 IU/mL), and IgE sensitization to specific allergens which is defined as any specific IgE (IgE ≥ 0.35 UA/mL) sensitization to either *Dermatophagoides pteronyssinus* (Der p 1), animal dander, Japanese cedar, birch, moth, or egg whites.

Outcomes, Exposure, and Confounders

We set the presence of early/late preterm birth, TPL, or PPRM as a measure of outcome. Maternal allergic features designated as explanatory variables included history of asthma, AR, AD, FA, drug allergy, contact dermatitis, natural, log-transformed nonspecific IgE level, high levels of nonspecific IgE, and IgE sensitization. We selected potential confounders on the basis of their potential association with the exposures and outcomes. We considered 4 categories of variables as potential confounding factors based on previous studies [4, 7, 28]. The maternal baseline characteristics included maternal age, primiparity, marital state, maternal education, annual family income, place of recruitment, and BMI during early pregnancy. The maternal comorbidities included a past history of hypertension, type 1 or 2 diabetes, and pregnancy-related variables including abnormal pregnancy (at least one of the following: pregnancy-induced hypertension, gestational diabetes mellitus, placenta abruption, ectopic pregnancy, placenta previa, hydatidiform mole, or other abnormal pregnancy). Maternal life style habits included smoking and/or alcohol use during pregnancy.

Table 1. Summary of participants' baseline characteristics among mothers in the JECS birth cohort ($N = 97,683$)

Characteristic	$N^{\dagger}$	N (%)
Preterm birth		
Late (34–36 weeks)		3,622 (3.7)
Early (22–33 weeks)	97,683	969 (1.0)
Preterm labor	97,683	19,120 (19.6)
PPROM	96,836	1,132 (1.2)
Infant gender, female	97,675	47,614 (48.7)
Maternal age, years		
<20		857 (0.9)
≥20 and <35	97,679	70,442 (72.1)
≥35		26,380 (27.0)
Primiparous	96,851	56,121 (57.9)
Current marriage	96,472	92,273 (95.6)
History of abnormal pregnancy	96,894	5,993 (6.2)
Hypertension	96,894	459 (0.5)
Type 1 or 2 diabetes	96,894	199 (0.2)
BMI at early pregnancy		
<18.5		15,697 (16.2)
≥18.5 and <25.0	97,136	71,091 (73.2)
≥25.0		10,348 (10.7)
Smoking during pregnancy, yes	96,171	4,650 (4.8)
Alcohol during pregnancy, yes	96,451	9,576 (9.9)
Education completed		
Junior high school		4,634 (4.8)
High school	95,642	70,337 (73.5)
University		20,671 (21.6)
Annual family income, >6 million yen	89,343	23,830 (26.7)
Place of recruitment		
Hokkaido		7,714 (7.9)
Fukushima/Miyagi		21,420 (21.9)
Chiba/Kanagawa		11,934 (12.2)
Koshin		6,976 (7.1)
Toyama		5,295 (5.4)
Aichi	97,683	5,414 (5.5)
Kyoto/Osaka/Hyogo		16,313 (16.7)
Tottori		2,944 (3.0)
Kochi		6,753 (6.9)
Fukuoka/Kumamoto/Miyazaki		12,074 (12.4)
Okinawa		846 (0.9)
Nonspecific IgE (≥170 IU/mL)	87,745	20,456 (23.3)
Log nonspecific IgE		
25th percentile		3.0
Median	87,745	4.1
75th percentile		5.1
IgE sensitization to specific allergens	86,857	64,244 (74.0)
IgE Der p 1 (≥0.35 UA/mL)	86,867	40,873 (47.1)
IgE Japanese cedar (≥0.35 UA/mL)	86,851	48,389 (55.7)
IgE hen egg (≥0.35 UA/mL)	86,862	887 (1.0)
IgE animal dander (≥0.35 UA/mL)	86,841	17,866 (20.6)
IgE moth (≥0.35 UA/mL)	86,846	24,347 (28.0)
Any allergic diseases	96,894	49,373 (51.0)
Asthma	96,894	10,611 (11.0)
AR	96,894	34,912 (36.0)
AD	96,894	15,251 (15.7)
Allergic conjunctivitis	96,894	9,631 (9.9)
FA	96,894	4,696 (4.8)
Drug allergy	96,894	2,505 (2.6)
Contact dermatitis	96,894	1,857 (1.9)

IgE, immunoglobulin E; Der p 1, *Dermatophagoides pteronyssinus*; PPRM, preterm premature rupture of the membranes; JECS, Japan Environment and Children's Study; AR, allergic rhinitis; AD, atopic dermatitis; FA, food allergy. [†] Number of participants without missing value.

Statistical Analyses

The frequencies and percentages of mothers experiencing each allergic disease and outcomes were illustrated in Venn diagrams and Upset plots enabling the visualization of 4 complications of allergic diseases and the intersections of multiple conditions about the outcomes. To examine the association between adverse perinatal outcomes and maternal allergic features, we used a multinomial logistic regression model for early and late preterm birth, designating non-preterm birth as a reference category. We used a binomial logistic regression model for TPL and PPRM. The results are shown as estimates of the unadjusted (univariate model) and adjusted (multivariable model) odds ratios (OR and aOR, respectively) and their associated 95% confidence intervals (CI). We estimated aORs using multivariable analysis considering the potential confounders, implementing the multiple imputation by a chained equation algorithm with 20 iterations (R package MICE, version 3.3.0) [35]. We also attributed a p value for the estimates in the tables for reference. This study was exploratory, and it aimed to assess the magnitude of the association between maternal allergy status and preterm birth, TPL, or PPRM. Therefore, we did not define the statistical significance of the p value at the design stage. All statistical analyses were assembled and conducted by a certified biostatistician (K.P.) using R statistical software, version 3.5.1 (The R Foundation, Vienna, Austria) [36].

Results

Characteristics of the Study Population

Figure 1 shows the flowchart of patient selection in this study. For this analysis, we included mothers with singleton deliveries at ≥22 weeks of gestation ($n = 98,221$). Mothers with unclear data for gestational age ($n = 2$) or with missing relevant data ($n = 536$) were excluded from the study. In total, 97,683 mothers were enrolled.

Table 1 shows the maternal characteristics. Based on maternal age, 857 participants (0.9%) were under 20 years old, 70,442 (72.1%) were older than 20 years and under 35 years, and 26,380 (27.0%) were aged 35 years and over. Primiparous births occurred in 56,121 (57.9%) mothers. We found that 3,622 (3.7%) mothers experienced early preterm birth (22–33 weeks of gestation), 969 (1.0%) experienced late preterm birth (34–36 weeks of gestation), and 19,120 (19.6%) mothers experienced TPL. PPRM occurred in 1,132 (1.2%) mothers. IgE sensitization to specific allergens was found in 74% of the mothers. The maternal prevalence of any allergic disease, AD, and asthma was 51, 15.7, and 11%, respectively. Figure 2 shows the overlapping of the history of 4 main allergic diseases (BA, AR, AD, and FA) among the mothers. Almost half of the mothers had a history of AR alone, but most had for AD, FA, and BA in various combinations. Figure 3 shows the overlapping of mothers experiencing each preterm-related outcome.

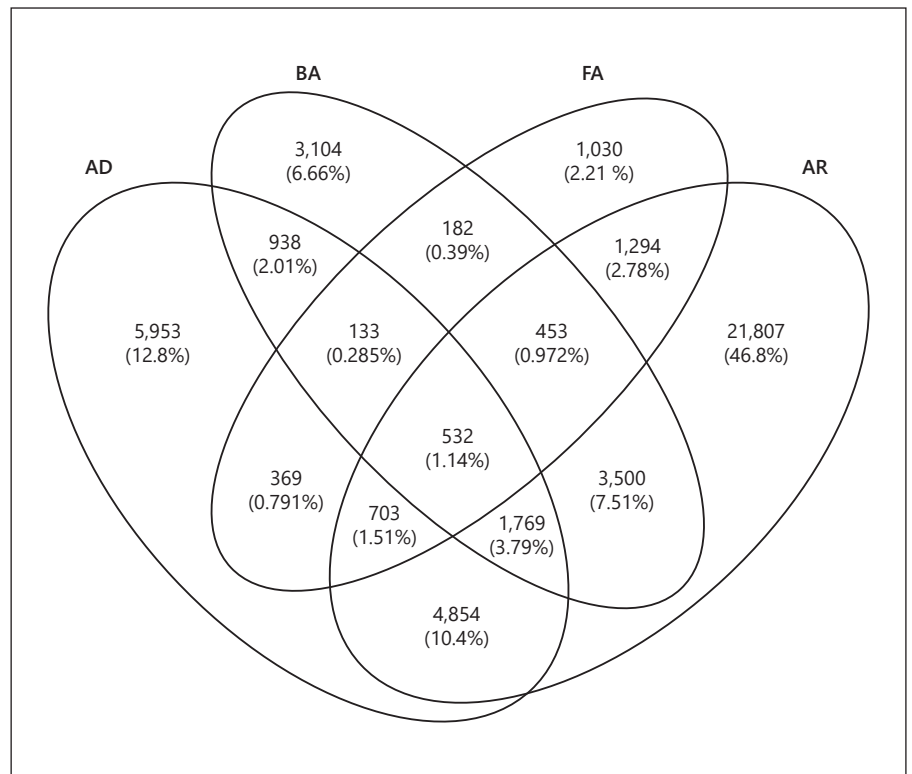


Fig. 2. Four main allergic disease combinations of participants (asthma, AR, AD, and FA). BA, bronchial asthma; AR, allergic rhinitis; AD, atopic dermatitis; FA, food allergy.

Associations between Maternal Allergic Features and Preterm Birth

Table 2 shows the associations between maternal allergic features and preterm birth. High levels of non-specific IgE (≥ 170), IgE sensitization to animal dander and moth, any maternal allergic diseases, and maternal history of AD showed a negative association with late preterm birth (aOR = 0.89 [0.82–0.97], aOR = 0.91 [0.84–1.00], aOR = 0.92 [0.84–1.00], aOR = 0.92 [95% CI = 0.86–0.99], and aOR = 0.86 [0.78–0.95], respectively). However, there was no significant association between AD, high levels of non-specific IgE, or IgE sensitization to animal dander and early preterm birth (aOR = 0.93 [0.78–1.12], aOR = 1.00 [0.85–1.16], and aOR = 0.98 [0.84–1.16], respectively). Although allergic conjunctivitis showed a negative association with early preterm birth (aOR = 0.76 [0.60–0.96]), we did not find the same association with late preterm birth (aOR = 1.01 [0.90–1.12]).

Table 3 shows the associations between the number of allergic diseases of participants and preterm birth as a post hoc analysis. There was a significant negative association between the number of allergic diseases and late preterm birth (aOR = 0.96 [0.93–0.99]).

Associations between Maternal Allergic Features and TPL

Table 4 shows the associations between maternal allergic features and TPL. In the multivariable logistic regression analysis, high levels of non-specific IgE were negatively associated with TPL (aOR = 0.95 [0.92–0.99]), and all the evaluated allergic diseases except AD were positively associated with TPL (any allergic diseases (aOR = 1.12 [1.08–1.15]), asthma (aOR = 1.11 [1.06–1.17]), rhinitis (aOR = 1.12 [1.08–1.16]), allergic conjunctivitis (aOR = 1.10 [1.04–1.16]), FA (aOR = 1.17 [1.09–1.26]), drug allergy (aOR = 1.35 [1.23–1.48]), and contact dermatitis (aOR = 1.34 [1.20–1.49]), respectively). In addition, there was a significant positive association between the number of allergic diseases and TPL (aOR = 1.07 [1.05–1.08]) (Table 3).

Associations between Maternal Allergic Features and PPRM

There were no significant associations between maternal allergic features and PPRM (Table 5).

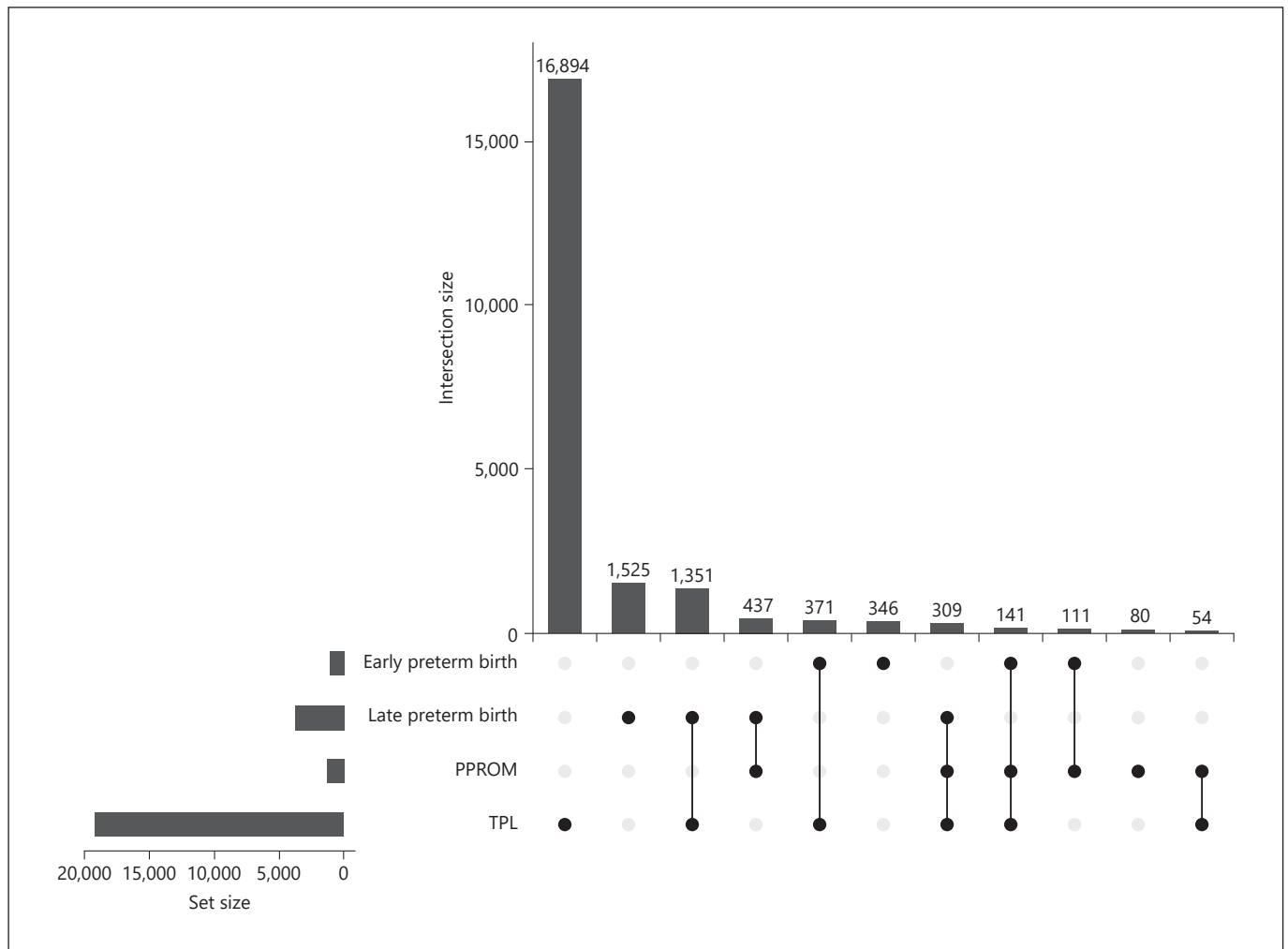


Fig. 3. Upset plot of preterm-related outcome combinations (early preterm birth, late preterm birth, TPL, and PPRM). TPL, threatened preterm labor; PPRM, preterm premature rupture of the membranes.

Discussion

In the present study, we succeeded in evaluating the associations of preterm birth, TPL, and PPRM with allergic features in pregnant Japanese women based on data collected from a nationwide birth cohort study. Late preterm birth showed a significant negative association with maternal history of AD. In contrast, maternal history of allergic disease, with the exception of AD, showed a positive association with TPL. Although early preterm birth showed a negative association with a maternal history of allergic conjunctivitis, the clinical significance of this result still needs careful consideration. Early preterm birth was found in only 1% of the mothers, and the 95% CI of the odds ratio was estimated broadly.

Maternal Allergic Features and Preterm Birth

In a previous study, Tronnes et al. [4] reported that severe maternal AD was associated with a decreased risk of preterm birth (relative risk [RR] = 0.90 [0.86–0.93]) in a Norwegian national cohort study that included 2 million births. The results of our study were consistent with this report. The underlying mechanisms for these associations are unclear in both of these epidemiological studies, but it is noteworthy that 2 different national cohort studies showed the same protective effects of AD against preterm birth. We also reported a negative association between log-transformed nonspecific IgE levels, high levels of nonspecific IgE, and sensitization to animal dander and late preterm birth. It has been suggested that high production of IgE

Table 2. Results of univariate and multivariable multinomial logistic regression for maternal allergic features and early/late preterm birth

Maternal allergic features	Early preterm birth				Late preterm birth			
	univariate		multivariable (for multiply imputed data)		univariate		multivariable (for multiply imputed data)	
	OR [†]	95% CI lower upper	aOR [†]	95% CI lower upper	OR [‡]	95% CI lower upper	aOR [‡]	95% CI lower upper
Log (nonspecific IgE)	1.00	0.96 1.05	1.00	0.96 1.05	0.97	0.95 0.99	0.97	0.95 0.99
High nonspecific IgE (≥ 170)	1.01	0.86 1.18	1.00	0.85 1.16	0.89	0.82 0.97	0.89	0.82 0.97
IgE sensitization to specific allergens (≥ 0.35)	0.95	0.82 1.11	0.98	0.84 1.14	0.95	0.88 1.03	0.96	0.89 1.04
IgE_Der p	0.87	0.76 0.99	0.89	0.77 1.01	0.93	0.87 1.00	0.94	0.87 1.01
IgE_Japanese cedar	0.91	0.79 1.04	0.95	0.82 1.08	0.97	0.90 1.04	0.99	0.92 1.06
IgE_hen egg	0.89	0.44 1.79	0.87	0.44 1.73	0.82	0.56 1.20	0.80	0.55 1.16
IgE_animal dander	0.96	0.81 1.14	0.98	0.84 1.16	0.90	0.82 0.98	0.91	0.84 1.00
IgE_moth	1.03	0.89 1.19	1.00	0.86 1.17	0.92	0.85 1.00	0.92	0.85 0.99
Any allergic diseases	0.95	0.84 1.08	0.95	0.84 1.09	0.93	0.87 0.99	0.92	0.86 0.99
Asthma	0.97	0.79 1.19	0.91	0.74 1.12	1.01	0.91 1.12	0.98	0.88 1.09
AR	0.91	0.79 1.04	0.91	0.80 1.04	0.95	0.88 1.02	0.94	0.88 1.01
AD	0.89	0.75 1.07	0.93	0.78 1.12	0.84	0.76 0.93	0.86	0.78 0.95
Allergic conjunctivitis	0.76	0.60 0.97	0.76	0.60 0.96	1.01	0.90 1.13	1.01	0.90 1.12
FA	1.25	0.96 1.64	1.18	0.90 1.55	0.99	0.84 1.15	0.95	0.81 1.12
Drug allergy	1.19	0.82 1.73	1.07	0.73 1.55	1.09	0.89 1.33	1.03	0.84 1.26
Contact dermatitis	1.04	0.66 1.64	0.93	0.59 1.48	0.84	0.64 1.09	0.80	0.61 1.04

aOR and 95% CIs were estimated with potential confounders including maternal age, primiparity, marital state, past history of hypertension, type 1 or 2 diabetes, abnormal pregnancy, BMI at early pregnancy, smoking and alcohol use during pregnancy, maternal education, annual family income, and place of recruitment. OR, odds ratio; aOR, adjusted odds ratio; CI, confidence interval; AR, allergic rhinitis; AD, atopic dermatitis; FA, food allergy. [†] (Early preterm birth)/(normal delivery). [‡] (Late preterm birth)/(normal delivery).

Table 3. Results of the post hoc analysis – the univariate and multivariable multinomial logistic regression for the number of allergic diseases[†] and early/late preterm birth, TPL, and PPRM

Outcome	Univariate				Multivariable (for multiply imputed data)			
	OR [‡]	95% CI		<i>p</i> value	aOR [‡]	95% CI		<i>p</i> value
		lower	upper			lower	upper	
Early preterm birth	0.95	0.89	1.01	0.111	0.94	0.88	1.01	0.071
Late preterm birth	0.97	0.93	1.00	0.037	0.96	0.93	0.99	0.018
TPL	1.06	1.04	1.07	<0.0001	1.07	1.05	1.08	<0.0001
PPROM	1.01	0.95	1.07	0.797	1.01	0.95	1.07	0.788

aOR and 95% CIs were estimated with potential confounders, including maternal age, primiparity, marital status, past history of hypertension, type 1 or 2 diabetes, abnormal pregnancy, BMI at early pregnancy, smoking and alcohol use during pregnancy, maternal education, annual family income, and place of recruitment. OR, odds ratio; aOR, adjusted odds ratio; CI, confidence interval; TPL, threatened preterm labor; PPRM, preterm premature rupture of the membranes. [†] Number of allergic diseases defined as the number of past histories of allergic diseases among mothers. [‡] (Each outcome)/(normal delivery).

Table 4. Results of univariate and multivariable binomial logistic regression for maternal allergic features and TPL

Maternal allergy features	Univariate				Multivariable (for multiply imputed data)			
	OR [†]	95% CI		<i>p</i> value	aOR [†]	95% CI		<i>p</i> value
		lower	upper			lower	upper	
Log (nonspecific IgE)	0.99	0.98	1.00	0.028	0.99	0.98	1.00	0.080
High nonspecific IgE (≥170)	0.94	0.91	0.98	0.004	0.95	0.92	0.99	0.017
IgE sensitization to specific allergens (≥0.35)	0.98	0.94	1.01	0.215	0.97	0.93	1.01	0.098
IgE_Der p	0.97	0.93	1.00	0.038	0.97	0.94	1.00	0.087
IgE_Japanese cedar	1.02	0.98	1.05	0.334	0.98	0.95	1.02	0.288
IgE_hen egg	0.94	0.79	1.11	0.472	0.97	0.82	1.15	0.732
IgE_animal dander	0.96	0.92	1.00	0.029	0.97	0.93	1.01	0.190
IgE_moth	0.97	0.93	1.00	0.078	0.97	0.93	1.00	0.082
Any allergic diseases	1.10	1.06	1.13	<0.001	1.12	1.08	1.15	<0.001
Asthma	1.10	1.04	1.15	<0.001	1.11	1.06	1.17	<0.001
AR	1.10	1.07	1.14	<0.001	1.12	1.08	1.16	<0.001
AD	1.00	0.96	1.05	0.949	1.01	0.97	1.05	0.717
Allergic conjunctivitis	1.08	1.03	1.14	0.003	1.10	1.04	1.16	<0.001
FA	1.12	1.04	1.20	0.002	1.17	1.09	1.26	<0.001
Drug allergy	1.33	1.21	1.46	<0.001	1.35	1.23	1.48	<0.001
Contact dermatitis	1.33	1.20	1.49	<0.001	1.34	1.20	1.49	<0.001

aOR and 95% CIs were estimated with potential confounders including maternal age, primiparity, marital state, past history of hypertension, type 1 or 2 diabetes, abnormal pregnancy, BMI at early pregnancy, smoking and alcohol use during pregnancy, maternal education, annual family income, and place of recruitment. OR, odds ratio; aOR, adjusted odds ratio; CI, confidence interval; TPL, threatened preterm labor; AR, allergic rhinitis; AD, atopic dermatitis; FA, food allergy. [†] (TPL)/(no TPL).

results from inflammation in AD; this is consistent with the observed negative association between AD and preterm birth. Recently, we reported that maternal history of AD was associated with an increased risk of SGA birth (aOR = 1.11 [1.00–1.24]) [10], presumably via in-

trauterine growth restriction. If maternal history of AD decreases preterm birth, then intrauterine growth restriction babies tend to be born as SGA babies. Therefore, our previous findings are also consistent with the current study.

Table 5. Results of univariate and multivariable binomial logistic regression for maternal allergic features and PPRM

Variable	Univariate				Multivariable (for multiply imputed data)			
	OR [†]	95% CI		<i>p</i> value	aOR [†]	95% CI		<i>p</i> value
		lower	upper			lower	upper	
Log (nonspecific IgE)	0.96	0.92	1.01	0.103	0.97	0.93	1.01	0.108
High nonspecific IgE (≥ 170)	0.95	0.81	1.10	0.455	0.95	0.82	1.10	0.520
IgE sensitization to specific allergens (≥ 0.35)	0.99	0.86	1.13	0.829	0.99	0.86	1.14	0.854
IgE_Der p	0.94	0.83	1.06	0.319	0.95	0.84	1.07	0.384
IgE_Japanese cedar	1.08	0.95	1.22	0.255	1.07	0.93	1.21	0.350
IgE_hen egg	1.08	0.59	1.96	0.812	1.05	0.59	1.88	0.868
IgE_animal dander	0.92	0.78	1.07	0.279	0.93	0.80	1.09	0.379
IgE_moth	1.01	0.88	1.16	0.915	0.99	0.86	1.13	0.841
Any allergic diseases	1.02	0.91	1.15	0.735	1.03	0.91	1.16	0.637
Asthma	0.93	0.77	1.13	0.459	0.91	0.75	1.10	0.318
AR	1.02	0.90	1.15	0.801	1.03	0.91	1.17	0.634
AD	0.94	0.80	1.11	0.480	0.96	0.81	1.13	0.593
Allergic conjunctivitis	1.17	0.97	1.41	0.095	1.17	0.97	1.41	0.095
FA	1.11	0.86	1.44	0.434	1.09	0.84	1.42	0.517
Drug allergy	1.22	0.87	1.71	0.260	1.17	0.83	1.64	0.376
Contact dermatitis	0.69	0.42	1.15	0.158	0.67	0.40	1.13	0.132

aOR and 95% CIs were estimated with potential confounders including maternal age, primiparity, marital state, past history of hypertension, type 1 or 2 diabetes, abnormal pregnancy, BMI at early pregnancy, smoking and alcohol use during pregnancy, maternal education, annual family income, and place of recruitment. PPRM, preterm premature rupture of the membranes; OR, odds ratio; aOR, adjusted odds ratio; CI, confidence interval; AR, allergic rhinitis; AD, atopic dermatitis; FA, food allergy. [†] (PPROM)/(no PPRM).

In the 1990s, Th2 immunity arose as an important factor of maternal tolerance toward fetal alloantigens during pregnancy, protecting fetuses from maternal Th1-cell attack [37]. However, Th2-dominant immunity was also reported in recurrent miscarriages [38]. Therefore, it is believed that an adequate balance of Th1/Th2 immunity (i.e., a response slightly shifted to a Th2-type immunity) may be suitable for the maintenance of pregnancy [39, 40]. These observations, combined with our present results, indicate that mothers with a history of allergic disease may tend to maintain an adequate balance of Th1/Th2 immunity during pregnancy, which may result in a decreased likelihood of preterm birth. Recently, the association between several chemokines and preterm birth has been highlighted by the use of multiplex methodologies [41]. Future studies are required to explore the mechanism by which IgE or chemokine levels affect pregnancy outcomes.

We did not find any association between maternal asthma and preterm birth in the current study. However, various studies including a large national cohort and meta-analysis have shown that maternal asthma increases the risk of adverse complications during pregnancy.

Tronnes et al. [4] reported that maternal asthma was associated with an increased risk of preterm birth (RR = 1.15 [1.10–1.21]) in their national cohort, and Murphy et al. [9] also reported a similar trend (RR = 1.41 [1.22–1.61]). They also reported that the relative risk of preterm birth was reduced to nonsignificant levels by active asthma management (RR = 1.07 [0.91–1.26]) in their meta-analysis [9]. Recently, Yland et al. [8] estimated the RRs of adverse perinatal outcomes, including preterm birth, by comparing pregnancies with differing asthma disease status. Their study found associations between asthma severity and SGA and between exacerbations late in pregnancy and preterm delivery and NICU admission [8]. Considering these trends, the control level and severity of maternal asthma during pregnancy plays an important role in the risk of adverse outcomes. In the present study, maternal asthma was associated with an increased risk of TPL but not of preterm birth. We used the information about lifetime prevalence of asthma reported by the mothers; it is possible that the effect of maternal asthma on preterm perinatal outcomes was underestimated in the current study. The effects of maternal asthma on adverse pregnancy outcomes are inconsistent across the

studies, potentially due to differences in the definition of exposure.

Although the relationships between maternal asthma and adverse pregnancy outcomes were well examined in the previous study, their pathophysiologic mechanisms were not fully understood. Demissie et al. [42] proposed several mechanisms, including the following: (1) a common underlying etiology for the irritability or hyperactivity of both uterine and bronchial smooth muscles; (2) hypoxia secondary to maternal asthma; (3) release of bioactive mediators; and (4) medications used to treat asthma during pregnancy [43]. We had hypothesized that immunological inflammation related to allergic diseases might affect the uterine environment, which may add an explanation to their hypothesis; however, further studies regarding the mechanism are necessary.

Maternal Allergic Features and TPL

TPL was much more common among our study participants than preterm birth; almost 20% of the mothers had a diagnosis of TPL, while 4.7% were diagnosed with preterm birth. We revealed that mothers with a history of any allergic disease showed a significant positive association with TPL, especially asthma, rhinitis, allergic conjunctivitis, FA, drug allergy, and contact dermatitis. In addition, it was also found that the odds of TPL increased as the number of histories of allergic disease among mothers increased. It was indicated that the number of diseases among mothers can be a proxy for a more severely affected population in the context of allergic inflammation. Kramer et al. [28] showed that women with physician-diagnosed asthma or hay fever symptoms in last 12 months were at an increased risk of TPL (RR = 2.21 [1.07–4.60] and RR = 2.50 [1.26–4.94], respectively). However, women with a history of eczema from childhood, eczema symptoms in last 12 months, or high maternal nonspecific IgE during pregnancy (>100, >240, and >750) did not demonstrate significant risk in their case-control study [28]. These results are consistent with those of the present study.

The current study showed that maternal drug allergy and contact dermatitis conferred a stronger association with TPL than the other assessed maternal allergic diseases. AD is characterized by a Th2 response to environmental antigens [44], but contact dermatitis is predominantly mediated by Th1 lymphocytes [45]. In drug hypersensitivity, mechanistically, drugs can induce all types of immunological reactions, but one of the most common is the T-cell-mediated reaction [46]. Specifically, non-IgE-mediated allergic reactions may play an important role in

the association between allergic diseases and TPL, as we found that mothers with high levels of nonspecific IgE showed a negative association with TPL. Therefore, we can hypothesize that cell-mediated immunological changes might affect TPL. When pregnant women have Th1-dominant immunity, they tend to have a history of non-IgE-mediated allergic diseases such as contact dermatitis or delayed-type drug allergy and can also be more prone to TPL during pregnancy. Further research is necessary to verify this hypothesis.

It should be noted that the risk factors for TPL and preterm birth were not identical in this study. Although preterm labor does not always lead to premature delivery (Fig. 3 shows that most mothers who experienced TPL in the current study did not result in preterm birth), pregnant women who have been diagnosed with preterm labor require careful follow-up, rest, and occasionally hospitalization including tocolytic treatment [23, 47]. However, it is known that prolonged bed rest can induce various problems in pregnant women such as thrombosis [19, 20], weight loss [48], and depressive symptoms [22]. The use of tocolytic drugs can also increase the risk of adverse side effects such as maternal lung edema, granulocytopenia, rhabdomyolysis, and fetal radiographic bone abnormalities [49–53]. Beta-2 receptor agonist is one of the most commonly used tocolytic agents in Japan, but Ogawa et al. [53] showed that exposure to beta-2 receptor agonist in utero may be a risk factor for childhood asthma [42]. Therefore, the prevention of TPL itself is very important.

Maternal Allergic Features and PPRM

The 2 previous studies on the association between maternal asthma and perinatal adverse outcomes including PPRM have yielded inconsistent results. Wen et al. [7] showed, in their retrospective cohort study, that maternal asthma conferred an increased risk of PROM (aOR = 1.49 [1.37–1.63]) and preterm labor (aOR = 1.78 [1.53–2.07]), but Rejno et al. [5] did not show any significant difference for either outcome in their prospective cohort study. In the current study, we found no significant association between maternal allergic diseases and PPRM, while TPL showed significantly higher odds. To examine this discordance, looking at the distribution of mothers diagnosed with TPL and PPRM, 16,894 mothers were diagnosed with TPL only, while only 504 mothers were diagnosed with both TPL and PPRM (shown in Fig. 3). From this, it was considered that one of the causes was that the number of mothers diagnosed with PPRM was extremely small and the detection power was insufficient. Further

studies are required to understand the association between maternal allergic features and PPRM.

Limitations and Strengths

One strength of the present study was that perinatal adverse outcomes were defined according to the doctor's diagnosis using data from medical charts in a large-scale national cohort. Additionally, this is the first study to assess the associations between maternal allergic profiles and TPL/PPROM – not only preterm birth – in an Asian population. We also examined various maternal allergic features including IgE production as explanatory variables, while most previous studies focused solely on maternal asthma.

However, an important limitation is to be considered when interpreting the results presented in this study. Information on the severity, timing of diagnosis, and treatments of the maternal allergic diseases and TPL was not collected in our questionnaire and medical record transcription. We used lifetime prevalence of maternal allergic diseases in the study; hence, disease activity during pregnancy was unclear. The diagnosis of TPL depended on each obstetrician; therefore, it may have ranged anywhere from a pregnant woman complaining of light uterine contractions in an outpatient clinic to a pregnant woman needing hospitalization (including tocolytic treatment) to control ongoing preterm labor. In fact, the prevalence of TPL in this study was higher than previously reported [17, 18], and most of them were expected to be well controlled or basically mild based on the fact that most women with TPL in this study did not have preterm births. We found some significant associations between maternal allergic diseases and preterm outcomes, although they may have been underestimated.

In summary, this study suggests that maternal allergic disease, with the exception of AD, increases the risk of TPL, whereas AD and high levels of nonspecific IgE display inverse associations with preterm birth. In addition, these relationships were significantly influenced by the number of the history of allergic disease. Our results highlighted the comorbidity of maternal allergic disorders and TPL and suggested that greater consideration is needed when following pregnant women with allergic diseases in a clinical setting, especially in the case of multiple allergic disorders. Screening and intervention for maternal allergic diseases may be considered to reduce the risk of TPL in these instances; however, further studies are required to confirm their usefulness. Accumulation of evidence on the relationships between maternal allergic features and TPL and preterm birth may lead to a

decrease in adverse pregnancy outcomes and an increase in the quality of life of pregnant women, and it may also ultimately save medical resources.

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Statement of Ethics

The JECS was conducted based on the Ethical Guidelines for Medical and Health Research Involving Human Subjects in Japan. The Ministry of the Environment's Institutional Review Board on Epidemiological studies and the Ethics Committees of all participating institutions approved the JECS protocol (No. 10091001). Written informed consent was obtained from all participants.

Conflict of Interest Statement

None of the authors have a conflict of interest in relation to this work. The authors have no ethical conflicts to disclose.

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Author Contributions

Research staff at the 15 regional centers of the JECS collected data. The final version of the data set (jecs-ag-20160424) was fixed and released by the National Center of the JECS (The National In-

stitute for Environmental Studies). K.P. conducted statistical analysis of the data set. All authors contributed to analysis of the study results. M.S. wrote the first draft of the manuscript. All authors approved the final version of the manuscript.

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